Comparison of effects of sustained isocapnic hypoxia on ventilation in men and women

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Sajkov, Dimitar, Alister Neill, Nicholas A. Saunders, and R. Douglas McEvoy. Comparison of the effects of sustained isocapnic hypoxia on ventilation in men and women. J. Appl. Physiol. 83(2): 599–607, 1997.—Sleep-related respiratory disturbances are more common in men than in premenopausal women. This might, in part, be due to different susceptibilities to the respiratory depressant effects of hypoxia. Therefore, we compared ventilation during 10 min of baseline room-air breathing and 20-min sustained isocapnic hypoxia (fractional inspired O2 = 11%, arterial saturation of O2 = 80%) followed by 10 min of breathing 100% O2 in normal men and in 10 women in the follicular phase of the menstrual cycle. Control measurements were made during two transitions from room air (10 min) to 100% O2 (10 min) and averaged. Inspired minute ventilation (VI) after 2 min of hypoxia was the same in men and women [131 ± 6.1% baseline for men, 136 ± 7.7% baseline for women; not significant (NS)] and declined to the same level after 20 min (115 ± 5.0% baseline for men, 116 ± 6.6% baseline for women; NS) associated with a similar decline in inspiratory time and tidal volume. Breathing frequency did not change. VI decreased transiently during subsequent 100% O2 breathing in both men and women, associated with reduced frequency and duty cycle and increased expiratory time. The fall in VI was significantly greater than that observed during control hypoxia experiments in men but not in women. We conclude that ventilatory responses to sustained isocapnic hypoxia do not differ between awake healthy men and women in the follicular phase of their menstrual cycle. However, after termination of isocapnic hypoxia, men appear to depress their ventilation to a greater degree than women.

METHODS

Subject Selection

Twenty subjects (age 19–47 yr; 10 men and 10 premenopausal women) were included in the study. With the use of history and physical examination and routine hematologic and biochemical tests, subjects were confirmed to be healthy. All women subjects were studied in the follicular phase of the menstrual cycle between days 5 and 10. Women taking oral contraceptives were excluded to minimize the respiratory stimulant effects of progesterone (32, 35). The study was approved by the Research and Ethics Committee of the Daw Park Repatriation General Hospital, and all subjects gave written informed consent.

Study Design

Each subject underwent a control study followed by an experimental (sustained isocapnic hypoxia) study. These were conducted on separate days in 18 of 20 subjects. In two subjects, the experiments were conducted on the same day, and at least 20 min separated the studies.

Subjects were asked to report to the laboratory at ~1000, after eating a light breakfast and after refraining from alcohol and caffeine for at least 8 h. All subjects were studied awake in a soundproof room separate from the monitoring room where physiological signals were recorded and the investigators manipulated the inspired gases (see Gas delivery during sleep, there is an increased prevalence of breathing disorders, such as snoring and sleep apnea syndromes, in men compared with women (25, 34). Exogenous factors such as smoking and alcohol consumption may contribute to this gender bias. However, gender differences in upper airway anatomy (8), physiological control of upper airway muscles (26), and ventilatory responses to chemical stimuli may also be important.

Hypoxia in the range of 70–90% arterial saturation of O2 (SaO2) is a strong respiratory stimulant. However, sustained isocapnic hypoxia for 20–30 min produces a biphasic ventilatory response in which an early stimulatory phase is followed by a roll-off or reduction of ventilation toward baseline values (4, 12, 13, 29, 30). Some investigators (5, 16, 20) have shown that, on cessation of hypoxic breathing, an immediate suppression of ventilation occurs below baseline values. Ventilatory depression during and after a sustained hypoxic stimulus is thought to occur because of the release of inhibitory neurotransmitters and neuromodulators, such as γ-aminobutyric acid and endogenous opioids (13). Hypoxia-induced depression of ventilation is possibly relevant to the pathogenesis of sleep-disordered breathing because it carries the potential to exaggerate sleep hypoventilation. Also, an undershoot of respiratory drive immediately posthypoxia is a potential cause for ventilatory instability and central or obstructive apneas (2, 15).

We are unaware of previous studies that have compared the effects of sustained isocapnic hypoxia in men and women. Although a number of studies have investigated the influence of gender on the ventilatory responses to progressive, short-term (5–10 min) isocapnic hypoxia, no consistent findings have emerged. In the awake state, women compared with men have been reported to have lower (32), higher (1), and equal (17, 27) hypoxic ventilatory response. However, the ventilatory response to progressive short-term hypoxia has been found to be more depressed in men than in women after alcohol consumption (23) and during non-rapid-eye-movement sleep (31). We hypothesized that men might also be more susceptible to the ventilatory depressant effects of sustained isocapnic hypoxia. Therefore, in the present study, we compared the ventilatory responses to sustained (20 min) isocapnic hypoxia in awake healthy men and women.
ery). Subjects were seated comfortably, listened to relaxing music through headphones, and were observed by video camera. The temperature in the laboratory was controlled and held constant at 21°C.

To confirm that subjects remained awake during the experiments, continuous recordings of electroencephalograms (EEG; C3–A1 placement), electrooculograms (EOG), and electromyograms (EMG) were performed. Continuous electrocardiogram recordings were also made.

Isocapnic hypoxia. Sustained isocapnic hypoxia experiments consisted of 10 min of baseline room-air breathing, followed by the rapid introduction of hypoxia (3 breaths of 100% N₂, followed by an inspired gas concentration of 11% O₂-89% N₂) that was continued for 20 min. Isocapnic conditions (± 1 mmHg) were maintained during hypoxia by a variable manual bleed of CO₂ into the inspiratory side of the breathing circuit. After 20 min of isocapnic hypoxia, 100% O₂ was administered for 10 min. The 100% O₂ was given to achieve a rapid increase in alveolar PO₂, thereby allowing changes in posthypoxic ventilation to be compared between subjects independent of individual differences in the time required to wash out the hypoxic gas from the lungs. The addition of CO₂ to the inspiratory line was ceased immediately on switching to 100% O₂ breathing.

Control. Control measurements were performed to establish the effects of hyperoxia (100% O₂) on ventilation. This was necessary to separate the known transient ventilatory depressant effect of hyperoxia per se (9, 11) from any ventilatory depressant effect of sustained hypoxia on baseline ventilation. In each control experiment, 10 min of baseline room-air breathing were followed by 10 min of 100% O₂ breathing. No attempt was made to control end-tidal PCO₂ (PETCO₂) in control experiments. At the end of the hypoxic period, subjects were given five breaths of N₂ before switching back to room-air breathing. Two sets of control measurements were undertaken sequentially in each subject to increase the number of observations of the normoxia-hypoxia transition, and the results were averaged.

Gas delivery. Gas mixtures were introduced to the inspiratory side of the breathing circuit through a five-way Gatlin-Shape valve (series 2440C, Hans Rudolph, Kansas City, MO). This valve has a single outlet, which was connected to the inspiratory tubing, and four separate inlets, three of which were attached to reservoir bags containing 100% O₂, 100% N₂, or 11% O₂-89% N₂ mixture, respectively. The fourth inlet was open to room air. The inlets were opened or closed rapidly and silently by balloon inflation, using a pressure source and a system of solenoid valves that was controlled remotely from the monitoring room.

Measurements

Ventilation. Ventilation was measured by using a tightly fitting Downs full-face mask (dead space = 75–100 ml, depending on facial configuration), with built-in unidirectional valves and an external CO₂ leak detector. A pneumotachograph (PT36, Erich Jäger, Germany) was placed in the inspiratory side of the circuit to measure flow, from which tidal volume (VT) was recorded by electronic integration. The resistance of the inspiratory circuit was <1 cmH₂O·l⁻¹·s⁻¹. Respiratory frequency (f), inspired minute ventilation (Vi), and indexes of ventilatory timing [i.e., duration of the respiratory cycle (Tr), inspiratory time (Ti), expiratory time (Te), inspiratory fraction of respiration (Ti/Tr), and inspiratory flow rate (VT/Ti)] were computed and averaged for selected 1-min periods during experiments (see Data Analysis and Statistics). Minute ventilation and VT were measured for every breath, but to enable the large quantity of data to be handled reasonably, measures of ventilatory timing were obtained by sampling alternate breaths when f was ≥10 breaths/min. When breathing f fell below 10 breaths/min, all breaths were sampled.

Because a pneumotachograph was used for measurement of flow and volume, it was necessary to correct the measurements of inspired gas volume for the different viscosities of the gas mixtures used. The major change in inspired gas viscosity in our experiments occurred during O₂ breathing. Correction factors used were derived by repeated 1-liter calibrations (1-liter calibration syringe, Hans Rudolph) with the use of the various gas mixtures employed in the experiments. The volume signal, using 1-liter of room air as the calibrating signal, was assigned a value of unity, and the derived correction factors for the other gas mixtures are shown in Table 1. These experimentally determined correction factors were within 2% of those determined theoretically by using Poiseuille’s equation.

Respiratory gases and SaO₂. Mask CO₂ and O₂ concentrations were continuously sampled (POET II models 602–3 and 602–1, Criticare Systems, Waukesha, WI) to provide PETCO₂ and end-tidal PO₂ (PETO₂). Pulse oximetry (finger probe) was recorded continuously by using the POET II 602–1 monitor. The minimum Sato₂ for each sampled period is reported.

All physiological signals were recorded with the use of a computerized data-acquisition system (Sleepwatch, Compumedics, Melbourne, Australia). Digital sampling speeds were 125 Hz (for EEG, EOG, and EMG) and 50 Hz (for respiratory signals).

Data Analysis and Statistics

The Student’s t-test was used to compare baseline variables between men and women, and the χ² test was used to compare categorical variables. Ventilatory parameters (Vi, VT, f, TT, Ti, Te, Ti/Tr, and VT/Ti) were calculated for minutes 2, 4, 6, 8, and 10 of the 10-min baseline periods and then averaged. Subsequent results were expressed in absolute terms and as a percentage of the corresponding average baseline value. Ventilatory parameters were measured for minutes 1, 2, 3, 5, 10, 15, and 20 during sustained isocapnic hypoxia and minutes 1, 2, 3, 5, and 10 during hyperoxic breathing (either posthypoxia or during control experiments). Data obtained at these times were used to graphically display the results.

To examine differences in the biphasic ventilatory response during sustained isocapnic hypoxia between the genders, we compared parameters of ventilation at baseline and at early (2 min) and late (20 min) hypoxia within and between the sexes by using two-way analysis of variance (ANOVA). In contrast to the ventilatory response during sustained isocapnic hypoxia, relatively little is known about the behavior of ventilation after sustained hypoxia. Therefore, to examine for differences after sustained isocapnic hypoxia, we included all data points (i.e., posthypoxia minutes 1, 2, 3, 5, and 10).

Table 1. Correction factors for various gas mixtures

<table>
<thead>
<tr>
<th>FIO₂ (balance N₂)</th>
<th>O₂</th>
<th>Room Air</th>
<th>Hypoxic Mixture</th>
<th>N₂</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.0</td>
<td>0.21</td>
<td>0.11</td>
<td>0.0</td>
</tr>
<tr>
<td>Volume correction factor</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Measured</td>
<td>0.898</td>
<td>1.00</td>
<td>1.017</td>
<td>1.031</td>
</tr>
<tr>
<td>Calculated</td>
<td>0.883</td>
<td>1.00</td>
<td>1.010</td>
<td>1.020</td>
</tr>
</tbody>
</table>

FIO₂, fractional inspired oxygen. Calculations made according to Poiseuille’s equation, assuming constant temperature and humidity.
from a given experimental intervention were first subjected to a one-way ANOVA for repeated measures to determine whether there were statistically significant differences observed with respect to time. Two-way ANOVA for repeated measures was used to determine whether, within a gender, there were differences between hyperoxic breathing after sustained isocapnic hypoxia vs. hyperoxic breathing after room-air breathing. Two-way ANOVA was also used to determine whether there were differences between genders within the same experimental intervention. When the F statistic reached statistical significance, pairwise comparisons were performed with the use of the Newman-Keuls procedure.

**RESULTS**

There was no difference in age, body mass index, smoking habits, and respiratory function between male and female volunteers (Table 2). Small, but statistically significant, differences were found for blood pressure, hemoglobin levels, and baseline V̇I, consistent with the known physiological differences between men and women for these variables.

**During Sustained Isocapnic Hypoxia**

The same hypoxic stimulus was produced in both men and women. The lowest SaO₂ was achieved at the end of the hypoxic period [SaO₂ = 79 ± 1.5% in men; 79 ± 1.0% in women; not significant (NS)], and the SaO₂ curves (Fig. 1) were virtually superimposed for men and women. Isocapnic conditions were maintained (PETCO₂ within 2–3 Torr) throughout the period of sustained hypoxia in both men and women (Fig. 1), with exception of the first minute of hypoxia in women, when a small fall in PETCO₂ occurred. PETCO₂ was slightly lower in women (P < 0.05) during baseline room-air breathing and throughout the experiment.

Hypoxia resulted in an early increase in V̇I in men and women, followed by a roll-off in V̇I during hypoxia (Fig. 2, Table 3). Expressed as a percentage of respective baseline values, the magnitude of these changes did not differ between men and women (Table 3). The acute hypoxic ventilatory response (HVR) calculated during the second minute of hypoxia and expressed as a change in ventilation vs. change in saturation per square meter of body surface area (BSA) (ΔV̇I/ΔSaO₂/BSA) was identical in men and women (0.17 ± 0.04 l·min⁻¹·%SaO₂⁻¹·m⁻²).

We found that isocapnic hypoxia induced a significant early rise in V̇I, Ti, and the duty cycle (Ti/Tt) in both men and women, with no significant change in breathing f, Te, and V̇I/Ti. The subsequent roll-off of V̇I during sustained hypoxia was due to a fall in V̇I, Ti, and Ti/Tt that was similar in magnitude for men and women (Table 3). The duty cycle was shorter in women compared with men during both room-air breathing and hypoxia.

**Table 2. Baseline characteristics in men and women volunteers**

<table>
<thead>
<tr>
<th></th>
<th>Men (n = 10)</th>
<th>Women (n = 10)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>33 + 2.4 (22–47)</td>
<td>29 ± 2.0 (19–41)</td>
<td>NS</td>
</tr>
<tr>
<td>BMI</td>
<td>24 ± 0.7 (19–26)</td>
<td>23 ± 1.2 (19–32)</td>
<td>NS</td>
</tr>
<tr>
<td>Smokers</td>
<td>4</td>
<td>5</td>
<td>NS</td>
</tr>
<tr>
<td>Mean BP, mmHg</td>
<td>93 + 2.7 (78–105)</td>
<td>85 ± 2.9 (67–97)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Hb, g/l</td>
<td>154 ± 2.6 (142–165)</td>
<td>153 ± 1.7 (127–143)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>FEV₁, %predicted</td>
<td>103 + 3.4 (82–116)</td>
<td>103 ± 3.4 (92–119)</td>
<td>NS</td>
</tr>
<tr>
<td>FVC, %predicted</td>
<td>101 + 2.2 (90–111)</td>
<td>100 ± 2.6 (85–114)</td>
<td>NS</td>
</tr>
<tr>
<td>MMEF, %predicted</td>
<td>91 ± 8.2 (64–130)</td>
<td>96 ± 4.4 (77–126)</td>
<td>NS</td>
</tr>
<tr>
<td>Baseline V̇I, l/min</td>
<td>8.4 ± 0.9 (5.2–12.1)</td>
<td>6.9 ± 0.2 (4.3–10.4)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>V̇I/BSA, l·min⁻¹·m⁻²</td>
<td>4.4 ± 0.2 (3.2–5.3)</td>
<td>3.9 ± 0.3 (2.6–5.7)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are means ± SE; n, no. of subjects. Nos. in parentheses, range; BMI, body mass index; BP, blood pressure; Hb, hemoglobin; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; MMEF, maximum midexpiratory flow; V̇I, inspired minute ventilation; BSA, body surface area; NS, not significant.
Table 3. Ventilatory parameters for men and women during sustained isocapnic hypoxia

<table>
<thead>
<tr>
<th></th>
<th>Room air (BL)</th>
<th>Sustained hypoxia</th>
<th>Room air (BL)</th>
<th>Sustained hypoxia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2 min</td>
<td>20 min</td>
<td>2 min</td>
<td>20 min</td>
</tr>
<tr>
<td><strong>Men</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>V̇i, l/min</strong></td>
<td>8.4 ± 0.37</td>
<td>10.9 ± 0.60 *</td>
<td>9.7 ± 0.56 †</td>
<td>6.9 ± 0.46 †</td>
</tr>
<tr>
<td>%BL</td>
<td>100 ± 0.0</td>
<td>131 ± 6.13 *</td>
<td>115 ± 4.95 †</td>
<td>100 ± 0.0</td>
</tr>
<tr>
<td><strong>Vr, liter</strong></td>
<td>0.58 ± 0.03</td>
<td>0.73 ± 0.06 *</td>
<td>0.65 ± 0.04</td>
<td>0.51 ± 0.05</td>
</tr>
<tr>
<td>%BL</td>
<td>100 ± 0.0</td>
<td>126 ± 5.53 *</td>
<td>113 ± 4.92</td>
<td>127 ± 9.15 †</td>
</tr>
<tr>
<td><strong>f, Breaths/min</strong></td>
<td>15.1 ± 1.03</td>
<td>15.0 ± 1.49</td>
<td>15.5 ± 1.05</td>
<td>14.2 ± 1.24</td>
</tr>
<tr>
<td>%BL</td>
<td>100 ± 0.0</td>
<td>99 ± 5.99</td>
<td>103 ± 4.00</td>
<td>100 ± 0.0</td>
</tr>
<tr>
<td><strong>Tₐ, s</strong></td>
<td>1.52 ± 0.09</td>
<td>1.96 ± 0.25 *</td>
<td>1.54 ± 0.10 †</td>
<td>1.39 ± 0.08 *</td>
</tr>
<tr>
<td>%BL</td>
<td>100 ± 0.0</td>
<td>126 ± 10.75 *</td>
<td>101 ± 3.59 †</td>
<td>119 ± 4.83 †</td>
</tr>
<tr>
<td><strong>Tₑ, s</strong></td>
<td>2.70 ± 0.23</td>
<td>2.45 ± 0.26</td>
<td>2.49 ± 0.17</td>
<td>2.66 ± 0.19</td>
</tr>
<tr>
<td>%BL</td>
<td>100 ± 0.0</td>
<td>91 ± 6.72</td>
<td>94 ± 4.44</td>
<td>89 ± 6.41</td>
</tr>
<tr>
<td><strong>T/Tₜ</strong></td>
<td>0.36 ± 0.01</td>
<td>0.44 ± 0.01 *</td>
<td>0.38 ± 0.01</td>
<td>0.32 ± 0.02 *</td>
</tr>
<tr>
<td><strong>Vr/Tₜ</strong></td>
<td>0.38 ± 0.02</td>
<td>0.39 ± 0.02</td>
<td>0.43 ± 0.02</td>
<td>0.37 ± 0.02</td>
</tr>
<tr>
<td><strong>PETCO₂, Torr</strong></td>
<td>39.4 ± 0.96</td>
<td>39.3 ± 0.71</td>
<td>39.0 ± 0.94</td>
<td>37.0 ± 0.83 †</td>
</tr>
<tr>
<td>%BL</td>
<td>100 ± 0.0</td>
<td>100 ± 1.24</td>
<td>99 ± 1.14</td>
<td>100 ± 0.0</td>
</tr>
</tbody>
</table>

Values shown are means ± SE. BL, baseline values; mean of alternate minutes during 10 min of room air breathing; V̇i, tidal volume; f, frequency; Tₐ, inspiratory time; Tₑ, expiratory time; T, duration of respiratory cycle; PETCO₂, end-tidal partial pressure of CO₂. *P < 0.05 compared with corresponding value in men. †P < 0.05 compared with baseline. **P < 0.05 compared with corresponding value in men.

After Sustained Isocapnic Hypoxia

Ventilation in men and women in the posthypoxic periods is shown in Fig. 3 and compared with the corresponding changes in ventilation during control hyperoxia experiments (shaded areas). Transient depression of V̇i (P < 0.05 compared with baseline) was observed at 1 min posthypoxia and during the first minute of the control hyperoxia experiments in both men and women (Fig. 3B). During control hyperoxia experiments, there was a trend toward a subsequent increase in V̇i, Vr, and at 3 min that was not sustained (Fig. 3, B-D). In men, the ventilatory depression observed at 1 min posthypoxia was significantly greater than for the corresponding period during the control hyperoxia experiment. This difference was not seen in women. In the first minute after hypoxia, Tₑ was increased significantly compared with the corresponding hypoxia control values in both men and women (Fig. 3F). This increase in Tₑ after hypoxia was associated with a reduction in duty cycle (Fig. 3G) in men and women and a significant fall in breathing f (Fig. 3D) at 1 min in men. During control hyperoxia experiments, there was no change in timing variables in men or women, with the exception of a small increase in Tᵢ in men at 1 min.

End-tidal CO₂ (Fig. 3A) did not change significantly from baseline levels at 1 min posthypoxia and during the first minute of the control hyperoxia experiments in men and women, and, therefore, could not explain the transient depression of V̇i that was observed in these different protocols. No attempt was made to maintain isocapnic conditions during hyperoxic breathing, and PETCO₂ was observed to fall in both men and women after about the third minute in both protocols (Fig. 3A).

**Discussion**

The main findings of this study were that the acute (2-min) response to isocapnic hypoxia and the subsequent roll-off in V̇i during hypoxia (20 min) were the same in men and women, whereas in the immediate posthypoxia period there was a transient depression of V̇i in men, exceeding that observed during control hyperoxia experiments, that was not observed in women. This suggests that men may be more susceptible to posthypoxic ventilatory depression, despite a similar pattern of ventilatory response to sustained isocapnic hypoxia in awake healthy men and premenopausal women in the follicular phase of their menstrual cycle.

**Ventilatory Changes During Sustained Isocapnic Hypoxia**

Both genders showed virtually identical biphasic responses to sustained isocapnic hypoxia (early augmentation of V̇i followed by roll-off or decrease in V̇i), with the roll-off in V̇i being due to a fall in Vr and a fall in Tᵢ and the Tᵢ/Tᵢ. This biphasic ventilatory response to sustained isocapnic hypoxia is similar to that reported in previous studies (12, 16, 24). The changes that we observed in ventilatory timing during the acute response and subsequent roll-off (e.g., increase and then roll-off in Tᵢ and Tᵢ/Tᵢ without a change in breathing f) are similar to those reported previously (12, 16, 24). The difference between the present study and these earlier studies is that we did not observe an increase in respiratory drive during hypoxia, as assessed by increased Vr/Tᵢ. Rather, the increase and subsequent decrease in Vr appeared to be associated mainly with changes in Tᵢ. This difference could potentially be explained by the different route of breathing employed. Two of these earlier studies (12, 16) used mouth breathing and noseclip, which are known to be associated with increased ventilatory drive (10). Furthermore, it is possible that the use of a face mask, rather than noninvasive methods such as inductive plethysmography.
Aitken et al. (1) reported higher HVR in 30 premenopausal women compared with 12 healthy, age-matched men, whereas Altkén et al. (1) reported higher HVR in 30 premenopausal women in their follicular phase compared with 37 age-matched men. Other studies found no gender differences in HVR (19, 27). Our results are in keeping with these latter studies, with the early (2 min) HVR being virtually identical in women and men (0.31 ± 0.07 and 0.33 ± 0.07 l·min⁻¹·%SaO₂⁻¹, women and men, respectively). The magnitude of the early (2 min) increment in Vt (31–36%) in the present study was lower than that reported in some other studies of sustained isocapnic hypoxia (12, 20, 29) but similar to another (16). This probably reflects the slower induction of hypoxia in our study (SaO₂ of ~90% during the second minute) compared with the studies of others (12, 29) where an SaO₂ of ~80% was achieved within the first 2 min. However, the acute hypoxic ventilatory response, expressed as percent change in SaO₂ (0.31 ± 0.07 and 0.33 ± 0.07 l·min⁻¹·%SaO₂⁻¹ for women and men, respectively) was also lower than reported in most earlier studies [e.g., 0.46–1.0, 0.69, and 1.47 l·min⁻¹·%SaO₂⁻¹ (see Refs. 32, 28, 27, respectively)]. These differences may in part be due to methodological differences. Our subjects breathed through the nose and used a face mask, whereas the subjects in the above studies breathed by using a mouthpiece and noseclip. Acute HVR has been shown to be higher during mouth breathing than during nasal breathing (10). Our study is the first comparison of hypoxic ventilatory responses in men and women during nasal breathing.

As shown in the present study, exposure to sustained isocapnic hypoxia causes a roll-off over a period of 10–15 min to a new steady-state level that is usually above the prehypoxic ventilation (12, 29, 30). The mechanisms of ventilatory depression during sustained isocapnic hypoxia remain unclear. Considerable evidence points to the accumulation of inhibitory neurotransmitters (e.g., γ-aminobutyric acid) in the brain during sustained isocapnic hypoxia (13), whereas other evidence suggests that, at least in adult men, ventilatory depression results from the effects of hypoxia on the peripheral chemoreflex (3, 4, 17, 21).

The effect of gender on hypoxia-induced ventilatory depression has not, to our knowledge, been systematically studied before. In the present study, men and women demonstrated the same ventilatory decline during 20 min of sustained isocapnic hypoxia, caused by a fall in Vt, rather than change in breathing f. Several earlier studies of sustained isocapnic hypoxia included both male and female volunteers (3–5, 12, 17, 21) but did not group data by gender. In four studies (3–5, 21) individual ventilatory responses were graphed, and in none of these studies was a gender difference in ventilatory roll-off apparent. In our study, the PETCO₂ in women was slightly, but significantly, less than that in men throughout the experiment. Our intention in this study was to measure the acute hypoxic ventilatory response and subsequent ventilatory depression at the physiological set point of CO₂, i.e., under eucapnic conditions. We did not, therefore, artificially increase the PETCO₂ in women to match that in the men. It is possible that our results comparing the acute and prolonged responses to isocapnic hypoxia between men and women would have been different had we done so.

**Ventilatory Changes After Sustained Isocapnic Hypoxia**

The method we adopted to terminate hypoxia was to switch the subject abruptly to 100% O₂ breathing, which was then continued for 10 min until the end of the experiment. This produced a rapid increase in saturation, thereby allowing the ventilatory off response to be compared between subjects independent of individual lung washout times. We also reasoned that sudden withdrawal of peripheral chemoreceptor drive would allow any central depressant effects of sustained isocapnic hypoxia to be better observed and compared between men and women. However, hypoxia without preceding hypoxia has been shown to produce immediate short-term ventilatory depression (9, 11, 22). Recent studies have shown that ventilation increases during sustained hyperoxia (6, 7). Therefore, it was important to conduct a control experiment to measure the effects of a sudden switch from breathing room air to breathing 100% O₂, to establish the magnitude of any ventilatory undershoot or depression related to preexisting hypoxic conditions, and to control for the effects of any subsequent augmentation of ventilation during sustained hyperoxia.

Room-air to hyperoxia transitions. Hyperoxia (100% O₂ breathing) after room-air breathing produced an ~15% decrease in Vt in both men and women in the first minute, which was similar in magnitude to the 8–12% depression reported previously in similar experiments (9, 11, 22). In contrast, Holtby et al. (20) were unable to show a significant posthyperoxia depression of ventilation, possibly due to their measurement technique (i.e., moving average of 7 breaths, searching for nadirs). The small transient decrease in Vt that we observed was not associated with statistically significant changes in respiratory timing or effort variables. In the present study, 3 min after the room-air to hyperoxia transition, there was a slight increase in Vt.
Fig. 3. Ventilatory response after sustained isocapnic hypoxia. Shaded areas, data (means ± SE) obtained after normoxia to hyperoxia transitions (i.e., control experiments). Other results (●) are means ± SE (bars) obtained after transition from 20 min of sustained isocapnic hypoxia to hyperoxia (i.e., hypoxia experiments). A: ET_{CO2}, end-tidal CO₂. B: V{sub i}, inspiratory minute ventilation. C: VT, tidal volume. D: Freq, frequency. E: T{sub i}, inspiratory time. F: T{sub e}, expiratory time. G: T{sub i}/T{sub T}, ratio of T{sub i} to total time. H: ratio of V{sub T} to T{sub T}. *P < 0.05 compared with baseline for control experiments. †P < 0.05 compared with baseline for hypoxia experiments. ‡P < 0.05 control vs. hypoxia experiments.
above baseline (in women) and an increase in Vt (in men) that was not sustained. During these control experiments, end-tidal CO₂ was not controlled, and there was a small progressive fall in PETCO₂, particularly after 5 min. These changes are consistent with previous reports of increased ventilation (6, 20) and reduced PETCO₂ (6, 9) during sustained poikilocapnic hyperoxic breathing. These changes are thought to be due to stimulation of medullary chemoreceptors by an increase in cerebrospinal CO₂ concentration, resulting from the combined effects of increased oxyhemoglobin levels during O₂ breathing (Haldane effect) and a reduction of cerebral blood flow (6).

Hypoxia-hyperoxia transitions. In posthypoxia experiments, there was a transient fall in Vt in the first minute of O₂ breathing, which, in contrast to control
experiments, was associated with a prolongation of **TE** and a decrease in respiratory duty cycle. The 1-min posthypoxia fall in **V̇I** appeared to be greater in men than in women and was significantly different from hyperoxic control values in men. Previous studies, predominantly of male subjects, have shown similar degrees of ventilatory depression after sustained isocapnic hypoxia (5, 16, 20). The changes in posthypoxia **TE** that we observed were similar to those reported by Georgopolous et al. (16) after 25 min of sustained isocapnic hypoxia and by Badr et al. (2) after 5 min of sustained isocapnic hypoxia in non-rapid-eye-movement sleep. Unlike those studies, we did not find a decrease in **VT** posthypoxia. These changes in **V̇I** and respiratory timing cannot be explained on the basis of changes in end-tidal **CO₂**, because **PETCO₂** was unchanged for the first 3 min posthypoxia.

The finding that there was no gender difference in ventilatory response, and particularly in the roll-off phenomenon, during sustained isocapnic hypoxia but that differences were observed in posthypoxic ventilatory depression may appear inconsistent. However, these two manifestations of hypoxic ventilatory depression may be caused by different neurophysiological/neurochemical phenomena. The hypoxic “on-response” and roll-off appear to be caused by changes in **Ti** and possibly respiratory drive, whereas the posthypoxia undershoot appears, from our study and previous work (2, 16), to be associated with changes in **Te**. In addition, it has been shown that adenosine antagonism with aminophylline seems to have a greater effect on sustained isocapnic hypoxia ventilatory roll-off than on posthypoxic undershoot (16).

**PETCO₂** did not increase during the transient falls in **V̇I** observed after the normoxia-hypoxia and hypoxia-hyperoxia transitions. We have no direct experimental evidence to explain this apparent discrepancy. The fact that it was observed in both experimental settings makes it unlikely that it was due to a reduction in metabolic rate after sustained hypoxia; rather, it was linked to O₂ breathing. Cardiac output is known to fall acutely during hyperoxic breathing (14). Therefore, we believe that the most likely explanation for isocapnic conditions being maintained in the presence of a transient fall in **V̇I** is that hypoxia caused an immediate fall in cardiac output and therefore an immediate fall in CO₂ flow to the lungs.

Also of note was that baseline **PETCO₂** was lower in women than men and remained so throughout the experiments. In a study of resting ventilation, metabolic rate, and hypoxic and hypercapnic ventilatory responses in 67 subjects, Aitken et al. (1) showed that women had lower metabolic rates (even after correction for BSA) but higher baseline ventilatory drives and lower **PETCO₂** than men. Women were studied in the follicular phase of their menstrual cycle, as in our study, so the difference was not a luteinizing effect. Therefore, it is possible that increased ventilatory drive in women may protect them from posthypoxic respiratory depression.

We conclude that awake healthy men and women in the follicular phase of their menstrual cycle show the same biphasic response to sustained isocapnic hypoxia. However, posthypoxic ventilatory depression is significantly greater compared with hyperoxic control measurements in men but not in women. The tendency for ventilation to return gradually to baseline levels on sudden removal of a respiratory stimulus is thought to be an important mechanism of maintaining respiratory stability (2, 15). Our findings suggest that after removal of a sustained hypoxic stimulus the ventilatory depressive effects of hypoxia are more prominent in men, possibly rendering them more susceptible to unstable patterns of breathing.

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