Effects of NREM sleep on dynamic within-breath changes in upper airway patency in humans

M. J. Morrell and M. S. Badr. Effects of NREM sleep on dynamic within-breath changes in upper airway patency in humans. J. Appl. Physiol. 84(1): 190–199, 1998—The purpose of our study was to compare inspiratory- and expiratory-related changes in retropalatal cross-sectional area (CSA) during wakefulness to those during non-rapid-eye-movement (NREM) sleep. We studied 18 subjects in whom the severity of sleep-disordered breathing varied. Relative changes in CSA were visualized by using fiber-optic endoscopy. For each breath analyzed (wakefulness n = 4–13; sleep n = 7–16), the CSA was measured at fixed points within inspiration and expiration (0, 25, 50, and 100% of the inspiratory and expiratory duration); these measurements were expressed as a percentage of the CSA that occurred at the start of inspiration. During wakefulness, there was a statistically significant increase in the retropalatal CSA (compared with the start of inspiration) only during early expiration (group mean: expiration, 0% = 112.6 ± 3.2 (SE)%; 25% = 122.8 ± 6.2%; 50% = 110.6 ± 3.8%). In contrast, during sleep, significant changes in CSA occurred during both inspiration and expiration (group mean: inspiration, 25% = 75.3 ± 6.0%; 50% = 66.7 ± 7.7%; 75% = 64.6 ± 8.1%; expiration, 0% = 126.8 ± 11.8%; 25% = 125.3 ± 6.9%). The expiratory-related increase in CSA was followed by narrowing such that at end expiration the caliber of the airway was returned to that occurring at the beginning of inspiration (group mean at end expiration = 98.6 ± 3.1%). The largest changes in CSA occurred in the subjects with an increased body mass index (BMI). We conclude that, during NREM sleep, significant changes in CSA occur during both inspiration and expiration and that the magnitude of these changes is significantly influenced by BMI.

Methods

Subjects

We studied 18 subjects who were recruited from a sleep clinic and from the general population. All subjects underwent full polysomnography. The anthropometric, polysomnographic, and clinical data are summarized in Table 1.

All subjects restricted their sleep before the study (no. of hours of sleep on the night before the study: 0–6 h). Sixteen subjects were studied overnight, and the remaining two (subjects SS and PS) were studied in the morning after a night of sleep deprivation. In three subjects (subjects JB, SC, and DH) oxymetazoline hydrochloride 0.05% (Goldline Laboratories) was used before the study to reduce nasal secretions. The experimental protocol was approved by the Human Subjects Committee of William S. Middleton Memorial Veterans Hospital and the University of Wisconsin Medical School, Madison.

Measurements

Electroencephalograms (EEG), electrooculograms (EOG), and chin electromyograms were recorded (model 7-B, Grass) by 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 (size 1, Hans Rudolph) attached to a nasal mask. Tidal volume (VT) was obtained from the integrated airflow signal. Rib cage and abdominal movements were monitored by using a current-coupled respiratory inductance plethysmography (Respirac, Ambulatory Monitoring). An estimate of arterial oxygen saturation was obtained by using a pulse oximeter with a finger probe (Biox 3700, Ohmeda).

Pharyngeal lumen visualization. A pediatric fiber-optic scope (3.2 mm OD; model SC-10, Olympus; or model FB-10X, Pentax Precision Instrument) was used to visualize the retropalatal airway. After topical anesthesia with a 10% lidocaine hydrochloride solution (Astra Pharmaceuticals), the scope was passed through the nares. The position of the scope was standardized across subjects by advancing the tip to touch the end of the soft palate and then withdrawing it 2–3 cm. Slight variation of the orientation of the scope among subjects ensured clear visualization of the retropalatal lumen. Once the fiber-optic scope was positioned, it was secured by using soft putty around the hole of the nasal mask through
After a period of wakefulness during which 3–5 min of data were collected for analysis (see Analysis below), the subject was allowed to go to sleep. If subjects reported that they normally breathed through the mouth while asleep, it was taped shut. Two subjects (subjects JB and SC) were unable to tolerate having their mouths taped. In these subjects we observed for any mouth breathing by ensuring there was no evidence of airflow leakage on the integrated airflow signal. During the sleep period the subject’s head position was fixed with the use of sand-filled bolsters.

All variables were monitored continuously throughout the study. During periods of wakefulness and stable sleep, when the retropalatal lumen was clearly visible (i.e., no secretions obscuring the image), the fiber-optic image and the respiratory signals were stored on-line on a computer.

Analysis

The wakefulness/sleep stage was scored according to standard criteria (22). Inspired VT, inspiratory time (TI), expiratory time (TE), total breath duration (TT), and inspired minute ventilation (Vi) were calculated breath by breath during a period of wakefulness and a period of sleep. For each analysis period, the breaths were consecutive. The sleep period (7–16 breaths) was selected by taking the period of deepest stable non-rapid-eye-movement (NREM) sleep (preferably stage IV) during which there was no arousal from sleep or any increase in EEG frequency and during which the retropalatal lumen was clearly visible with no respiratory artifacts, e.g., swallowing, coughing, and so on. In six of the eighteen subjects, we were unable to identify a period of stable stage IV sleep during which the airway lumen was visible. In these subjects, analysis periods were taken from stable stage II NREM sleep. The wakefulness period (4–13 breaths) was selected from the period that was closest in time to the sleep analysis period during which the retropalatal airway was clearly visible and the respiratory signal was free from swallowing. In sixteen of the eighteen subjects, the wakefulness period was taken from the short period of wakefulness before the sleep study. Two subjects were unable to stay awake long enough for collection of the wakefulness data before the sleep data. In these subjects, the wakefulness period data were taken from the postsleep period data. In four subjects (subjects CB, BW, KC, and RH), the number of

### 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>Neck Girth, cm</th>
<th>AHI, events/h</th>
<th>Arousal Index, events/h</th>
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<td>30</td>
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<td>66.36</td>
<td>21.7</td>
<td>33</td>
<td>0</td>
<td>1.3</td>
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<td>39</td>
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<td>75.00</td>
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<td>82.73</td>
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<tr>
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<td>122.73</td>
<td>42.0</td>
<td>45</td>
<td>60.0</td>
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F, female; M, male; BMI, body mass index; AHI, apnea/hypopnea index. *Subjects reported light, intermittent snoring. †Subjects studied with simultaneous esophageal pressure measurements.

which it was passed. A continuous image of the retropalatal lumen was obtained from a closed-circuit video camera (Endovision 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 (34). The images were also recorded onto videotape, along with the airflow signal that was modulated (FM-1 mod/demod, Wolf Industries) and recorded onto an audio track of the videotape.

Esophageal pressure (Pes). In a subgroup of four subjects, measurements of Pes were made. In these subjects a pressure-tipped catheter (model TC-500XG, Millar) was threaded through the mask and passed into the nostril opposite the one that contained the fiber-optic scope. The tip of the catheter was positioned in the mid-one-third of the esophagus, ~40 cm from the nares. A check that Pes reflected pleural pressure was made by asking the subjects to cough and sniff and ensuring that the respective pressure swings were positive and negative.

Protocol

Subjects were asked to report to the laboratory 1 h before their normal sleep time. Sleep-staging electrodes and respiratory bands were attached, and the subject then lay supine on the bed. For the subjects in whom Pes was measured, local anesthesia was given and the pressure catheter was passed into the esophagus. In all subjects, the fiber-optic scope was passed into the upper airway and positioned as described above to visualize the retropalatal airway. 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 attached 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. The remaining transducers were then attached, and further fine adjustments to the orientation of the scope were made. The subject was then instructed to take several deep breaths; during this procedure, the position of the scope on the longitudinal pharyngeal axis was confirmed. After a period of wakefulness during which 3–5 min of data were collected for analysis (see Analysis below), the subject was allowed to go to sleep. If subjects reported that they normally breathed through the mouth while asleep, it was taped shut. Two subjects (subjects J B and SC) were unable to tolerate having their mouths taped. In these subjects we observed for any mouth breathing by ensuring there was no evidence of airflow leakage on the integrated airflow signal. During the sleep period the subject’s head position was fixed with the use of sand-filled bolsters.

All variables were monitored continuously throughout the study. During periods of wakefulness and stable sleep, when the retropalatal lumen was clearly visible (i.e., no secretions obscuring the image), the fiber-optic image and the respiratory signals were stored on-line on a computer.

Analysis

The wakefulness/sleep stage was scored according to standard criteria (22). Inspired VT, inspiratory time (TI), expiratory time (TE), total breath duration (TT), and inspired minute ventilation (VI) were calculated breath by breath during a period of wakefulness and a period of sleep. For each analysis period, the breaths were consecutive. The sleep period (7–16 breaths) was selected by taking the period of deepest stable non-rapid-eye-movement (NREM) sleep (preferably stage IV) during which there was no arousal from sleep or any increase in EEG frequency and during which the retropalatal lumen was clearly visible with no respiratory artifacts, e.g., swallowing, coughing, and so on. In six of the eighteen subjects, we were unable to identify a period of stable stage IV sleep during which the airway lumen was visible. In these subjects, analysis periods were taken from stable stage II NREM sleep. The wakefulness period (4–13 breaths) was selected from the period that was closest in time to the sleep analysis period during which the retropalatal airway was clearly visible and the respiratory signal was free from swallowing. In sixteen of the eighteen subjects, the wakefulness period was taken from the short period of wakefulness before the sleep study. Two subjects were unable to stay awake long enough for collection of the wakefulness data before the sleep data. In these subjects, the wakefulness period data were taken from the postsleep period data. In four subjects (subjects CB, BW, KC, and RH), the number of
consecutive wakefulness breaths available for analysis was
limited due to excess secretions that prevented visualization
of the retropalatal lumen and produced discomfort and fre-
quent swallowing.

During the period of sleep used for analysis, the occurrence
of airflow limitation was assessed by an experienced observer
from the profile of the airflow trace on the paper record.
Inspiratory flow limitation was considered to be present if the
inspiratory flow was "flattened" compared with that which
occurred during wakefulness or if snoring occurred.

Analysis of retropalatal CSA. The retropalatal CSA was
obtained for each digitized frame (5 frames/s) by manually
outlining the retropalatal lumen by using appropriate com-
puter software (Sigma Scan, Jandel). During this process, the
investigator was blinded to the phase of respiration. An
example of an outlined image is shown in Fig. 1. Before this
study, we validated our ability to outline an image reproduc-
ibly. In this validation, the CSA of a tube with approximately
the same CSA as the retropalatal airway was outlined 10
times by the same investigator. For this exercise the coeffi-
cient of variation was 10%.

For each breath, the CSA of the retropalatal lumen at the
start of inspiration was defined as 100%, and the within-
breath changes of luminal CSA were referenced to this
measurement. In a subgroup of four subjects, in whom Pes
was measured, the relative changes in CSA were validated
against absolute changes in CSA. The absolute changes in
CSA were calculated by using the dimensions of the pressure
catheter as a reference (II). The CSA was measured at fixed
points within inspiration and expiration (0, 25, 50, 75, and
100% of inspiratory and expiratory duration). At the transi-
tion between inspiration and expiration, the frame during
which flow crossed zero was defined as the end of inspiration
(100%), and the subsequent digitized frame (i.e., 0.2 s later)
was used as the start of expiration (0%). For the purposes of
presentation, the subjects were divided into groups (gp1-
gp3) on the basis of the apnea/hypopnea index (AHI; AHI gp1 =
<1 event/h of sleep; AHI gp2 = >1 but <5 events/h of sleep;
AHI gp3 = >5 events/h of sleep) and on the basis of body mass
index (BMI; BMI gp1 = <25 kg/m²; BMI gp2 = >25 but <30
kg/m²; BMI gp3 = >30 kg/m²).

For the subjects in whom Pes was measured (n = 4), the
changes in retropalatal CSA were compared with the changes
in Pes. The analysis period for this comparison was the same
as that described above.

Statistical analysis. All statistical analyses were per-
formed on the complete data sets of 18 subjects. Comparison
of the mean values of respiratory variables, VT, Ti, Te, Tr,
and Vt, between the wakefulness and sleep conditions was
performed using a one-factor analysis of variance. Signifi-
cant within-breath changes in CSA were tested for separately
during wakefulness and sleep by using a one-factor analy-
sis of variance; post hoc comparison of the CSA at each time
period throughout inspiration and expiration with that occur-
ring at the start of inspiration was performed by using
Fisher's least significant difference statistic.

A stepwise regression model was used to test the statistical
dependence of retropalatal CSA on age and two conventional
markers of sleep-disordered breathing, AHI and BMI. A
separate analysis was performed at each of the four time
periods within inspiration and the five time periods during
expiration.

RESULTS

All subjects had periods of regular breathing during
wakefulness and sleep during which clear pictures of
the upper airway were obtained. In one subject (subject
DW) we were unable to measure Pes due to technical
problems; however, this did not affect our ability to use
the dimensions of the pressure catheter to calculate
absolute CSA. In one subject (subject SM), the sleep-
related changes of retropalatal CSA were atypical; this
subject was therefore not included in the group analy-
ysis, and these data are presented separately.

Respiratory Measurements During Wakefulness
and NREM Sleep

The group mean levels for each respiratory variable
during wakefulness and NREM sleep are shown in
Table 2. NREM sleep was associated with a significant
reduction in Vt compared with wakefulness (P = 0.012).
The sleep-related fall in ventilation was associated
with a significant sleep-related prolongation of Ti (P =
0.015).

During sleep, in 10 of the 18 subjects studied, evi-
dence of inspiratory flow limitation occurred. In two
subjects (subjects SC and DH) there was no evidence of
inspiratory flow limitation during the period of regular
breathing used for analysis; however, during other
parts of the night snoring did occur.

Within-Breath Changes in Retropalatal CSA During
Wakefulness and NREM Sleep

Examples of the changes in retropalatal CSA during
wakefulness and sleep, in one normal subject (subject
PS) and one patient with mild sleep-disordered breath-
ing (subject KC), are shown in Fig. 2. Note that, during

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Fig. 1. An example of a fiber-optic image
of retropalatal airway (B) with anatomic
landmarks marked (A). B: the epiglottis
can be clearly seen in pharyngeal lumen;
A: the unlabeled outlined structure oppo-
site epiglottis is the "fused" appearance of
corniculate cartilages and part of aryteno-
epiglottic fold. Outline of pharyngeal lu-
men (used to calculate cross-sectional area
(CSA)) is indicated in A.
wakefulness, the changes in the CSA were minimal. In contrast, during sleep, narrowing of the retropalatal airway occurred during inspiration; this was followed by an increase in CSA during the transition from inspiration to expiration and a subsequent gradual decrease in CSA during late expiration. Similar patterns are seen in the normal subject and the patient with mild sleep-disordered breathing; however, the magnitude of the changes is much smaller in the normal subject compared with in the patient with sleep-disordered breathing.

Table 2. Respiratory variables during wakefulness and sleep

<table>
<thead>
<tr>
<th>Variable</th>
<th>Wakefulness</th>
<th>NREM Sleep</th>
</tr>
</thead>
<tbody>
<tr>
<td>V̇I, l/min</td>
<td>8.35 ± 0.55</td>
<td>6.18 ± 0.62</td>
</tr>
<tr>
<td>VT, liter</td>
<td>0.53 ± 0.03</td>
<td>0.41 ± 0.04</td>
</tr>
<tr>
<td>TT, s</td>
<td>3.77 ± 0.16</td>
<td>3.94 ± 0.15</td>
</tr>
<tr>
<td>TI, s</td>
<td>1.54 ± 0.09</td>
<td>1.80 ± 0.11</td>
</tr>
<tr>
<td>TE, s</td>
<td>2.22 ± 0.12</td>
<td>2.12 ± 0.08</td>
</tr>
</tbody>
</table>

Values are means ± SE; n = 18 subjects. NREM, non-rapid eye movement; V̇I, inspired minute ventilation; VT, inspired tidal volume; TT, total breath duration; TI, inspiratory time; TE, expiratory time.

For each individual, the within-breath changes in the CSA of the retropalatal airway during wakefulness are shown in the first three panels of Fig. 3A. In the left panels, the subjects are divided into groups on the basis of AH1 and in the right panels on the basis of BMI. The mean (±SE) values for each group are shown in the bottom panel. The changes during sleep are shown in Fig. 3B. For all subjects during wakefulness (n = 18), compared with the CSA at the start of inspiration, the changes in retropalatal CSA were significant only during early expiration when the airway became wider [group mean: expiration, 0% = 112.55 ± 3.18 (SE)% (P < 0.01); 25% = 122.78 ± 6.17% (P < 0.001); 50% = 110.64 ± 3.80% (P < 0.05)]. In contrast, during sleep, the retropalatal CSA narrowed significantly during inspiration [group mean: inspiration, 25% = 75.25 ± 6.00% (P < 0.05); 50% = 66.70 ± 7.71% (P < 0.01); 75% = 64.61 ± 8.08% (P < 0.01)] and widened significantly during early expiration [group mean: expiration, 0% = 126.81 ± 11.77% (P < 0.05); 25% = 125.31 ± 6.92% (P < 0.05)]. The expiratory-related increase in CSA was followed by narrowing, such that the caliber of the airway was returned to “baseline” before the subse-

Fig. 2. Examples of retropalatal CSA (●) and respiratory airflow (V̇; ○) in 1 normal subject (subject PS; A and C) and 1 subject with mild sleep-disordered breathing (subject KC; B and D) during wakefulness (A and B) and sleep (C and D). Measurements of CSA are expressed as %maximum CSA that occurred during 2 breaths shown. Fiber-optic images illustrate retropalatal CSA at different phases of respiratory cycle.
quent inspiration (group mean: 100% of expiration = 98.57 ± 3.07%).

Within the group of normal subjects and patients studied, the sleep-related changes in retropalatal CSA appeared to be more pronounced in the patients with significant sleep-disordered breathing compared with the normal subjects. On the other hand, the patients with relatively low AHI had similar changes in CSA to those of more severely apneic subjects. When the subjects were divided according to BMI, changes in CSA were smaller in the nonobese compared with the most obese subjects, although in terms of this index, subjects with moderate BMI were similar to the normal subjects.

Stepwise regression analysis of data from all subjects revealed that BMI was a better predictor of the sleep-related changes in airway caliber than AHI. During early and late inspiration, airway narrowing was significantly dependent on BMI (inspiration: 25%, P = 0.02; 75%, P = 0.02; 100%, P = 0.01); during expiration the changes in CSA were significantly dependent on BMI only during early expiration (expiration: 25%, P = 0.03). The sleep-related changes in CSA were significantly dependent on AHI only at the beginning of expiration (expiration: 0%, P = 0.04). During wakefulness, neither BMI nor AHI had any significant predictive value with respect to changes in CSA at any point during the respiratory cycle. Age was not a significant predictor of changes in CSA, during wakefulness or sleep.

In one subject (subject SM), the sleep-related changes of the retropalatal CSA were atypical. The sleep-related within-breath changes in retropalatal CSA in this individual are shown in Fig. 4. Mean retropalatal...
The purpose of the present study was to investigate the sleep-related changes in upper airway caliber throughout the respiratory cycle (i.e., during inspiration and expiration) within a population comprising normal subjects and patients with varying degrees of sleep-disordered breathing. The main findings of our study were that 1) during wakefulness, there were

During sleep, the CSA at end expiration returned to the same level as that occurring at the start of inspiration. These findings validate our use of normalization to compare relative changes in CSA across subjects.

Pattern of Retropalatal Narrowing: Lateral vs. Anterior/ Posterior (AP)

Eleven subjects showed substantial narrowing of the retropalatal CSA during inspiration (i.e., >80%). In these subjects, the pattern of sleep-related inspiratory pharyngeal narrowing was variable. In seven of the subjects, the magnitude of airway narrowing was similar in the AP and lateral dimensions. In four of these, the AP and lateral narrowing occurred simultaneously, in two the AP narrowing occurred first, and in the remaining subject lateral narrowing occurred first. In three subjects, the airway narrowing was clearly predominantly lateral, and in one it was predominantly AP.

Relationship of Retropalatal Narrowing vs. Pes

The changes in retropalatal CSA and Pes that occurred during wakefulness and sleep are shown for three subjects in Fig. 6. Notice that, during sleep, within each subject, inspiratory-related narrowing was associated with a more negative Pes. Interestingly, however, narrowing during expiration was not associated with equivalent changes in Pes. The expiratory dissociation of changes in CSA and Pes was clearly seen during sleep in two subjects (subjects RH and LN).

**DISCUSSION**

Comparison between the absolute and relative changes in CSA is shown for four subjects in Fig. 5. Note that when the CSA is expressed in square millimeters the relative within-breath changes of the airway luminal size are preserved. In two of the subjects, sleep-related changes in the absolute CSA occurred at the start of inspiration; however, in one there was a reduction in airway size and in the other, an increase.
statistically significant within-breath changes in retro-palatal CSA during expiration only; 2) during sleep, there were significant changes in inspiratory and expiratory CSA; the minimum CSA occurred at midinspiration, and the maximum CSA occurred at the beginning of expiration; and 3) subjects with an increased BMI had the largest changes in CSA.

Validity of Techniques and Methodology

Fiber-optic endoscopy has several limitations that need to be considered in an interpretation of the findings of the present study. First, we were unable to measure absolute CSA in all subjects. Previously, several methods have been used to calibrate fiber-optic images of the upper airway lumen (11, 14, 16, 17). These approaches require visualization of a structure of known dimensions, such as a pressure catheter, or the angle formed by the vocal cords. In our study, we were not always able to visualize the vocal cords from the retropalatal level. However, in four subjects we were able to calculate the absolute CSA between wakefulness and sleep by using the Pes catheter. In these subjects, the absolute CSA of the airway showed the same pattern and magnitude of narrowing as the changes expressed as a percent; these results support our use of relative measurements of CSA. However, due to the small number of subjects, we were unable to compare our findings with a previous report in which sleep was associated with a reduction in the CSA of the pharyngeal lumen (33).

Our measurement of relative changes in CSA could have been influenced by any movement of the fiber-optic scope. To prevent this, the orientation of the fiber-optic scope was fixed by anchoring it to the mask, and images were analyzed only if there was judged to be no change in the relationship of the scope to anatomic landmarks in different planes (e.g., soft palate, epiglottis, vocal cords). In addition, in five subjects we assessed any potential caudal-rostral movement of the airway relative to the scope by observing the scope through the mouth during deep breathing. We did not see the scope move during slow or rapid deep breathing in any of these subjects. Furthermore, we found that the magnitude of the CSA changes was similar during periods of regular breathing and periods of breathing at a larger VT. Thus we are confident that the observed changes were real and not due to movement of the scope.

An important consideration in the present study was our ability to accurately and reproducibly detect the edge of the airway lumen. Each image was outlined manually. The edge of the soft palate was used to define the longitudinal level at which the CSA was calculated (Fig. 1). Breaths in which the airway lumen was not clearly visible were rejected; if there was any doubt, the image was independently analyzed by a second investigator. In addition, our validation identified a coefficient of variation of 10% in the outlining of an image of known diameter; as a result of this, we suggest that changes of <20% should be interpreted with caution. However, during sleep, the magnitude of the CSA changes were greater than this in most cases (Fig. 3B).

Finally, fiber-optic endoscopy does not allow simultaneous visualization of multiple anatomic levels of the pharyngeal airway. We chose to visualize the retropalatal airway for practical and theoretical reasons. Previous studies have indicated that this is the site of maximum narrowing in patients with sleep apnea (2, 20, 28). In addition, the soft palate is clearly visible at this level and provides an anatomic marker.

Dynamic Changes in Pharyngeal Patency During Eupnic Breathing

We have shown that the retropalatal lumen narrowed during inspiration, widened at the transition from inspiration to expiration (late inspiration to early expiration), and then narrowed again in expiration. During wakefulness, these changes were significant

Fig. 6. Changes in retropalatal CSA (■) and esophageal pressure (Pes; □) in 3 subjects (A and B, C and D, E and F) during wakefulness (A, C, and E) and sleep (B, D, and F). Measurements of CSA are expressed as %CSA that occurred at start of inspiration.
only at the start of expiration; during sleep, statistically significant changes occurred in both inspiration and expiration.

Previous studies have measured dynamic changes in airway caliber during wakefulness (17, 28, 29). Studies by using cine-computerized tomography scanning have shown that, in patients with sleep apnea, the smallest retropalatal CSA occurred at end expiration (28). Another study using fiber-optic imaging showed that, in awake nonsnoring subjects, the smallest retropalatal CSA occurred either at the beginning of inspiration or at the end of expiration. In our study, during wakefulness the minimum retropalatal CSA occurred during early inspiration (25% of inspiration), although this narrowing was not significant. This difference in findings between our study and the study using cine-computerized tomography scanning may be accounted for by differences in the severity of disease in the patients studied. Overall, the pattern of airway narrowing observed in our investigation during wakefulness was small compared with that occurring during sleep.

Influence of AHI and BMI on Pharyngeal Patency During NREM Sleep

In the present study, during sleep, patients with a higher AHI had greater changes in CSA throughout a breath (see Fig. 3B). These findings suggest that subjects with significant sleep apnea are more predisposed to sleep-related retropalatal airway changes (or, indeed, vice versa). However, interestingly the AHI was a significant predictor of changes in retropalatal CSA only during early expiration. The lack of relationship between inspiratory-related narrowing and AHI may have been due to the fact that, counting the number of apneas/hypopnea per hour of sleep may not be an accurate measurement of pharyngeal dynamics. For example, many episodes of hypopnea may be missed given the standard 4% desaturation requirement to score hypopnea used in our laboratory. Furthermore, the AHI given in Table 1 is an aggregate index reflecting the body position and sleep state distribution of a whole night; factors that are not controlled for among subjects. By contrast, our data were obtained over a short period under relatively standard conditions of supine NREM sleep. Clearly, a more relevant estimate of AHI would have been one obtained under these conditions.

We noted that BMI was a better predictor of sleep-related inspiratory airway narrowing than AHI. This may have been due to the fact that BMI, which is a major determinant of the susceptibility to upper airway obstruction during sleep, would be associated with factors likely to exert most influence during supine sleep. In patients with obstructive sleep apnea, increased pharyngeal fat deposits have been reported (9, 30, 31); these increased deposits presumably augment extraluminal pressure. Koenig and Thach (15) have shown, in anesthetized rabbits, that external mass loading of the upper airway increases inspiratory resistance. In humans, Ryan and Love (26) have shown that, during wakefulness, obese patients have a more collapsible pharyngeal airway. Taken together, these studies support the idea that, during inspiration, pharyngeal dynamics are influenced by body weight via cervical adipose tissue.

Both BMI and AHI were significant predictors of the increase in retropalatal CSA that occurred during expiration. However, the respective influence of AHI and BMI occurred at different time periods during expiration. It has been shown that, in patients with a high AHI, pharyngeal compliance is increased relative to normal subjects (26, 13). This may render the pharyngeal airway of these patients more responsive to the positive intraluminal pressure generated at the start of expiration, and the subsequent decrease in intraluminal pressure during midexpiration. This suggestion is supported by studies that have found that the upper airway may be more compliant during expiration compared with during inspiration (18, 24).

Sleep-related changes in retropalatal CSA varied among subjects, even in those with a similar AHI or BMI. Because of the wide variability of sleep-disordered breathing within the population of normal subjects and patients studied, we were not able to formally analyze our data by dividing our subjects into subgroups. It is likely that some of the variability in CSA within our study population may be due to other factors that we were unable to control for, such as different NREM sleep states, age, gender, and physiological variables such as muscular characteristics and vascular tone. We found that chronological age did not have a significant influence on the susceptibility of the airway to collapse. However, in the present study, we were unable to test for the effect of other factors due to our limited data set. It is likely that sleep state may have influenced retropalatal CSA because upper airway resistance is known to increase in stage IV sleep relative to stage II sleep (10). Similarly, gender may influence airway collapsibility, although interestingly, Rainer and White (21) found no significant difference between men and women in pharyngeal resistance measured during wakefulness. Finally, in patients with upper airway resistance syndrome, narrowing of the airway and the subsequent arousal from sleep occurs in the absence of apnea/hypopnea (6). In the present study, several patients had significant narrowing of the airway and a low AHI, which would be consistent with a diagnosis of upper airway resistance syndrome. However, by using the same statistical approach described for chronological age, we were unable to demonstrate any statistical effect of an arousal index (number of arousals per hour of sleep) on within-breath changes in CSA.

Sleep-Related Changes in Airway Shape

We have described airway caliber by measuring CSA. Previous studies have reported that the narrowing of the pharynx during wakefulness is mainly attributable to a reduction of the area in the lateral dimension (28, 30); however, another study has documented slightly larger changes in AP vs. lateral dimension (17). In the
present study, the pattern of narrowing varied across subjects. Our findings indicate that, although reductions in the lateral dimension of the airway may be the predominant site of narrowing in some patients, in others narrowing occurs primarily in the AP dimension. However, in the majority of subjects, we observed narrowing in both the AP and lateral dimensions.

Mechanisms of Dynamic Changes in CSA

The findings of this study show that the smallest retropalatal CSA occurred during inspiration. If the pharyngeal airway is thought of as a collapsible tube, these changes in CSA can be explained by changes in transmural pressure and/or compliance of the pharyngeal wall. During inspiration, upper airway intraluminal pressure will be reduced as intrathoracic pressure becomes more subatmospheric. Intraluminal pressure may also be decreased by the reduction of hydrostatic pressure associated with the acceleration of gas in a narrowed airway (the Bernoulli effect). These processes are likely to be more pronounced during sleep because the compliance of the pharyngeal wall is increased (4).

In the present study, we were unable to separate out the effects of any sleep-related increase in compliance vs. the effects of augmented collapsing pressures. Nevertheless, it is likely that both these factors contributed to the significant sleep-related inspiratory narrowing that occurred in the patients with more severe sleep apnea.

In this study we found that the largest retropalatal CSA occurred during early expiration. The subsequent decrease in CSA during the second half of expiration may have represented a passive return to the baseline CSA, reflecting the progressive decay of positive intraluminal pressure during expiration. Alternatively, expiration may have been associated with narrowing of the upper airway caused by active contraction of the pharyngeal constrictor muscles (7), changes in lung volume per se (3), or increasing thoracic caudal traction and increasing ventrolateral neck traction (35).

In conclusion, our study has shown that, during NREM sleep, eupnic breathing is associated with significant changes in airway caliber that occur during both inspiration and expiration and that these changes are greatest in patients with increased BMI. We suggest that these dynamic changes in airway CSA throughout the respiratory cycle may be important in inducing airway collapse during breaths preceding an obstructive apnea. In addition, we put forward the idea that the changes in expiratory CSA may have implications for the therapeutic treatment of obstructive sleep apnea by using positive pressure therapy.

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