Effect of REM sleep on retroglossal cross-sectional area and compliance in normal subjects

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Rowley, James A., Carrie S. Sanders, Brian R. Zahn, and M. Safwan Badr. Effect of REM sleep on retroglossal cross-sectional area and compliance in normal subjects. J Appl Physiol 91: 239–248, 2001.—It has been proposed that the upper airway compliance should be highest during rapid eye movement (REM) sleep. Evidence suggests that the increased compliance is secondary to an increased retroglossal compliance. To test this hypothesis, we examined the effect of sleep stage on the relationship of retroglossal cross-sectional area (CSA; visualized with a fiber-optic scope) to pharyngeal pressure measured at the level of the oropharynx during eupneic breathing in subjects without significant sleep-disordered breathing. Breaths during REM sleep were divided into phasic (associated with eye movements, PREM) and tonic (not associated with eye movements, TREM). Retroglossal CSA decreased with non-REM (NREM) sleep and decreased further in PREM (wake 156.8 ± 48.6 mm², NREM 104.6 ± 65.0 mm² (P < 0.05 wake vs. NREM), TREM 83.1 ± 46.4 mm² (P = not significant NREM vs. TREM), PREM 73.9 ± 39.2 mm² (P < 0.05 TREM vs. PREM)]. Retroglossal compliance, defined as the slope of the regression CSA vs. pharyngeal pressure, was the same between all four conditions (wake −0.7 ± 2.1 mm²/cmH₂O, NREM 0.6 ± 3.0 mm²/cmH₂O, TREM −0.2 ± 3.3 mm²/cmH₂O, PREM −0.6 ± 5.1 mm²/cmH₂O, P = not significant). We conclude that the intrinsic properties of the airway wall determine retroglossal compliance independent of changes in the neuromuscular activity associated with changes in sleep state.

upper airway; imaging; nasopharynx; rapid eye movement sleep

RAPID EYE MOVEMENT (REM) sleep is a distinct neurophysiological state associated with significant changes in breathing pattern and ventilatory control compared with both wakefulness and non-rapid-eye movement (NREM) sleep (4, 18, 37). Because data from sleep studies show that obstructive apneas are more frequent and longer during REM sleep (5, 30), it has been hypothesized that upper airway mechanics would also be influenced by REM sleep. We recently investigated the effect of REM sleep on retropalatal compliance during eupneic breathing by using an experimental system in which we simultaneously image the upper airway by use of a fiber-optic scope and measure the pharyngeal pressure (Pph) at the site of airway narrowing (25). Using this experimental approach, we found that retropalatal cross-sectional area (CSA) decreased significantly during NREM sleep but did not decrease further in either tonic (not associated with rapid eye movements) or phasic (associated with rapid eye movements) REM sleep (TREM and PREM, respectively). We also found that retropalatal compliance is highest during NREM sleep, with the compliance during TREM and PREM similar to that seen in wakefulness.

This result was unexpected for several reasons. First, upper airway neuromuscular activity, particularly of the genioglossus muscle, is lowest during REM sleep (26, 27, 42). Second, it has been shown that the genioglossus reflex to negative pressure is inhibited during REM sleep, resulting in an increased upper airway collapsibility in normal subjects during REM sleep (34). Third, it has recently been demonstrated that the site of obstruction during REM sleep in patients with obstructive sleep apnea is more often in the oropharynx than in the nasopharynx (2). Thus we hypothesized that one explanation for our findings of decreased compliance in REM sleep compared with NREM sleep was that we had studied the nasopharynx rather than the oropharynx. Thus in this work we investigated the effect of REM sleep on retroglossal CSA and compliance. Our hypothesis was that retroglossal compliance would be increased during REM compared with NREM sleep.

METHODS

Subjects

The experimental protocol was approved by the Human Investigation Committee of the Wayne State University School of Medicine and the Detroit Veterans Affairs Medical Center. Informed, written consent was obtained from all subjects. We studied 10 subjects who were recruited from the general population. Four subjects complained of light habitual snoring but did not have any sleep-disordered breathing.

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(as evidenced by apneas or hypopneas) on baseline polysomnography. The anthropometric, polysomnographic, and clinical data are summarized in Table 1.

**REM Enhancement**

We enhanced our ability to achieve REM sleep in heavily instrumented subjects in several ways. First, we severely restricted the sleep of our subjects before their study. Subjects were instructed to sleep no more than 5 h the night before the study and were then kept awake the night of the study until ~5–6 AM. Thus all subjects had been awake for ~24 h before the study. Second, we studied the subjects starting at 5:00 AM, which is the time of the day at which the majority of people have the highest propensity for REM sleep (3). Finally, we kept interruptions to a minimum after the initial data collection for wakefulness and NREM sleep. Seven of the 10 subjects underwent the above REM enhancement. The remaining three subjects were medical residents or students and were studied after an all-night call in the hospital.

**Measurements**

Electroencephalograms (EEG), electrooculograms (EOG), and chin electromyograms (EMG) were recorded (model 7-B, Grass) using the international 10–20 system of electrode placement (EEG: C3–A2 and C4–A1; EOG F7–A2 and F8–A2). Airflow was measured by a pneumotachometer (model 3700A, Hans Rudolph) attached to a nasal mask. Tidal volume (Vt) was obtained from the integrated airflow signal. Airway pressures were measured using a pressure-tipped catheter (Model TC-500XG, Millar), which was threaded through the mask (see Protocols for positioning). The pharyngeal lumen was visualized by using a pediatric fiber-optic bronchoscope (FB10X, Pentax). Lidocaine (2%) was atomized into the pharynx through the mouth to provide retroglossal anesthesia, and 2% lidocaine jelly was used to provide both lubrication and anesthesia to the nostril through which the scope was passed. The position of the scope was standardized across subjects by advancing the tip to touch the tip of the epiglottis and then withdrawing it 2–3 cm. Slight variation of the orientation of the scope among subjects ensured clear visualization of the retroglossal lumen. Once the fiber-optic scope was positioned, it was secured by use of soft putty around the hole of the nasal mask through which it was passed. A continuous image of the retroglossal lumen was obtained from a closed-circuit video camera (Endosvision 3000, Pentax Precision Instrument) connected to the scope. The video image and the respiratory signals were digitized at 5 frames/s and 25 Hz, respectively, by using specially developed software.

**Protocols**

**Night 1: Airway visualization protocol.** The subjects were sleep restricted as described above. All subjects were instructed to use oxymetazoline hydrochloride 0.05% (Goldline Laboratories) 12 h before the study start time. An additional dose was given before the start of the study if the subject had subjective nasal stuffiness. At ~5 AM, sleep-staging electrodes and respiratory bands were attached, and the subjects then lay supine in the bed. Local anesthesia was given, the pressure catheter was passed through one nostril, and the fiber-optic scope was then passed through the opposite nostril and positioned as described above. With use of the fiber-optic scope, the pressure catheter tip was positioned at the level of the oropharynx lumen to measure Pph. The nasal mask was then carefully lowered onto the face and secured. At this point, the exact position of the fiber-optic scope was adjusted, and the scope plus the attach video camera were placed in a clamp suspended above the subject’s head. The mask was carefully sealed, including the hole through which the scope was inserted. A check for air leakage around the mask was made by occluding the airflow during an attempted inspiration and expiration. After a period of wakefulness during which 3–5 min of data were collected for analysis, the subject was allowed to go to sleep. During the sleep period, the subject’s head position was fixed with the use of sand-filled bolsters.

All variables were continuously monitored throughout the study. The fiber-optic image and the respiratory signals were acquired to the computer on-line during wakefulness, stage 2 sleep, slow-wave sleep, and REM sleep. Data were acquired only during periods in which the retroglossal lumen was clearly visible (i.e., no secretions obscuring the image). The study was terminated after a period of stable REM sleep was achieved during which there was sufficient time to collect both clear fiber-optic images and respiratory signals.

**Night 2: Pressure-flow relationship protocol.** For this study, the subjects were requested to restrict their sleep to 6 h the night before the study, and the subject was studied beginning at 11 PM after ~18 h of sleep deprivation. Sleep staging electrodes and respiratory bands were attached. Supraglottic pressure was measured by positioning the pressure catheter tip in the hypopharynx by observing the tip of the catheter disappear behind the tongue. The subject was laid supine on the bed and the nasal mask was placed on the face and secured. A check for air leakage around the mask was made. The remaining transducers were then attached. After a period of wakefulness during which 3–5 min of data was collected for analysis, the subject was allowed to fall asleep. During this study, the subject’s head position was not fixed. All variables were monitored continuously throughout the study until a period of stable REM sleep was achieved.

**Table 1. Anthropometric, polysomnographic and clinical data for each subject**

<table>
<thead>
<tr>
<th>Subject</th>
<th>Gender</th>
<th>Age, yr</th>
<th>Height, m</th>
<th>Weight, kg</th>
<th>BMI, kg/m²</th>
<th>REM Latency, min</th>
<th>REM Time, min</th>
<th>%IFL</th>
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</thead>
<tbody>
<tr>
<td>TJ</td>
<td>M</td>
<td>27</td>
<td>1.95</td>
<td>75.0</td>
<td>21.8</td>
<td>183</td>
<td>6</td>
<td>0</td>
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<tr>
<td>DA</td>
<td>M</td>
<td>39</td>
<td>1.88</td>
<td>68.2</td>
<td>21.6</td>
<td>96</td>
<td>13</td>
<td>2.3</td>
</tr>
<tr>
<td>MP</td>
<td>M</td>
<td>36</td>
<td>1.83</td>
<td>81.8</td>
<td>24.5</td>
<td>96</td>
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<td>95.8</td>
</tr>
<tr>
<td>KD</td>
<td>F</td>
<td>25</td>
<td>1.85</td>
<td>75.0</td>
<td>24.4</td>
<td>34</td>
<td>32</td>
<td>65.8</td>
</tr>
<tr>
<td>AT</td>
<td>F</td>
<td>23</td>
<td>1.65</td>
<td>49.1</td>
<td>18.0</td>
<td>197</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>CS</td>
<td>F</td>
<td>21</td>
<td>1.71</td>
<td>60.0</td>
<td>20.5</td>
<td>189</td>
<td>10</td>
<td>4.0</td>
</tr>
<tr>
<td>JB</td>
<td>M</td>
<td>27</td>
<td>1.77</td>
<td>100.1</td>
<td>31.9</td>
<td>39</td>
<td>2</td>
<td>100</td>
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<tr>
<td>AH</td>
<td>M</td>
<td>22</td>
<td>1.97</td>
<td>140.2</td>
<td>36.1</td>
<td>60</td>
<td>26</td>
<td>2.7</td>
</tr>
<tr>
<td>AC</td>
<td>F</td>
<td>25</td>
<td>1.63</td>
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<td>58</td>
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<td>28</td>
<td>1.75</td>
<td>93.2</td>
<td>30.4</td>
<td>59</td>
<td>3</td>
<td>0</td>
</tr>
</tbody>
</table>

M, male; F, female; BMI, body mass index; REM, rapid eye movement sleep; %IFL, percentage of breaths with inspiratory flow limitation.
the study, and respiratory signals were acquired onto the computer on-line during wakefulness, stage 2 sleep, slow-wave sleep, and REM sleep.

**Data Analysis**

**Night 1.** Wakefulness/sleep stage was scored according to standardized criteria (22). Inspired tidal volume (VT), inspiration time (TI), total breath duration (TT), breathing frequency (f), and inspired minute ventilation (VI) were calculated breath by breath during a period of wakefulness, stage 2 sleep, slow-wave sleep, and REM. Each breath during REM sleep was scored as either tonic REM (TREM) or phasic REM (PREM). PREM breaths were scored if a rapid EOG deflection >50 μV in amplitude occurred within the 1 s preceding inspiration or any time during the inspiratory cycle. TREM breaths were scored during periods of ocular quiescence between the phasic eye bursts (25, 42). For each of the five stages, ~6–12 breaths were analyzed. Breaths for analysis were selected during a period of time in which there was no arousal from sleep or any increase in EEG frequency and during which the retroglossal lumen was clearly visible. For the wake and NREM stages, consecutive breaths were obtained during a period in which the breathing was regular and stable. For the REM stages, breaths were selected in relation to eye bursts present (PREM) or absent (TREM).

The retroglossal CSA was obtained for each digitized frame (5 frames/s) by manually outlining the retroglossal lumen using computer software (SigmaScan, Jandel Scientific) as shown in Fig. 1. The landmarks for outlining included the base of the tongue anteriorly, the lateral pharyngeal walls, and the posterior pharyngeal wall at the level of the glottic opening. The epiglottis was also used as a reference landmark, generally by its location in the center of the outlined image. During this process, the investigator was blinded to the phase of respiration but not to the stage of sleep. The reproducibility of this technique has been previously validated by our laboratory (38). For each image, the scanning software provided an area in pixels. We converted these relative areas to absolute areas by using the dimensions of the pressure catheter as a reference (25).

Retroglossal compliance (compliance of the upper airway; Cua) was determined as follows. We plotted the CSA of the digitized frames for each breath (both inspiration and expiration) against the Pph that corresponded to each image of that breath. We defined the Cua as the slope of the regression line, CSA vs. Pph. Inspiratory and expiratory Cua were determined in a similar fashion using only the CSA and Pph data for inspiration or expiration.

**Night 2.** Wakefulness/sleep stage was scored according to standardized criteria (22). Inspired VT, TI, TT, VI, and f were calculated for 10–15 breaths during a period of wakefulness, stage 2 sleep, slow-wave sleep, PREM, and TREM as described for night 1. A pressure-flow loop was plotted for each breath. All trials were averaged, and a composite pressure-flow loop was plotted for each subject. To generate a composite pressure-flow plot of breaths of different duration, pressure and flow were sampled at equally distributed points in both inspiration and expiration. Inspiratory resistance (Rua) at a fixed flow of 0.2 l/s was computed from each loop as a numeric representation of the linear part of the pressure-flow loop.

**Additional analysis.** Each of the 10 subjects also had 50–100 breaths analyzed for the presence of inspiratory flow limitation (IFL) as part of another research project. IFL was defined as a 1-cmH2O or greater decrease in supraglottic pressure without any corresponding increase in flow during inspiration. For each subject, the percentage of IFL breaths (%IFL) was calculated as the number of IFL breaths divided by total breaths. Each subject’s %IFL is presented in Table 1.

**Statistical Analysis**

**Night 1.** All statistical analyses were performed on the complete data set of 10 subjects using SigmaStat2.0 (Jandel Scientific). Comparisons of the mean values TI, TT, VT, Vi, f, and Cua, as well as the CSA at the beginning of inspiration (CSAI) were carried out by use of a one-way analysis of variance (ANOVA) with repeated measures, with sleep stage as the factor. To compare the inspiratory and expiratory Cua, we first changed all values to the absolute values because we were interested in comparing absolute changes in CSA per unit change in Pph; statistical analysis was then performed by using a two-way ANOVA with repeated measures, with sleep stage and phase of breath (inspiration or expiration) as the factor. For comparisons that reached significance (P < 0.05), post hoc analysis was performed by using the Student-Newman-Keuls method.

**Night 2.** All statistical analyses were performed on the data set of nine subjects. One subject (DW) relocated before participating in the resistance measurement night. Comparison of the mean values, TI, TT, VT, Vi, and Rua were carried out by using a one-way ANOVA with repeated measures with sleep stage as the factor. For comparisons that reached significance (P < 0.05), post hoc analysis was performed by using the Student-Newman-Keuls method.

**RESULTS**

Table 1 presents demographic variables for each of the 10 subjects as well as the REM latency and number of minutes of REM for each subject. Resistance data for another subject (AC) was previously reported (25). Because of the similarities seen between stage 2 and slow-wave sleep on preliminary analysis and because we were most interested in comparing REM sleep to...
NREM sleep, we combined the data for stage 2 and slow-wave sleep into one category, NREM sleep, before the final statistical analyses were performed.

Effect of Sleep Stage on Ventilatory Data

The group mean levels for each respiratory variable during wakefulness and sleep stages for each of the two nights are shown in Table 2. For night 1, wakefulness was associated with a higher \( V_t \) compared with each of the other three sleep stages \((P < 0.001)\). The increased \( V_t \) was secondary to an increased \( V_t \) in wakefulness compared with the three sleep stages \((P = 0.001)\). There was no difference in \( V_t \) and \( V_t \) between any of the sleep stages. There were no differences in \( f \), \( T_i \), and \( T_T \) between wake and any of the stages of sleep. For night 2, wakefulness was associated with a higher \( V_t \) compared with each of the three sleep stages \((P = 0.003)\). There was a trend toward an increased \( V_t \) in wakefulness compared with the three sleep stages \((P = 0.06)\). There were no differences between wakefulness and the sleep stages for \( f \), \( T_i \), or \( T_T \).

Effect of REM Sleep on CSA

The effect of sleep stage on the group mean CSAI is shown in Fig. 2. A one-way ANOVA with repeated measures indicated that sleep stage had a significant effect on CSAI \((P < 0.001)\). Post hoc analysis showed that the mean CSAI became significantly smaller as the subjects progressed from wakefulness to NREM sleep \((104.6 \pm 65.0 \text{ vs. } 156.8 \pm 48.6 \text{ mm}^2)\) in wakefulness; \(P < 0.05\). There was no significant difference between NREM and TREM sleep \([83.1 \pm 46.4 \text{ mm}^2], \(P = \text{not significant (ns)}\) compared with NREM] but there was a further decrease in CSA in PREM sleep \((73.9 \pm 39.2 \text{ mm}^2), P < 0.05\) compared with TREM sleep.

Effect of REM Sleep on Cua

An example of the CSA-Pph curves for one subject is illustrated in Fig. 3B. In wake, NREM, and PREM, CSA changed little over the change in pressure. There were larger changes in CSA during TREM, with an increase in CSA during early inspiration and narrowing in late expiration.

Individual and group mean retroglossal Cua for each stage of sleep are shown in Fig. 4. For the group as a whole, there was no significant effect of sleep stage on Cua \((P = 0.001)\). The increased Cua was secondary to an increased \( V_t \) in wakefulness compared with the three sleep stages \((P = 0.001)\). There was no correlation between the CSAI and Cua during any stage of sleep.

### Table 2. Respiratory variables during wakefulness and sleep

<table>
<thead>
<tr>
<th>Variable</th>
<th>Night 1</th>
<th>Night 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>( V_t )</td>
<td>Wake: 7.4 ± 1.4</td>
<td>Wake: 7.7 ± 2.0</td>
</tr>
<tr>
<td></td>
<td>NREM: 5.1 ± 1.2</td>
<td>NREM: 5.7 ± 3.1</td>
</tr>
<tr>
<td></td>
<td>TREM: 5.8 ± 1.6</td>
<td>TREM: 6.1 ± 1.6</td>
</tr>
<tr>
<td></td>
<td>PREM: 5.0 ± 1.5</td>
<td>PREM: 5.4 ± 1.7</td>
</tr>
<tr>
<td>( V_t )</td>
<td>Wake: 0.46 ± 0.11</td>
<td>Wake: 0.50 ± 0.19</td>
</tr>
<tr>
<td></td>
<td>NREM: 0.33 ± 0.12</td>
<td>NREM: 0.33 ± 0.14</td>
</tr>
<tr>
<td></td>
<td>TREM: 0.38 ± 0.12</td>
<td>TREM: 0.36 ± 0.10</td>
</tr>
<tr>
<td></td>
<td>PREM: 0.31 ± 0.14</td>
<td>PREM: 0.31 ± 0.11</td>
</tr>
<tr>
<td>( f )</td>
<td>Wake: 16.5 ± 2.8</td>
<td>Wake: 16.2 ± 3.5</td>
</tr>
<tr>
<td></td>
<td>NREM: 16.0 ± 2.0</td>
<td>NREM: 17.1 ± 4.4</td>
</tr>
<tr>
<td></td>
<td>TREM: 15.6 ± 2.0</td>
<td>TREM: 17.1 ± 2.5</td>
</tr>
<tr>
<td></td>
<td>PREM: 16.7 ± 2.5</td>
<td>PREM: 18.8 ± 3.9</td>
</tr>
<tr>
<td>( T_i )</td>
<td>Wake: 1.5 ± 0.3</td>
<td>Wake: 2.0 ± 0.5</td>
</tr>
<tr>
<td></td>
<td>NREM: 1.6 ± 0.2</td>
<td>NREM: 1.6 ± 0.2</td>
</tr>
<tr>
<td></td>
<td>TREM: 1.6 ± 0.3</td>
<td>TREM: 1.6 ± 0.2</td>
</tr>
<tr>
<td></td>
<td>PREM: 1.3 ± 0.3</td>
<td>PREM: 1.5 ± 0.2</td>
</tr>
<tr>
<td>( T_T )</td>
<td>Wake: 3.8 ± 1.0</td>
<td>Wake: 4.2 ± 1.1</td>
</tr>
<tr>
<td></td>
<td>NREM: 3.8 ± 0.5</td>
<td>NREM: 3.8 ± 0.4</td>
</tr>
<tr>
<td></td>
<td>TREM: 4.3 ± 1.6</td>
<td>TREM: 3.7 ± 0.6</td>
</tr>
<tr>
<td></td>
<td>PREM: 3.7 ± 0.6</td>
<td>PREM: 3.4 ± 0.5</td>
</tr>
</tbody>
</table>

Values are means ± SD. NREM, non-REM sleep; TREM, tonic REM breaths not associated with eye movement; PREM, phasic REM breaths associated with eye movement. Vi, inspired minute ventilation; Vt, inspired tidal volume; f, frequency; Ti, inspiratory time; TT, total breath time. *P < 0.001 wake vs. NREM, TREM, PREM; †P = 0.001 wake vs. NREM, TREM, PREM; ‡P = 0.06 wake vs. NREM, TREM, PREM.
The effect of phase of respiration on Cua for each sleep stage is shown in Fig. 5. A two-way ANOVA with repeated measures found that neither sleep stage or phase of respiration had significant effects on Cua. In other words, the inspiratory Cua was not significantly different than the expiratory Cua. The large standard deviations found for this set of data in expiration is largely due to two subjects, one with and one without habitual snoring, who had a larger Cua in expiration than in inspiration. There was no correlation between the Rua and Cua during any stage of sleep.

**Effect of REM Sleep on Upper Airway Resistance**

Resistance at a fixed flow during the linear part of the pressure-flow relationship was measured during the stages of sleep in 9 of the 10 subjects (Fig. 6). For the group of 9 subjects, Rua during NREM was 8.3 ± 1.6 cm H2O/cm H2O. There was no effect of sleep stage or phase of respiration on Cua.
There were no significant differences in Rua between the stages of sleep.

DISCUSSION

The aim of the present study was to investigate the effect of REM sleep on retroglossal CSA and compliance in a group of subjects without significant sleep-disordered breathing. There were two main findings from our study. First, the retroglossal CSA was significantly smaller during PREM compared with NREM sleep, with no difference in CSA between NREM and TREM sleep. This is in contrast to our findings in the nasopharynx, where there was no further narrowing of the retropalatal airway in REM sleep compared with NREM sleep (25). Second, Cua during eupneic breathing, defined as the slope of the regression line for CSA plotted against Pph, was similar to that during wakefulness in all stages of sleep. These findings indicate that, in a group of subjects without significant sleep-disordered breathing, the oropharynx was equally non-compliant during wakefulness and NREM and REM sleep.

Validity of Techniques and Methodology

Fiber-optic endoscopy has several limitations that need to be considered when interpreting the findings. These have been discussed in detail in earlier papers (19, 25). Briefly, CSA measurements could be influenced by movement of the fiber-optic scope. To prevent this, the orientation of the scope was fixed by anchoring it to the mask, the position of the subject’s head was fixed by a sand pillow, and only images in which there was no change in the relationship of the scope to anatomic landmarks in different planes were analyzed. Second, an important consideration is the ability to accurately and reproducibly detect the edge of the airway lumen. To ensure this, only images in which the airway lumen was clearly visible were analyzed. Third, only 6–12 images were analyzed per stage of sleep. Reasons for the limited number of breaths included the need to manually outline the pharyngeal lumen of each image, poor visualization of the pharyngeal lumen, and, for REM, a limited number of breaths available to analyze because of the criteria used to choose phasic and tonic breaths and because we had only one REM period for each subject. Despite the small numbers, we believe that the images analyzed are representative because of the similarity of changes in CSA and the lack of change in Cua across the 10 subjects. In addition, we note that the CSA values we obtained were similar to values obtained by other investigators using fiber-optic imaging (11), computerized tomography (29), and acoustic reflection (17). We note that four of the subjects had short REM periods lasting 2 min or less. However, we believe that the breaths chosen for analysis are representative because other investigators have shown that the effects of REM sleep on ventilatory parameters and cardiovascular flow are related to the rapid eye movements and occur with the onset of REM sleep (12, 42).

A potential limitation of our study protocol is that we sleep-deprived the subjects. Sleep deprivation has been shown to result in an increase in snoring and sleep-disordered breathing (16). However, we do not believe that the sleep deprivation influenced our results. First, if sleep deprivation increases sleep-disordered breathing, we would have expected more compliant airways in our subjects. Second, Leiter et al. (16) studied the effect of 24-h sleep deprivation on genioglossus EMG activity and found that sleep deprivation decreased the genioglossus EMG response to CO2 rebreathing but only in subjects older than 30 years of age; 8 of our 10 subjects were under 30 years of age. Finally, Series et al. (33) found that the critical closing pressure of the upper airway did not change after 24 h of sleep deprivation, suggesting that global upper airway neuromuscular activity was unchanged after sleep deprivation.

The measurement of pharyngeal compliance as defined requires several assumptions. First, we are not measuring true pharyngeal airway compliance, because measurement of pharyngeal volume in sleeping, spontaneously breathing subjects is not practical. We believe that pharyngeal CSA is a reasonable substitute, as have others who have measured Cua (10, 15). Second, an accurate compliance measurement using area requires that the pressure be measured at the same level as the changes in area, as we have done in

Fig. 6. Upper airway resistance at fixed flow (Rua) for each subject is plotted for wakefulness, NREM, TREM, and PREM sleep. Mean ± SD is also shown for each stage (hexagon). There was no significant effect of sleep stage on Rua (P = ns).

11.4 cmH2O·l−1·s−1, during TREM 3.8 ± 3.1 cmH2O·l−1·s−1, and during PREM 4.7 ± 3.7 cmH2O·l−1·s−1. There were no significant differences in Rua between the stages of sleep.
this study. Third, the measurement of compliance assumes that the pressure being measured is a transmural pressure because the extraluminal pressure is assumed to be constant (15, 20). Finally, the relative contributions to the transmural pressure (23), such as the genioglossus (28), contribute minimally to the upper airway and the pressure surrounding the airway (attributed to structures such as the tongue, tonsils, and pharyngeal fat pads) cannot be ascertained with this method, primarily because it is difficult to measure the pressure surrounding the airway in a human.

It must be noted that we made pharyngeal compliance measurements over a small range of Pph (4–5 cmH2O) because we were specifically interested in studying the effect of REM sleep on compliance during eupneic breathing. Thus the compliance measurements may be different from those made under experimentally manipulating the Pph with externally applied pressure over a larger range of pressures (10–20 cmH2O) (10, 15). By measuring compliance in this fashion in the static upper airway, it has been observed that the pharyngeal compliance changes with the pharyngeal CSA (10, 11). Because the upper airway is a dynamic structure, we believe that the measurement of Cua is best made during eupneic breathing and that this approach allows us to make unique observations on the effect of sleep stage on the upper airway.

Our study was based on the premise the genioglossus muscle activity is reduced during REM sleep. Older investigations (26, 27) showed decreases in tonic activity of the genioglossus and other upper airway muscles during REM sleep. Recent work showed a decrease in genioglossus peak inspiratory activity between NREM and PREM sleep but not between NREM and TREM sleep (42). Recently it has also been shown that the reflex increase in genioglossus activity to negative pressure is decreased in REM sleep (34). Overall, the evidence suggests that genioglossus activity decreases in REM sleep, particularly in PREM sleep. In addition, we have made the assumption that a potential increase in resistive load secondary to the fiber-optic scope has not resulted in a compensatory increase in upper airway neuromuscular activity needed to maintain airway caliber (7). This assumption is based on two investigations that show no increase in genioglossus activity during inspiratory resistive loading (9, 21). However, we did not make any direct measurements of muscle activity, particularly of the genioglossus muscle. This was for practical reasons because further interventions may interfere with sleep, especially REM sleep. It is also unclear whether the measurement of one particular muscle would be adequate to make correlations between EMG activity and mechanical output given the complexity of the upper airway and the multiple muscles involved in determining CSA and compliance. However, the lack of EMG measurements precludes drawing firm conclusions regarding the effect of upper airway dilators on upper airway CSA and compliance.

Effect of REM Sleep on the Retroglossal Airway

The finding of decreasing CSA as the subjects progressed from wakefulness to NREM sleep to PREM sleep without changes in retroglossal compliance suggests that airway patency and compliance are determined by different factors in the oropharynx. Because the tongue comprises the anterior wall of the oropharynx, it would be expected that the retroglossal CSA is primarily determined by the genioglossus muscle. Several studies have shown that passive maneuvers that move the tongue forward dilate the airway (35), as does stimulation of the genioglossus muscle (14, 28, 36). Alternatively, inhibition of genioglossus activity would be expected to result in decreased airway patency. We note a correlation between the decreased peak genioglossus activity in PREM sleep compared with TREM sleep found by Wiegand et al. (42) and our decreased CSA in PREM sleep compared with TREM and NREM sleep. Thus our data supports the conclusion that genioglossus activity is a determinant of retroglossal CSA.

Retroglossal compliance, however, did not change between wakefulness and any stage of sleep, including PREM sleep. Compliance was also the same between inspiration and expiration, despite the phasic activity present during inspiration. This suggests that the neuromuscular activity, including the phasic activity, of the genioglossus is not a determinant of upper airway stiffness. The dissociation between CSA and compliance that we have noted is consistent with the work of previous investigators. In an isolated upper airway model in dogs, it has been shown that upper airway muscle activation leads to dilation of the upper airway (36). However, activation did not result in a shift of the slope of the pressure-volume curve (6). Schnall et al. (28) determined that electrical stimulation of the genioglossus did not result in decreased Rua during eupneic breathing in normal awake subjects. Although CSA was not directly measured, Rowley and colleagues showed that passive maneuvers that move the tongue (23) and hypoglossal nerve transection (24) did not change the critical closing pressure in a feline isolated upper airway model, suggesting that the genioglossus muscle plays a minor role in upper airway collapsibility. We conclude that these studies, in addition to our present data, suggest that genioglossus activity is an important determinant of airway CSA but not of Cua or collapsibility. Instead, retroglossal compliance is likely determined by the nonneuromuscular properties of the airway wall. In the oropharynx, which is dominated by the tongue, the intrinsic stiffness of the genioglossus is the most likely determinant of the nonneuromuscular properties.

In summary, our results indicate that the genioglossus is an important determinant of retroglossal structure and function but that influence is different for CSA and compliance. The size of the oropharynx is influenced by genioglossus neuromuscular activity, as evidenced during PREM sleep in which there is both...
decreased activity and decreased patency. In contrast, during the respiratory cycle, the nonneuromuscular properties of the genioglossus favor airway stiffness resulting in a low retroglossal compliance.

**Retropalatal vs. Retroglossal CSA and Compliance**

The results of this study contrasted in several important ways from our findings in the nasopharynx (25). First, in the nasopharynx we found that the CSA was decreased in NREM sleep compared with wakefulness but did not decrease further in REM sleep. Retropalatal CSA is primarily determined by the muscles of the palate, including the tensor and levator palatini muscles. The neuromuscular activity of both of these muscles has been shown to decrease significantly during NREM sleep (39, 40). If neuromuscular activity is the key determinant of upper airway size as proposed above, the results could indicate that although neuromuscular activity to retroglossal muscles (such as the genioglossus) decreases during REM sleep, the neuromuscular activity of muscles important to retropalatal CSA does not decrease. This has not been studied recently in a systematic fashion, but an older study suggests that there is no neuromuscular activity of these muscles during REM sleep (27). Therefore, nonneuromuscular properties of the upper airway must also influence baseline CSA in the nasopharynx. Nonneuromuscular determinants of upper airway size include the intrinsic properties of the muscles, connective tissue, and bony structures. We have previously hypothesized that increased blood flow to the nasopharynx during REM sleep increased the stiffness of the nasopharynx during REM. Theoretically, this increased stiffness could act to enlarge the retropalatal CSA. Alternatively, the bony structures of the nasopharynx, including the pterygoid hamulus, could act to keep the airway open during periods of decreased neuromuscular activity.

Second, retroglossal compliance did not change between sleep stages, whereas we previously found that retropalatal compliance was increased during NREM sleep compared with REM sleep. Because of the absence of neuromuscular activity in REM sleep, we hypothesized that nonneuromuscular properties of the upper airway wall, particularly the vascular perfusion of the upper airway, were the principal determinants of retropalatal stiffness in REM compared with NREM sleep. Our present data would indicate that nonneuromuscular properties are the primary determinants of retroglossal compliance during all stages of sleep. The difference in our findings for the two different sites is likely because of the large influence the tongue plays in the oropharynx. In particular, we speculate that the stiffness of this large muscle may not be influenced by changes in vascular perfusion as is the stiffness of relatively thin muscles such as the tensor and levator palatini.

**Implications**

Our findings have several important implications regarding the determinants of Cua in the sleeping human. First, sleep stage has differential effects on upper airway structure and function depending on the site of upper airway investigated. This would indicate that the study of either area in isolation may not allow the proper insight on overall upper airway pathophysiology.

Therefore, studies investigating the role of neuromuscular activity in upper airway function should include muscles that are found in both the nasopharynx (such as the tensor palatini) and the oropharynx (such as the genioglossus). Additionally, other measures of upper airway function, such as Rua, critical closing pressure, or response to inspiratory resistance loading, may provide a better measure of upper airway mechanics because they measure the overall function of the upper airway, not just that of the nasopharynx or oropharynx.

Second, given the decrease in retroglossal CSA during REM sleep, it would be expected that Rua would increase during REM sleep as well. However, our own present data and those of other investigations show that Rua is the same or decreased during REM sleep (8, 25, 41). This finding of unchanged resistance despite decreasing CSA has two potential explanations. First, Rua may be determined primarily by the pharyngeal narrowing at the nasopharynx, not at the oropharynx. Because retropalatal CSA does not change between NREM and REM sleep, it would be expected that there would be no change in resistance. Second, it is possible that Rua and CSA do not correlate despite the known effect of increasing resistance with decreasing radius of a tube. That relationship is based on a solid, uniform tube. Given that the upper airway is not a solid or uniform structure, there could be additional determinants of resistance.

Third, as discussed above, the differential effect of REM sleep on retroglossal CSA and compliance indicates that upper airway neuromuscular activity is an important determinant of retroglossal CSA but not of compliance. In other words, the genioglossus dilates but does not stiffen the upper airway. Thus, when researchers use the term “upper airway dilator” for the genioglossus, it is important to realize that the effect of the genioglossus is on upper airway CSA only. Because there were minimal changes in CSA during eupneic breathing in both wake and sleep, we believe that our data support the conclusion that the main mechanical corollary of phasic inspiratory activity is to prevent further narrowing of the airway, rather than to open the airway, during inspiration (1).

Fourth, the relatively noncompliant airway in all stages of sleep, despite known changes in neuromuscular activity (26, 42) and the finding of similar compliance in inspiration and expiration, all support the conclusion that the nonneuromuscular properties, not neuromuscular activity, are the critical determinants of retroglossal compliance during sleep.
cullar determinants of airway wall stiffness include the tissue characteristics of the airway wall muscles, which have been shown to correlate with passive muscle elastance (31, 32). Other nonneuromuscular determinants could include the connective tissues, caudal tracheal traction (23), and tissue blood perfusion (13).

In conclusion, our study has shown that baseline retroglottal CSA progressively decreases during NREM and REM sleep and that eugnmonic breathing during REM sleep is associated with a similar retroglottal compliance compared with that during wakefulness and NREM sleep. Our data suggest that the neuromuscular activity of the genioglossus is an important determinant of retroglottal CSA but that intrinsic properties of the airway wall determine retroglottal compliance independent of changes in the neuromuscular activity. We believe that these data on retroglottal compliance confirm our previous hypothesis that the nonneuromuscular properties of the airway wall are a more important determinant of upper airway stiffness during sleep than is upper airway neuromuscular activity. Future research should be directed at elucidating which mechanical properties are critical to determining Cua.

REFERENCES


