Neuromechanical control of upper airway patency during sleep

Susheel P. Patil, Hartmut Schneider, Jason J. Marx, Elizabeth Gladmon, Alan R. Schwartz, and Philip L. Smith

Department of Medicine, Division of Pulmonary and Critical Care Medicine, Johns Hopkins University, Baltimore, Maryland

Submitted 6 March 2006; accepted in final form 26 September 2006

OBSERVATIONS SLEEP APNEA is a prevalent disorder characterized by repetitive upper airway obstruction that results in recurrent hypoxemia and arousal from sleep (32, 48). Although it is well known that pharyngeal occlusion is the primary cause of sleep apnea, the precise mechanisms leading to upper airway obstruction are incompletely understood. Moreover, the critical pressure of the upper airway (Pcrit), a measurement of upper airway collapsibility, is elevated in sleep apnea patients compared with normal subjects during sleep (11, 13, 57, 63). There remains considerable debate as to whether observed differences in pharyngeal collapsibility are due to alterations in anatomically imposed mechanical loads or in dynamic neuromuscular responses (32, 50, 64). Imaging studies in patients with sleep apnea have consistently demonstrated narrowing of the pharynx due to alterations in soft tissues and fat deposition that presumably increase pharyngeal collapsibility (4, 15, 51). However, despite the alterations in pharyngeal anatomy and elevations in pharyngeal collapsibility observed in sleep apnea patients (4, 15, 51), recent evidence suggests that mechanical loads may account for only one-third of the variability in sleep apnea severity (69).

Dynamic neuromuscular control of the upper airway (17, 36, 37, 48, 68) differs between sleep apnea patients and normal subjects, particularly during wakefulness. Specifically, during the waking state, it has been proposed that patients with anatomically narrowed upper airways require increased genioglossal muscle activity to compensate for the narrowing of the upper airway. Dynamic responses to upper airway obstruction can compensate for pharyngeal mechanical loads and stabilize airway patency during both wake and sleep (35, 49, 58–60). Acute upper airway obstruction results in alterations in lung volume, intraluminal airway pressures, and gas exchange, which activate the upper airway musculature and lower pharyngeal collapsibility (30, 35, 49, 58–60). Several investigators have suggested that dynamic responses to upper airway obstruction require coordinated action among numerous rather than any single pharyngeal muscle (2, 9, 25, 26, 52). Despite the presence of extensive literature, the extent to which both mechanical loads and dynamic neuromuscular responses contribute to airflow obstruction has not been systematically evaluated during sleep.

The major goal of this study was to quantitate the effect of upper airway mechanical loads and dynamic responses on sleep apnea pathogenesis. We hypothesized that compared with normal subjects, sleep apnea patients would be characterized by elevations in mechanical loads and impaired dynamic responses to airflow obstruction. In contrast, normal individuals would maintain upper airway patency during sleep due to reduced mechanical loads and/or vigorous dynamic responses in the presence of elevated mechanical loads. We utilized established methods for characterizing upper airway mechanical properties and dynamic responses to airflow obstruction to test these predictions. Since obesity, age, and sex are known risk factors for sleep apnea, our study groups were carefully matched for these factors.

MATERIALS AND METHODS

Study Population

Patients from the Johns Hopkins Sleep Disorders Center with moderately severe obstructive sleep apnea [apnea-hypopnea index (AHI) > 20 events/h] and a matched normal group of healthy volunteers from the community (AHI < 5 events/h and flow-limited breathing for less than half the night) were recruited. The groups were matched for age, sex, and body mass index (BMI). The study was approved by the institutional review board on human research, and all subjects provided written informed consent.

Address for reprint requests and other correspondence: S. P. Patil, Johns Hopkins Sleep Disorders Center, Asthma and Allergy Bldg., 5501 Hopkins Bayview Circle, Rm. 4B30A, Baltimore, MD 21224 (e-mail: spatil@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.
Assessment of Sleep

An overnight sleep study was performed in subjects to determine the presence or absence of obstructive sleep apnea using techniques previously described (46). Sleep staging and arousals were scored using standard criteria (47). Airflow was monitored using a differential pressure transducer (Validyne ± 2 cmH2O, Northridge, CA) connected to nasal cannula. Thoracoabdominal movements were monitored using piezo-electrode strain gauges (Sleepmate, Midlothian, VA), and oxyhemoglobin saturation was monitored continuously via pulse oximetry (Ohmeda, Louisville, CO). Signals were acquired digitally scored for obstructive apneas and hypopneas as previously described (46). Severity of obstructive sleep apnea was defined by the AHI as determined by the number of obstructive apneas and hypopneas per hour.

Experimental Set-Up for Pharyngeal Critical Pressure Measurements

Following the baseline sleep study, patients underwent polysomnography while wearing a tight-fitting nasal mask for an additional one to two nights. Signals were amplified (Grass 78D Polygraph, Grass Instruments, Quincy, MA) and acquired digitally (Windaq, Akron, OH). Nasal pressure (PN) was measured continuously at the level of the mask, and airflow measurements were obtained using a pneumotachograph (Hans Rudolph, Kansas City, MO) attached to a differential pressure transducer placed between the nasal mask and a continuous positive airway pressure (CPAP) unit designed to apply holding pressure. A minimum of two series of stepwise reductions in pressures between continuous positive airway pressure (CPAP) unit designed to apply holding pressure. A minimum of two series of stepwise reductions in

Assessment of the Active Critical Pressure

A standardized protocol for assessing the active Pcrit was implemented as previously described (11, 12, 53, 55–57, 63). After at least 3 min of stable stage 2 sleep at holding pressure, the PN was reduced in a step-wise fashion by 1–2 cmH2O and sustained for at least 10 min of NREM sleep before the PN was reduced again. As PN was sequentially lowered, stable flow-limited breathing was first observed (see Fig. 1, active) followed by periods of recurrent hypopneas and apneas. The PN was lowered until apneas developed or the individual developed prolonged awakenings. If a prolonged awakening occurred, the protocol was resumed after patients reinitiated 3 min of stable stage 2 NREM sleep to a slightly higher PN. Analyses were performed during periods of stable stage 2 NREM sleep or if there was a consistent, stable pattern of hypopneas or apneas during stage 1 sleep that prevented the establishment of deeper levels of NREM sleep.

EMGgg Monitoring

To document the differences in neuromuscular activity between the passive and active state, EMGgg was monitored in a subsample of apneic (n = 5) and normal (n = 5) subjects. Two fine wire-hook needles were placed perorally, as previously described (36). The raw EMGgg signal was amplified and band-pass filtered between 30 and 3,000 Hz (Grass 78D Polygraph, Grass Instruments, Quincy, MA) (36). The signal was rectified and integrated (time constant 100 ms) to determine a component of muscular activity for a moving time-average signal (Windaq Advanced CODAS; DATAQ Instruments; Akron, OH). The EMGgg signal was quantified as a percentage of maximal awake maneuver (tongue thrust or maximal tongue protrusion against the maxillary ridge) (36). At least three of each maneuver were obtained until a consistent maximal response was achieved.

Data Analysis

Passive and active pressure-flow analyses. The passive Pcrit of the upper airway was determined by plotting the maximal inspiratory airflow (VImax) from breaths 2–5 against PN under the hypotonic conditions during stable non-REM sleep (3, 43). Each of these breaths was assessed for the presence or absence of inspiratory airflow limitation. To determine VImax, we determined the level of bias flow in the breathing circuit at each PN level. Our measurement assumed that inspiratory and expiratory tidal volumes are equal over breaths 2–5. Under these circumstances, the mean airflow level will equal the bias flow rate through the breathing circuit. The mean flow rate was then used to establish a baseline zero flow level for measurements of maximal inspiratory airflow. When esophageal pressure measurements were present for a subject, inspiratory flow limitation was defined as the presence of a plateau in inspiratory airflow in association with a continued fall in esophageal pressure by at least 1 cmH2O beyond the onset of the plateau. Flow limitation in the absence of esophageal pressure was determined using established criteria (18, 33). Flow limitation was considered to be present when a flattened flow vs. time contour was visualized. Breaths associated with arousal were excluded from analyses. The flow-limited segment of the VImax vs. PN relationship was identified using a median segmented regression approach as previously described (43). The regression equation was solved for Pcrit (PN at which zero airflow is present; Fig. 2). The resistance upstream to the site of obstruction (passive Rus) was calculated as the inverse of the regression slope (63).

Determination of the Active Pcrit was calculated in a similar fashion. When stable flow limitation was present, PN and VImax were obtained from nine breaths at the end of a 10-min period of stable NREM sleep. At PNS where the predominant pattern of breathing was periodic, the last three breaths of the final three hypopneas or apneas at each PN level were sampled. Median segmented regression of VImax vs. PN identified the flow-limited segment of the pressure-flow relationship and provided the active Pcrit and the active Rus (Fig. 2)
The difference between the active and passive $P_{crit}$ ($P_{critA}$/$P_{critP}$; Fig. 2) was considered as a measure of the strength of dynamic neuromuscular responses to upper airway obstruction. We recognized that lowering the PN would eventually result in periodic obstructive hypopneas and obstructive apneas and arousals from sleep (24). Under such circumstances, sleep and breathing instabilities may confound our assessment of the dynamic responses to upper airway obstruction and the active $P_{crit}$. To address this issue, we identified a PN transition threshold between periods of stable and unstable sleep and breathing in the active condition. This threshold was defined by the level of PN and corresponding $V_{max}$ at which instability was observed (Fig. 2, point A). The PN range above the transition threshold was used to define the steady-state portion of the active pressure-flow relationship.

To determine dynamic responses to sustained periods of upper airway obstruction during periods of stable stage 2 sleep and breathing, two parameters were derived. First, the PN at the transition threshold during the active condition was compared with the PN of the passive pressure-flow relationship at the same level of $V_{max}$ (see Fig. 2, point B; $\Delta P_{A-P}$). $\Delta P_{A-P}$ represented the subject’s ability to preserve upper airway patency during steady-state sleep and maintain stable breathing patterns by recruiting dynamic neuromuscular responses (analogous to $\Delta P_{critA-P}$). Second, we examined the level of airflow obstruction required to induce periodic breathing in normal and sleep apnea subjects. The subject’s susceptibility to periodic breathing was defined as the level of $V_{max}$ at the transition threshold at which periodicity breathing began along the active pressure-flow relationship (transition threshold; see Fig. 2, point A).

In one normal subject, measurements of passive and active pressure-flow relationships were obtained during stage 3 sleep due to insufficient data collected during stage 2 sleep. Sensitivity analyses including and excluding the data collected in this subject demonstrated no significant differences in the results. The data for the subject were therefore included for all analyses. In three normal females (see Table 2), the active $P_{crit}$ was indeterminate due to awakenings from sleep at negative PN levels. Nevertheless, before the awakenings, subjects 5, 9, and 16 demonstrated partial upper airway obstruction (i.e., inspiratory flow-limitation) at a PN of -7.2, -8.4, and -13.7 cmH2O, respectively. In these three subjects, the active $P_{crit}$ was assumed to be equal to the lowest PN associated with flow-limited breathing before arousal. Imputing the active $P_{crit}$ with a value that was equal to the lowest PN obtained would increase the average active $P_{crit}$ and decrease the $P_{critA-P}$ in the normal group and thus bias against our primary hypothesis. Sensitivity analyses of the active $P_{crit}$ and compensatory neuromuscular responses ($P_{critA-P}$) excluding these three subjects did not change our findings. Therefore, we present the active $P_{crit}$ and $P_{critA-P}$ data in RESULTS excluding these three subjects. In contrast, $\Delta P_{A-P}$ and the $V_{max}$ at the transition threshold...
were obtained in the three normal female subjects, whose data were therefore included for analyses.

**EMGGG analyses.** Tonic and peak phasic EMGGG values were determined for breaths at a Pn level equivalent to the passive Perit during the passive and active conditions (see Fig. 1). Tonic activity was defined as the lowest activity present during inspiration. Peak phasic activity was defined as the maximal activity during inspiration. The difference between tonic EMGGG activity during the passive condition (Fig. 1, bracket B) and holding pressure (Fig. 1, bracket A) was calculated. Similarly, the difference between tonic EMGGG activity during the active condition (Fig. 1, active) and holding pressure (Fig. 1, bracket A) was determined. This difference represents the relative activation of upper airway tonic EMGGG during passive or active conditions compared with the holding pressure level. Corresponding calculations were performed to determine the relative activation of peak phasic EMGGG activity during passive or active conditions compared with the holding pressure level. The change in tonic and peak phasic EMGGG activity from the passive to the active condition (ΔEMGGG,A-P) was also calculated.

**Statistical analysis.** All statistical analyses were performed using STATA 8 (Stata, College Station, TX). The primary outcomes in the study were the differences between the active and passive Perit (ΔPeritA-P), the difference in pressures between the active and passive conditions at the Vmax transition threshold (ΔPΔA-P), the passive Perit, and the active Perit between apneic and normal subjects. Secondary outcomes included differences in Rus, the transition threshold at which periodic breathing began in the active condition below which periodic breathing was observed (see MATERIALS AND METHODS for additional details).

The mean (SD) holding pressure was 9.0 (SD 2.3) and 5.7 cmH2O (SD 1.9) (P = 0.0007) for obstructive sleep apnea patients and normal subjects, respectively. The mean passive Perit was elevated in patients with obstructive sleep apnea compared with normal subjects [−0.05 (SD 2.4) and −4.5 cmH2O (SD 3.0), respectively; P = 0.0003], suggesting increased airway collapsibility under conditions of reduced neuromuscular activity. However, there was no significant difference in the passive Rus between obstructive sleep apnea periods.
Table 2. Individual demographic and upper airway characteristics of participants

<table>
<thead>
<tr>
<th>Subj No.</th>
<th>Sex</th>
<th>Age, yr</th>
<th>BMI, kg/m²</th>
<th>NREM AHI, events/h</th>
<th>Passive Perit, cmH₂O</th>
<th>Rus, cmH₂O·1⁻¹·s⁻¹</th>
<th>Dynamic Responses</th>
<th>Active Perit, cmH₂O</th>
<th>Rus, cmH₂O·1⁻¹·s⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>−0.8</td>
<td>8.6</td>
<td>−8.4</td>
<td>−6.7</td>
<td>−7.6</td>
</tr>
<tr>
<td>1</td>
<td>M</td>
<td>32</td>
<td>28</td>
<td>2.6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>47</td>
<td>30</td>
<td>2.1</td>
<td>−0.1</td>
<td>21.7</td>
<td>−24.1</td>
<td>−13.3</td>
<td>−24.2</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>57</td>
<td>27</td>
<td>2.7</td>
<td>−0.7</td>
<td>21.8</td>
<td>−3.8</td>
<td>−6.3</td>
<td>−4.5</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>35</td>
<td>39</td>
<td>5.7</td>
<td>−1.0</td>
<td>17.1</td>
<td>−7.3</td>
<td>−3.5</td>
<td>−8.3</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>62</td>
<td>37</td>
<td>1.0</td>
<td>−3.2</td>
<td>9.4</td>
<td>−7.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>48</td>
<td>25</td>
<td>2.3</td>
<td>−4.0</td>
<td>16.6</td>
<td>−3.1</td>
<td>−4.6</td>
<td>−7.2</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>43</td>
<td>24</td>
<td>4.6</td>
<td>−4.5</td>
<td>24.6</td>
<td>−3.0</td>
<td>−1.6</td>
<td>−7.5</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>28</td>
<td>30</td>
<td>2.5</td>
<td>−4.8</td>
<td>29.9</td>
<td>−6.5</td>
<td>−5.7</td>
<td>−11.3</td>
</tr>
<tr>
<td>9</td>
<td>F</td>
<td>42</td>
<td>26</td>
<td>0.2</td>
<td>−5.4</td>
<td>68.8</td>
<td>−5.9</td>
<td>−18.1</td>
<td>−11.3</td>
</tr>
<tr>
<td>10</td>
<td>M</td>
<td>25</td>
<td>27</td>
<td>1.6</td>
<td>−5.9</td>
<td>18.2</td>
<td>−0.3</td>
<td>0.4</td>
<td>−6.2</td>
</tr>
<tr>
<td>11</td>
<td>F</td>
<td>35</td>
<td>31</td>
<td>0.2</td>
<td>−5.9</td>
<td>30.5</td>
<td>−5.2</td>
<td>−6.4</td>
<td>−11.0</td>
</tr>
<tr>
<td>12</td>
<td>F</td>
<td>36</td>
<td>31</td>
<td>1.8</td>
<td>−6.2</td>
<td>42.8</td>
<td>−15.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>M</td>
<td>43</td>
<td>23</td>
<td>0.8</td>
<td>−7.6</td>
<td>6.6</td>
<td>−6.6</td>
<td>−2.9</td>
<td>−14.2</td>
</tr>
<tr>
<td>14</td>
<td>F</td>
<td>20</td>
<td>38</td>
<td>1.9</td>
<td>−7.9</td>
<td>24.3</td>
<td>−7.4</td>
<td>−0.8</td>
<td>−15.3</td>
</tr>
<tr>
<td>15</td>
<td>F</td>
<td>22</td>
<td>24</td>
<td>0.7</td>
<td>−7.9</td>
<td>17.1</td>
<td>−8.3</td>
<td>0.0</td>
<td>−16.2</td>
</tr>
<tr>
<td>16</td>
<td>F</td>
<td>34</td>
<td>31</td>
<td>1.3</td>
<td>−8.6</td>
<td>25.8</td>
<td>−4.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>−4.5</td>
<td>24.0</td>
<td>−6.9</td>
<td>−6.1</td>
<td>−11.1</td>
</tr>
<tr>
<td>SD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3.0</td>
<td>15.0</td>
<td>5.7</td>
<td>5.4</td>
<td>5.3</td>
</tr>
</tbody>
</table>

| OSA patients | | | | | | | | | |
| 17 | F | 50 | 27 | 24.4 | 4.7 | 3.9 | −2.8 | 0.4 | 1.8 | 16.0 |
| 18 | M | 34 | 32 | 74.1 | 3.6 | 13.0 | 1.0 | 1.3 | 4.6 | 14.0 |
| 19 | M | 56 | 30 | 37.0 | 1.7 | 30.5 | −4.2 | −3.7 | −2.5 | 33.4 |
| 20 | M | 30 | 31 | 74.0 | 1.0 | 18.4 | −2.8 | −0.3 | −1.8 | 32.0 |
| 21 | F | 50 | 23 | 69.0 | 0.9 | 19.4 | 0.8 | 1.1 | 1.7 | 22.8 |
| 22 | F | 52 | 40 | 56.0 | 0.8 | 17.3 | −5.7 | −0.4 | −4.9 | 42.5 |
| 23 | M | 31 | 27 | 32.3 | 0.4 | 16.5 | 1.5 | −1.1 | −1.1 | 18.4 |
| 24 | M | 36 | 24 | 52.2 | 0.7 | 16.4 | 2.0 | 1.5 | 2.7 | 10.4 |
| 25 | M | 38 | 32 | 62.4 | 0.2 | 12.3 | 0.8 | 0.4 | 1.0 | 10.9 |
| 26 | M | 56 | 26 | 35.2 | −0.6 | 25.7 | −4.2 | −3.4 | −4.8 | 30.4 |
| 27 | M | 52 | 32 | 72.6 | −0.7 | 24.4 | 0.9 | 0.4 | 0.2 | 21.0 |
| 28 | M | 31 | 32 | 70.7 | −1.6 | 24.6 | −0.5 | 1.1 | −2.1 | 31.3 |
| 29 | F | 35 | 37 | 62.4 | −1.8 | 22.2 | −2.9 | −5.6 | −4.7 | 11.2 |
| 30 | F | 35 | 35 | 75.3 | −3.0 | 16.5 | 0.9 | 0.3 | −2.1 | 15.0 |
| 31 | M | 28 | 23 | 38.8 | −3.0 | 24.8 | −4.9 | −3.2 | −7.9 | 35.4 |
| 32 | M | 27 | 27 | 35.7 | −4.6 | 16.2 | −1.8 | −2.2 | −6.4 | 15.0 |
| Mean |     |     |     |     | 54.5 | −0.05 | 18.6 | −1.6 | −0.8 | −1.6 | 22.5 |
| SD   |     |     |     |     | 17.9 | 2.4   | 6.5   | 2.4  | 2.2  | 3.5  | 10.2 |

Individual data for normal subjects and OSA patients. BMI, body mass index; Perit, critical pressure; Rus, upstream resistance; ΔPcritₐ₋ₚ = active Perit−passive Perit; ΔPₐ₋ₚ = difference in active and passive nasal pressure at transition threshold (see Fig. 2).

patients and normal subjects [18.6 (SD 6.5) and 24.0 cmH₂O·1⁻¹·s⁻¹ (SD 15.0), respectively; P = 0.27].

Active Properties

The mean active Perit (see Fig. 3A) was also significantly elevated in obstructive sleep apnea patients compared with normal subjects [−1.6 (SD 3.5) and −11.1 cmH₂O (SD 5.3), respectively; P < 0.0001], suggesting increased upper airway collapsibility during conditions of intact neuromuscular activity. There was no significant difference in the active Rus between obstructive sleep apnea patients and normal subjects [22.5 (SD 10.3) and 31.5 cmH₂O·1⁻¹·s⁻¹ (SD 18.3), respectively; P = 0.17].

Dynamic Responses to Upper Airway Obstruction

Dynamic responses to upper airway obstruction were greater in normal subjects than sleep apnea patients, as reflected by the ΔPcritₐ₋ₚ [−6.9 (SD 5.7) vs. −1.6 cmH₂O (SD 2.4), respectively; P = 0.0004] and the ΔPₐ₋ₚ [−6.1 (SD 5.4) vs. −0.8 cmH₂O (SD 2.2), respectively; P = 0.0006]. The mean passive and active pressure-flow relationships are shown for normal subjects and obstructive sleep apnea patients in Fig. 4.

To determine whether normal subjects and sleep apnea patients differed in their tendency to develop periodic breathing, we compared Vmax at the transition threshold between the two groups (Figs. 2 and 4). Vmax at the transition threshold was similar in both groups [263 (SD 62) and 217 ml/s (SD 82) in normal and sleep apnea subjects, respectively; P = 0.08], indicating that both groups developed periodic breathing at comparable levels of airflow obstruction.

Differences in dynamic responses to upper airway obstruction in normal compared with and apneic subjects could be related to differences in upper airway mechanical loads (i.e., passive Perit) between the two groups. To address this concern, we compared the dynamic responses to upper airway obstruction in a subgroup of normal subjects [n = 7 (6 male, 1 female); age 41.4 yr (SD 10.2), BMI 29.0 kg/m² (SD 5.1)] and sleep apnea patients [n = 6 (4 male, 2 female); age 35.3 yr (SD 10.7), BMI 29.8 kg/m² (SD 5.5); P > 0.2 for all characteristics] with comparable passive Perit [−2.0 (SD 2.3) vs. −2.4
cmH\textsubscript{2}O (SD 1.4), respectively). Despite comparable mechanical loads (Fig. 3B), the normal subjects had greater dynamic responses to upper airway obstruction than sleep apnea patients as demonstrated by $\Delta P_{\text{crit}}$ [−8.0 (SD 7.4) vs. 2.2 cmH\textsubscript{2}O (SD 2.2), respectively; $P = 0.03$] and $\Delta P_{\text{crit}_{\text{passive}}} [−6.0 (SD 3.7) vs. −2.2 \text{ cmH}_{2}\text{O (SD 2.5), respectively, $P = 0.03$}].

**EMG\textsubscript{GG} Responses**

Tonic and peak phasic EMG\textsubscript{GG} activity were studied in a subsample of obstructive sleep apnea subjects [$n = 5$ (4 males, 1 female) age 40.2 yr (SD 11.3), BMI 31.4 kg/m\textsuperscript{2} (SD 6.7)] and normal subjects [$n = 5$ (4 males, 1 female), age 42.2 yr (SD 13.6), BMI 28.2 kg/m\textsuperscript{2} (SD 5.9); $P > 0.5$ for all characteristics]. The change in tonic EMG\textsubscript{GG} activity between the passive and holding pressure states compared with the change in tonic EMG\textsubscript{GG} activity between the active and holding pressure states demonstrated significant differences in normal subjects [4.7% (SD 4.2) vs. 14.1% (SD 13.9), $P = 0.03$] and apneic subjects [2.4% (SD 2.1) vs. 12.7% (SD 9.7), $P = 0.03$]. Similarly, the change in peak phasic EMG\textsubscript{GG} activity between passive and...
holding pressure states compared with the change in peak phasic EMG activity between active and holding pressure states demonstrated significant differences in normal subjects [9.7% (SD 4.1)] vs. [22.6% (SD 10.8), P = 0.03] and apneic subjects [6.1% (SD 9.1)] vs. [31.2% (SD 18.5), P = 0.03]. However, no significant difference in the tonic EMG activity or peak phasic EMG activity was found between normal subjects and obstructive sleep apnea patients during either the holding pressure, passive, or active conditions. Furthermore, no significant relationship between any measure of EMG activity and ΔPcrit was found.

DISCUSSION

We demonstrated that patients with obstructive sleep apnea were characterized by defects in upper airway mechanical properties and dynamic responses to upper airway obstruction compared with matched normal controls, as evidenced by elevations of upper airway critical pressures under passive and active conditions. In sleep apnea patients, the passive Pcrit was uniformly elevated to levels known to produce severe airflow obstruction during sleep, suggesting that mechanical loads play a key role in the pathogenesis of obstructive sleep apnea. The passive Pcrit was also elevated to a similar degree in a subgroup of our normal subjects, suggesting that some normal individuals have mechanical defects which place them at risk for the disorder. Despite the presence of elevated mechanical loads, these normal subjects demonstrated a markedly greater response in ΔPcrit compared with sleep apnea patients who had comparable levels of mechanical loads (passive Pcrit; see Fig. 3B). This finding suggests that neuromuscular responses to airway obstruction improve upper airway patency during sleep and offset mechanical loads in normal subjects. The present study suggests that increased mechanical loads and blunted neuromuscular responses are both required for the development of obstructive sleep apnea.

Our approach to studying the upper airway during sleep is based on a Starling resistor model in which upper airway patency is determined primarily by the critical pharyngeal pressure (44, 54). The critical pressure has previously been shown to describe a continuum of pharyngeal collapsibility from health to varying degrees of upper airway obstruction including snoring, hypopneas, and apneas (11, 57). As summarized in Fig. 3, in normal sleeping subjects with intact neuromuscular responses, the active Pcrit is markedly negative and the upper airway remains patent compared with obstructive sleep apnea patients in whom the Pcrit is close to atmospheric pressure and the upper airway occludes spontaneously at sleep onset. Furthermore, a range of critical pressures can be obtained that is characterized by a relative threshold above which recurrent apneas and hypopneas begin to occur (apnea-hypopnea threshold; see Fig. 5) (11). The present study confirmed that an active Pcrit greater than approximately −5 cmH2O distinguished most obstructive sleep apnea patients (14 of 16 subjects) from normal subjects (15 of 16 subjects) (11).

In the present study, the passive Pcrit was higher than the apnea-hypopnea threshold in all sleep apnea patients, indicating the presence of increased mechanical loads as previously reported (3, 22, 43, 54, 67). Moreover, the passive Pcrit measurements were comparable to previous values obtained under conditions of minimal or absent neuromuscular tone, suggesting that mechanical loads are similar during the sleep state and anesthesia (5, 6, 20). Elevations in passive Pcrit observed in apneic patients compared with normal subjects cannot be attributed to overt anthropometric differences between the groups since our groups were matched for age, sex, and obesity. Furthermore, subjects with obvious alterations known to increase mechanical loads were excluded (e.g., tonsillar hypertrophy, microagnathia) (39, 66). Nevertheless, subtle structural changes (29, 51) or differences in regional adiposity (16, 38, 61) could explain elevations in upper airway mechanical loads.

A major finding in the present study was the observation that normal subjects could be divided into two subgroups based on the passive Pcrit. Half of the normal subjects demonstrated a passive Pcrit that was below the apnea-hypopnea threshold of −5 cmH2O, which was sufficient to maintain upper airway patency, regardless of their ability to further lower their critical pressure during the active state. In the remaining normal subjects, the passive Pcrit was greater than −5 cmH2O, placing them at risk for obstructive sleep apnea (see Fig. 5). Nevertheless, these normal subjects compensated for increases in mechanical loads by increasing airflow over a wide range of PNS (ΔP<sub>A</sub>−P) during the active condition and by lowering the active Pcrit below the apnea-hypopnea threshold (increased ΔPcrit<sub>A</sub>−P). In contrast, obstructive sleep apnea patients failed to compensate for the increased mechanical loads by lowering their Pcrit during the active state and demonstrated reduced ΔP<sub>A</sub>−P and ΔPcrit<sub>A</sub>−P responses, suggesting the presence of blunted neuromuscular responses. It is unlikely that blunted neuromuscular responses in sleep apnea patients were due to...
baseline differences in mechanical loads between the normal and sleep apnea groups because $\Delta PA_p$ and $\Delta Pcrit_{A_p}$ remained low in sleep apnea subjects after matching both groups for the level of mechanical loads (see passive $Pcrit$, Fig. 3B). The finding suggests that nonmechanical factors, i.e., neuromuscular factors, most likely account for the differences in the $\Delta PA_p$ and $\Delta Pcrit_{A_p}$ between the two groups.

The mechanism for the lack of $\Delta PA_p$ and $\Delta Pcrit_{A_p}$ responses in obstructive sleep apnea patients is unclear. Recent evidence suggests that neuromuscular responses account for approximately two-thirds of the variability in sleep apnea severity (69), suggesting that compensatory neuromechanical mechanisms account for active responses to upper airway obstruction and play a dominant role in preventing upper airway collapse during sleep. As the upper airway collapses during sleep, an integrated compensatory neuromuscular response can maintain airway patency, as reflected by decreases in the active $Pcrit$. Several mechanisms might account for blunt dynamic responses to airflow obstruction in apneic patients. First, a loss of pharyngeal mechanoreceptors input (1, 23, 28) may result from chronic exposure to upper airway obstruction and mucosal inflammation. Second, neuromuscular activity may be inadequate or waking neuromuscular reflex responses are lost during sleep (17, 36, 37, 48, 68). Third, decreases in ventilatory response to hypercapnia and hypoxemia in sleep apnea patients (10, 14, 27, 42) indicate insensitivity of central chemoreflex pathways that predispose to recurrent airway collapse. Fourth, instability in the chemical control system, as reflected by measurements of loop gain, has been observed in specific strata of sleep apnea patients, which may contribute to recurrent airway obstruction (22, 41, 67, 71).

Recently, it has been suggested that hyperventilation following arousals during sleep may also contribute to upper airway collapse and destabilize breathing patterns due to altered loop gain (21, 70). In the present study, we demonstrated that periodic breathing began at comparable levels of upper airway obstruction in both normal and sleep apnea subjects, indicating a similar propensity for periodic breathing. Moreover, the experimental findings in normal subjects indicate that if the upstream pressure is lowered sufficiently, the normal dynamic neuromuscular responses can be overwhelmed, leading to periodic obstructive hypopneas and apneas, as would occur spontaneously in obstructive sleep apnea patients (11, 24).

In a limited number of sleep apnea patients and normal subjects, we monitored $EMGG$ activity to document the presence of neuromuscular activation. Although $EMGG$ activity increased in the active compared with the passive state in both groups, neither tonic nor peak phasic between-group differences were observed, and no relationship between measures of $EMGG$ activity and $\Delta Pcrit_{A_p}$ or $\Delta PA_p$ was identified in either group. There are several potential explanations for why $EMGG$ responses did not differ between the two groups and did not correlate with $\Delta Pcrit_{A_p}$ or $\Delta PA_p$. First, the genioglossus muscle is only one of many muscles controlling pharyngeal patency and may not represent composite neuromuscular responses to airflow obstruction. Second, we only monitored EMG activity in approximately one-third of our subjects and may have inadequate power to discern differences in neuromuscular responses. Third, it is possible that neuromuscular and airflow responses to upper airway obstruction may be dissociated (54), suggesting that the genioglossus activity may reflect rather than control the state of pharyngeal patency (8, 30, 31). Finally, the conversion of electrical activity to pharyngeal muscle pressure may be impaired in sleep apnea patients and could account for the lack of difference in $EMGG$ between normal and sleep apnea subjects despite differences in dynamic airflow responses.

Our study has several limitations. First, our passive upper airway state represents a hypotonic upper airway rather than anatomic airway. Nevertheless, our passive $Pcrit$ measurements in both normal and sleep apnea subjects are comparable to those reported under the atomic condition (5, 6, 20). Second, recurrent obstructive apneas and hypopneas in the active condition were associated with sleep-wake instability, which might have confounded the active response. Nevertheless, our active $Pcrit$ measurements were made under comparable conditions of NREM sleep in both groups, who exhibited similar susceptibility to $(V_{max}$ at the transition threshold) (57, 63). Furthermore, evidence for activation was observed over the entire active pressure-flow relationship, regardless of whether sleep and breathing patterns were stable ($\Delta PA_p$ or not stable ($\Delta Pcrit_{A_p}$). Third, while subjects were carefully matched for anthropometric and demographic characteristics, it is possible that differences in body fat distribution (16, 38, 61) and/or hormonal status (7, 40, 45, 72) may account for differences in passive and/or active $Pcrit$ between groups.

The major implication of the present study is that defects in both upper airway mechanical (passive $Pcrit$) and neuromuscular control ($\Delta Pcrit_{A_p}$ or $\Delta PA_p$ must be present to develop obstructive sleep apnea (Fig. 5). If the mechanical loads on the upper airway result in a passive $Pcrit$ that is greater than approximately $−5$ cmH$_2$O, obstructive sleep apnea will occur if the individual is unable to adequately recruit neuromuscular responses ($\Delta Pcrit_{A_p}$ or $\Delta PA_p$) and lower the active $Pcrit$ by $<5$ cmH$_2$O threshold. In contrast, if the mechanical loads result in a passive $Pcrit$ of less than approximately $−5$ cmH$_2$O, obstructive sleep apnea will not occur, regardless of the neuromuscular responses ($\Delta Pcrit_{A_p}$ or $\Delta PA_p$) recruited to further lower the active $Pcrit$. Thus, we propose a “two-hit” hypothesis, where defects in both upper airway mechanical and neuromuscular control are necessary for the development of obstructive sleep apnea.

The precise factors causing these mechanical and neuromuscular defects, however, remain undefined. For example, it is known that weight loss leads to substantial decreases in the active $Pcrit$ (53), which account for improvements in sleep apnea severity (62). Nevertheless, it is unclear whether improvements in upper airway function with weight loss are due to mechanical or neuromuscular factors. Given the increasing prevalence of obesity in Western society, a substantial proportion of the general population may be at risk for developing obstructive sleep apnea (73). Our findings lead us to speculate that obesity leads to defects in mechanical and neuromuscular control of upper airway function. In future studies, partitioning of upper airway collapsibility into its mechanical and neuromuscular components could serve to examine the therapeutic effects of pharmacological agents, upper airway surgery, oral appliance devices, and weight loss on upper airway collapsibility and as intermediate physiological traits for studies examining the genetic susceptibility to obstructive sleep apnea.
ACKNOWLEDGMENTS

We acknowledge the technical assistance of Luis E. Pichard in data collection and analyses. We also thank Drs. David Pearse and Naresh Punjabi for insightful comments to improve the manuscript.

Present address of J. J. Marx: St. Joseph’s Medical Center; 7601 Osler Dr., 2nd Floor, Towson, MD 21204.

GRANTS

The study was supported by National Heart, Lung, and Blood Institute Grants HL-50381 and HL-37379 and National Research Service Award Grant HL-68418. The study was also supported by Johns Hopkins Bayview Medical Center General Clinical Research Center Grant M01-RR-02719.

REFERENCES


