Effect of gender on the development of hypcapnic apnea/hypopnea during NREM sleep

X. S. ZHOU, S. SHAHABUDDIN, B. R. ZAHN, M. A. BABCOCK, AND M. S. BADR

John D. Dingell Veterans Affairs Medical Center, and Division of Pulmonary and Critical Care Medicine, Wayne State University School of Medicine, Detroit, Michigan 48201

Received 15 March 1999; accepted in final form 14 February 2000

Zhou, X. S., S. Shahabuddin, B. R. Zahn, M. A. Babcock, and M. S. Badr. Effect of gender on the development of hypcapnic apnea/hypopnea during NREM sleep. J Appl Physiol 89: 192–199, 2000.—We hypothesized that a decreased susceptibility to the development of hypcapnic central apnea during non-rapid eye movement (NREM) sleep in women compared with men could be an explanation for the gender difference in the sleep apnea/hypopnea syndrome. We studied eight men (age 25–35 yr) and eight women in the midluteal phase of the menstrual cycle (age 21–43 yr); we repeated studies in six women during the midfollicular phase. Hypcapnia was induced via nasal mechanical ventilation for 3 min, with respiratory frequency matched to euepnic frequency. Tidal volume (VT) was increased between 110 and 200% of eupneic control. Cessation of mechanical ventilation resulted in hypcapnic central apnea or hypopnea, depending on the magnitude of hypcapnia. Nadir minute ventilation in the recovery period was plotted against the change in end-tidal PCO2 (PETCO2) per trial; minute ventilation was given a value of 0 during central apnea. The apneic threshold was defined as the x-intercept of the linear regression line. In women, induction of a central apnea required an increase in VT to 155 ± 29% (mean ± SD) and a reduction of PETCO2 by −4.72 ± 0.57 Torr. In men, induction of a central apnea required an increase in VT to 142 ± 13% and a reduction of PETCO2 by −3.54 ± 0.31 Torr (P = 0.002). There was no difference in the apneic threshold between the follicular and the luteal phase in women. Premenopausal women are less susceptible to hypcapnic disfacilitation during NREM sleep than men. This effect was not explained by progesterone. Preservation of ventilatory motor output during hypcapnia may explain the gender difference in sleep apnea.


apneic threshold; control of breathing; central apnea; hypcapnia; ventilation; mechanical; follicular; luteal; progesterone

SLEEP APNEA/HYPOPNEA SYNDROME is more prevalent in men than in women (29). Differences in upper airway structure/function and/or ventilatory control during sleep could explain the gender difference. The relative contribution of each mechanism is uncertain.

The differences in upper airway structure between genders have clearly been shown during wakefulness, inasmuch as men have larger pharynges and tracheae (4, 26). Likewise, upper airway resistance (Rua) is higher in men than in women, and upper airway dilating muscle response to negative pressure is reduced in men relative to women (16a). However, no gender comparison has been done during sleep. Furthermore, the difference in upper airway structure does not account for the reported difference in the prevalence of central sleep apnea (see below).

Gender differences in ventilatory control have also been documented during wakefulness, including increased sensitivity to CO2, in men relative to women (1, 8, 26, 27). Likewise, the higher prevalence of central sleep apnea in men than in women suggests a gender difference in CO2 chemosensitivity and/or higher propensity to sleep discontinuity (29). Thus the precise mechanism(s) underlying gender differences in the occurrence of sleep apnea remains uncertain.

In a previous study investigating the effect of induced central apnea on upper airway patency, we experienced substantial difficulty inducing central apneas in women relative to men (2). Thus we hypothesized that women are less susceptible to hypcapnic disfacilitation during NREM sleep than men. This effect was not explained by progesterone. Preservation of ventilatory motor output during hypcapnia may explain the gender difference in sleep apnea.

METHODS

The experimental protocol was approved by the Human Investigation Committee of the Wayne State University School of Medicine and the Detroit Veterans Affairs Medical Center. Informed written consent was obtained from all subjects. We studied eight men (age 29 ± 2 yr) and eight women in the midluteal phase of the menstrual cycle (age 32 ± 3 yr) (Table 1). An additional study was performed on six of the women during the follicular phase of the menstrual cycle (Table 2). All subjects were healthy nonsnorers and were not receiving any medication; none of the women were taking birth control drugs. Studies during the luteal phase were conducted between days 17 and 21 of the menstrual cycle, and studies during the follicular phase were conducted between cycle days 6 and 11 (with day 1 being the 1st day of menses). Menstrual cycle phase was confirmed by progesterone assay (follicular phase <1.5 ng/ml; luteal phase >2.5 ng/ml).

The costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

http://www.jap.org
Table 2. Comparison of the P ETCO2

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age, yr</th>
<th>Ht, cm</th>
<th>Wt, kg</th>
<th>BMI, kg/m2</th>
</tr>
</thead>
<tbody>
<tr>
<td>BJ</td>
<td>28</td>
<td>175</td>
<td>79.5</td>
<td>26.0</td>
</tr>
<tr>
<td>XH</td>
<td>25</td>
<td>180</td>
<td>67.5</td>
<td>20.8</td>
</tr>
<tr>
<td>YS</td>
<td>27</td>
<td>162</td>
<td>54.9</td>
<td>20.9</td>
</tr>
<tr>
<td>WA</td>
<td>26</td>
<td>181</td>
<td>75.0</td>
<td>22.9</td>
</tr>
<tr>
<td>RM</td>
<td>27</td>
<td>175</td>
<td>75.0</td>
<td>24.5</td>
</tr>
<tr>
<td>PM</td>
<td>35</td>
<td>180</td>
<td>81.2</td>
<td>25.3</td>
</tr>
<tr>
<td>GS</td>
<td>30</td>
<td>180</td>
<td>76.4</td>
<td>23.6</td>
</tr>
<tr>
<td>NTF</td>
<td>36</td>
<td>165</td>
<td>66.4</td>
<td>24.4</td>
</tr>
<tr>
<td>Mean</td>
<td>29.3</td>
<td>174.8</td>
<td>72.1</td>
<td>23.5</td>
</tr>
<tr>
<td>±SD</td>
<td>±4.1</td>
<td>±7.4</td>
<td>±8.7</td>
<td>±1.9</td>
</tr>
</tbody>
</table>

Women

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age, yr</th>
<th>Ht, cm</th>
<th>Wt, kg</th>
<th>BMI, kg/m2</th>
</tr>
</thead>
<tbody>
<tr>
<td>CF</td>
<td>21</td>
<td>167</td>
<td>60.0</td>
<td>21.5</td>
</tr>
<tr>
<td>SK</td>
<td>21</td>
<td>153</td>
<td>45.0</td>
<td>19.2</td>
</tr>
<tr>
<td>XX</td>
<td>33</td>
<td>163</td>
<td>54.5</td>
<td>20.5</td>
</tr>
<tr>
<td>YL</td>
<td>36</td>
<td>165</td>
<td>56.8</td>
<td>20.9</td>
</tr>
<tr>
<td>AC</td>
<td>27</td>
<td>163</td>
<td>56.8</td>
<td>21.5</td>
</tr>
<tr>
<td>LP</td>
<td>43</td>
<td>168</td>
<td>63.2</td>
<td>22.5</td>
</tr>
<tr>
<td>NF</td>
<td>34</td>
<td>160</td>
<td>43.2</td>
<td>16.9</td>
</tr>
<tr>
<td>GL</td>
<td>39</td>
<td>155</td>
<td>50.0</td>
<td>20.8</td>
</tr>
<tr>
<td>Mean</td>
<td>31.8</td>
<td>161.6</td>
<td>53.7</td>
<td>20.5</td>
</tr>
<tr>
<td>±SD</td>
<td>±8.1</td>
<td>±5.3</td>
<td>±7.1</td>
<td>±1.7</td>
</tr>
</tbody>
</table>

BMI, body mass index.

ng/ml). Subjects were instructed to restrict their sleep on the night before the study (total sleep time 4–6 h). The study was done during regular sleep hours.

Measurements. An appropriate-sized tight-fitting nasal continuous positive airway pressure mask (Respironics, Murrysville, PA) was glued to the face with liquid latex to prevent mask leaks and was connected to the ventilation circuit. Tape was placed over the mouth to restrict subjects to nasal breathing. Airflow was measured by heated pneumotachometer (model 3710, Hans Rudolph, Kansas City, MO) connected to the mask leaks and was connected to the ventilation circuit. Tape was placed over the mouth to restrict subjects to nasal breathing. Airflow was measured by heated pneumotachometer (model 3710, Hans Rudolph, Kansas City, MO) connected to the mask. Tidal volume (VT) was obtained by

ter (model 3710, Hans Rudolph, Kansas City, MO) connected to the mask. Tidal volume (VT) was obtained by

ter (model 3710, Hans Rudolph, Kansas City, MO) connected to the mask. Tidal volume (VT) was obtained by

ter (model 3710, Hans Rudolph, Kansas City, MO) connected to the mask. Tidal volume (VT) was obtained by

ter (model 3710, Hans Rudolph, Kansas City, MO) connected to the mask. Tidal volume (VT) was obtained by

ter (model 3710, Hans Rudolph, Kansas City, MO) connected to the mask. Tidal volume (VT) was obtained by

ter (model 3710, Hans Rudolph, Kansas City, MO) connected to the mask. Tidal volume (VT) was obtained by

ter (model 3710, Hans Rudolph, Kansas City, MO) connected to the mask. Tidal volume (VT) was obtained by

ter (model 3710, Hans Rudolph, Kansas City, MO) connected to the mask. Tidal volume (VT) was obtained by

measure ribcage and abdominal respiratory efforts (Respitrace, Ambulatory Monitoring). This was used as a redundant measurement of ventilation and timing. Inspiratory muscle activity was obtained by surface electromyogram (EMG) electrodens (Medi-Trace, Buffalo, NY) placed 2–4 cm above the right costal margin in the anterior axillary line. End-tidal P CO2 (P ETCO2) was measured with a gas analyzer (model CD-3A, AEI Technologies, Pittsburgh, PA).

To confirm the central etiology of apnea and to ascertain upper airway mechanics, supraglottic pressure was measured with a solid-state catheter (model MPC-500, Millar Instruments, Houston, TX). A 10% lidocaine spray was used to provide topical anesthesia to one nostril and the pharynx before catheter insertion. The catheter was threaded through a hole in the nasal mask, through the nose, and positioned in the hypopharynx just below the base of the tongue, as determined by visual inspection of the tip. Airflow, measured by the pneumotachometer through the nasal mask, and supraglottic pressure, measured with the catheter, were recorded using Biobench data acquisition software (National Instruments, Austin, TX) on a separate computer. Pressure-flow loops were used to confirm the absence of inspiratory flow limitation (22). Rua was determined from the linear portion of the inspiratory arm of the pressure-flow loops. Rua throughout inspiration was determined from the slope of the pressure-flow curve and expressed in centimeters H2O per liter times seconds. Satisfactory pressure-flow loops were obtained in 12 subjects (6 men and 6 women). Control Rua was calculated for the five control breaths before MV. The nadir breath for hypopnea trials was selected as a representative “low-drive” recovery break.

Electroencephalograms, electrooculograms, and chin EMG were attached using the international 10–20 system of electrode placement (electroencephalogram: C3-A2, C4-A1, Oz-A2; electrooculogram: F7-A2 and F8-A1). Data were logged onto a polygraph recorder (model 78, Grass, West Warwick, RI), and sleep stage was scored according to standard methodologies (17).

MV protocol. Hyperventilation was achieved using a pressure support ventilator (Quantum PSV, Healthdyne Technologies, Marietta, GA). The nasal mask dead space was determined to be 110.5 ± 1.5 ml. Accumulation of CO2 in the circuit was prevented by the biased flow provided by the ventilator and from an expiratory mushroom valve in-line between the pneumotachometer and the ventilator tubing. No rebreathing of CO2 took place, as shown by P CO2 at the start of inspiration equivalent to room air values. During the control and recovery periods, the ventilator was set at an expiratory positive airway pressure (EPAP) of 2.0 cmH2O. This was the minimum EPAP allowed by the device. During periods of hyperventilation, the ventilator was set in spontaneous timed mode, with timing matched to each subject’s

Table 2. Comparison of the PetCO2 and progesterone levels during the luteal and follicular phases of the menstrual cycle

<table>
<thead>
<tr>
<th>PetCO2, Torr</th>
<th>Wakefulness</th>
<th>NREM sleep</th>
<th>AP, mmHg</th>
<th>Progesterone, ng/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lu</td>
<td>Fol</td>
<td>Lu</td>
<td>Fol</td>
<td>Lu</td>
</tr>
<tr>
<td>XX</td>
<td>44.2</td>
<td>45.7</td>
<td>48.8</td>
<td>49.1</td>
</tr>
<tr>
<td>YL</td>
<td>45.3</td>
<td>44.7</td>
<td>48.2</td>
<td>48.7</td>
</tr>
<tr>
<td>AC</td>
<td>44.5</td>
<td>44.7</td>
<td>48.6</td>
<td>49.6</td>
</tr>
<tr>
<td>LP</td>
<td>44.7</td>
<td>45.4</td>
<td>47.6</td>
<td>48.5</td>
</tr>
<tr>
<td>NF</td>
<td>44.4</td>
<td>46.5</td>
<td>48.9</td>
<td>51.2</td>
</tr>
<tr>
<td>GL</td>
<td>48.3</td>
<td>47.4</td>
<td>52.0</td>
<td>50.8</td>
</tr>
<tr>
<td>Mean</td>
<td>45.2</td>
<td>45.7</td>
<td>49.0</td>
<td>49.6</td>
</tr>
</tbody>
</table>

PETCO2, end-tidal P CO2; AP, apneic threshold; NREM, non-rapid eye movement; Lu, luteal; Fol, follicular.
eupneic rate. Hyperventilation was achieved by increasing the inspiratory pressure of the ventilator during expiration. The inspiratory pressure was increased by 1.0 cmH2O from an initial level of 2.0 cmH2O each successive trial, which resulted in increased VT (range 110–230% of eupneic control). Spontaneous respiratory effort remained in most trials, as evidenced by persistence of an initial negative deflection of supraglottic pressure signal and persistent, albeit reduced, diaphragmatic EMG activity. MV was continued for 3 min and was terminated during expiration, to an EPAP of 2.0 cmH2O. The post-MV period, or recovery period, was observed for posthyperventilatory inhibition. The ensuing hypocapnia resulted in hypopnea or central apnea, depending on the magnitude of hypocapnia. Apnea was defined as a period of no airflow for ≥5.0 s. Stable NREM sleep in stage 2 or slow-wave sleep was selected for each trial. Each trial was repeated twice, and trials were selected for analysis only if the sleep state remained stable throughout the trial, including the recovery. Trials were separated by ≥3 min.

Data analysis. We analyzed only trials with stable sleep state, as evidenced by the absence of arousal (20) or ascent to a lighter sleep state. PETCO2 was averaged over 10 breaths during wakefulness at the beginning of the study. For each trial, the control period was represented by the average of five breaths immediately preceding the onset of MV. The hyperventilation data were the calculated averages of the last five mechanically ventilated breaths before the ventilator was turned back to an EPAP of 2.0 cmH2O. The change in PETCO2 was calculated as the difference between the control period and the last five MV breaths. The change in PETCO2 was plotted against the changes in PETCO2 for each trial. In addition, apnea length was measured and plotted vs. the corresponding change in PETCO2 for each apnea trial.

Statistical analysis. Linear regression analysis was performed on the change in V̇E and the change in PETCO2 to determine the PETCO2 threshold associated with zero V̇E (apnea). Thus the predicted apneic threshold was defined as the x-intercept of the linear regression line. Unpaired Student's t-tests were performed to compare the men and women (luteal phase). Paired Student's t-tests were used to compare the six women during the luteal and follicular phases. One-way repeated-measures ANOVA was used to compare the six women during the luteal and follicular phases. One-way repeated-measures ANOVA was used to compare the six women during the luteal and follicular phases.

RESULTS

A representative polygraph record of one hypopneic trial is shown in Fig. 1. MV was initiated during expiration in stable NREM sleep. Ventilator frequency was matched to the subject's spontaneous eupneic breathing. V̇E increased to 125% of control and resulted in a mild hypocapnia (ΔPETCO2 = -2.2 Torr from control). Note the persistence of spontaneous inspiratory effort during MV, as evidenced by initial negative deflection on mask pressure signal and persistence of inspiratory EMG activity. Cessation of MV resulted in a decreased V̇T (55% of control), with no corresponding change in breathing frequency. Figure 2 shows a representative polygraph record of one trial in which a central apnea occurred when the MV was terminated.
over control, and the $P_{ET\text{CO}_2}$ was decreased $-6.23$ Torr below control. After the MV was removed, the flow and $V_T$ fell to zero. Also, there was no negative deflection on the supraglottic pressure recording (not shown), and there was no inspiratory EMG activity, also suggesting no effort to breathe (central apnea).

For the men, a total of 125 trials were recorded: 88 produced hypopneas, and 37 were apneic trials. Among the women (luteal phase), there were 134 successful trials: 106 produced hypopnea, and 28 were apneic trials. To induce apnea in the men, the $V_T$ was increased $142 \pm 13\%$ above eupneic control, and the subsequent apnea length was $24.8 \pm 9.4$ s (range 5.4–47.0 s). In women, the $V_T$ was increased $155 \pm 29\%$ (luteal phase) above eupneic control to produce an apnea; the subsequent apnea length was $20.8 \pm 8.3$ s (range 8.8–46.8 s). No differences were found between the two groups with regard to $P_{ET\text{CO}_2}$ during wakefulness ($44.5 \pm 0.3$ and $45.3 \pm 0.5$ Torr for men and women, respectively) and $P_{ET\text{CO}_2}$ during the NREM control period ($47.9 \pm 0.6$ and $48.8 \pm 0.5$ Torr for men and women, respectively).

Representative plots of the data [$V_E$ (percentage of control) vs. change in $P_{ET\text{CO}_2}$] from the hypopneic and the apneic trials are shown for one man (Fig. 3A) and one woman (Fig. 3B). The linear regression line was fitted to the data from the hypopneic trials only, and the equation of the linear regression line was used to calculate the apneic threshold. The man differed from the woman in the slope, the predicted apneic threshold, and the apneic threshold from the first apneic trial. The predicted apneic threshold was very close to the apneic threshold measured for the first apneic trial; this was also true for the group (see below).

The mean group data for men and women for the calculated apneic threshold and the apneic threshold measured for the first apneic trial are shown in Fig. 4. There was a significant difference between the men and the women for the calculated apneic threshold ($P = 0.004$) and for the measured apneic threshold ($P < 0.001$). No difference was found between the calculated and the measured apneic threshold within each group. The slopes of the linear regression equations were substantially different ($P = 0.006$) between the men and the women (Fig. 4A), which indicates higher chemoresponsiveness in the men than in the women.

To determine whether ventilatory changes were due to changes in $R_u$, the $R_u$ was measured from the linear portion of the pressure-flow curve for the men and the women ($n = 6$ in each group; Fig. 5). $R_u$ during the control period was not different between men and women ($8.8 \pm 1.1$ and $8.5 \pm 1.5$ cmH$_2$O·l$^{-1}$·s for men and women, respectively), nor was $R_u$ different after MV ($8.5 \pm 1.5$ and $9.0 \pm 2.1$ cmH$_2$O·l$^{-1}$·s for men and women, respectively). Thus reduced ventilatory output was not associated with changes in $R_u$ in men and women.

Six of the women were studied again during the follicular phase to ascertain whether the phase of the menstrual cycle influenced the apneic threshold. Eighty-seven trials were conducted (64 resulted in hypopnea and 23 in apnea) in the six women during the follicular phase tests. Achievement of central apnea during the follicular phase required an increase in $V_T$...
to 165 ± 37% of control and a reduction of PetCO₂ by −4.9 ± 0.3 Torr. Comparison of the subset of women studied at the two phases of the menstrual cycle revealed no difference in the calculated or the measured apneic threshold (Fig. 6, B and C). In addition, there was no difference in chemoresponsiveness, as shown by the change in ventilation relative to the change in PetCO₂ between the luteal and the follicular phases (Fig. 6A).

DISCUSSION

The purpose of this study was to examine whether there was a gender difference in the susceptibility to hypocapnic apnea/hypopnea during sleep. Our data showed that the change in PetCO₂ necessary to cause a central apnea was significantly different between men and women. This difference may not be due to progesterone, inasmuch as no difference in the change in PetCO₂ at the apneic threshold was found in the six women studied during the luteal and the follicular phases of the menstrual cycle.
This gender comparison allows us to propose that healthy young women are less susceptible than men to hypocapnic central apnea during NREM sleep. However, our sample size is relatively small, owing to the difficulty in conducting interventional studies in heavily instrumented subjects. Therefore, caution is mandated in interpreting our findings, inasmuch as our data may not be representative of a large cross-sectional study’s reflection of the whole population.

Role of gender in the development of hypocapnic apnea/hypopnea. We considered several explanations for the difference in the occurrence and magnitude of posthyperventilation inhibition of ventilatory motor output, including differences in upper airway caliber, metabolic rate, and chemoresponsiveness.

The gender difference in apneic threshold cannot be explained by a difference in upper airway mechanics or baseline P\textsubscript{ET}\textsubscript{CO\textsubscript{2}}. Although a patent upper airway may facilitate the development of arterial and, hence, medullary hypocapnia, we included only nonsnorers without evidence of significant sleep-induced upper airway narrowing. This was evidenced by the absence of snoring and the absence of inspiratory flow limitation on pressure-flow loops (n = 12) (22). Likewise, our findings could not be explained by differences in metabolic rate. Although data are limited, the available studies demonstrate no difference in metabolic rate between women and men during sleep (6, 28). Furthermore, it is unlikely that MV per se would decrease metabolic rate preferentially in one gender.

The gender difference in hypocapnic response indicates a difference in chemoresponsiveness, at least in the hypocapnic range. Our findings are in contrast to previous studies showing no gender difference in the hypercapnic ventilatory response during NREM sleep (25). Women have been shown to have lower hypoxic and hypercapnic ventilatory responses than men during wakefulness but not during NREM sleep (1, 25, 26). Whether the response to hypocapnia during NREM sleep is different between men and women is unknown. Similarly, whether the difference is unique to the CO\textsubscript{2} stimulus or whether it encompasses other stimuli (i.e., hypoxia) remains to be determined.

We were intrigued by the apparent difference in chemoresponsiveness between our study and previous studies in awake subjects. Unfortunately, studies on chemoresponsiveness are difficult to interpret, inasmuch as sleep per se has a variable effect on airway resistance, which could reduce the response to any stimulus. In addition, Rua is affected by changes in ventilatory motor output (2). Therefore, the ventilatory response to CO\textsubscript{2} depends on the level of CO\textsubscript{2}, the baseline Rua, and its response to chemoreceptor stimuli. It is possible that previous studies included men with high Rua. The higher Rua in men than in women may have dampened the ventilatory response to hypercapnia, masking a higher CO\textsubscript{2} chemoresponsiveness in men. In contrast, all our subjects were nonsnorers with normal upper airway mechanics.

Mechanism(s) of gender-related differences in chemoresponsiveness. We considered several possibilities to explain the gender difference in chemoresponsiveness. Specifically, we considered 1) the protective role of progesterone and/or estrogen vs. 2) the destabilizing role of testosterone. Progesterone is a known ventilatory stimulant that leads to increased ventilation in humans (8, 27) and is presumed to protect premenopausal women from sleep-disordered breathing. The ventilatory effects of progesterone are more pronounced during the luteal than during the follicular phase of the menstrual cycle (27). In contrast, estrogen, by itself, has been shown not to affect ventilation (8) but, in combination with progesterone, will elevate ventilation (8, 18). However, the lack of difference between the follicular and luteal phases argues against progesterone alone or a progesterone-estrogen combination as underlying factors minimizing the propensity for the development of central apnea.

Although gender difference in ventilatory control has been attributed to female hormones, testosterone is also known to influence ventilation (21, 27). There is substantial evidence implicating testosterone as a destabilizer of respiration in sleeping humans (11, 13, 19). For example, testosterone administration to hypogonadal men results in increased hypoxic ventilatory response during wakefulness and an increased frequency of apnea and hypopnea during sleep (27). In a
group of seven obese men, six exhibited episodes of desaturation and disordered breathing and one was hypogonadal and did not experience any desaturations or disordered breathing (9). Several case studies have shown the development of upper airway obstruction after testosterone administration (11). The available data, taken together, support our interpretation that the gender difference in the apneic threshold was due to testosterone effect. This interpretation remains speculative in the absence of studies directly investigating the ventilatory effects of testosterone during sleep.

Implications for sleep apnea. The noted difference in the apneic threshold between men and women suggests that women are less susceptible to the development of central apnea. Evidence in the literature suggests a male propensity for the development of central sleep apnea. For example, Franklin et al. (7) studied 20 consecutive patients with central sleep apnea, and only 1 was a woman. In another study of 327 screened patients, 14 patients were selected because they met the criteria of central apnea index >5 or apnea-hypopnea index >10; only 1 of these 14 subjects was a woman (5). Thus central apnea appears to be more prevalent in men.

The gender difference in the susceptibility to hypocapnic inhibition may also influence the development of obstructive sleep apnea. We and others have shown that individuals with a collapsible upper airway during sleep and with evidence of inspiratory flow limitation are dependent on the ventilatory motor output to preserve upper airway patency (2, 10, 16, 27). For example, mild hypocapnic hypopnea was associated with increased Rua or worsening inspiratory flow limitation only in snoring subjects who demonstrated inspiratory flow limitation during eupnea (2). Thus hypocapnia may cause a significant reduction in ventilatory motor output and subsequent upper airway narrowing in a snoring man but less ventilatory inhibition and, hence, less upper airway compromise in a woman with similar snoring and baseline upper airway mechanics.

Central apnea rarely occurs as a single event. Instead, several factors conspire to perpetuate breathing instability during sleep after central apnea. First, when the ventilatory motor output totally ceases during apnea, the inertia of the ventilatory control system will prevent the resumption of rhythmic breathing until the arterial PCO2 increases 4–6 Torr above eu-

pnea. The noted difference in the apneic threshold until the arterial PCO2 increases 4–6 Torr above eu-

pnea, the inertia of the ventilatory control system when the ventilatory motor output totally ceases during sleep instabilities during sleep after central apnea. First, several factors conspire to perpetuate breathing instability during sleep.

We thank A. T. Taylor for help with data analysis and Dr. James Rowley for critical review of the manuscript.

This work was supported by the Veterans Affairs Medical Service and the National Heart, Lung, and Blood Institute. M. S. Badr is a Career Investigator of the American Lung Association.

REFERENCES


