Long-term facilitation of ventilation is not present during wakefulness in healthy men or women

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OBSTRUCTIVE SLEEP APNEA (OSA) is more common in men than in women (36). The reason for this gender difference is currently unknown; however, it is potentially related to differences in central respiratory control, upper airway neuromuscular control, or upper airway anatomy. Several studies have compared the airway anatomy in healthy men and women and reported that the cross-sectional area of the pharynx is larger in men than in women (8, 9, 19). However, only one study has corrected for the difference in body size between genders, and this study did not find a gender difference in pharyngeal cross-sectional area (9). The resting activity of the upper airway dilator muscles has been implicated in the pathogenesis and high male prevalence of OSA; however, the activity of the largest airway dilator, the genioglossus, has been reported to be similar between men and women (13, 26, 35) in all but one study (27). The central control of respiration may also play a role in the pathogenesis of OSA because the airway is more prone to collapse during periods of low respiratory drive (5, 25). Theoretically, it would seem that if periods of low drive were prevented and respiratory cycling minimized, then the upper airway would be stabilized and airway collapse less likely.

Long-term facilitation (LTF) is the progressive increase in inspired minute ventilation (V̇) that persists for minutes to hours after cessation of a repetitive hypoxic stimulus. LTF is a centrally mediated, serotonin-dependent process (4) that has been shown to exist in various awake animals (1, 10, 23, 33). LTF not only prevents periods of low drive but also could, at least theoretically, minimize respiratory cycling and therefore stabilize the upper airway. There is disagreement in the literature regarding the existence of LTF in humans (2, 3, 20, 21, 31). These studies have been predominantly conducted in men, and thus far there have been no gender comparisons of LTF in humans. Progesterone is a known respiratory stimulant that increases not only resting ventilation (11) but also the hypoxic ventilatory response (32). Recently, LTF has been reported to be greater in diestrus than estrus in female rats (37). It is therefore possible that LTF may be influenced by female sex hormones and may be different between genders. If LTF were more readily elicited or more pronounced in women than in men, then it could provide partial protection from respira-
tory cycling in women and may help protect them from further sleep-disordered breathing events. LTF is seen in both the hypoglossal and phrenic motoneurons in animals (4). It would therefore appear likely that the genioglossus muscle activity would increase during and after repetitive hypoxia. However, the genioglossus has been reported to be depressed during repetitive hypoxia in healthy male subjects, whereas diaphragm activity and ventilation were not different from the resting level (no LTF) (20). However, there is evidence to suggest that repetitive hypoxia may augment upper airway dilator activity. Aboubakr et al. (2) reported that repetitive hypoxia during sleep in patients with partial upper airway obstruction results in a progressive reduction of upper airway resistance (Rua) without changing Vt (2). It is therefore possible that the genioglossus muscle may be facilitated or depressed during repetitive hypoxia. The response of the genioglossus may differ between genders because other respiratory depressants (alcohol and benzodiazepines) that cause selective depression of genioglossus or hypoglossal nerve activity (7, 15) do not depress the genioglossus as much in women as men (15), and the depression is reduced in male cats when pretreated with progesterone (29).

We therefore conducted the present study to determine 1) whether LTF of ventilation occurs in healthy men and/or women and 2) whether depression or facilitation of genioglossus and diaphragm muscles occurs during repetitive hypoxia and whether this is the same in both genders.

METHODS

Subjects. Twelve men and thirteen women gave informed written consent and participated in the study. All subjects were healthy nonsmokers with normal lung function (spirometry and body plethysmography) and did not take any regular medication, including the oral contraceptive pill. Subjects had regular menstrual cycles not longer than 35 days and were tested in the luteal menstrual phase (days 20–24) as confirmed by plasma progesterone levels (ACS:180 Progesterone assay, Chrion Diagnostics, Chrion Healthcare, Victoria, Australia). Three women were subsequently found to be anovulatory (plasma progesterone <7 nmol/l in the luteal phase), and their results were excluded from the analysis. The study was approved by the Research and Ethics Committee of the Repatriation General Hospital (Daw Park, South Australia).

Equipment and measurements. Subjects wore a nasal mask (Gel mask, Respironics, Murrysville, PA) with a two-way non-rebreathing valve attached (series 2600, Hans Rudolph, Kansas City, MO). On the inspiratory side, the breathing valve was connected to a pneumotachograph (model PT36, Erich Jaeger, Würzburg, Germany) and a Gatlin-shaped valve system (series 2440C, Hans Rudolph) for delivery of inspiratory gases. The Gatlin-shaped valve consisted of one output port attached to the pneumotachograph and four inputs, three of which were connected to foil bags (300 liters, Scholle Industries, Adelaide, Australia) containing the following inspiratory gas mixes: 50% O2 in N2, 100% N2, and 9% O2 in N2. The fourth port was open to room air. Each port could be rapidly occluded or opened with a pneumatically driven solenoid valve and balloon. Only one input port was open at a time, and all changes between ports were conducted during expiration. The inspiratory flow signal (pneumotachograph) was electronically integrated to give inspiratory tidal volume (Vt). Inspiratory (Ti), expiratory (Te) and total breath (Tt) times were determined from the flow signal, and Vt was calculated on a breath-by-breath basis. Mask pressure (P\textsubscript{mask}) and end-tidal P\textsubscript{C02} and P\textsubscript{O2} (P\textsubscript{ETCO2} and P\textsubscript{ETO2}, respectively) were measured continuously from the mask (P\textsubscript{mask}: model 78542A, Hewlett Packard, Andover, MA; P\textsubscript{ETO2} and P\textsubscript{ETCO2}: POET II model 602-3, Criticare Systems Waukesha, WI).

Epiglottic pressure (P\textsubscript{cho}) was measured with a pressure-tipped catheter (model MPC-500, Millar, Houston, TX) advanced 1 cm below the tongue base under direct visualization after both nostrils were decongested (0.05% oxymetazoline HCl) and the nostril through which the catheter was passed was anesthetized (2% lignocaine). The pressure at the level of the choanae (P\textsubscript{cho}) was determined with a second pressure-tipped catheter (model MPC-500, Millar) inserted through the same nostril. The choanal catheter was advanced until it touched the posterior nasopharyngeal wall, and it was then retracted 0.5 cm. The peak inspiratory supraglottic (epiglottis to nares), nasal (choanae to nares), and pharyngeal (epiglottis to choanae) airway resistances (Rua, Rna, and Rph, respectively) were calculated. The electromyogram (EMG) of the genioglossus was recorded in the standard manner (22) with two intramuscular electrodes (316SSST wire, Medwire, Mt. Vernon, NY) inserted 4 mm either side of the frenulum to a depth of 1.5–2 cm after surface anesthesia (4% lignocaine). The surface diaphragmatic EMG was recorded from the pair of electrodes placed in the right sixth, seventh, and eighth intercostal spaces adjacent to the costal margin that produced the highest inspiratory phasic activity. These positions were chosen to minimize intercostal and abdominal muscle artifact on the diaphragm signal (16). The electrocardiogram (ECG) was also recorded and used to blank ECG artifact from the diaphragmatic EMG signal (CWE, Ardmore, PA). Both genioglossal and blanked diaphragmatic EMGs were bandpass filtered (0.03–1 kHz, rectified, and moving time averaged (MTA) with a time constant of 100 ms. For each breath, the end-expiratory tonic (tonic) and peak inspiratory phasic (phasic) EMG activities were determined from the MTA signal. The electroencephalogram C\textsubscript{3}-A\textsubscript{2} and right electrocorticogram were measured to confirm wakefulness (Compumedics S series preamplifier, Abbotsford, Victoria, Australia), and ear arterial O2 saturation (SaO2) was recorded continuously (POET II model 602-1 Criticare systems).

All data were acquired on an IBM laptop computer using an analog-to-digital converter (DATAQ Instruments, Akron, Ohio).
OH) at a sampling rate of 200 Hz for all signals other than EMGs (1,000 Hz).

**Protocol.** Subjects presented to the laboratory in the morning after a light breakfast without caffeine. They were instrumented (as described above) and lay supine with one pillow. Maximal EMG activity of the genioglossus muscle was determined by performing three of each of the following maneuvers: swallows, deep sniffs, and maximal tongue protrusions against the top teeth. Care was taken to ensure that all subjects gave maximal efforts during the tongue protrusions by strong verbal encouragement and ensuring a plateau in muscle activity was reached before each maneuver was ceased.

After these maneuvers, subjects were given earphones through which they listened to the radio and were instructed to relax, keep their eyes open, stay awake, and breathe only through their nose. They were informed that during hypoxia they might experience slight dizziness or breathlessness but that these responses were normal and to remain relaxed. After 5 min of baseline room air breathing, subjects were exposed to ten 2-min episodes of hypoxia separated by 2 min of room air. The hypoxic gas was 9% O2 in N2 blended with room air, as necessary via a three-way tap, to maintain SaO2 at 80%. Each hypoxic period was initiated with three breaths of 100% N2 to cause a rapid fall in SaO2 and terminated with one breath of 50% O2. Isocapnia was maintained during and after repetitive hypoxia by manually bleeding CO2 into the inspiratory tubing. Subjects breathed room air for a further 25 min after the tenth hypoxic period before the maximal EMG maneuvers were repeated. The highest activity recorded during the maneuvers was taken to be the maximal activity of the genioglossus. The EMG activity was then expressed as a percentage of maximal activity by scaling the moving-time-averaged EMG between electrical zero and the maximum activity level. This well-established technique (22) allowed the genioglossal EMG signals to be averaged within and between subjects and compared between genders.

**Data analysis and statistical procedures.** Breaths that were contaminated with movement artifact, swallowing, sighs, or sleep were removed from analysis. All variables were averaged at 30-s intervals to condense the 70 min of breath-by-breath data. Resting variables were determined from the average of the 5 min immediately before the start of the repetitive hypoxia. Anthropometric and resting characteristics were compared between men and women by two-sample Student’s t-tests. The maintenance of isocapnia was assessed with an ANOVA for repeated measures on PETCO2 data for the entire protocol. All measured variables (V1, VT, Tr, TE, Tr, phasic and tonic EMG activity of the genioglossus and diaphragm, SaO2, Pspi, Pmask, peak inspiratory flow, Rua, Rna, and Rph) were compared between men and women with two-way ANOVA for repeated measures, including the Greenhouse-Geisser correction for multisample asphericity (18). Separate ANOVAs were used to 1) detect LTF or depression of respiratory drive (data during the second minute of normoxia between hypoxic exposures and during recovery after the tenth hypoxic exposure analyzed) and 2) detect “roll-off” during repetitive hypoxia (data during the second minute of each hypoxic exposure analyzed). LTF was also calculated in the manner described by Babcock and Badr (3). This involved determining whether the V1 was >10% above the resting level at 5 and 20 min after the tenth hypoxic exposure.

**RESULTS**

Adequate ventilatory and diaphragm EMG data were obtained in all 22 subjects. One of either the Pmask or Pcho pressure signals was inadequate in five subjects (large drift in 3 subjects and catheter failure in 2 subjects), so all pressure and resistance data were excluded in these subjects. The genioglossal signal was poor in two subjects (intermittent signal in 1 subject and complete signal loss in the other subject mid protocol). Analysis of the genioglossus and diaphragm muscle activity was therefore limited to 20 subjects.

**Resting data.** The 12 men and 10 women studied did not differ in terms of age, body mass index, or lung function (Table 1). Although resting V1 was not different between genders, there were significant differences in breathing pattern, VT, and PETCO2, at rest (Table 2). The low PETCO2 in women with equivalent V1 is likely to be due to the elevated plasma progesterone level in the 10 women studied (22.4 ± 1.1 nmol/l). The resting level of genioglossal activity did not differ between genders, and Pspi, Pcho, and Rua were also not different between men and women (Table 2).

**Repetitive isocapnic hypoxia.** SaO2 at rest, during or after repetitive isocapnic hypoxia did not differ between genders (Fig. 1). There were no time or gender × time interaction effects for PETCO2 during and after hypoxia, indicating adequate maintenance of isocapnia (Fig. 1).

**Table 2. Resting breathing characteristics in men and women**

<table>
<thead>
<tr>
<th></th>
<th>Men (n = 12)</th>
<th>Women (n = 10)</th>
<th>Significance (P Value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>V1, l/min</td>
<td>7.67 ± 0.32</td>
<td>7.59 ± 0.49</td>
<td>0.893</td>
</tr>
<tr>
<td>PETCO2, Torr</td>
<td>40.92 ± 0.67</td>
<td>36.77 ± 0.68</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>VT, liter</td>
<td>0.56 ± 0.00</td>
<td>0.43 ± 0.03</td>
<td>0.021</td>
</tr>
<tr>
<td>f, breaths/min</td>
<td>14.34 ± 1.03</td>
<td>17.76 ± 1.06</td>
<td>0.031</td>
</tr>
<tr>
<td>T1, s</td>
<td>2.04 ± 0.15</td>
<td>1.63 ± 0.06</td>
<td>0.025</td>
</tr>
<tr>
<td>T2, s</td>
<td>2.41 ± 0.21</td>
<td>1.85 ± 0.14</td>
<td>0.038</td>
</tr>
<tr>
<td>Phasic EMGg, %maximum</td>
<td>4.91 ± 1.61</td>
<td>7.34 ± 2.63</td>
<td>0.443</td>
</tr>
<tr>
<td>Tonic EMGg, %maximum</td>
<td>1.68 ± 0.51</td>
<td>2.91 ± 1.01</td>
<td>0.300</td>
</tr>
<tr>
<td>Pspi, cmH2O</td>
<td>-2.65 ± 0.33</td>
<td>-2.75 ± 0.35</td>
<td>0.837</td>
</tr>
<tr>
<td>Pcho, cmH2O</td>
<td>2.45 ± 0.32</td>
<td>2.40 ± 0.39</td>
<td>0.952</td>
</tr>
<tr>
<td>Rua, cmH2O</td>
<td>2.67 ± 0.69</td>
<td>3.00 ± 0.63</td>
<td>0.732</td>
</tr>
</tbody>
</table>

Values are means ± SE; n, no. of subjects except *n* = 10 men, †n = 7 men. V1, resting inspired minute ventilation; PETCO2, end-tidal PCO2; VT, tidal volume; f, breathing frequency; T1, inspiratory time; T2, expiratory time; phasic EMGg, peak inspiratory phasic genioglossus electromyogram activity; tonic EMGg, end expiratory tonic genioglossus electromyogram activity; Pspi, epiglottic pressure; Pcho, choanal pressure; Rua, supraglottic (upper airway) resistance.
The increase in \(V_I\) during the hypoxic periods did not differ between men and women, and there was no gender \(\times\) time interaction effect. Similarly, the normoxic ventilation between hypoxic exposures and during recovery was not different between genders (Fig. 1). There was no significant change of \(V_I\) over time during normoxic periods of the protocol, indicating that no depression or facilitation of ventilation occurred in either gender. There were also no gender differences in \(V_T\), \(T_i\), \(T_e\), and \(T_r\) during the hypoxic periods, or in the normoxic periods during or after repetitive hypoxia, indicating that these variables also showed no facilitation or depression (Fig. 1). When the \(V_I\) data were analyzed by the method described by Babcock and Badr [(3); see METHODS] to determine whether individual subjects demonstrated LTF, we found that one male and one female subject fit their criteria for LTF of ventilation. None of the anovulatory women fitted this criteria for LTF of ventilation.

Ria and genioglossus and diaphragm muscle responses were more variable than the \(V_I\) data; however, the same patterns existed. There were no gender differences or gender \(\times\) time interaction effects in any of these variables during the hypoxic periods or in the...
2-min normoxic periods between hypoxic exposures. However, after the tenth hypoxic exposure, the inspiratory phasic genioglossus muscle activity was lower than baseline in women and lower in women than in men (Fig. 2). This occurred despite unchanged \( V_i \), diaphragm muscle activity, and \( R_{ua} \) during this recovery time.

**DISCUSSION**

In this study, the ventilatory and respiratory muscles responses to repetitive eucapnic hypoxia were compared between healthy young men and women during wakefulness. We found that there was no LFT of ventilation, diaphragm, or genioglossus muscle activity during or after repetitive hypoxia. The genioglossus muscle activity was depressed in women during recovery from repetitive hypoxia; however, this was not apparent in men.

**Resting gender differences.** Although resting \( V_i \) was not different between genders, there were significant differences in the pattern of breathing in the young men and women studied. Resting \( V_t \) was lower in women than in men; however, breathing frequency was higher in women because of lower \( T_i \) and \( T_e \) (Table 2). \( P_{etco2} \) was lower in women than in men, consistent with the respiratory-stimulating effects of progesterone. Previous gender comparisons of breathing at rest report that women in the follicular menstrual phase have lower \( V_i \) and \( V_t \) than men but equal breathing frequency and arterial \( P_{CO2} \) (14, 28, 34). In women during the luteal menstrual phase, however, ventilation has been reported to be higher than in the follicular phase, such that ventilation is not different compared with men (14, 34). The findings of the present study are consistent with these previous studies. The relevance, if any, of these differences in resting breathing pattern to the present study and to the high male prevalence of sleep-disordered breathing syndromes is uncertain. There were no gender differences in the resting genioglossus muscle activity or \( R_{ua} \).

**LTF of ventilation.** LTF of ventilation is the prolonged increase in ventilation after repetitive stimulation of the carotid bodies that has been proposed to stabilize breathing patterns. Although LTF has been extensively studied in various animal models, there have been relatively few studies in humans. In the early 1990s, there were two abstract reports from the same laboratory, one showing LTF in 14 healthy volunteers (31) and the second showing LTF in 14 OSA patients but not in 5 healthy controls (21). Since these initial reports, McEvoy et al. (20) studied 11 male volunteers during wakefulness and failed to find evidence of LTF. These three studies all used the same “2 min on-2 min off” hypoxia protocol, causing desaturation to \( \approx 80-85\% \). More recently, Babcock and Badr (3) have used a “3 min on-5 min off” hypoxia protocol (inspired \( O_2 \) fraction = 8\%) during sleep in healthy subjects and reported no LTF of ventilation in the group although some individuals appeared to demonstrate LTF. These authors commented that the presence or absence of LTF in an individual subject appeared to be related to whether the subjects snored and had inspiratory flow limitation (LTF existed in snorers). More recently, the same laboratory has conducted a similar study in OSA patients (2) with optimal or suboptimal continuous positive airway pressure (to allow inspiratory flow limitation) levels during sleep. Using the same 3 min on-5 min off protocol, the authors were unable to demonstrate LTF in either continuous positive airway pressure condition. In the present study, we have again failed to find evidence of LTF of ventilation in men during wakefulness and this
Genioglossus and diaphragm muscle activity and Rua. The genioglossus and diaphragm muscles both show inspiratory phasic activity that increases during respiratory stimulation and decreases with generalized respiratory depression. These relative changes in muscle activity are often proportional, suggesting that the hypoglossal and phrenic motoneuron outputs are coupled. However, there are situations when the activity of the two muscles differ. These include after alcohol (15) and benzodiazepine (17) ingestion in humans and after anesthesia and cyanide brain hypoxia in animals (30). Repetitive eucapnic hypoxia has previously been reported to also cause preferential depression of genioglossal activity in healthy men during wakefulness without altering diaphragmatic activity (20). In the present study of normal individuals during wakefulness, there was a statistically significant reduction in genioglossus muscle activity after the tenth hypoxic exposure in women but not in men. Given the variable nature of genioglossus EMG signals, power calculations were performed to determine the minimum detectable difference of genioglossus activity in both men and women. These calculations revealed that with the coefficient of variation of genioglossal activity measured at rest in the 10 women studied, a change in genioglossal activity below 87% of the resting level could be detected with 80% power (hence the power was adequate). In men, however, the coefficient of variation in genioglossal activity was almost twice that of women (20.9 in men, 12.8 in women) such that only changes below 79% of baseline could be detected with 80% power. It is therefore possible that the nonsignificant result in men was the result of type II error. However, it must be noted that the genioglossal data in men did not appear to show a trend toward depression during the 5- and 20-min recovery times despite being below baseline for the last three hypoxic episodes.

Repetitive (20) and sustained (24) isocapnic hypoxia has been shown to disproportionately suppress genioglossal compared with diaphragmatic activity. Why the present findings differ from the earlier studies using repetitive hypoxia (20) is uncertain. The present protocol was almost identical to that previous study with the exception that the hypoxic gas used in our study was a 9% O2 in N2 gas compared with an 11% O2 gas in the earlier study. Despite this, the level of hypoxemia was similar between studies (85% SaO2 in the earlier study and 82% in the present study), probably reflecting the fact that the earlier study was conducted at moderate altitude. In the earlier study, each hypoxic period was terminated with one breath of 100% O2, whereas in the present study each hypoxic period was terminated with one breath of 50% O2. We believe that unlikely that these differences would result in the different findings between studies. If anything, the subjects in the present protocol would be likely to experience more central depression because of the lower SaO2 levels achieved. There are some differences in the subject characteristics between studies, with the 11 subjects used in the earlier study having a mean age of 36 yr. This is noticeably older than our subjects (mean of 25 yr) and may contribute to the inability in this study to detect a reduction in genioglossal activity in men if this phenomenon is, at least in part, age related. Therefore, it is possible that the inability to demonstrate depression of the respiratory phasic genioglossal activity in the men in the present study results from either the high variability of the genioglossus in these men and/or the age of the experimental subjects.

Previous studies in humans during non-rapid eye movement sleep (2, 3) have indicated that Rua decreases after repetitive hypoxia perhaps, implying facilitation of upper airway dilator muscles, although muscle activity was not measured in either study. Data from this and a previous study in wakefulness (20) do not support relative augmentation of genioglossal activity with repetitive hypoxia in healthy human subjects.

Methodological considerations. There are several important methodological issues to consider when interpreting these results. First, some forms of neuroplasticity are protocol specific, and the results of this study do not preclude the possibility that other protocols may elicit LTF in human volunteers. Second, the development of LTF is not always instantaneous with some studies demonstrating a gradual increase in ventilation (12) after cessation of repetitive hypoxia. Thus, although previous human data do not appear to show such a slow increase in ventilation, the possibility remains that LTF occurred after completion of the study. Age alters LTF in a gender-dependent manner in rats (37, 38). The subjects studied in the present study were relatively young (25 yr), and if similar age and gender interactions occur in humans, then it is possible that older adults may demonstrate LTF that is different between men and women.

The level of inspired O2 was adjusted in the present study to target an SaO2 of 80% in both men and women. If the hypoxic ventilatory response was different between men and women, then one gender may have received a lower O2 concentration in the inspirate than the other. However, SaO2 and V̇E were not different between genders, indicating that the stimuli for LTF was probably not different between genders.

An additional consideration regards the recording of genioglossal and diaphragmatic EMGs. The electrical
activity of any muscle may not represent the functional changes in muscle force or movement. If the electromechanical coupling of the genioglossus and diaphragm muscle differed between genders, then any EMG comparison would be of limited significance regarding muscle force generation or perhaps upper airway caliber. However, we are unaware of any data showing a gender difference in electromechanical coupling of upper airway dilator muscles. The surface recording of diaphragm muscle activity can be confounded by activation of abdominal muscles during respiration; however, we placed the diaphragm EMG electrodes in positions to minimize abdominal muscle contamination.

Finally, this study was conducted during wakefulness, which limits the significance of the findings with regard to sleep-disordered breathing. However, we believe that if a fundamental difference in the control of ventilation or development of LTF existed during wakefulness, it would likely be of importance with regard to the control of breathing during sleep. Previous investigators have suggested (3) that serotonin-mediated LTF of ventilation may depend on the level of raphe neuron activity. The activity of raphe neurons is near maximal during wakefulness, possibly making further release of serotonin and therefore LTF difficult to elicit. This would not, however, explain the apparent inability to demonstrate LTF of ventilation during sleep in humans (2, 3).

In summary, we have found no evidence of LTF of ventilation or of genioglossal or diaphragm muscle activity in healthy men or women during wakefulness. The present findings in awake men and women are consistent with previous reports in awake men (20), sleeping normal subjects (3), and OSA patients (2) and suggest that LTF of ventilation is either absent or at least very difficult to elicit in humans. The genioglossus muscle was depressed in women during recovery from repetitive hypoxia, as has previously been shown in men (20). Our results do not support the hypothesis that different ventilatory or respiratory muscle responses to repetitive hypoxia could explain the gender difference in OSA and other related sleep breathing disorders.

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REFERENCES


