Ventilatory responses to carbon dioxide at low and high levels of oxygen are elevated after episodic hypoxia in men compared with women

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Morelli, Chris, M. Safwan Badr, and Jason H. Mateika. Ventilatory responses to carbon dioxide at low and high levels of oxygen are elevated after episodic hypoxia in men compared with women. J Appl Physiol 97: 1673–1680, 2004. First published July 23, 2004; doi:10.1152/japplphysiol.00541.2004.—We hypothesized that the acute ventilatory response to carbon dioxide in the presence of low and high levels of oxygen would increase to a greater extent in men compared with women after exposure to episodic hypoxia. Eleven healthy men and women of similar race, age, and body mass index completed a series of rebreathing trials before and after exposure to eight 4-min episodes of hypoxia. During the rebreathing trials, subjects initially hyperventilated to reduce the end-tidal partial pressure of carbon dioxide (PET CO₂) below 25 Torr. Subjects then rebreathed from a bag containing a normocapnic (42 Torr), low (50 Torr), or high oxygen gas mixture (150 Torr). During the trials, PET CO₂ increased while the selected level of oxygen was maintained. The point at which minute ventilation began to rise in a linear fashion as PET CO₂ increased was considered to be the carbon dioxide set point. The ventilatory response below and above this point was determined. The results showed that the ventilatory response to carbon dioxide above the set point was increased in men compared with women before exposure to episodic hypoxia, independent of the oxygen level that was maintained during the rebreathing trials (50 Torr: men, 5.19 ± 0.82 vs. women, 4.70 ± 0.77 l·min⁻¹·Torr⁻¹; 150 Torr: men, 4.33 ± 1.15 vs. women, 3.21 ± 0.58 l·min⁻¹·Torr⁻¹). Moreover, relative to baseline measures, the ventilatory response to carbon dioxide in the presence of low and high oxygen levels increased to a greater extent in men compared with women after exposure to episodic hypoxia (50 Torr: men, 9.52 ± 1.40 vs. women, 5.97 ± 0.71 l·min⁻¹·Torr⁻¹; 150 Torr: men, 5.73 ± 0.81 vs. women, 3.83 ± 0.56 l·min⁻¹·Torr⁻¹). Thus we conclude that enhancement of the acute ventilatory response to carbon dioxide after episodic hypoxia is sex dependent.

long-term facilitation; carbon dioxide set point; chemoreflex sensitivity; sex

SLEEP-DISORDERED BREATHING is more prevalent in men than women (9). This discrepancy may exist in part because disproportionate increases in minute ventilation for a given level of carbon dioxide and/or oxygen occur in men compared with women immediately after apnea (18). This increase could induce hypcapnia, a reduction in central respiratory drive, and ultimately partial or complete closure of the upper airway (3, 4, 31). Disproportionate increases in ventilation might be due in part to an enhanced ventilatory response to hypercapnia and/or hypoxia in men compared with women. This postulation has been substantiated consistently by studies that have shown that the ventilatory response to carbon dioxide is increased in healthy men compared with women during both wakefulness (2, 32, 38, 39, 42, 44) and sleep (47). In contrast, some studies have reported that the ventilatory response to hypoxia is greater in men compared with women (32, 42, 44), whereas other studies have reported the opposite finding (2) or that no sex difference exists (41).

Inconsistent findings from studies that have examined sex differences in the ventilatory response to hypoxia may exist to some extent because variable levels of carbon dioxide were combined with the hypoxic stimulus. Recent studies have shown that the ventilatory response to hypoxia is negligible in the presence of hypocapnia (10, 28, 35) but increases in the presence of hypercapnia. Moreover, the response to hypoxia under conditions of hypocapnia does not vary between men and women (41). Given these findings, sex differences may become more evident in the presence of increased carbon dioxide levels. Therefore, the first aim of our investigation was to determine whether sex differences in the ventilatory response to a constant level of hypoxia (i.e., isooxic hypoxia) were dependent on the existing level of carbon dioxide.

Apart from the impact that hypcapnia may have on the ventilatory response to hypoxia, our group recently showed in awake humans that the ventilatory response to progressive increases in carbon dioxide, while low oxygen levels were maintained, was increased after short-term exposure to episodic hypoxia (24). Moreover, preliminary findings from this study (24) indicated that a greater increase in the ventilatory response to carbon dioxide in the presence of isooxic hypoxia and hyperoxia occurred in men compared with women after episodic hypoxia. Thus sex differences in the ventilatory response to carbon dioxide and oxygen may be amplified by exposure to episodic hypoxia, which is a hallmark of recurring apnea. This modification may have important implications for sleep-disordered breathing because it could perpetuate and exacerbate respiratory events in men compared with women. Thus the second and primary objective of the present investigation was to determine whether increases in the acute ventilatory response to carbon dioxide in the presence of isooxic
hypoxia and hyperoxia, after exposure to episodic hypoxia, are sex dependent.

**METHODS**

Protocol overview. The Human Investigation Committees of Wayne State University School of Medicine and Detroit Veterans Affairs Medical Center approved the experimental protocol. Eleven healthy men and 11 healthy women visited our laboratory on two occasions after informed consent was obtained. During the first visit to the laboratory, subjects completed two rebreathing trials and were exposed to two 4-min episodes of hypoxia to ensure that they were accustomed to the experimental apparatus and protocol. Before the second visit, subjects were asked to avoid eating or drinking caffeinated beverages on the morning of the experiment. Moreover, subjects arrived at the same time of day (i.e., 8 AM) to avoid any influence that circadian rhythms might have on the measured responses. During the second visit, four rebreathing experiments were completed before and after exposure to episodic hypoxia protocol. Thus a total of eight rebreathing trials were completed.

Modified rebreathing protocol. Read’s modified rebreathing protocol (21, 22, 24, 27, 28) was employed during the four rebreathing trials completed before and on average 50 min after exposure to episodic hypoxia. Each rebreathing trial was separated by 5 min of rest. During each of these trials, the subjects initially breathed room air for 5 min. Subsequently, the subjects hyperventilated for 5 min while being coached to maintain an end-tidal partial pressure of carbon dioxide (PETCO2) between 22 and 25 Torr. This period of hyperventilation was employed to lower the stores of carbon dioxide so that the carbon dioxide set point for ventilation could be delineated during rebreathing (i.e., the point where ventilation increases linearly as PETCO2 increases). In previous studies, our laboratory referred to this point as the ventilatory recruitment threshold (23, 24). Furthermore, the reduction in carbon dioxide stores allowed us to measure minute ventilation below the set point (i.e., basal ventilation).

After the 5-min period of hyperventilation, the subjects were switched from room air to a rebreathing bag. The end-tidal partial pressure of oxygen (PetO2) in the bag during four of the eight experiments completed was 50 Torr, whereas the PetO2 for the remaining four experiments was 150 Torr. These pressures of oxygen were maintained throughout the rebreathing experiment. The PetCO2 in the bag at the start of the rebreathing experiment was 42 Torr. The trials from hereon will be referred to as the isoxic hypoxic (50 Torr) and hyperoxic (150 Torr) carbon dioxide-rebreathing trials.

Rebreathing began at the end of expiration and was followed by three rapid and deep breaths that produced equilibration of the PETCO2. Subsequently, breath-by-breath PETCO2 was plotted against time and fitted with at least squares regressions. The equation for this line provided a predicted value of PetCO2 vs. time, thereby minimizing interbreath variability associated with the measurement of this variable. Thereafter, minute ventilation was plotted against the predicted PETCO2.

A 16-bit analog-to-digital converter (model AT-MIO-16XE-50, National Instruments) digitized the analog signals for online computer analysis using software specifically designed for this purpose. The software calculated tidal volumes, breathing frequency, minute ventilation, PETCO2, and PetO2 on a breath-by-breath basis. 

Episodic hypoxia protocol. During episodic hypoxia, subjects breathed through a face mask that was attached to a two-way valve. The inspiratory portion of the valve was connected to a stopcock. Subjects inspired either room air or the contents from one of two bags attached to the stopcock that contained either 8% oxygen-balance nitrogen or 100% oxygen. Before the initial exposure to hypoxia, subjects breathed room air for 15 min so that baseline values of minute ventilation and carbon dioxide could be determined. Subsequently, subjects were exposed to eight 4-min episodes of hypoxia separated by 5 min of normoxia. During the hypoxic episodes, subjects inspired the gas mixture that consisted of 8% oxygen-balance nitrogen. At the completion of each episode, hypoxia was abruptly terminated with two breaths of 100% oxygen to rapidly bring the PetO2 to the normoxic range. After the last exposure to hypoxia (8th episode), respiration was monitored for 15 min of recovery.

Data analysis. Average values of minute ventilation, tidal volume, breathing frequency, and PETCO2 were determined for the last 5 min of the 15-min baseline period recorded immediately before episodic hypoxia, the last minute of each hypoxic episode, the last minute of normoxia that separated each hypoxic episode, and for minutes 0–5, 6–10, and 11–15 of recovery from episodic hypoxia.

Average values of minute ventilation, tidal volume, breathing frequency, and PETCO2 were determined for the baseline periods measured immediately before completion of the rebreathing trials. Thus measures from four baseline periods were obtained before and after exposure to episodic hypoxia. Subsequently, average values obtained from the baseline periods recorded before exposure to episodic hypoxia were averaged, as were the values from the baseline periods recorded after exposure, to make statistical comparisons. A similar analysis was completed for the time constant values that were obtained from the exponential decline that was chosen to fit any waning of ventilatory “poststimulus potentiation” that might have occurred after hyperventilation (see below).

The data collected during the rebreathing experiments were analyzed by using a spreadsheet designed for this purpose. Before analysis, the three deep breaths that were required for gas equilibration, in addition to sighs or swallows that were detected by the software during the experiment, were excluded from further analysis.

Subsequently, breath-by-breath PETCO2 was plotted against time and fitted with at least squares regressions. The equation for this line provided a predicted value of PetCO2 vs. time, thereby minimizing interbreath variability associated with the measurement of this variable. Thereafter, minute ventilation was plotted against the predicted PetCO2.

Subsequently, each of these plots was fitted with a model made up of the sum of two segments separated by one breakpoint. Model fitting was based on minimizing the sum of least squares for nonlinear regressions by using commercial software (Sigmplot 7.0, SPSS). The first segment of the response was an exponential decline to a final value (i.e., basal ventilation). This value was taken as a measure of minute ventilation below the carbon dioxide set point. The exponential decline was chosen to fit any waning of ventilatory poststimulus potentiation that might have occurred after hyperventilation. However, poststimulus potentiation is often not observed so that the time constant of the response may be <1 s (12).

The second segment was characterized by a breakpoint followed by a linear increase in minute ventilation that occurred in conjunction with a rise in PetCO2. The breakpoint was taken as a measure of the carbon dioxide set point. The set point measured while PetO2 was maintained at 150 Torr was thought to originate from the central chemoreflex, while the set point measured when PetO2 was main-

J Appl Physiol • VOL 97 • NOVEMBER 2004 • www.jap.org
tained at 50 Torr was thought to derive from the sum of the central and peripheral chemoreflex.

The slope of the line fitted to minute ventilation after the breakpoint was taken as a measure of the chemoreflex sensitivity to increases in PETCO2. Our laboratory previously referred to the slope as a measure of chemoreflex responsiveness (23, 24). We assumed that the average slope recorded from the hyperoxic carbon dioxide-rebreathing trials (PETO2 = 150 Torr) represented central chemoreflex sensitivity, whereas the slope recorded from the hypoxic carbon dioxide-rebreathing trials (PETCO2 = 50 Torr) represented the combined peripheral and central chemoreflex sensitivity (12).

Statistical analysis. An unpaired t-test was used to compare age, height, weight, body mass index and body surface area between men and women. A two-way analysis of variance with repeated measures in conjunction with Student-Newman-Keuls post hoc test was used to determine whether 1) baseline measures of minute ventilation, tidal volume, breathing frequency and PETCO2, and 2) whether the time constant of the hyperventilatory poststimulus potentiation observed at the onset of rebreathing trials, were significantly different between men and women, before vs. after exposure to episodic hypoxia. A similar analysis was employed to determine whether minute ventilation, tidal volume, breathing frequency, and PETCO2 recorded during each hypoxic episode, during each normoxic period that separated the hypoxic episodes, and during the 15 min of recovery recorded immediately after episodic hypoxia were different from baseline measures and sex dependent. A randomized block three-way analysis of variance in conjunction with Student-Newman-Keuls post hoc test was used to compare 1) the carbon dioxide set points measured from men and women during the isoxic hyperoxic and hypoxic carbon dioxide-rebreathing trials before and after episodic hypoxia, 2) the ventilatory response measured from men and women above the carbon dioxide set point (i.e., chemoreflex sensitivity) during isoxic hyperoxic and hypoxic carbon dioxide-rebreathing trials, and 3) basal ventilation measured from men and women below the carbon dioxide set point during the isoxic hyperoxic and hypoxic carbon dioxide-rebreathing trials before and after episodic hypoxia. The levels of the main factors were timing of the rebreathing experiments (before vs. after episodic hypoxia), oxygen concentration (hypoxic vs. hyperoxic carbon dioxide-rebreathing trials), and sex (male vs. female). Given that chemoreflex sensitivity recorded from the male group was greater than measures recorded from the female group before exposure to episodic hypoxia the difference in central and central + peripheral chemoreflex sensitivity was calculated before vs. after episodic hypoxia in both groups. A two-way analysis of variance in conjunction with Student-Newman-Keuls was used to determine whether the difference varied between sexes. The levels of the main factors were sex (male vs. female) and oxygen concentration (hypoxic vs. hypoxic rebreathing trials). Pearson product-moment correlation analysis was performed between measures of chemoreflex sensitivity and body surface area, height, weight, and body mass index for data combined from the male and female groups. Data are presented as means ± SE. A value of P < 0.05 was considered significant.

RESULTS

Both groups were composed of seven Caucasians, three Asians, and one African-American. The average height, weight, and body surface area were significantly greater in the men compared with women (P < 0.001); however, age and body mass index were similar (Table 1).

During episodic hypoxia, the tidal volume response measured from the male group was significantly greater than the female response (P < 0.01) (Fig. 1). In contrast, no difference in the minute ventilation and breathing frequency response was measured (Fig. 1). The ventilatory response to each episode of hypoxia in both men and women was accompanied by a decrease in PETCO2 compared with baseline (P < 0.003 in all cases) (Fig. 1).

Minute ventilation, tidal volume, and breathing frequency during the normoxic periods that separated the hypoxic episodes was similar to measures obtained under baseline conditions (Fig. 1). Conversely, our findings showed that minute ventilation (P < 0.01) and tidal volume (P < 0.001) were above baseline values for the initial 5 min of recovery in men but not in women (Fig. 1). Examination of the data revealed that the increase in the average values was due to increases in minute ventilation and tidal volume during the initial 60–90 s of recovery. After the initial 5 min of recovery, minute ventilation and tidal volume returned to baseline values for the remainder of recovery in men, although tidal volume remained elevated in men compared with women for the middle (P < 0.01) and last (P < 0.01) 5 min of recovery (Fig. 1). In both groups, the absence of an increase in respiratory activity during the 15-min recovery period, compared with baseline, was accompanied by a reduction in PETCO2 (P < 0.05) (Fig. 1).

Tidal volume measured before the rebreathing trials completed before exposure to episodic hypoxia was greater in men compared with women (P < 0.05) (Table 2). A similar trend was observed for minute ventilation (P = 0.07) (Table 2), whereas PETCO2 and breathing frequency were not significantly different. Minute ventilation, tidal volume, and breathing frequency measured before the rebreathing trials completed before exposure to episodic hypoxia were not significantly different from measures obtained after exposure to episodic hypoxia in both men and women (Table 2). Conversely, PETCO2 was higher in both groups before compared with after exposure to episodic hypoxia (P < 0.05) (Table 2). The time constant of the poststimulus potentiation induced by hyperventilation before rebreathing was similar between the sexes both before and after exposure to episodic hypoxia (men before vs. after episodic hypoxia, 7.78 ± 1.39 vs. 6.34 ± 0.85 s; women before vs. after episodic hypoxia, 8.98 ± 1.46 vs. 8.89 ± 1.45 s).

Basal ventilation (i.e., ventilation measured below the carbon dioxide set point) measured during the isoxic hypoxic (men, 10.6 ± 1.8 vs. women, 9.0 ± 0.9 l/min) and hyperoxic (men, 8.9 ± 1.5 vs. women, 7.9 ± 0.9 l/min) rebreathing trials was not significantly different between sexes before episodic hypoxia. These relationships remained the same after exposure to episodic hypoxia. The ventilatory response to carbon dioxide above the carbon dioxide set point (i.e., slope of the minute ventilation vs. PETCO2 relationship) in the presence of low (P < 0.05) and high (P < 0.01) oxygen levels was greater in men compared with women before exposure to episodic hypoxia (Fig. 2). These relationships remained after exposure to episodic hypoxia (P < 0.01) (Fig. 2). More interestingly, the ventilatory response during the hypoxic (P < 0.01) and hyperoxic (P < 0.05) carbon dioxide-rebreathing trials was greater

### Table 1. Anthropometric measures for men and women

<table>
<thead>
<tr>
<th></th>
<th>Age, yr</th>
<th>Height, cm</th>
<th>Weight, kg</th>
<th>Body Mass Index, kg/m²</th>
<th>Body Surface Area, m²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>28.1 ± 2.3</td>
<td>175.5 ± 2.5*</td>
<td>74.8 ± 2.5*</td>
<td>24.3 ± 0.5</td>
<td>1.9 ± 0.04*</td>
</tr>
<tr>
<td>Women</td>
<td>28.3 ± 1.9</td>
<td>162.8 ± 1.5</td>
<td>61.8 ± 1.5</td>
<td>23.3 ± 0.4</td>
<td>1.7 ± 0.03</td>
</tr>
</tbody>
</table>

Values are means ± SE. *Significantly different from women, P < 0.001.
after compared with before episodic hypoxia in men. An increase was also observed in the women for the hypoxic rebreathing trials (P < 0.05) (Fig. 2). After standardizing for the difference in baseline measures, the increase in the ventilatory response to carbon dioxide in the presence of low and high oxygen levels oxygen remained significantly greater in men compared with women after episodic hypoxia (P < 0.05) (Fig. 2). No significant correlations existed between the ventilatory responses measured during the isooxic hypoxic and hyperoxic carbon dioxide-rebreathing trials and height, weight, body mass index, and body surface area.

Before and after exposure to episodic hypoxia, the carbon dioxide set point during the isooxic hyperoxic and hypoxic carbon dioxide-rebreathing trials was not significantly different between men and women, although a trend toward an increase was observed in the men (P < 0.06) (Fig. 3). Moreover, within the male and female groups, the carbon dioxide set point during both the hyperoxic and hypoxic rebreathing trials was not altered after compared with before episodic hypoxia (Fig. 3).

**DISCUSSION**

The primary finding of our study was that the ventilatory response to carbon dioxide in the presence of low and high oxygen levels was enhanced after episodic hypoxia in men compared with women. This sex difference existed even though long-term facilitation (25, 26, 34), which is a phenomenon that is characterized by respiratory activity that remains elevated for several minutes to hours after exposure to episodic hypoxia, was not evident.

**Critique of the methods.** The modified rebreathing technique has been discussed extensively in a number of prior publications (12, 20, 22–24, 27, 28). We refer the reader to our laboratory’s published work that comprehensively critiques the rebreathing method and the experimental design employed in the present study (24).

Corne and colleagues (10) implied recently that the carbon dioxide set-point measured during modified rebreathing trials represents the point at which the decline in poststimulus potentiation intersects with the increase in end-tidal carbon dioxide. This is unlikely the case because poststimulus potentiation is often not observed. Furthermore, when it is observed after hypocapnic (21, 22, 28) or isocapnic hyperventilation (J. Duffin, personal communication), the time constant is much shorter than the time required to attain the recruitment threshold (21, 22, 28). Nevertheless, even if the hypothesis is correct, our finding that the time constant measures were similar between sexes both before and after episodic hypoxia suggests that the impact of poststimulus potentiation on the set point or other measures did not vary throughout the experimental protocol.

It may be argued that the slope of the minute ventilation vs. PETCO2 relationship (i.e., chemoreflex sensitivity) measured during the isooxic hyperoxic and hypoxic carbon dioxide-rebreathing trials should have been corrected for body surface area, because this measure was significantly different between groups. However, we did not find a correlation between height,

| Table 2. Respiratory parameters in men and women before and after exposure to episodic hypoxia |
|-----------------------------------------------|-----------------|-----------------|-----------------|-----------------|
|                                               | Men             | After           | Women           | After           |
| Minute ventilation, l/min                     | 11.2±0.6        | 10.7±0.7        | 9.6±0.4         | 9.7±0.4         |
| Tidal volume, ml                             | 787.8±50.0†     | 720.7±42.1*     | 658.9±28.9      | 643.8±23.3      |
| Breathing frequency, breaths/min              | 15.1±1.1        | 15.5±1.2        | 15.2±0.7        | 15.3±0.8        |
| End-tidal partial pressure of carbon dioxide, Torr | 41.4±1.3†      | 40.3±1.4        | 40.5±0.8†       | 39.6±0.7       |

Values are means ± SE. *Significantly different from women, P < 0.05. †Significantly different from values measured after exposure to episodic hypoxia, P < 0.05.
weight, body mass index, or body surface area and the slope of the minute ventilation vs. \( P_{\text{ET CO}_2} \) relationship, which suggests that a correction for body surface area was not warranted. The lack of a correlation between body surface area and ventilatory response has been reported in a previous study (44). Moreover, although Aitken et al. (2) showed sex differences in ventilatory control between extremes in height and weight (see comparison between “short” vs. “tall” group), additional results showed that a group deemed “average” had a blunted ventilatory response compared with both the short and tall groups. This finding suggests that height, weight, and body surface area did not impact on the ventilatory responses as implied by the comparisons between extreme groups (i.e., short and tall).

**Ventilatory response to isooxic hypoxic and hyperoxic carbon dioxide rebreathing before episodic hypoxia.** The ventilatory response to carbon dioxide in the presence of isoxic hypoxia and hyperoxia was greater in men compared with women before exposure to episodic hypoxia, when carbon dioxide levels were above the set point. The increase in the ventilatory response to isoxic hyperoxic carbon dioxide rebreathing observed in the men is consistent with most published studies completed during wakefulness (2, 32, 38, 39, 42, 44) and may reflect the impact of sex steroids on the control of ventilation. Thus increased levels of testosterone or decreased levels of total estrogen or estradiol that are typical of the male sex hormone profile compared with women might be responsible for the sex difference in the ventilatory response to isoxic hyperoxic carbon dioxide rebreathing. This suggestion is supported by studies that have shown that the administration of testosterone enhances the ventilatory response to chemical stimuli (46) and that increases in circulating levels of estrogen attenuates the ventilatory response to electrical stimulation of the mesencephalic locomotor region in cats (16).

We also showed that the ventilatory response to isoxic hypoxic carbon dioxide rebreathing was increased in men compared with women. This finding is similar to results obtained in some studies that examined sex differences in the acute ventilatory response to hypoxia (32, 42, 44) but is in contrast to other studies (2, 41). One possible reason for the equivocal findings is that menstrual cycle status was not controlled in some investigations. Thus women in the luteal phase of the menstrual cycle may exhibit an increased ventilatory response to hypoxia compared with men because progesterone has been shown to be a respiratory stimulant (6). However, diametrically opposed findings were obtained from studies that examined the ventilatory response to hypoxia in men and women in the follicular phase of the menstrual cycle (2, 44). Moreover, findings from our study and a past investigation (47) showed that differences existed between sexes even though women participating were not restricted to a given phase of the menstrual cycle.

Thus inconsistent findings from studies that have examined sex differences in the ventilatory response to hypoxia may in part be due to the impact that carbon dioxide has on the hypoxic ventilatory response. Recent findings have shown that ventilation does not vary in response to changes in \( P_{\text{ET CO}_2} \) below the carbon dioxide set point but does increase when carbon dioxide levels are above the set point (2, 32).

Fig. 2. Histograms showing the average chemoreflex sensitivity obtained from the rebreathing trials completed by men and women while oxygen was maintained at 50 Torr (central + peripheral chemoreflex; A) or 150 Torr (central chemoreflex; B) before (black bars) and after (white bars) exposure to episodic hypoxia. Moreover, histograms showing the difference between chemoreflex sensitivity measured before and after episodic hypoxia (gray bars) for men and women are shown. Note that before exposure to episodic hypoxia central and central + peripheral chemoreflex sensitivity was greater in men compared with women. Additionally, note that the increase in central and central + peripheral chemoreflex sensitivity after episodic hypoxia was greater in men compared with women. Values are means \( \pm \) SE. *Significantly different from women, \( P < 0.05 \). 8Significantly different from baseline \( P < 0.05 \).

Fig. 3. Histograms showing the average carbon dioxide set point obtained from the rebreathing trials completed by both men and women while oxygen was maintained at 150 Torr (central chemoreflex) or 50 Torr (central + peripheral chemoreflex) before (black bars, central chemoreflex; dark gray bars, central + peripheral chemoreflex) and after (white bars, central chemoreflex; light gray bars, central + peripheral chemoreflex) exposure to episodic hypoxia protocol. Note that in men and women the carbon dioxide set points were similar before and after exposure to episodic hypoxia. Values are means \( \pm \) SE.
dioxide is above the set point (11, 28, 35). Thus the absence of a sex difference in the ventilatory response to hypocapnic hypoxia may occur because the response in both men and women are equally disfacilitated by the existing hypocapnia (41). Moreover, sex differences in the ventilatory response to isocapnic hypoxia (2, 32, 42, 44) could vary on the basis of the level of $P_{et\text{CO}_2}$ chosen to represent isocapnia, because the degree to which the chosen level of carbon dioxide is above the set point, which was not measured in previous studies, may vary. Additionally, given that ventilation is influenced by behavioral stimuli during wakefulness (11), it is possible that in some cases the level of carbon dioxide chosen to reflect isocapnia is not a true representation and consequently that the level selected may be below the carbon dioxide set point. Our postulation that carbon dioxide might have a role in the measure of the hypoxic ventilatory response is supported by our results that showed that the ventilatory response to hypoxia was not different between sexes when carbon dioxide was below the carbon dioxide set point but was greater in men in the presence of hypocapnia.

**Ventilatory response to isocapnic hypoxic and hypercapnic carbon dioxide rebreathing after episodic hypoxia.** In support of our laboratory’s previous findings (24), we showed that, despite the absence of long-term facilitation, the ventilatory response to isocapnic hypoxic carbon dioxide rebreathing was enhanced in both men and women after exposure to episodic hypoxia. Moreover, we showed that this enhancement manifests itself most prominently in men compared with women. The increase observed is similar to previous results that showed that the acute ventilatory response to hypoxia in humans was increased after exposure to chronic intermittent hypoxia for days or weeks (1, 14, 22) or continuous hypoxia for $\geq 3$ h (17, 21, 40). This similarity exists even though exposure to episodic hypoxia in the present study was relatively short compared with the duration of exposures employed previously. Moreover, we found that the increase in the ventilatory response to hypoxia was due solely to a change in the slope of the ventilatory response. In contrast, other studies have reported that increases in the ventilatory response to hypoxia after exposure to continuous or chronic episodic hypoxia may be due in part to changes in the set point (1, 21, 22). Whether the difference is a consequence of duration of exposure to hypoxia (minutes vs. hours or days), pattern of exposure (acute episodic vs. continuous or chronic episodic hypoxia), and/or hypocapnic severity remains to be determined.

The sample size of most of the studies that examined the acute ventilatory response to hypoxia after exposure to chronic hypoxia was small (no greater than an $n = 12$), and the male to female ratio reported was no less than 2:1, thus conclusions regarding sex differences were not addressed and cannot be compared with our findings. Indeed, no study to our knowledge has directly obtained measures of the acute ventilatory response to hypoxia in both sexes during or after chronic exposure to hypoxia. However, one study (29) that measured the acute ventilatory response to hypoxia and hypercapnia during days 2, 7, and 12 in women residing at high altitude compared these measures with values obtained from men exposed to a similar altitude in previous investigations (36, 45). No difference in the slope of the acute response to hypoxia or hypercapnia existed between sexes. A few other studies examined whether the rate of the ventilatory increase that is known to occur during exposure to continuous or chronic episodic hypoxia (i.e., ventilatory acclimatization to hypoxia) is sex dependent (15, 19). On the basis of the literature, if one assumes that peripheral chemoreceptor adaptation (see *Mechanisms responsible for the ventilatory response to isocapnic hypoxic and hyperoxic carbon dioxide rebreathing after episodic hypoxia* for further discussion) is in part responsible for ventilatory acclimatization then these studies could provide insight into whether the rate of chemoreceptor adaptation differs between sexes. Unfortunately, the data have been equivocal, with one study showing that the rate of ventilatory acclimatization was greater in women (15) and another that showed no difference (19). Thus additional studies are required to determine whether alterations in the acute ventilatory response to hypoxia after chronic exposure to hypoxia are sex dependent.

The increase in the acute ventilatory response to isocapnic hypoxic carbon dioxide rebreathing that we observed after 30 min of episodic hypoxia is in contrast to the reduction in the ventilatory response that Mahamed and Duffin (22) observed under similar conditions after exposure to 20 min of continuous hypoxia. These authors suggested that the reduction in the acute response mirrored the typical decline in ventilation that is often observed during short-term exposure (i.e., 20–30 min) to isocapnic continuous hypoxia (i.e., ventilatory roll-off) (34). This difference between our results and Mahamed and Duffin (22) reflects previous findings observed in awake (30) and anesthetized rats (5). Thus exposure to episodic hypoxia may have dramatically different effects on the ventilatory response to isocapnic hypoxic carbon dioxide rebreathing than exposure to continuous hypoxia over a similar time frame.

Whether this difference is sex dependent remains to be determined, because a direct comparison of the ventilatory response to hypoxia after exposure to short-term episodic and continuous hypoxia in women has not been completed. However, Sajkov et al. (37) did show that “ventilatory roll-off” is not sex dependent. If one accepts the findings of Mahamed and Duffin (22) that the reduction in the acute response after exposure to chronic hypoxia mirrors ventilatory roll-off then the male and female ventilatory response to hypoxia after episodic and continuous hypoxia may be similar.

In our laboratory’s previous study, we observed a trend toward an increase in the ventilatory response to isocapnic hyperoxic carbon dioxide rebreathing after exposure to episodic hypoxia (24). In our present investigation, this increase was found to be statistically significant in the men but not the women. Our finding is similar to results obtained by Ainslie et al. (1) and Tansely et al. (40), who showed that the ventilatory response to carbon dioxide was significantly increased after 8 h of daily exposure to hypoxia for 2 wk and 48 h of exposure to continuous hypoxia, respectively. Alternatively, Mahamed et al. (21, 22) showed that no change in the ventilatory response to carbon dioxide occurred after 20 min of daily exposure to hypoxia for 2 wk or after 3 h of continuous exposure to hypoxia. The lack of a response observed by Mahamed et al may wholly or in part be due to differences in the duration of exposure to continuous or chronic intermittent hypoxia, because in both experiments the duration of exposure was less than that used by Ainslie et al. (1) and Tansley et al. (40).

It is possible that we would have observed greater increases in the ventilatory response to isocapnic hyperoxic carbon dioxide rebreathing in the men participating in our studies if we had...
employed additional episodes of hypoxia. Similarly, additional episodes of hypoxia may have led to statistically significant increases in the ventilatory responses to carbon dioxide in the presence of both low and high oxygen levels in the women participating in our investigation. Moreover, greater increases may have been observed if the duration of time between exposure to episodic hypoxia and completion of the isocapnic hyperoxic carbon dioxide rebreathing trials thereafter was reduced. However, these speculations require further investigation.

Mechanisms responsible for the ventilatory response to isocapnic hypoxia and hyperoxic carbon dioxide rebreathing after episodic hypoxia. The increase in the ventilatory response to slow-wave sleep was enhanced after exposure to chronic episodic hypoxia or continuous hypoxia. Conversely, sustained central nervous system hypoxia (43) or hypercapnia (without hypoxia) isolated to the carotid body (7) did not lead to ventilatory acclimatization to hypoxia. However, it is unlikely that the increase in sensitivity that we measured was due solely to increased carotid body sensitivity because the ventilatory response to isocapnic hypoxic carbon dioxide rebreathing was elevated in men. Thus enhanced processing of carotid body input to the central nervous system or enhanced neuromuscular translation into breathing likely contributed to the enhanced ventilatory response to hypoxia. This postulation is supported by findings that showed in anesthetized rats that the phrenic neurogram response to electrical stimulation of the carotid sinus nerve, which was sectioned distally from the carotid bodies, was enhanced after chronic exposure to hypoxia compared with baseline and a control group not exposed to chronic hypoxia (13). Thus a mechanism in the central nervous system may contribute to the ventilatory response to isocapnic hypoxic carbon dioxide rebreathing because the carotid body (7) did not lead to ventilatory acclimatization to hypoxia. However, it is unlikely that the increase in sensitivity that we measured was due solely to increased carotid body sensitivity because the ventilatory response to isocapnic hypoxic carbon dioxide rebreathing was elevated in men. Thus enhanced processing of carotid body input to the central nervous system or enhanced neuromuscular translation into breathing likely contributed to the enhanced ventilatory response to hypoxia. This postulation is supported by findings that showed in anesthetized rats that the phrenic neurogram response to electrical stimulation of the carotid sinus nerve, which was sectioned distally from the carotid bodies, was enhanced after chronic exposure to hypoxia compared with baseline and a control group not exposed to chronic hypoxia (13). Thus a mechanism in the central nervous system may facilitate the response of the peripheral and central chemoreflex after exposure to episodic hypoxia. Moreover, the degree to which this mechanism impacts on the chemoreflex response may be sex dependent.

Physiological significance. Our findings may have implications for the control of breathing during sleep. Increases in the ventilatory response to hypcapnia and hypoxia after exposure to episodic hypoxia might promote the occurrence of apneas and hypopneas. Disproportionate increases in ventilation (i.e., hyperventilation) for a given level of oxygen could drive carbon dioxide levels below the apneic threshold, ultimately resulting in a reduction in central respiratory drive to chest wall and upper airway muscles. The decrease in ventilatory motor output could subsequently lead to partial or complete closure of the upper airway (3, 4, 31). Moreover, factors that might stabilize breathing (26) and reduce the impact that enhanced ventilatory responses have on apnea occurrence might not be activated consistently, because we did not observe long-term facilitation of breathing after episodic hypoxia. Finally, because the ventilatory response to hypcapnia and hypoxia was greater in men than women after exposure to episodic hypoxia, then the prevalence of apnea may follow a similar trend if increases in chemoreflex sensitivity are in part responsible for the development of apnea. This possibility is in line with the reported finding that the prevalence of obstructive sleep apnea is greater in men compared with women (9).

GRANTS

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REFERENCES