Upper airway neuromuscular compensation during sleep is defective in obstructive sleep apnea

Brian M. McGinley, Alan R. Schwartz, Hartmut Schneider, Jason P. Kirkness, Philip L. Smith, and Susheel P. Patil

Johns Hopkins Sleep Disorders Center, Division of Pulmonary and Critical Care Medicine, Johns Hopkins University, Baltimore, Maryland

Submitted 14 November 2007; accepted in final form 7 April 2008

McGinley BM, Schwartz AR, Schneider H, Kirkness JP, Smith PL, Patil SP. Upper airway neuromuscular compensation during sleep is defective in obstructive sleep apnea. J Appl Physiol 105: 197–205, 2008. First published April 10, 2008; doi:10.1152/japplphysiol.01214.2007—Obstructive sleep apnea is the result of repeated episodes of upper airway obstruction during sleep. Recent evidence indicates that alterations in upper airway anatomy and disturbances in neuromuscular control both play a role in the pathogenesis of obstructive sleep apnea. We hypothesized that subjects without sleep apnea are more capable of mounting vigorous neuromuscular responses to upper airway obstruction than subjects with sleep apnea. To address this hypothesis we lowered nasal pressure to induce upper airway obstruction to the verge of periodic obstructive hypopneas (cycling threshold). Ten patients with obstructive sleep apnea and nine weight-, age-, and sex-matched controls were studied during sleep. Responses in genioglossal electromyography (EMGGG) activity (tonic, peak phasic, and phasic EMGGG), maximal inspiratory airflow (Vₘₐₓ), and pharyngeal transmural pressure (Pₜₘ) were assessed during similar degrees of sustained conditions of upper airway obstruction and compared with those obtained at a similar nasal pressure under transient conditions. Control compared with sleep apnea subjects demonstrated greater EMGGG, Vₘₐₓ, and Pₜₘ responses at comparable levels of mechanical and ventilatory stimuli at the cycling threshold, during sustained compared with transient periods of upper airway obstruction. Furthermore, the increases in EMGGG activity in control compared with sleep apnea subjects were observed in the tonic but not the phasic component of the EMG response. We conclude that sustained periods of upper airway obstruction induce greater increases in tonic EMGGG, Vₘₐₓ, and Pₜₘ in control subjects. Our findings suggest that neuromuscular responses protect individuals without sleep apnea from developing upper airway obstruction during sleep.

METHODS

Subjects

Patients with moderate to severe obstructive sleep apnea [non-rapid eye movement (NREM) apnea-hypopnea index (AHI) > 20 events/h] and control subjects (NREM AHI ≤ 10 events/h), some of whom had a history of snoring, were recruited from the Johns Hopkins Sleep Disorders Center. Subjects were matched for age, gender, and body-mass index (BMI). Subjects were excluded if they had a history of a concurrent sleep disorder (e.g., narcolepsy, restless legs syndrome, previous upper airway surgery, significant pulmonary disease or gas exchange abnormalities, or use of supplemental oxygen). The institutional review board on human research approved the study, and all subjects provided written informed consent.

Experimental Approach

Our approach to the assessment of neuromuscular responses to upper airway obstruction exploits specific experimental paradigms for manipulating the nasal pressure during sleep that partition the relative contribution of upper airway structural and neuromuscular properties to the maintenance of upper airway patency (25). Nasal pressure was lowered in a stepwise manner and sustained for ~10 min of NREM sleep to induce upper airway obstruction and allow time for subjects to respond to the imposed nasal pressure. Upper airway obstruction reduces nasal pressure to the verge of periodic obstructive hypopneas (cycling threshold). Ten patients with obstructive sleep apnea and nine weight-, age-, and sex-matched controls were studied during sleep. Responses in genioglossal electromyography (EMGGG) activity (tonic, peak phasic, and phasic EMGGG), maximal inspiratory airflow (Vₘₐₓ), and pharyngeal transmural pressure (Pₜₘ) were assessed during similar degrees of sustained conditions of upper airway obstruction and compared with those obtained at a similar nasal pressure under transient conditions. Control compared with sleep apnea subjects demonstrated greater EMGGG, Vₘₐₓ, and Pₜₘ responses at comparable levels of mechanical and ventilatory stimuli at the cycling threshold, during sustained compared with transient periods of upper airway obstruction. Furthermore, the increases in EMGGG activity in control compared with sleep apnea subjects were observed in the tonic but not the phasic component of the EMG response. We conclude that sustained periods of upper airway obstruction induce greater increases in tonic EMGGG, Vₘₐₓ, and Pₜₘ in control subjects. Our findings suggest that neuromuscular responses protect individuals without sleep apnea from developing upper airway obstruction during sleep.

Address for reprint requests and other correspondence: Brian McGinley, Johns Hopkins Asthma and Allergy Center, 5501 Hopkins Bayview Circle, Rm. 4B68, Baltimore, MD 21224 (e-mail: bmcginley@jhmi.edu).

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.
to recruit neuromuscular responses. Specifically, as the nasal pressure was reduced, increasing degrees of upper airway obstruction could elicit neuromuscular responses that mitigated the obstruction and stabilized ventilation (active state, Fig. 1). Dynamic responses to upper airway obstruction could thereby stabilize breathing patterns during sleep. Further reductions in nasal pressure, however, could ultimately overwhelm these neuromuscular responses in both sleep apnea and control subjects and result in periodic hypopneas and apneas that fragment sleep (active state, Fig. 1). We assessed upper airway neuromuscular responses by targeting the nasal pressure just prior to the development of ventilatory instability, which imposed a maximal challenge to compensatory neuromuscular mechanisms without disrupting sleep. This pressure has previously been termed the cycling threshold (C_r) (25).

At the C_r, we assessed the stimulus to ventilation by measuring the mechanical loads imposed on the upper airway and consequent alterations in ventilation. Mechanical loads were assessed by measuring the degree of upper airway obstruction during abrupt, transient decreases in nasal pressure to the C_r, when neuromuscular activity was relatively quiescent or hypotonic (passive state, Fig. 1) (30). During sustained periods of breathing against these loads (active state), ensuing perturbations in ventilation and negative airway pressure were assessed to quantify the stimulus to upper airway neuromuscular responses. (5, 25, 30). The strength of these neuromuscular responses during sleep was calculated as the differences in genioglossal electromyography (EMG_GG), maximal inspiratory airflow (V_{Imax}), and transmural pressure between sustained periods of upper airway obstruction at the C_r and transient periods of upper airway obstruction.

**Experimental Procedures**

**Assessment of sleep.** Baseline sleep studies were performed for all subjects on EMBLA (Somnologica, Medcare). Physiologic signals monitored included electroencephalograms (C3-A2, C3-O1), left and right electrooculograms, electrocardiogram (modified V2 lead), thoracic and abdominal inductive plethysmography, submental electromyogram, oxyhemoglobin saturation via pulse oximetry (Ohmeda, Louisville, CO), and airflow via nasal cannula (Salter Adult Nasal Cannulas, Salter Labs, Arvin, CA) attached to a pressure transducer (Gould-Statham P-10, Gould, Oxnard, CA) at the level of the nasal mask. Sleep staging was performed according to standard criteria (28). Respiratory arousals were identified according to the American Academy of Sleep Medicine criteria (2), and respiratory events were scored according to previously reported standard laboratory criteria (27).

**Experimental setup.** Subjects returned for a second sleep study to assess EMG_GG activity and V_{Imax} responses to time-dependent manipulations in nasal pressure during sleep. Signals were amplified (Grass 78D Polygraph, Grass Instruments, Quincy, MA), and acquired digitally (Windaq/200, Dataq Instruments, Akron, OH). In addition to the physiologic signals acquired during the baseline night, respiratory effort was measured with a pneumotachograph (No. 5, Hans Rudolph, Kansas City, MI) attached to a differential pressure transducer (Validyne, Northridge, CA) placed between a tight-fitting nasal mask (Comfort Classic, Respironics, Murrysville, PA) and a continuous positive airway pressure (CPAP) unit designed to apply pressures between −20 and 20 cmH2O (MAP, Germany). Body position was monitored visually with infrared video cameras so that patients could be maintained in the supine position.

Genioglossal EMG. During the second polysomnogram, two stainless steel Teflon-coated fine hook wires (California Fine Wire, Grover Beach, CA) were inserted into the base of the tongue under light local anesthesia (4% lidocaine), 3 mm lateral to the frenulum, at a depth of 25 mm, by means of a 25-gauge needle that was inserted and quickly advanced to the level of the hyoid bone. Genioglossal EMG was recorded using an EMG amplifier (Classic, Respironics, Murrysville, PA) and a continuous positive airway pressure (CPAP) unit designed to apply pressures between −20 and 20 cmH2O (MAP, Germany). Body position was monitored visually with infrared video cameras so that patients could be maintained in the supine position.

EEG, electroencephalogram; EMG, electromyogram; EMG_GG, genioglossal electromyogram; V_{Imax}, maximal inspiratory airflow; SpO_2, oxyhemoglobin saturation; P_{ES}, esophageal pressure.

**Fig. 1.** Induction of upper airway obstruction during active and passive periods of experimental protocol is displayed for control subject. **Top left:** subject was maintained at holding pressure of −5 cmH2O during stable stage 2 NREM sleep. Nasal pressure (P_N) was lowered in stepwise manner by 1–2 cmH2O approximately every 10 min. **Bottom left:** at P_N of −3 cmH2O, subject maintains steady-state sleep and ventilatory pattern (left). Ventilatory pattern is notable for inspiratory flow limitation indicated by flat inspiratory flow contour. When P_N was lowered further to −5 cmH2O, subject developed unstable sleep and ventilatory patterns with recurrent hypopneas (middle). P_N at which subject transitioned from stable to unstable ventilatory pattern was defined as cycling threshold (C_r). **Top right:** subject was maintained at same holding pressure (5 cmH2O) during stable stage 2 NREM sleep, then challenged with series of acute drops in P_N over period of 5 breaths. **Bottom right:** decompressed view of passive period is displayed at same P_N immediately above C_r identified during active period (−3 cmH2O). Comparisons between active period above C_r and passive period at same P_N demonstrate marked increases in both inspiratory airflow and genioglossal electromyography (EMG_GG) activity during active period. EEG, electroencephalogram; fEMG_GG, EMG_GG moving time average; SpO_2, oxyhemoglobin saturation; P_{ES}, esophageal pressure.
removed, leaving the wires in place. Placement was confirmed visually on the raw EMGGG signal when phasic activation was seen with baseline breathing, and during maximal maneuvers that included tongue thrust, swallowing, and hyperventilation. The raw EMGGG signals were bandpass filtered between 30 and 3,000 Hz (Grass 78D Polygraph, Grass Instruments).

Induction of upper airway obstruction. Once subjects fell into stage 2 NREM sleep, nasal CPAP was increased to a pressure that alleviated inspiratory flow limitation (holding pressure) (5, 25, 30). Airflow and EMGGG responses to sustained and acute reductions in nasal pressure were then assessed. As previously described, sustained upper airway obstruction was induced by stepwise reductions in nasal pressure (P_N) by 1–2 cmH_2O over 5- to 10-min periods (active state, Fig. 1) (25). The nasal pressure was lowered sequentially until recurrent obstructive hypopneas or obstructive apneas developed (Fig. 1, C_T). If prolonged periods of awakening occurred, the protocol was resumed after patients reinitiated 3 min of stable stage 2 NREM sleep at a slightly higher nasal pressure.

Acute upper airway obstruction was subsequently induced by rapidly lowering the nasal pressure for five breaths (passive state) from an elevated “holding” nasal pressure that alleviated upper airway obstruction, which was then relieved by returning to the holding pressure for a minimum of one minute (Fig. 1) (5, 25, 31). This process was repeated by lowering the nasal pressure sequentially by 1–2 cmH_2O until complete upper airway obstruction was induced. If prolonged arousals occurred, the protocol was resumed after patients reinitiated 3 min of stable stage 2 NREM sleep at the holding pressure. Each subject underwent a minimum of two series of passive pressure reductions that included near-zero airflow.

Analysis

Pressure-flow analyses. As nasal pressure was progressively lowered, V_imax decreased until the upper airway occluded during both the passive and active conditions (30). V_imax was determined for flow-limited breaths as previously described (25). Esophageal pressure measurements were present in a subset of subjects, and inspiratory flow limitation was defined in these subjects as the presence of a plateau in inspiratory airflow in association with a continued fall in esophageal pressure by at least 1 cmH_2O beyond the onset of the plateau. Flow limitation in the presence of an abdominal strain gauge was determined using the criterion of Hosselet et al. (11). PN vs. V_imax plots were constructed for both the passive and active conditions (24).

Quantifying Mechanical Loads and Ventilatory Parameters at the Cycling Threshold

As the nasal pressure was lowered to the C_T and mechanical loads imposed on the upper airway increased, perturbations in ventilation and esophageal pressure swings occurred. When upper airway obstruction was sustained, the resultant changes in ventilation and esophageal pressure swings elicited a neuromuscular response to defend upper airway patency. To determine the comparability of the neuromechanical stimulus at the C_T between sleep apnea and control subjects, we measured the mechanical loads and ventilatory parameters at the C_T.

Mechanical loads. The mechanical loads imposed on the upper airway at the C_T were assessed by determining the transmural pressure (P_TM) across the pharynx. The passive P_TM was defined as the difference in P_N at the C_T and the P_N at which the upper airway occluded during the passive condition (P_N at C_T - passive Pcrit).

Ventilatory parameters. When mechanical loads were imposed at C_T, we accounted for ventilatory disturbances that resulted by measuring the following ventilatory parameters during the holding condition and active condition at C_T: minute ventilation (L/min), tidal volume (ml), respiratory rate, duty cycle (inspiratory time/total respiratory time), maximal inspiratory airflow (V_imax), and negative airway pressure assessed by the magnitude of esophageal pressure swings (see Table 2).

Upper Airway Neuromuscular Responses

To assess the neuromuscular responses at the C_T, we measured EMGGG and its mechanical effect on upper airway patency. The relative strength of the upper airway neuromuscular responses (EMG_GG) and the change in upper airway patency (V_imax and transmural pressure) between the active condition and the passive condition was calculated at a similar level of nasal pressure (within ± 1 cmH_2O). The mean number of breaths analyzed for each subject was 13 ± 2 breaths in the holding, 6 ± 1 breaths in the passive, and 9 ± 1 breaths in the active condition. The number of breaths analyzed did not differ between the control and sleep apnea groups during any condition.

EMGGG responses. The raw EMGGG signals were rectified and integrated (time constant 200 ms) offline for a moving time average signal (Windaq Advanced CODAS; DATAQ Instruments; Akron, OH). The EMGGG signal was referenced to electrical zero and normalized to the maximal effort maneuver while awake that yielded the highest signal (tongue thrust, swallow, hyperventilation). These maneuvers were repeated 2–3 times by each subject. The EMGGG signal was sampled during stable stage 2 NREM sleep as an instantaneous measurement at three points in the respiratory cycle, as follows: 1) tonic (just prior to the start of phasic onset), 2) at V_imax, and 3) peak phasic (largest activity during inspiration) (Fig. 2). Additionally, phasic EMGGG activity (within breath peak phasic-tonic activity) was calculated for each breath.

EMGGG activity was assessed in each individual at the holding pressure and during both the passive and active periods of induced upper airway obstruction. Breaths associated with microarousals from sleep were excluded from the analysis. As described above (see Experimental Approach), we compared EMGGG responses during the active condition at the C_T to responses at a similar nasal pressure level during the passive condition. To isolate differences in EMGGG activi...
ity between active and passive conditions, EMG$_{GG}$ activity during these conditions was referenced to levels at the holding pressure.

Transmural pressure responses. Pharyngeal transmural pressure during the active condition at the CT (active $P_{TM}$) was defined as: $|P_N - P_C|$. The contribution of neuromuscular activation to alterations in $P_{TM}$ was assessed by comparisons between the active $P_{TM}$ and passive $P_{TM}$.

Flow responses. $V_{max}$ was assessed as described previously (25). The relative contribution of neuromuscular activation to upper airway patency was assessed by comparisons of $V_{max}$ and $P_{crit}$ (see Statistical Analysis, below) between the passive and active conditions. To assess the relationship between EMG$_{GG}$ activity and $V_{max}$, we correlated EMG$_{GG}$ and $V_{max}$ between the passive and active conditions for each subject. We then assessed whether changes in EMG$_{GG}$ and $V_{max}$ were correlated within the control and sleep apnea groups.

Statistical Analysis

Descriptive statistics were used to describe the characteristics of subject groups as means with standard errors of the mean unless otherwise stated. Multiple mixed-model regression with repeated measures was used for comparisons of EMG$_{GG}$ and $V_{max}$ between conditions at the holding pressure and passive and active periods of upper airway obstruction within and between groups (control and sleep apnea subjects). Sign-rank tests were used to assess changes in ventilation, nasal pressure, transmural pressure, and $P_{crit}$ between conditions within the control and sleep groups, and a rank-sum test was used to assess for differences between groups. Assessment of the correlation between EMG$_{GG}$ and $V_{max}$ was performed with a pairwise correlation within disease groups. All statistics were performed using Stata 9 (Stata, College Station, TX). For all analyses, statistical significance was defined as $P \leq 0.05$.

RESULTS

Subject Characteristics

Nineteen subjects, 10 with obstructive sleep apnea (5 men/5 women) and 9 without obstructive sleep apnea (4 men/5 women) were studied. Patients with and without sleep apnea were comparable with respect to age, BMI, and gender, but there was a marked difference in AHI between the two groups (Table 1).

Subjects’ upper airway properties were characterized physiologically during sleep with assessments of $P_{crit}$. As expected, the $P_{crit}$ was elevated in sleep apnea subjects compared with control subjects, respectively, during both the passive (0.7 ± 0.6 cmH$_2$O vs. 3.0 ± 1.0 cmH$_2$O, $P = 0.01$) and active (0.8 ± 1.0 cmH$_2$O vs. 11.2 ± 2.2 cmH$_2$O, $P < 0.01$) conditions (see Fig. 5). All subjects in the sleep apnea group had an active $P_{crit}$ greater than 4 cmH$_2$O, a range consistent with sleep apnea. Five of the nine control subjects had an active $P_{crit}$ of less than 8 cmH$_2$O, a range consistent with normal breathing patterns during sleep, and four subjects were within a range of 8 to 4 cmH$_2$O, which was consistent with primary snoring (9).

Active Responses in a Control and Sleep Apnea Subject

In Fig. 3, we illustrate representative EMG$_{GG}$ and airflow responses in a control and a sleep apnea subject during the active and passive conditions at the CT. During the active condition, a steady flow-limited inspiratory pattern was maintained in both the control and sleep apnea subject. Compared with the sleep apnea subject, the control subject demonstrated marked neuromuscular activation (Fig. 3, left) during the active
condition. In the passive condition, both control and sleep apnea subjects demonstrated little change in neuromuscular activity from the holding pressure condition (Fig. 3, right).

Quantifying Mechanical Loads and Ventilatory Parameters at the Cycling Threshold

To examine the comparability of the neuromechanical stimulus that elicited neuromuscular responses at the CT, we assessed the passive PTM and the change in both ventilation and negative airway pressure from the holding pressure to the CT during the active condition.

Mechanical loads. Nasal pressure was similar in the control and sleep apnea groups, respectively, during the holding condition (7.0 ± 1.0 cmH2O vs. 9.6 ± 0.8 cmH2O, P = 0.06). While the absolute PN was lower in controls at the CT (0.6 ± 1.1 cmH2O vs. 4.5 ± 0.9 cmH2O, P = 0.02), the passive PTM was similar in control and sleep apnea groups (3.5 ± 0.7 cmH2O vs. 3.8 ± 0.6 cmH2O, P = 0.8, see Fig. 5), indicating similar mechanical loads at the CT.

Ventilatory parameters. Assessment of ventilation demonstrated that both groups transitioned from a stable to an unstable breathing pattern (i.e., cycling threshold) at similar levels of minute ventilation, tidal volume, respiratory rate, Vmax, and inspiratory duty cycle (Table 2, P > 0.05). In the subset of subjects with esophageal pressure monitoring, esophageal pressure swings were similar in the control (n = 6) and sleep apnea (n = 4) groups, respectively, during both the

Table 2. Ventilatory parameters during the holding and active conditions

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>Sleep Apnea</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Holding</td>
<td>Active at CT</td>
</tr>
<tr>
<td>VE, l/min</td>
<td>7.9 ± 0.7</td>
<td>6.8 ± 0.7*</td>
</tr>
<tr>
<td>VT, ml</td>
<td>539 ± 61</td>
<td>460 ± 61*</td>
</tr>
<tr>
<td>RR, BPM</td>
<td>15 ± 1</td>
<td>15 ± 1</td>
</tr>
<tr>
<td>Vmax, ml/s</td>
<td>325 ± 36</td>
<td>258 ± 21*</td>
</tr>
<tr>
<td>Inspiratory duty</td>
<td>cycle</td>
<td></td>
</tr>
<tr>
<td>SpO2, %</td>
<td>0.43 ± 0.01</td>
<td>0.48 ± 0.02*</td>
</tr>
<tr>
<td>PES, cmH2O</td>
<td>-1.8 ± 0.5</td>
<td>-9.3 ± 2.0*</td>
</tr>
</tbody>
</table>

VE, minute ventilation; VT, tidal volume; Vmax, maximal inspiratory flow; RR, respiratory rate; BPM, breaths per minute; Inspiratory duty cycle, inspiratory time/total respiratory time; SpO2, oxyhemoglobin saturation; PES, peak esophageal pressure swing. *P < 0.05 vs. holding condition.

Fig. 3. Representative recordings from control subject (top) and sleep apnea (bottom) are presented during active and passive conditions. Comparisons were made in EMGGg activity and Vmax between passive and active conditions at same nasal pressure, indicated by dashed arrow. Control subject has marked increase in both EMGGg and Vmax in active compared with passive condition. In contrast, sleep apnea subject demonstrates only small change in EMGGg and Vmax between active and passive condition. Abd, abdominal piezoelectrode strain gauge.
Cycling Threshold

Upper Airway Neuromuscular Responses at the

Comparisons of EMGGG activity during periods of passive and active upper airway obstruction are performed within control and sleep apnea groups at 3 points within respiratory cycle: 1) tonic, 2) at V\textsubscript{max}, and 3) peak phasic, and at calculated phasic value (peak phasic – tonic activity). *P < 0.05 within groups between passive and active conditions; †P < 0.05 between groups at passive and active conditions.

holding and active conditions (Table 2). Thus, the mechanical loads and the ventilatory parameters at the C\textsubscript{T} were similar, which suggests that the stimuli to elicit neuromuscular responses were comparable in both groups.

**Upper Airway Neuromuscular Responses at the Cycling Threshold**

**EMGGG responses.** During the holding condition, there was no difference in EMGGG activity between control and sleep apnea subjects.

There were no differences in EMGGG activity at any point in the respiratory cycle (Fig. 4). The control subjects demonstrated greater increases in tonic, V\textsubscript{max}, and peak phasic EMGGG activity (P < 0.05) compared with sleep apnea subjects (Fig. 4). In contrast, the phasic component of the EMGGG response was similar for both groups (Fig. 4, far right). Thus, neuromuscular responses were due to increased tonic rather than phasic activity, which was greater in control compared with sleep apnea subjects.

To assess for the possibility that a lower absolute P\textsubscript{N} could account for the increased neuromuscular responses observed in control compared with sleep apnea subjects, we extended our analyses of EMGGG responses to a subset of control (n = 5) and sleep apnea (n = 5) subjects who were matched for the P\textsubscript{N} at the C\textsubscript{T} (2.9 ± 0.8. cmH\textsubscript{2}O vs. 2.5 ± 1.0 cmH\textsubscript{2}O, P = 0.7). There were no differences in EMGGG activity at any point in the respiratory cycle between control and sleep apnea subjects at either the holding or passive condition. Comparing the active to the passive condition, the tonic EMGGG activity was higher in control compared with sleep apnea subjects respectively (16.1 ± 2.7% vs. 6.7 ± 2.8%, P = 0.02), while phasic activity remained similar (7.7 ± 4.3% vs. 13.7 ± 4.4%, P = 0.3). In other words, significant differences in tonic EMGGG persisted between control and sleep apnea subjects who were matched for P\textsubscript{N} at the C\textsubscript{T} as already reported for the groups as a whole. These data indicate that differences in absolute P\textsubscript{N} do not account for the increased recruitment of tonic EMGGG responses observed in control compared with sleep apnea subjects.

**Table 3. Nasal, critical closing, and transmural pressures**

<table>
<thead>
<tr>
<th>PTID</th>
<th>P\textsubscript{N}</th>
<th>Per\textsubscript{crit}</th>
<th>P\textsubscript{TM}</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Holding</td>
<td>C\textsubscript{T}</td>
<td>Passive</td>
</tr>
<tr>
<td><strong>Control</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>7.1</td>
<td>-0.3</td>
<td>-4.7</td>
</tr>
<tr>
<td>2</td>
<td>6.6</td>
<td>0.3</td>
<td>-0.6</td>
</tr>
<tr>
<td>5</td>
<td>3.5</td>
<td>-4.0</td>
<td>-7.9</td>
</tr>
<tr>
<td>6</td>
<td>10.0</td>
<td>3.9</td>
<td>1.3</td>
</tr>
<tr>
<td>8</td>
<td>4.6</td>
<td>-3.4</td>
<td>-6.8</td>
</tr>
<tr>
<td>12</td>
<td>4.5</td>
<td>-2.5</td>
<td>-2.5</td>
</tr>
<tr>
<td>14</td>
<td>7.0</td>
<td>3.3</td>
<td>-1.0</td>
</tr>
<tr>
<td>18</td>
<td>12.8</td>
<td>4.5</td>
<td>-2.0</td>
</tr>
<tr>
<td>19</td>
<td>7.4</td>
<td>3.2</td>
<td>-2.5</td>
</tr>
<tr>
<td><strong>Mean ± SE</strong></td>
<td>7.0±1.0</td>
<td>0.6±1.1</td>
<td>-3.0±1.0</td>
</tr>
<tr>
<td><strong>Sleep Apnea</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>8.3</td>
<td>6.1</td>
<td>-2.0</td>
</tr>
<tr>
<td>4</td>
<td>12.5</td>
<td>3.7</td>
<td>1.2</td>
</tr>
<tr>
<td>7</td>
<td>9.0</td>
<td>3.6</td>
<td>1.6</td>
</tr>
<tr>
<td>9</td>
<td>13.4</td>
<td>10.3</td>
<td>3.9</td>
</tr>
<tr>
<td>11</td>
<td>9.4</td>
<td>3.6</td>
<td>-0.6</td>
</tr>
<tr>
<td>15</td>
<td>9.3</td>
<td>2.9</td>
<td>-1.0</td>
</tr>
<tr>
<td>17</td>
<td>10.7</td>
<td>5.5</td>
<td>3.9</td>
</tr>
<tr>
<td>20</td>
<td>4.0</td>
<td>-1.4</td>
<td>-4.5</td>
</tr>
<tr>
<td>22</td>
<td>9.9</td>
<td>5.1</td>
<td>1.6</td>
</tr>
<tr>
<td>23</td>
<td>9.3</td>
<td>6.1</td>
<td>3.1</td>
</tr>
<tr>
<td><strong>Mean ± SE</strong></td>
<td>9.6±0.8</td>
<td>4.5±0.9*</td>
<td>0.7±0.6*</td>
</tr>
</tbody>
</table>

PTID, patient identification number; P\textsubscript{N}, nasal pressure; Per\textsubscript{crit}, critical closing pressure; P\textsubscript{TM}, pharyngeal transmural pressure. *P < 0.05 vs. control group.
Transmural pressure responses. Despite comparable mechanical loads and ventilatory responses at the CTr, the active Pcrt was lower (see Subject Characteristics, above), and the active PtM was greater in control than sleep apnea subjects (11.8 ± 2.7 cmH2O vs. 3.9 ± 0.7 cmH2O, P < 0.01, see Fig. 5; Table 3). The change in pharyngeal transmural pressure from the passive to the active condition may account for the change in VImax observed below.

Flow responses. VImax increased during the active compared with the passive condition in both controls and sleep apnea subjects, but control subjects exhibited a greater increase in VImax (Fig. 6). Thus, active responses in VImax and tonic EMGGG were greater in control than sleep apnea subjects, which suggest that compensatory neuromuscular responses contributed more to the maintenance of upper airway patency in the controls.

Relationships Between Changes in EMGGG and VImax

To examine the relationship between EMGGG activity and airway patency (VImax), we compared responses in these parameters within and among subjects. Both EMGGG and VImax increased from the passive to the active condition, and were positively correlated in 14 of 19 subjects. The EMGGG and VImax responses, however, were variable, and did not correlate within either the control or sleep apnea groups. Thus the individual responses suggest a role for EMGGG activation in maintaining upper airway patency.

DISCUSSION

There were three major findings in our study. First, genio-glossus neuromuscular activity was recruited progressively over time in response to sustained exposure to upper airway obstruction during sleep. Second, tonic EMG responses were greater in control than sleep apnea subjects, whereas the phasic component of the response did not differ. Third, despite comparable mechanical loads and ventilatory disturbances at the CTr, controls demonstrated a larger increase in maximal inspiratory airflow and transmural pressure between the passive and active conditions, suggesting a greater contribution of compensatory neuromuscular activity to the maintenance of upper airway patency. Our findings suggest that upper airway neuromuscular activation maintains upper airway patency during sleep and prevents individuals without sleep apnea from developing upper airway obstruction during sleep.

Our findings are consistent with previous studies of upper airway neuromuscular control, which have also suggested differences between control and sleep apnea subjects (7, 19, 20). Investigators have demonstrated that neuromuscular activity is elevated during wakefulness in patients with sleep apnea compared with normal subjects (19), and suggested that this activity might be required to maintain upper airway patency during wakefulness in the presence of an anatomically compromised upper airway. Younes (34) extended the concept that sleep apnea is associated with structural compromise of the upper airway, and demonstrated that alterations in upper airway anatomy is associated with increasing sleep apnea severity. Nevertheless, structural loads did not fully account for the variability in sleep apnea severity, suggesting that upper airway neuromotor responses also play a pivotal role in the maintenance of pharyngeal patency during sleep. Fogel et al. (7) highlighted the importance of neuromuscular activity by...
demonstrating greater reductions at sleep onset in sleep apnea compared with controls. Over time, neuromuscular responses to airflow obstruction during sleep can restore upper airway patency (13) and stabilize breathing patterns to some degree (25, 30). Nevertheless, unstable sleep and breathing patterns can confound the assessment of upper airway neuromuscular control. To eliminate the impact of sleep and breathing instability, we induced a stable level of upper airway obstruction by targeting the nasal pressure at the C_T. Utilizing this experimental paradigm, we found that the neuromuscular contribution to the maintenance of upper airway patency was greater in control than in matched sleep apnea subjects. In contrast to our previous study, which did not discern significant differences in EMGGG responses to airflow obstruction during sleep (25), differences in EMGGG responses were detected in the current study due to an enlarged sample size and a more robust analytic approach that included comparisons of EMGGG under steady-state conditions.

The increase in upper airway neuromuscular activity during sleep in control subjects primarily resulted from recruitment of tonic rather than phasic responses to upper airway obstruction. Tonic genioglossal activity has been shown to decline substantially with sleep onset, and to a greater degree in sleep apnea compared with control subjects (7). This tonic activity may be a result of increased output from the brainstem respiratory central pattern generator (4), or by influences of peripheral mechanoreceptors (10, 17, 18) and chemical stimuli (8, 14). In contrast, based on studies utilizing topical anesthesia applied to the pharynx, phasic genioglossal activity appears to be augmented primarily by local pharyngeal receptors, which elicit a local reflex neural response (3, 10, 15, 16, 26). The findings in our study suggest that the differences in neuromuscular activity between sleep apnea and control subjects are most likely the result of centrally mediated processes affecting tonic genioglossal activity, while the fact that phasic responses in apneics were comparable to controls suggests that local pharyngeal reflex responses to upper airway obstruction appear intact in both groups.

Despite similarities in mechanical and chemical stimuli, EMGGG, V_{max}, and transmural pressure responses differed substantially between control and sleep apnea groups. Our findings suggest that tonic activity of the genioglossus, a major upper airway dilator muscle, contributes to the maintenance of pharyngeal patency (V_{max}) during sleep. This notion is also supported by previous studies demonstrating that selective electrical stimulation of the genioglossus muscle increases V_{max} and relieves upper airway obstruction during sleep and anesthesia (6, 12, 22, 29). As further evidence for the role of the genioglossus in stabilizing the upper airway, we found that V_{max} and EMGGG responses to upper airway obstruction correlated positively in 14 of 19 subjects. Nevertheless, the strength of this correlation varied widely, suggesting differences in the mechanical efficiency of neural activity (23). Alternatively, we cannot exclude the possibility that other pharyngeal dilator muscles might have also contributed to the observed change in airflow during sleep. In contrast to EMGGG activity, the airflow and transmural pressure responses to sustained periods of upper airway obstruction provided composite measures of neural activation to the upper airway muscles. Comparing these responses between groups, we found that upper airway neuromuscular responses accounted for a substantial improvement in upper airway patency in the control compared with sleep apnea subjects (Figs. 5 and 6).

There were several limitations in the present study. First, we recognize that differences in the absolute nasal pressure at the C_T may have contributed to differences in neuromuscular responses. In a subset of control and sleep apnea subjects who were matched for P_N at the C_T, however, increased tonic EMGGG responses persisted in control compared with sleep apnea subjects indicating that differences in absolute P_N did not account for the increased recruitment of tonic EMGGG responses observed in control compared with sleep apnea subjects. Second, measurements of EMG activity are known to be relative and are difficult to compare between subjects. Nevertheless, we standardized the placement and assessment of EMGGG initially and monitored the signal’s stability during sleep. To further characterize EMGGG responses to upper airway obstruction, we referenced this activity during the passive and active obstructive breathing conditions to that during unobstructed breathing at the holding pressure level. Third, stringent criteria were applied to stage sleep (2); however, we recognize that subtle EEG changes reflecting an arousal might have gone undetected, thus altering the neural activity. Fourth, EMGGG signals were calibrated relative to the maximal signal produced during maneuvers performed in the wake state, which can be dependent on variable degrees of patient effort.

Implications

There are three implications of our study. First, we have established a standardized approach for the assessment of upper airway neuromuscular responses while controlling for the degree of upper airway obstruction and for the stability of sleep and ventilation. Second, our findings imply that centrally mediated tonic activity of the genioglossus is diminished during sleep in subjects with sleep apnea, and serve to focus basic research on elucidating underlying central mechanisms for this defect in upper airway neuromuscular control. Third, our findings are consistent with a deficit in tonic control that could be either inherent or acquired. An acquired deficit might result from either centrally mediated hypoxic injury (33), or localized upper airway vibratory damage (1, 21). Further study assessing the genetic and pathophysiologic basis for this defect in tonic genioglossal control is required.

GRANTS

The study was supported by National Heart, Lung, and Blood Institute Grants HL-50381, HL-37379, and HL-077137. This publication was also made possible by Grant UL1-RR-025005 from the National Center for Research Resources (NCRR), a component of the National Institutes of Health (NIH), and NIH Roadmap for Medical Research. Its contents are solely the responsibility of the authors and do not necessarily represent the official view of NCRR or NIH. Information on NCRR is available at http://www.ncrr.nih.gov. Information on Re-engineering the Clinical Research Enterprise can be obtained from http://nihroadmap.nih.gov/clinicalresearch/overview-translational.asp.

REFERENCES


J Appl Physiol • VOL 105 • JULY 2008 • www.jap.org


