INTRODUCTION

IN OBSTRUCTIVE SLEEP APNEA (OSA), REPETITIVE COLLAPSE OF THE UPPER AIRWAY DURING SLEEP RESULTS IN MULTIPLE EPISODES OF HYPOXEMIA AND subsequent repetitive arousals that fragment sleep. These events and the associated autonomic and neurohumoral disturbances are considered to lead to the many symptoms and signs of OSA and contribute to the long-term morbidity.\(^1,2\) The repetitive arousals are a dominant mechanism causing excessive daytime sleepiness. However, the increases in drive to the inspiratory muscles and the work of breathing during apneas and hypopneas may cause more-subtle symptoms and effects on neural control mechanisms for both respiratory and upper airway muscles.

Upper airway patency is dependent on the balance between the tendency of the airway to collapse, induced by the subatmospheric intraluminal pressure during inspiration, and upper airway dilator muscle activity and intrinsic passive properties. Upper airway negative pressure is the key force provoking airway occlusion during sleep and is related to airflow and the cross-sectional area of the airway. In healthy control subjects, a transient negative pressure causes a reflex increase in upper airway dilator muscle activity.\(^3,6\)

This is mediated by mechanoreceptors in the upper airway sensitive to changes in airway pressure\(^3,4,7\) and proprioceptive afferents in the tongue.\(^8\) This reflex is significantly attenuated in non-rapid eye movement sleep in healthy subjects\(^9,10\) and is not sufficient to maintain airway patency during sleep.\(^11\) In people with OSA, this reflex is not attenuated, compared with control subjects, during wakefulness\(^12\) and probably also not during sleep.\(^13,14\) However, upper airway muscle activity is reduced relatively more in OSA patients during sleep than in control subjects,\(^13\) and this probably contributes to more-frequent airway collapse.

The current study examined the reflex responses of the inspiratory pump muscles to brief airway occlusion in patients with OSA of varying severity and a control group of healthy subjects. The brief airway occlusion causes a sudden loading of the inspiratory muscles and a sudden decrease in airway pressure. This situation is functionally equivalent to the stretch reflex or loading reflex seen in limb muscles. A short-latency inhibitory reflex response is generated in inspiratory muscles, in response to airway occlusion,\(^15,16\) opposite in direction to the reflex facilitation of upper airway dilator muscles in response to negative pressure. Previous studies have shown that the inhibitory response to airway occlusion in inspiratory pump muscles is likely to be mediated by inspiratory muscle afferents.\(^15,17\) However, this does not imply that airway receptors cannot influence the reflex response. The initial inhibitory response to loading, which may be an important protective reflex to prevent aspiration,\(^15\) is of interest because the equivalent response in limb muscles (stretch reflex) usually consists of 2 phases of excitation with no intervening inhibition.\(^18-21\)

This suggests that there is a functionally different organization of the reflex pathways for inspiratory, compared with limb, muscles, perhaps to allow for integration with airway and chemoreceptor signals at the level of the medulla.

In subjects with asthma, the inhibitory reflex is prolonged, compared with nonasthmatic subjects, possibly because they experience chronically increased airway resistance, which intermittently loads their inspiratory muscles.\(^22\) We hypothesized that the
Inhibitory Reflexes in Obstructive Sleep Apnea—Jeffery et al

**Table 1**—Characteristics of Control and Subjects With Obstructive Sleep Apnea Syndrome

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Moderate OSAS</th>
<th>Severe OSAS</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. (men)</td>
<td>9 (6)</td>
<td>9 (8)</td>
<td>10 (7)</td>
</tr>
<tr>
<td>Age, y</td>
<td>42±3 (28-55)</td>
<td>50±5 (31-76)</td>
<td>49±3 (37-66)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>26±1 (23-32)</td>
<td>31±2 (20-44)</td>
<td>31±2 (25-45)</td>
</tr>
<tr>
<td>RDI</td>
<td>6±1 (3-10)</td>
<td>22±1 (14-29)</td>
<td>50±5 (37-63)</td>
</tr>
<tr>
<td>Min O₂ sat, %</td>
<td>93±3 (90-95)</td>
<td>90±1 (84-94)</td>
<td>83±2 (70-89)</td>
</tr>
<tr>
<td>ESS score</td>
<td>5±1 (1-10)</td>
<td>7±1 (2-14)</td>
<td>12±1b (6-20)</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SEM (range) unless otherwise indicated. OSAS refers to obstructive sleep apnea syndrome; BMI, body mass index; RDI, respiratory disturbance index, i.e., number of respiratory events (apneas and hypopneas) per hour of sleep time; min O₂ sat, minimum oxygen saturation overnight; ESS, Epworth Sleepiness Scale.

aSignificant difference from the Control group, p < .05.
bSignificant difference from the Control and Moderate groups, p < .05.

reflex control of inspiratory muscles would be different in subjects with OSA because they experience frequent and extended periods of increased inspiratory muscle loading during sleep. The present study was designed to assess the inspiratory muscle inhibitory reflex of subjects with OSA. This reflex may be important in controlling the way the inspiratory muscles respond to nocturnal airway obstruction.

**METHODS**

Polysomnographic studies and inspiratory muscle reflex studies were performed on separate days (within a week) on a total of 28 subjects: 19 with obstructive sleep apnea (9 moderate and 10 severe) and 9 control subjects. The sex ratio, mean age, and body mass index are provided in Table 1. Age and body mass index were not significantly different between groups. At the time of the study, no subjects were receiving any treatment for OSA. The protocol was approved by the University of New South Wales ethics committee, and the studies were conducted according to the Declaration of Helsinki. Informed consent was obtained from each subject.

**Polysomnography**

All subjects underwent a full overnight polysomnography study. The sleep recordings were performed on a Sominomed Somnostar 4100. Standard techniques and criteria were used to record the electroencephalogram, electromyogram (EMG), and electrocuculogram and to score the 30-second epochs of electroencephalogram recordings into sleep stages.23 Also recorded were the respiratory effort of the rib cage and abdomen, oral nasal flow using a thermistor and nasal pressure, electrocardiogram, and oxygen saturation. Respiratory events were scored according to established criteria.24 The scoring assigned each subject a respiratory disturbance index (RDI). This was measured as the number of respiratory events (apneas and hypopneas) per hour of sleep time. The RDI was used to group the subjects into 3 groups; a control group (RDI ≤ 10), a moderate OSA group (RDI 10-30), and a severe OSA group (RDI > 30). The RDI, Epworth Sleepiness Scale,24,25 and minimum oxygen saturation measured during polysomnography are shown in Table 1.

**Figure 1**—Nomenclature of electromyogram (EMG) responses. A, Experimental set up depicting surface electrodes placed over right and left scalenes, right parasternal intercostals, and right lateral chest wall (overlying diaphragm). Subjects breathed on a mouth piece through a 2-way valve that could be occluded by the inflation of a balloon in the inspiratory port. B, Typical rectified average of scalene EMG for 30 trials. Measurements of latency were made at the onset of the inhibitory response (IR onset), the peak of the inhibitory response (IR peak), the onset of the excitatory response (ER onset), and the peak of the excitatory response (ER peak). The onset of the occlusion occurs at the dashed line, which corresponds, to the sudden decrease in mouth pressure traces.

For the study of inspiratory muscle reflexes, subjects were assessed awake and seated. EMG activity was recorded from 3 obligatory inspiratory muscles using surface electrodes (Ag/AgCl, 10-mm diameter; Red Dot, 3M, Ontario Canada) positioned over right and left scalenes, parasternal intercostals, and lateral chest wall overlying the diaphragm (Figure 1a). To record from the scalene muscles, one electrode was placed in the posterior triangle of the neck (posterior to the sternocleidomastoid muscle and anterior to trapezius) at the level of the cricoid cartilage with another electrode approximately 4 cm inferior. Electrodes were applied to both right and left scalene muscles. For parasternal intercostal muscles, one electrode was placed over the right second or third intercostal space 2 to 3 cm from the edge of the sternum, while the other was placed on the sternum such that the interelectrode distance was approximately 4 cm. Electrodes were placed on the lateral chest wall, one on the anterior axillary line in the seventh intercostal space overlying costal diaphragm, and the other 4 cm inferiorly in the eighth intercostal space. The latter electrodes are likely to record EMG during inspiration from both the underlying costal diaphragm and any other active muscles (abdominal and
Table 2—Reflex Inhibition Latencies and Amplitudes for all Muscle Groups for Control Subjects and Those with Moderate and Severe OSA

<table>
<thead>
<tr>
<th>Muscle Group</th>
<th>Control (9)</th>
<th>Moderate OSA (8)</th>
<th>Severe OSA (8)</th>
</tr>
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<tbody>
<tr>
<td>R Scalene</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IR&lt;sub&gt;onset&lt;/sub&gt;, ms</td>
<td>38 ± 2</td>
<td>39 ± 3</td>
<td>44 ± 2</td>
</tr>
<tr>
<td>IR&lt;sub&gt;peak&lt;/sub&gt;, ms</td>
<td>60 ± 3</td>
<td>69 ± 3&lt;sup&gt;a&lt;/sup&gt;</td>
<td>76 ± 5&lt;sup&gt;ab&lt;/sup&gt;</td>
</tr>
<tr>
<td>IR&lt;sub&gt;peak&lt;/sub&gt;%, %</td>
<td>43 ± 3</td>
<td>40 ± 4</td>
<td>37 ± 6</td>
</tr>
<tr>
<td>ER&lt;sub&gt;onset&lt;/sub&gt;, ms</td>
<td>83 ± 5</td>
<td>99 ± 5&lt;sup&gt;a&lt;/sup&gt;</td>
<td>105 ± 9&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>ER&lt;sub&gt;peak&lt;/sub&gt;, ms</td>
<td>103 ± 7</td>
<td>119 ± 9</td>
<td>138 ± 14&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>L Scalene</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IR&lt;sub&gt;onset&lt;/sub&gt;, ms</td>
<td>40 ± 2</td>
<td>40 ± 4</td>
<td>41 ± 2</td>
</tr>
<tr>
<td>IR&lt;sub&gt;peak&lt;/sub&gt;, ms</td>
<td>62 ± 3</td>
<td>69 ± 3&lt;sup&gt;a&lt;/sup&gt;</td>
<td>67 ± 4&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>IR&lt;sub&gt;peak&lt;/sub&gt;%, %</td>
<td>38 ± 2</td>
<td>46 ± 5</td>
<td>38 ± 5</td>
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<tr>
<td>ER&lt;sub&gt;onset&lt;/sub&gt;, ms</td>
<td>84 ± 4</td>
<td>95 ± 4&lt;sup&gt;a&lt;/sup&gt;</td>
<td>97 ± 9&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>ER&lt;sub&gt;peak&lt;/sub&gt;, ms</td>
<td>104 ± 6</td>
<td>117 ± 5</td>
<td>124 ± 11&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Parasternal intercostal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control (3)</td>
<td>47 ± 3</td>
<td>61 ± 11</td>
<td>60 ± 15</td>
</tr>
<tr>
<td>IR&lt;sub&gt;onset&lt;/sub&gt;, ms</td>
<td>62 ± 3</td>
<td>80 ± 13</td>
<td>93 ± 6</td>
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<tr>
<td>IR&lt;sub&gt;peak&lt;/sub&gt;, ms</td>
<td>35 ± 13</td>
<td>28 ± 6</td>
<td>19 ± 10</td>
</tr>
<tr>
<td>IR&lt;sub&gt;peak&lt;/sub&gt;%, %</td>
<td>79 ± 6</td>
<td>97 ± 16</td>
<td>143 ± 16&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>ER&lt;sub&gt;onset&lt;/sub&gt;, ms</td>
<td>100 ± 15</td>
<td>115 ± 16</td>
<td>151 ± 22</td>
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<tr>
<td>ER&lt;sub&gt;peak&lt;/sub&gt;, ms</td>
<td>18 ± 8</td>
<td>29 ± 1</td>
<td>17 ± 18</td>
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<td>Lateral chest wall (diaphragm)</td>
<td></td>
<td></td>
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<tr>
<td>Control (7)</td>
<td>44 ± 2</td>
<td>59 ± 8</td>
<td>54 ± 11</td>
</tr>
<tr>
<td>IR&lt;sub&gt;onset&lt;/sub&gt;, ms</td>
<td>63 ± 2</td>
<td>82 ± 10</td>
<td>80 ± 11</td>
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<tr>
<td>IR&lt;sub&gt;peak&lt;/sub&gt;, ms</td>
<td>21 ± 4</td>
<td>29 ± 2</td>
<td>31 ± 10</td>
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<tr>
<td>IR&lt;sub&gt;peak&lt;/sub&gt;%, %</td>
<td>80 ± 4</td>
<td>111 ± 11&lt;sup&gt;1b&lt;/sup&gt;</td>
<td>102 ± 5&lt;sup&gt;ab&lt;/sup&gt;</td>
</tr>
<tr>
<td>ER&lt;sub&gt;onset&lt;/sub&gt;, ms</td>
<td>93 ± 5</td>
<td>118 ± 9</td>
<td>138 ± 21&lt;sup&gt;ab&lt;/sup&gt;</td>
</tr>
<tr>
<td>ER&lt;sub&gt;peak&lt;/sub&gt;, ms</td>
<td>29 ± 11</td>
<td>12 ± 3</td>
<td>20 ± 14</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SEM. Numbers in parentheses in first column indicate number of subjects with measured responses. IR<sub>onset</sub> refers to the onset of the inhibitory response; IR<sub>peak</sub>, the peak of the inhibitory response; ER<sub>onset</sub>, the onset of the excitatory response; ER<sub>peak</sub>, the peak of the excitatory response.

<sup>a</sup>Significant difference from the Control group, p < .05.

<sup>b</sup>Significant difference from the Control group when left and right scalenes data are combined, p < .05.

<sup>c</sup>Significant difference from the Control and Moderate groups, p < .05.

intercostal). EMG signals were filtered (53 Hz-1.0 kHz), sampled (at 2 kHz), and stored on a computer via a CED 1401 interface (Cambridge Electronic Design, Cambridge, UK).

The occlusion procedures were the same as those used previously by Butler and colleagues. Subjects breathed through a low-resistance airway at a target inspiratory flow of about 0.5 L per second (achieved using visual feedback displayed on a computer monitor). Inspiratory flow was measured by a pneumotachometer, and lung volume was obtained by integration of the flow signal. Airway occlusion lasting 250 ms was applied during mid-inspiration using a silent balloon valve in the inspiratory port (Hans Rudolph, #9300, Kansas City, MO). The occlusion was delivered during randomly chosen breaths (approximately 1 in every 3 breaths) and produced a small negative change in mouth pressure (measured proximal to the occlusion valve) of 2 to 8 cm H2O within approximately 10 milliseconds. This occlusion halts inspiratory flow and, therefore, halts the shortening of, and loads, the inspiratory muscles. Although subjects detected the occlusion, it may occur.

Due to full wave rectification of the EMG signals and sudden repolarization at the onset of the inhibition, a slight overestimation of the onset latency of the initial inhibition may occur. However, this applies to data obtained in both the OSA and control subjects.

Statistics

Measurements for each average of 30 trials were averaged across the 3 sets such that each subject had one value for each measured variable. A one-way analysis of variance using posthoc all pairwise comparisons procedures (Student-Newman-Keuls method) was performed to determine differences between the responses to airway occlusion of the control subjects and subjects with moderate and severe OSA. Left and right scalenes were analyzed both individually and combined. Pearson correlations were also performed on each reflex latency variable versus the RDI. Spearman rank correlations were performed if the data were not normally distributed. For scalenes, the median of the left and right scalenes for each subject was used for correlation analysis. Statistical significance was set at the 5% level. Values are given as means ± SEM. Values for left and right scalenes were averaged for each subject.
RESULTS

Short- and long-latency EMG responses to airway occlusion were observed for the recordings from the scalenes, parasternal intercostals, and the lateral chest wall. The reflex responses at each site consisted of a short-latency inhibition followed by an excitatory response. These responses were evident in both the single trials as well as the averaged rectified EMG traces (Figure 2). A reflex response was seen in at least one site in all subjects. However, responses were consistently clearest in recordings from the scalenes. For left and right scalenes, responses could be measured in all 9 control subjects, all 9 subjects with moderate OSA, and 8 of 10 subjects with severe OSA. For parasternal intercostal muscles, responses were measured in 3 control subjects, 4 with moderate OSA, and 4 with severe OSA. For lateral chest wall recordings (overlying diaphragm), responses were measured in 7 control subjects, 4 with moderate OSA, and 4 with severe OSA. The recordings obtained from the parasternal intercostals and lateral chest wall could not be measured in some subjects due to an insufficient signal-to-noise ratio during quiet breathing. The mean decrease in airway pressure produced by the occlusion was similar for control subjects and those with moderate and severe OSA (-3.9% ± 0.4%, -3.7% ± 0.5%, and -3.8% ± 0.3%, respectively).

The main finding was that the duration of the inhibitory response in the inspiratory muscles was prolonged in those subjects with moderate and severe OSA compared with control subjects. This is clear in both the single trials and averaged data from the scalenes from a typical subject from each subject group (control, moderate OSA, and severe OSA) shown in Figure 2. Group data for the reflexes from each muscle are shown in Table 2. There is a trend for a prolonged inhibition with moderate OSA and even more so with severe OSA for all the muscles (see Table 2, IRpeak and ERonset values). The differences were only significant in some cases (indicated in Table 2) probably due to sample size. The latency to the IRpeak and ERonset for scalenes (right and left combined) and ERonset for parasternal intercostals and diaphragm (recorded from over the lateral chest wall) were significantly delayed in subjects with severe OSA (p < .05). The latency to the ERpeak was also significantly delayed for the scalenes (right and left combined) and recording from over the lateral chest wall in subjects with severe OSA (p < .05; Table 2). This is consistent with a prolonged inhibition. The onset latency of the inhibitory response and the amplitudes of the inhibitory response and excitatory response were not significantly different between subject groups for any of the inspiratory muscles.

Correlations also showed significant relationships between the severity of OSA (as determined by RDI) and the duration of the inhibitory response for all 3 inspiratory muscles (Figure 3). The RDI was positively correlated with the latency to ERonset (duration of inhibition) for scalenes, parasternal intercostals, and recordings from over the lateral chest wall (p < .05). RDI was also positively correlated with the latency to IRpeak but was only significant...
DISCUSSION

The aim of this study was to determine whether the reflex responses of human inspiratory pump muscles to a brief airway occlusion (or inspiratory muscle loading) during wakefulness was altered in subjects with moderate to severe OSA compared with healthy control subjects. The study showed a prolongation of the short-latency reflex inhibitory response and delay of the subsequent excitatory response reaching the inspiratory motoneurons of the scalenes, parasternal intercostals, and diaphragm of subjects with OSA, compared with control subjects without OSA. The increased duration of the inhibitory response observed in subjects with OSA correlated positively with OSA severity. Those subjects with more-severe OSA had more prolonged IRs.

We are not aware of previous studies that have tested the reflex control of inspiratory pump muscles in subjects with OSA. Most work on reflexes in sleep to date has focussed on upper airway dilator muscles. Upper airway reflexes sensitive to changes in airway pressure play a dominant role in driving phasic activity in upper airway dilator muscles. During inspiration, when upper airway pressure becomes more negative, there is a reflex facilitation of the upper airway dilator muscles (including genioglossus and tensor palatini). This acts to enlarge the upper airway and thereby reduce the chance of upper airway collapse.

Isolated negative pressure changes in the upper airway can also potently inhibit inspiratory pump muscles in dogs. However, our previous studies in control subjects without respiratory disorders have shown, by exclusion, that the reflex inhibitory response to airway occlusion is most likely to be mediated via inspiratory pump muscle afferents and, thus, is not dependent on upper airway pressure receptors or receptors in the lung. Nevertheless, these results do not rule out the possibility that upper airway re-

Figure 3—Responses to airway occlusion of right scalene muscle. Correlations between respiratory disturbance index (RDI) and latencies to peak of the inhibitory response (IRpeak) (left panels), onset of the excitatory response (ERonset) (middle panels), and peak excitatory response (ERpeak) (right panels) for A, scalenes (median), B, parasternal intercostals and C, recordings from the lateral chest wall (overlying diaphragm). r values are shown for each graph. *Denotes a significant correlation, p < .05.
ceptors may modulate the reflex and contribute to differences in the reflex responses in OSA. This is one explanation proposed for the similar increase in the duration of the inhibitory response to airway occlusion in subjects with asthma.22

Two possible causes of a change in a reflex response are (1) alteration or addition of afferent input to pontomedullary inspiratory neurones or motoneurons (either tonically or dynamically in response to the stimulus) or (2) the response to a "normal" afferent input is altered along the reflex pathway (via changes in interneurone, motoneuron and/or pontomedullary inspiratory neurone excitability).

Afferent input from the upper airway may be altered if the receptors are sensitized, for example, in cases in which airway resistance is consistently high or if there is chronic inflammation or tissue trauma due to repetitive collapse of the upper airway.35 With these types of chronic changes, the altered afferent input may be an additional "tonic" inhibitory reflex input onto inspiratory neurones active throughout inspiration and/or expiration.33,34 A tonic inhibition is not necessarily apparent in normal breathing, as it would simply be overcome by appropriate increases in neural drive. However, the ongoing inhibition in combination with the short-latency inhibitory reflex would show an apparent prolongation of the inhibition. Similarly, an increased "dynamic" input from sensitized upper airway receptors could interact with the short-latency inhibitory response to airway occlusion to prolong the duration of the inhibition in the inspiratory pump muscles. Mechanisms of the pathways potentially involved in the reflex have been reviewed.35

Alternatively, in OSA, the response to "normal" afferent input may be altered or amplified at some point in the reflex pathway. Although the short-latency inhibitory response to airway occlusion appears to be mediated by muscle afferents, the reflex pathway is not known. It is possible that the pontomedullary respiratory centers are involved.15,16 Thus, afferent fibers activated by the airway occlusion may reflexly affect the final output of inspiratory motoneurons either at the level of the medulla or spinal cord. Changes in the sensitivity of these cells to descending and/or reflex input could prolong the inhibitory response to airway occlusion seen here in OSA subjects. How might changes in sensitivity of inspiratory neurones come about? Chronic repetitive loading of the inspiratory muscles during sleep may result in long-term adaptive changes in pontomedullary inspiratory neurones, interneurones, or spinal motoneurons. In human limb muscles, repetitive or endurance training can increase or decrease spinal reflexes depending on the desired performance.37,38 H reflexes can be suppressed by balance training39 and are also reduced in ballet dancers during standing.40,41 This suppression appears to be due to changes in reciprocal inhibition between muscles acting on the ankle. Resistance training has also shown decreases in the response to a descending corticospinal volley in a human hand muscle evoked by transcranial electrical stimulation.42 This suggests that plastic changes can occur within the corticospinal pathway that do not involve the motor cortex. Other studies have shown increases in H reflexes32,33 and short-latency stretch reflex amplitude with repetitive voluntary and electrical stimulation training.45-47 Training-related plasticity within the spinal cord may occur at multiple sites, at the motoneurons, the afferent synapses onto motoneurons, and their interneurones, and, in addition, descending inputs to the motoneurons or descending presynaptic inhibition may alter during training.37 These types of changes may also occur at the level of the pontomedullary inspiratory neurones.

Another consideration is that if the afferents activated by the airway occlusion synapse onto pontomedullary inspiratory neurones, changes in chemosensitivity could prolong the short-latency inhibitory reflex to airway occlusion. Normally, during sleep, there is an increase in the level of CO2 allowed in the face of increased mechanical loads such that mild to moderate levels of hypercapnia are tolerated and, thus, decreases the likelihood of arousal.2,14 As the severity of OSA increases, sensitivity of ventilatory responses to hypoxia and hypercapnia is further reduced.48 Nocturnal hypoventilation, most pronounced during rapid eye movement sleep,49 is thought to lead to a gradual desensitization of responses to CO2 and worsening daytime hypoventilation in OSA.50 Decreased sensitivity to CO2 may reduce the overall drive to medullary inspiratory neurones. Therefore, the rate of recovery from reflex inhibition (if it occurred at a brainstem level) may be slower than usual. This would increase the duration of the inhibition.

A confounding factor in this study may have been the relatively low number of subjects. Although the difference was not significant, the subjects with OSA were slightly older and heavier than control subjects. The use of surface electrodes in more-obese subjects makes it difficult to achieve high signal-to-noise ratio signals. This reduced the number of successful recordings, particularly from the paraseminal intercostal muscles and diaphragm, which resulted in some nonsignificant findings. Also, the influences of increased age, decreased chest wall compliance, and chronic sleep deprivation on the reflex are not yet known. Nevertheless, the duration of the reflex inhibitory response to the same external stimulus was prolonged in the OSA subjects across the range of ages and was also positively correlated to RDI. Whether these findings can be extrapolated to sleep is not known.

Irrespective of the caveats, this study has revealed a novel change in a major somatic reflex controlling output to the inspiratory pump muscles. In OSA, one teleologic advantage of prolonged inhibition of inspiratory muscles in response to airway occlusion during sleep might be that the increased time of inhibition of inspiratory pump muscles could reduce the development of an even higher negative pressure when the airway collapses. This may result in the recovery of airway patency with a relatively lower level of upper airway muscle activation. However, it is not clear from this study whether the more prolonged inhibition is a consequence or a cause of more-severe OSA. Prolonged inhibitory reflexes of inspiratory pump muscles in response to airway occlusion may reflect a generalized depression of inspiratory motoneurons, including those that innervate upper airway muscles, that may contribute to increases in RDI during sleep. Alternatively, if the differences in the reflex are a consequence of OSA, then the reflexes may have altered due to chronic repetitive loaded breathing during sleep due to airway collapse, chronic repetitive episodes of hypoxia during sleep, or altered upper airway afferent input. These changes may result in altered or additional afferent input (either tonically or dynamically in response to the occlusion) or neural amplification of the response to a "normal" afferent input somewhere along the reflex pathway. Some insight into these possibilities may be gained from the study of apnea syndromes that are not accompanied by airway obstruction.

Further studies are necessary to elucidate the neural pathways and influence of sleep state on these reflexes to airway occlusion in order to understand the mechanism and the effect of the prolonged inhibition in subjects with OSA.
ACKNOWLEDGEMENTS

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