Ventilatory sensitivity to carbon dioxide before and after episodic hypoxia in women treated with testosterone

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Ahuja D, Mateika JH, Diamond MP, Badr MS. Ventilatory sensitivity to carbon dioxide before and after episodic hypoxia in women treated with testosterone. J Appl Physiol 102: 1832–1838, 2007. First published February 1, 2007; doi:10.1152/japplphysiol.01178.2006.—We hypothesized that the ventilatory threshold and sensitivity to carbon dioxide in the presence of sustained hypoxia and hyperoxia during wakefulness would be increased following testosterone administration in premenopausal women. Additionally, we hypothesized that the sensitivity to carbon dioxide increases following episodic hypoxia and that this increase is enhanced after testosterone administration. Eleven women completed four modified carbon dioxide rebreathing trials before and after episodic hypoxia. Two rebreathing trials before and after episodic hypoxia were completed with oxygen levels maintained at 150 Torr, the remaining trials were repeated while oxygen was maintained at 50 Torr. The protocol was completed following 8–10 days of treatment with testosterone or placebo skin patches. Resting minute ventilation was greater following treatment with testosterone compared with placebo (testosterone 11.38 ± 0.43 vs. placebo 10.07 ± 0.36 l/min; P < 0.01). This increase was accompanied by an increase in the ventilatory sensitivity to carbon dioxide in the presence of sustained hyperoxia (VSCO₂ hyperoxia) compared with placebo (3.6 ± 0.5 vs. 2.9 ± 0.3; P < 0.03). No change in the ventilatory sensitivity to carbon dioxide in the presence of sustained hypoxia (VSCO₂ hypoxia) following treatment with testosterone was observed. However, the VSCO₂ hypoxia was increased after episodic hypoxia. This increase was similar following treatment with placebo or testosterone patches. We conclude that treatment with testosterone leads to increases in the VSCO₂ hypoxia, indicative of increased central chemoreflex responsiveness. We also conclude that exposure to episodic hypoxia enhances the VSCO₂ hypoxia, but that this enhancement is unaffected by treatment with testosterone.

episodic hypoxia; placebo; carbon dioxide rebreathing; ventilatory threshold

THE IMPACT OF TESTOSTERONE on sleep apnea prevalence and severity in men has been recognized for over two decades (8, 30). Pilot studies reported initially that the apnea/hypopnea index increased in hypogonadal men after testosterone administration (26, 33), although the response to administration was variable. Nevertheless, Liu and colleagues (19) showed using a well-controlled experimental design that testosterone administration exacerbated sleep apnea in older men. Elevated testosterone levels may also promote apnea in women because elevated androgen levels caused by polycystic ovarian syndrome is associated with a greater apnea/hypopnea index compared with healthy controls (15). Furthermore, because free testosterone levels have been reported to rise across the menopausal transition (6), it is possible that androgen levels may in part be responsible for the increase in the prevalence of apnea that has been reported in postmenopausal compared with premenopausal women (36, 41).

Elevated testosterone levels might impact on apnea severity in part by altering the ventilatory response to carbon dioxide. This response is characterized by a threshold that delineates the point at which ventilation increases linearly in response to increases in carbon dioxide. The threshold is referred to as the apneic threshold during sleep (10) and as the ventilatory threshold during wakefulness (24). The slope of the ventilatory response to carbon dioxide above the thresholds is a measure of ventilatory sensitivity (24). Below the thresholds, ventilation does not respond to increases in carbon dioxide during sleep and wakefulness, although ventilation may be sustained by arousal and behavioral stimuli during wakefulness (37). Increasing ventilatory sensitivity or a shift of the ventilatory/apneic threshold closer to resting levels of carbon dioxide may promote apnea severity (10).

The impact of elevated androgen levels on ventilatory control in women is not well established, because only one study to our knowledge has investigated this relationship. Zhou and colleagues (42) demonstrated during non-rapid eye movement (NREM) sleep that the application of testosterone resulted in a shift of the apneic threshold closer to resting levels of carbon dioxide and an increase in ventilatory sensitivity to a reduction in carbon dioxide levels (i.e., hypocapnia). Whether or not this change in sensitivity was largely a consequence of modifications in metabolic rate or chemoreflex sensitivity was not determined. Additionally, the ventilatory response to stimuli typically experienced during and immediately following an apnea (i.e., hypocapnia and/or hypoxia) was not investigated. Consequently, inferences as to whether central and/or peripheral chemoreflex sensitivity was altered following testosterone administration were not possible. Lastly, the possibility that the results obtained were a consequence of an order effect could not be ruled out because of the experimental design.

In the present investigation, we employed a crossover randomized design to examine the ventilatory threshold and sensitivity to carbon dioxide in the presence of sustained hyperoxia and hypoxia, below and above the ventilatory threshold, during wakefulness in women following treatment with testosterone or placebo. We hypothesized that the ventilatory threshold and ventilatory

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sensitivity to carbon dioxide in the presence of sustained hypoxia (VSCO$_2$ hypoxia) would be principally impacted following treatment with testosterone in women, because this response has been consistently greater in mammals with elevated (e.g., men) compared with reduced (e.g., women and hypogonadal men) testosterone levels (1, 5, 17, 28, 31, 38, 40).

In addition to the impact of testosterone on the ventilatory threshold and/or sensitivity, a variety of studies have suggested that these measures are also mutable following exposure to continuous or episodic hypoxia (18, 21, 22, 24, 27). Mateika and colleagues (24) showed recently that the ventilatory sensitivity to carbon dioxide in the presence of hypoxia (VSCO$_2$ hypoxia) increased following exposure to episodic hypoxia. Additionally, Morelli and colleagues (27) showed that the increase was greater in men compared with women. The greater increase observed in men following episodic hypoxia could be a consequence of testosterone levels. This possibility might have important implications for women with elevated androgen levels, because potential increases in the ventilatory response that may exist because of hormonal modifications could be further exacerbated by exposure to episodic hypoxia, which is a hallmark of obstructive sleep apnea. Thus the second aim of our investigation was to determine whether treatment with testosterone leads to a greater increase in the VSCO$_2$ hypoxia or VSCO$_2$ hypoxia after episodic hypoxia in women during wakefulness following treatment with testosterone compared with placebo.

METHODS

Protocol overview. The Human Investigation Committees of Wayne State University School of Medicine and John D. Dingell Veterans Affairs Medical Center approved the experimental protocol. Eleven healthy premenopausal women (age 24.9 ± 1.3 yr, height 65.9 ± 0.7 in., weight 137.9 ± 5.3 lb.) visited the laboratory on three occasions after informed consent was obtained. The subjects recruited were not on birth control pills or other forms of medication. Before each visit subjects were advised to have a minimum of 7 h of sleep before the study and to fast for a minimum of 3 h before visiting the laboratory. On each occasion, subjects arrived at the same time of the day to account for the influence of circadian rhythms on the measured variables. During the first visit to the laboratory, subjects underwent a physical examination and pregnancy test. Once the inclusion criteria (i.e., healthy and not pregnant) were fulfilled, subjects completed one rebreathing trial and were exposed to two 4-min episodes of hypoxia to ensure familiarization with the experimental protocol and apparatus. The subjects were then given either 8–10 testosterone (Androderm Watson Pharmaceuticals) or placebo patches (Watson Pharmaceuticals) in a randomized fashion. The subjects were blinded. The first testosterone or placebo patch was administered at the onset of the menstrual cycle, and a new patch was given another 8–10 patches that were either placebo or testosterone patches. Subjects who had previously received testosterone patches received placebo patches and vice versa. Subjects started wearing their second set of patches at the onset of the menstrual cycle. Consequently, subjects began wearing the second set of patches ~1 mo after the second visit to the laboratory. After wearing the patches for 8–10 days, subjects returned to the laboratory for a third visit. During the third visit to the laboratory, the protocol completed by the subjects was identical to that described for the second laboratory visit.

Modified rebreathing protocol. A modified rebreathing protocol was employed to measure the ventilatory threshold and sensitivity to carbon dioxide before and after episodic hypoxia (12, 13, 24). Each rebreathing trial was separated by 20 min of rest. During each rebreathing trial, the subjects initially breathed room air for 5 min; subsequently, subjects hyperventilated for 5 min while being coached to maintain PETCO$_2$ between 20 and 25 Torr. This period of hyperventilation was employed to lower the stores of the carbon dioxide so that the point where ventilation begins to rise with increases in PETCO$_2$ (i.e., the ventilatory threshold) could be delineated. After the desired PETCO$_2$ was maintained for at least 5 min, subjects were switched from room air to a rebreathing bag. As mentioned, two hypoxic (i.e., 150 Torr) and two hypoxic (i.e., 50 Torr) rebreathing trials were completed before as well as after episodic hypoxia. The PETCO$_2$ in the bag at the start of the rebreathing experiment was 42 Torr.

Rebreathing began at the end of expiration and was followed by three rapid and deep breaths that produced rapid equilibration of the PCO$_2$ in the bag, lungs, and arterial blood to that of mixed venous blood. The presence of a plateau in carbon dioxide during the equilibration was a prerequisite for the continuation of the test, and if a plateau was not observed after three deep breaths, the test was aborted. Rebreathing continued until PETCO$_2$ increased at least 10 Torr above the threshold or the minute ventilation reached 100 l/min. Conditions of quiet wakefulness were maintained, and noise in the laboratory was minimized to reduce any behavioral stimuli that might affect breathing.

During the rebreathing trials, the subjects wore a tight-fitting mask. The mask was connected to a pneumotachograph (model RSS100-HR, Hans Rudolph, Kansas, MO) that was used to monitor breath-by-breath changes in ventilation. The pneumotachograph was attached to one side of a three-way valve that allowed us to switch the subjects from room air to the rebreathing bag. The PETCO$_2$ and PETCO$_2$ were sampled from the pneumotachograph side of the three-way valve using oxygen and carbon dioxide analyzers (model 17518 and model 17515, Vacumed). The end-tidal gas that was sampled for monitoring was returned to the bag during rebreathing. The oxygen level in the bag during rebreathing was maintained by a flow of oxygen that was computer controlled. If oxygen decreased below the desired threshold

with a clot activator (BD Diagnostics, Franklin Lakes, NJ). The sample collected was tested for the steroid hormones progesterone, estrogen, estradiol, and testosterone. Subsequently, subjects assumed a supine position, and the required monitoring equipment was attached (see Modified rebreathing protocol for details regarding monitoring equipment). During the second visit, four rebreathing trials were completed before and four rebreathing trials after exposure to episodic hypoxia. Thus a total of eight rebreathing trials were completed. Two of the four rebreathing trials completed before or after episodic hypoxia occurred while oxygen was sustained at a partial pressure of end-tidal PO$_2$ (PETPO$_2$) of 50 Torr. The remaining trials were completed with the oxygen level sustained at 150 Torr. Before the subjects completed each rebreathing trial, baseline measures of ventilation and end-tidal PCO$_2$ (PETCO$_2$) were obtained. The episodic hypoxia protocol, completed while subjects were in the supine position, consisted of eight 4-min episodes of hypoxia separated by 5-min recovery periods. The first hypoxic episode was preceded by a 15-min baseline period, and the last hypoxic episode was followed by a 15-min recovery period.

Once the experimental protocol was completed, subjects were given another 8–10 patches that were either either placebo or testosterone patches. Subjects who had previously received testosterone patches received placebo patches and vice versa. Subjects started wearing their second set of patches at the onset of the menstrual cycle. Consequently, subjects began wearing the second set of patches ~1 mo after the second visit to the laboratory. After wearing the patches for 8–10 days, subjects returned to the laboratory for a third visit. During the third visit to the laboratory, the protocol completed by the subjects was identical to that described for the second laboratory visit.

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Episodic hypoxia. During the episodic hypoxia, the subjects breathed through a facemask that was attached to a two-way valve. The inspiratory port of the valve was connected to a stopcock. Subjects breathed either room air or from one of the bags attached to the stopcock. One of the bags contained 8% oxygen-balanced nitrogen. The other bag contained 100% oxygen. Before the first episode of 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 recovery. During the episodes of hypoxia the subjects inspired the gas mixture consisting of 8% oxygen-balanced nitrogen. After the completion of every episode of hypoxia, hypoxia was abruptly terminated with a single breath of 100% oxygen to rapidly bring the PETCO2 to the normoxic range. After the last episode of hypoxia (8th episode) respiration was monitored for 15 min.

**Data analysis.** The data collected during the rebreathing trials was analyzed using a spreadsheet designed for this purpose. Before the analysis, the three deep breaths that were required for equilibration in addition to sighs and swallows were excluded from further analysis. Minute ventilation was then plotted against PETCO2. The ventilation vs. PETCO2 plot was divided into two segments. The first segment was characterized by a sustained level of ventilation in response to increases in carbon dioxide (i.e., basal ventilation). The second segment was characterized by a break point followed by a linear increase in minute ventilation as the PETCO2 increased. The breakpoint was taken as a measure of the ventilatory threshold to carbon dioxide. The threshold measured during the rebreathing trials during which PETCO2 was sustained at 150 Torr was assumed to represent the central chemoreflex sensitivity. The slope recorded during the rebreathing trials in the presence of sustained hypoxia (PETCO2 = 50 Torr) was assumed to be a measure of central chemoreflex sensitivity. The slope recorded during the rebreathing trials in the presence of sustained hypoxia (PETCO2 = 50 Torr) was assumed to be a measure of peripheral and central chemoreflex sensitivity. The measures of basal ventilation, threshold, and sensitivity collected during the hypoxic rebreathing trials completed before episodic hypoxia were averaged as were the measures obtained after episodic hypoxia. Similar averages were obtained for the data collected during completion of the hyperoxic rebreathing trials. Lastly, breath-by-breath values of minute ventilation recorded during the last 2 min of hypoxic episodes 1–4 following administration of the placebo or testosterone patches were averaged. This measure was assumed to be mediated by the peripheral chemoreflex alone. The data for each episode were averaged because the ventilatory response to each individual hypoxic episode was similar in all subjects. This ventilatory response to episodic hypoxia was used as a corollary measure to support the findings obtained from the carbon dioxide rebreathing trials completed in the presence of sustained hypoxia.

**Statistics.** To examine the impact of testosterone and episodic hypoxia on chemoreflex sensitivity, a two-way ANOVA with repeated measures in conjunction with Student-Newman-Keuls post hoc test was also employed to compare baseline ventilation, basal ventilation, and the rate of rise of carbon dioxide during rebreathing measured throughout the placebo and testosterone studies. A paired t-test was used to compare the ventilatory response to episodic hypoxia and hormone levels between the placebo and testosterone trials. All results are presented as means ± SE. A value of $P \leq 0.05$ was considered significant.

**RESULTS**

Figure 1 shows that serum testosterone concentration was significantly greater after testosterone administration compared with placebo ($P < 0.003$). In contrast, estradiol, $17\beta$-estradiol and progesterone were unchanged following testosterone administration.

Baseline ventilation was increased after testosterone administration (testosterone $11.38 \pm 0.43$ vs. placebo $10.07 \pm 0.36$ l/min; $P < 0.01$). The increase was a consequence of differences in breathing frequency (testosterone $17.6 \pm 0.7$ vs. placebo $16.9 \pm 0.8$ breaths/min; $P < 0.03$) and tidal volume (testosterone $671.2 \pm 26.1$ vs. placebo $643.2 \pm 20.9$ ml; $P > 0.2$). Measures of PETCO2 were similar under both conditions (testosterone $40.3 \pm 0.6$ vs. placebo $-39.7 \pm 0.9$ Torr; $P > 0.76$).

In contrast to baseline minute ventilation, Fig. 2 shows that basal ventilation (i.e., ventilation below the ventilatory threshold during rebreathing trials) following testosterone administration was similar to placebo during carbon dioxide rebreathing trials completed in the presence of sustained hypoxia (Fig. 2A) and hypoxia (Fig. 2B) either before or after exposure to episodic hypoxia (hypoxia: testosterone vs. placebo, $P > 0.75$; hypoxia: testosterone vs. placebo, $P > 0.30$). Moreover, following testosterone or placebo treatment, basal ventilation before exposure to episodic hypoxia was similar to measures obtained after exposure during both the hyperoxic and hypoxic rebreathing trials (hypoxia: before vs. after, $P > 0.82$; hypoxia: before vs. after, $P > 0.19$). No change in the ventilatory threshold to carbon dioxide in the presence of sustained episodic hypoxia.” A similar analysis was completed to determine the effect of testosterone and/or episodic hypoxia on the central or the central + peripheral chemoreflex thresholds. A two-way ANOVA in conjunction with Student-Newman-Keuls post hoc test was also employed to compare baseline ventilation, basal ventilation, and the rate of rise of carbon dioxide during rebreathing measured throughout the placebo and testosterone studies. A paired t-test was used to compare the ventilatory response to episodic hypoxia and hormone levels between the placebo and testosterone trials. All results are presented as means ± SE. A value of $P \leq 0.05$ was considered significant.
hyperoxia (Fig. 3A) and hypoxia (Fig. 3B) was evident after testosterone administration compared with placebo, before or after exposure to episodic hypoxia (hyperoxia: testosterone vs. placebo, \( P < 0.01 \); hypoxia: testosterone vs. placebo, \( P = 0.99 \)). In contrast, the ventilatory response to carbon dioxide in the presence of sustained hypoxia (Fig. 4B) was greater after compared with before episodic hypoxia following administration of testosterone or placebo patches (\( P < 0.01 \)).

**DISCUSSION**

The primary findings of our study are that the \( V\text{SCO}_2 \) hyperoxia was increased following administration of testosterone patches before or after exposure to episodic hypoxia (\( P > 0.83 \)). Additionally, the ventilatory response to steady-state isocapnic hypoxia following testosterone administration was similar to the response measured under placebo conditions (\( P > 0.99 \); Fig. 5) even though the stimulus under both conditions was similar (arterial oxygen saturation: placebo vs. testosterone 84 ± 0.9 vs. 84 ± 0.8%, \( P > 0.99 \); \( \text{PETCO}_2 \): placebo vs. testosterone −39.4 ± 0.5 vs. 39.6 ± 0.7 Torr; \( P > 0.99 \)).

In contrast, the ventilatory response to carbon dioxide in the presence of sustained hypoxia (Fig. 4B) was greater after compared with before episodic hypoxia following administration of testosterone or placebo patches (\( P < 0.01 \)).

**Fig. 2.** Histograms showing the average minute ventilation measured below the ventilatory threshold (i.e., basal ventilation) during carbon dioxide rebreathing in the presence of sustained hyperoxia (A) and hypoxia (B) following administration of placebo and testosterone patches before and after exposure to episodic hypoxia. Note that basal ventilation following testosterone administration was similar to placebo before or after exposure to episodic hypoxia. Additionally, note that basal ventilation measured before exposure to episodic hypoxia was similar to measures obtained after episodic hypoxia.

Hyperoxia (Fig. 3A) and hypoxia (Fig. 3B) was evident after testosterone administration compared with placebo, before or after exposure to episodic hypoxia (hyperoxia: testosterone vs. placebo, \( P > 0.70 \); hypoxia: testosterone vs. placebo, \( P > 0.46 \)). Additionally, the ventilatory thresholds measured before compared with after exposure to episodic hypoxia were similar following testosterone or placebo administration (Fig. 3).

In contrast, a significant increase in the \( V\text{SCO}_2 \) hyperoxia was observed after testosterone administration compared with placebo (3.6 ± 0.5 vs. 2.9 ± 0.3; \( P < 0.03 \)) before exposure to episodic hypoxia (Fig. 4A). This increase was not accompanied by changes in metabolic rate during the rebreathing trials, because the rate of rise of carbon dioxide during the rebreathing trials completed under conditions of sustained hyperoxia were similar following placebo and testosterone administration (0.052 ± 0.002 vs. 0.054 ± 0.002 Torr/s; \( P > 0.5 \)). The \( V\text{SCO}_2 \) hypoxia after testosterone administration was similar to measures obtained under placebo conditions (Fig. 4B) either before or after exposure to episodic hypoxia (\( P > 0.83 \)). Similarly, the ventilatory response to steady-state isocapnic hypoxia following testosterone administration was similar to the response measured under placebo conditions (\( P > 0.99 \); Fig. 5) even though the stimulus under both conditions was similar (arterial oxygen saturation: placebo vs. testosterone 84 ± 0.9 vs. 84 ± 0.8%, \( P > 0.99 \); \( \text{PETCO}_2 \): placebo vs. testosterone −39.4 ± 0.5 vs. 39.6 ± 0.7 Torr; \( P > 0.99 \)).
for 8–10 days in healthy women compared with placebo. Conversely, the \( V^{\text{SCO}_2}_{\text{hypoxia}} \) was unaffected by testosterone administration. Additionally, our results showed that exposure to episodic hypoxia led to an increase in the \( V^{\text{SCO}_2}_{\text{hypoxia}} \); however, the increase was independent of treatment with placebo or testosterone skin patches.

**Impact of testosterone on baseline ventilation and the ventilatory response to carbon dioxide before exposure to episodic hypoxia.** Our results showed that baseline ventilation increased after treatment with testosterone. Given that the studies were completed during wakefulness, the increase observed might have occurred because of changes in behavioral/arousal stimuli (37). However, we believe this scenario is unlikely because we found that basal ventilation (i.e., ventilation below the ventilatory threshold), which is primarily influenced by behavioral/arousal stimuli (13), was unaltered after treatment with testosterone. Similarly, the increase in baseline ventilation was not likely due to alterations in the ventilatory threshold, the \( V^{\text{SCO}_2}_{\text{hypoxia}} \), or the ventilatory response to isocapnic hypoxia measured during the episodic hypoxia protocol, because these variables remained unchanged following testosterone administration. In contrast, an increase in the \( V^{\text{SCO}_2}_{\text{hyperoxia}} \) might have been principally responsible for the increase in baseline ventilation because it was increased following testosterone treatment.

Given our assumptions (see Data analysis), the lack of an increase in the \( V^{\text{SCO}_2}_{\text{hypoxia}} \) and the ventilatory response to isocapnic hypoxia suggest that the combined central + peripheral chemoreflex sensitivity and the peripheral chemoreflex alone remained unaltered following testosterone administration. In contrast, the increase in \( V^{\text{SCO}_2}_{\text{hyperoxia}} \) suggests that testosterone impacted on one of the components comprising the central chemoreflex pathway (i.e., central chemoreceptors, medullary respiratory neurons, spinal motoneurons), particularly because the metabolic rate was similar before and after testosterone administration.

The impact of testosterone on the central chemoreflex is possible given that sex hormone receptors (i.e., testosterone and estrogen receptors) have been located in a number of regions in the central nervous system, including the hypoglossal nucleus, ventrolateral nucleus tractus solitarius, and spinal respiratory motoneurons (3, 4, 32). Testosterone might have impacted on the central chemoreflex directly or indirectly through conversion to estradiol via aromatase (16). However, we have no evidence that testosterone impacted on the central chemoreflex via conversion to estradiol, because serum measures of estradiol and estrogen levels remained unaltered following testosterone administration. Nevertheless, unaltered serum hormonal levels cannot rule out that estrogen and progesterone levels were elevated within the central nervous system.

The increase in \( V^{\text{SCO}_2}_{\text{hyperoxia}} \) we observed is similar to the results of Zhou and colleagues (42), who reported that the ventilatory sensitivity to reductions in carbon dioxide below baseline values is increased during NREM sleep following...
testosterone administration in women. We have extended these findings by demonstrating directly that the change in ventilatory sensitivity is not a consequence of changes in metabolic rate or treatment order. Moreover, we have provided evidence that suggests that changes in ventilatory sensitivity observed in Zhou and colleagues study were mediated primarily by alterations in central chemoreflex sensitivity. In contrast, our findings appear to be contradictory to Mateika and colleagues (25) previously published results that showed that testosterone depression in men also led to an increase in the VSCO2 hypoxia. However, the discrepancy between the two studies may be a consequence of different hormone profiles. The hormone profile induced for a 2-mo time period in the men that participated in our laboratory’s previous study (25) resembled that of postmenopausal women (i.e., testosterone, estradiol, luteinizing hormone, and follicle-stimulating hormone were suppressed). Thus the suppression of other hormones may have been responsible for the increase in central chemoreflex sensitivity observed previously, or the impact of testosterone on chemoreflex sensitivity is altered in the presence of variations in levels of other hormones.

The increase in the VSCO2 hypoxia that we observed was not coupled with alterations in the ventilatory threshold, which is in contrast to Zhou and colleagues (42), who reported both an increase in the apneic threshold and the ventilatory sensitivity to carbon dioxide. Further investigation is required to determine whether arousal state (i.e., wake vs. sleep) and/or the methodology used to measure the ventilatory response to carbon dioxide (i.e., modified rebreathing of carbon dioxide in the presence of sustained hypoxia during wakefulness vs. normoxic hypopnea induced by mechanical hyperventilation during sleep), might account for the difference. Conversely, treatment with testosterone for more than 1 wk may be required to induce pervasive alterations in the ventilatory threshold. Indeed, our laboratory previously showed that suppressing testosterone for 2 mo in men lead to alterations in both the ventilatory threshold during wakefulness and the apneic threshold during sleep (25).

The increase in the VSCO2 hypoxia that we observed after testosterone administration in healthy young women supports the premise that increased endogenous levels of testosterone in women, which occur in conjunction with ovarian tumors (11), polycystic ovary syndromes (15, 39), or menopause (6), might lead to alterations in the ventilatory sensitivity to carbon dioxide. An increase in ventilatory sensitivity could lead to hyperventilation in the face of elevated carbon dioxide levels. This could lead ultimately to a reduction in carbon dioxide that extends below the apneic threshold during sleep, leading to the development of a central apnea and possibly an obstructive apnea (2). Thus an increase in ventilatory sensitivity to carbon dioxide could be responsible wholly, or in part, for the increased prevalence of sleep apnea that has been reported in these populations. However, the increase in ventilatory sensitivity in our study was caused by an increase in testosterone concentration (i.e., placebo 0.5 ± 0.06 vs. testosterone 6.1 ± 1.5 ng/ml) over a short time duration (i.e., 7 days) that was significantly greater than total testosterone concentration reported typically (e.g., 0.9–1.5 ng/ml) for patients suffering from polycystic ovary syndrome (20). Thus further study is required to determine whether smaller elevations in testosterone, typically characteristic of postmenopausal women or women with polycystic ovary syndrome, sustained over a long duration of time induces increases in sensitivity similar to that observed in the present study.

Our findings also support the premise that the greater ventilatory response to carbon dioxide observed previously in men compared with women (1, 5, 17, 28, 34, 38, 40) is due in part to differences in testosterone levels. Conversely, our findings appear to dismiss previous suggestions by some investigators that gender differences in the ventilatory sensitivity to carbon dioxide are due solely to differences in height, weight, body mass index, lung volume, or body surface area (1, 28, 38). Thus differences in the prevalence of sleep apnea between men and women may also be due in part to differences in the ventilatory sensitivity to carbon dioxide that may be a consequence of hormonal differences.

Impact of testosterone on the ventilatory response to carbon dioxide after exposure to episodic hypoxia. An increase in the VSCO2 hypoxia was observed following exposure to episodic hypoxia. This finding is similar to our laboratory’s previous results (24, 27). Our laboratory also showed previously that the increased ventilatory response was greater in men compared with women (27), and it was hypothesized that this gender difference was due to differences in sex hormones. Our results do not support this hypothesis because exposure to episodic hypoxia induced a similar increase in the VSCO2 hypoxia after treatment with placebo and testosterone patches. Consequently, a mechanism other than elevated levels of testosterone was likely responsible for the increase in the ventilatory response to hypoxia observed following episodic hypoxia and testosterone administration. Recent work has suggested that the release of reactive oxygen species following exposure to episodic hypoxia might be responsible for the enhancement of carotid body discharge, which could lead to increases in the VSCO2 hypoxia (29). Whether gender differences exist within this mechanism is speculative and requires further investigation.

Our finding that the VSCO2 hypoxia increased following exposure to episodic hypoxia suggests that chemoreflex sensitivity may not remain constant during sleep in individuals that experience repeated apneic episodes accompanied by hypoxemia, but rather it may increase over the night as indicated by the work of Mahamed and colleagues (23). If this is the case, and increases in chemoreflex sensitivity exacerbate sleep apnea, then apnea severity may increase from the beginning to the end of the night in individuals suffering from sleep apnea. This suggestion is supported by a few clinical studies (7, 9, 14, 35) that have reported that apnea severity increases from the beginning to the end of the night independent of other factors (e.g., sleep stage).

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