Gender differences in upper airway compliance during NREM sleep: role of neck circumference

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Rowley, James A., Carrie S. Sanders, Brian R. Zahn, and M. Safwan Badr. Gender differences in upper airway compliance during NREM sleep: role of neck circumference. J Appl Physiol 92: 2535–2541, 2002. First published March 1, 2002; 10.1152/japplphysiol.00553.2001.—It has been proposed that the gender difference in sleep apnea prevalence is related to gender differences in upper airway structure and function. Because a smaller upper airway is felt to be related to gender differences in upper airway structure and function, we hypothesized that men would have smaller retropalatal cross-sectional area and higher compliance during sleep compared with women. Using upper airway imaging, we measured upper airway cross-sectional area and retropalatal compliance in wakefulness and non-rapid eye movement (NREM) sleep in 15 men and 15 women without sleep-disordered breathing. Cross-sectional area at the beginning of inspiration tended to be larger in men compared with women in both wakefulness [194.5 ± 21.3 vs. 138.8 ± 12.0 (SE) mm²] and NREM sleep (111.1 ± 17.6 vs. 83.3 ± 11.9 mm²; P = 0.058). There was no significant difference, however, after correction for body surface area. Retropalatal compliance also tended to be higher in men during both wakefulness (5.9 ± 1.4 vs. 3.1 ± 1.4 mm²/cmH₂O; P = 0.006) and NREM sleep (12.6 ± 2.7 vs. 4.7 ± 2.6 mm²/cmH₂O; P = 0.055). However, compliance was similar in men relative to women after correction for neck circumference. We conclude that the gender difference in retropalatal compliance is more accurately attributed to differences in neck circumference between the genders.

METHODS

The experimental protocol was approved by the Human Investigation Committee of the Wayne State University School of Medicine and the John D. Dingell Veterans Affairs Medical Center. Informed written consent was obtained from all subjects.

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 by using a pressure-tipped catheter (model TC-500XG, Millar), which was threaded though the mask (see Protocol for positioning).

The retropalatal lumen was visualized by using a pediatric fiber-optic bronchoscope (FB10X, Pentax). Topical short-acting anesthesia was applied as follows: first, 2% lidocaine was used. 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.
atomized into the pharynx through the mouth; second, 10% lidocaine spray was used to anesthetize both nares; and finally, a 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 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 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. The images were also recorded onto videotape, along with the airflow signal, which was modulated (FM-1 mod/demod, Wolfe Industries) and recorded onto an audio track of the videotape.

Protocol. All subjects were instructed to use 0.05% oxymetazoline hydrochloride (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. Sleep staging electrodes were attached, and the subjects then lay supine in the bed. Local anesthesia was given, and the pressure catheter was passed through one nostril. 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 retropalatal rim to measure pharyngeal pressure (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 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. After a period of wakefulness during which 3–5 min of data were collected for analysis (see below), the subjects were allowed to go to sleep. During the sleep period each 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, and, if achieved, slow-wave sleep. Data were acquired only during periods in which the retropalatal lumen was clearly visible (i.e., no secretions obscuring the image). The study was terminated after either 1 h of stage 2 sleep or after a period of slow-wave sleep.

Data analysis. Wakefulness/sleep stage was scored according to standardized criteria (17). Inspired Vt, inspiratory time (Ti), total breath time (TrTOT), breathing frequency, and inspired minute ventilation (Vi) were calculated breath by breath for 12–15 consecutive breaths during a period of wakefulness, stage 2 sleep, and, if obtained, slow wave sleep. Breath 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 retropalatal lumen was clearly visible.

The retropalatal CSA was obtained for each digitized frame (5 frames/s) by manually outlining the retropalatal lumen using computer software (SigmaScan, Jandel). During this process, the investigator was blinded to the phase of respiration. An example of an outlined image is shown in Fig. 1.

The reproducibility of this technique has been previously validated by our laboratory (29). 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 (22).

The CSAs obtained with use of this method were further analyzed as follows. First, the CSA was measured at the beginning of inspiration (CSAI; first frame after which flow crossed from negative to positive) and expiration (CSAE; first frame after which flow crossed from positive to negative). We defined the percent change in CSA (%ΔCSA) by the following equation: (CSAI-wake – CSAE-NREM)/CSAI-wake. Second, 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 (Fig. 2). As in our earlier studies, we defined Cua as the slope of the regression line that would be drawn through the plot of CSA vs. Pph.

Statistical analysis. Analyses were performed using SigmaStat software (Jandel). Comparisons of the mean values of VT, Vi, breathing frequency, Tt, TrTOT, CSAI, CSAE, and Cua were performed by using two-way analysis of variance with repeated measures, with sleep stage and gender as the factors. %ΔCSAI was compared between genders by using a t-test. If there were statistically significant differences between genders for a variable, analyses of covariance (ANCOVA) were performed for the parameter with gender as the factor of primary interest and neck circumference (NC) as the covariate.

RESULTS

We studied 30 subjects, 15 men and 15 women, who were recruited from the general population. None had sleep complaints before study, and none had sleep-disordered breathing during a baseline sleep study. There was no difference between the men and women
in age (women, 24.5 ± 4.0 yr vs. men, 27.0 ± 6.6 yr; \( P = \text{not significant (NS)} \)) or body mass index (BMI; women, 25.2 ± 5.8 kg/m\(^2\) vs. men, 25.9 ± 4.8 kg/m\(^2\)). However, for those subjects in which it was measured (14 men and 12 women), NC was larger in the men (women, 34.9 ± 4.5 cm vs. men, 39.7 ± 1.7 cm; \( P = 0.001 \)).

Ventilatory data are presented in Table 1. There was no effect of either gender or sleep stage on T\( \text{I}, \text{TOT} \) or 22.0 mm\(^2\) in women and men, respectively; CSA\( \text{E} \) was lower in men during wakefulness than in women (men, 17.6 mm\(^2\) vs. women, 18.6 mm\(^2\); \( P = 0.008 \)). There tended to be a difference in Cua between men and women during wakefulness and NREM sleep (\( P = 0.055 \)). However, we noted that there was one outlier in the women that could be affecting the data. Subject AB was a 27-yr-old woman with a BMI of 32.9 kg/m\(^2\), NC of 38 cm, and no evidence of flow limitation on baseline polysomnography. Removal of the data for this subject resulted in a group mean Cua for women of 2.1 ± 1.0 mm\(^2\)/cmH\(_2\)O in wakefulness and 2.3 ± 1.1 mm\(^2\)/cmH\(_2\)O in NREM. In the subsequent ANOVA, Cua was significantly increased in men compared with women (\( P = 0.002 \)) and in NREM sleep compared with wakefulness (\( P = 0.015 \)). There was also an interaction between the two factors, indicating that Cua was only higher in men during NREM sleep (\( P = 0.022 \)). However, because the men and women were not matched for NC, we performed an ANCOVA with Cua during NREM sleep as the variable to be compared and NC as the covariate. The data for subject AB were included in this analysis. After correction for NC in an ANCOVA, there was no significant difference in NREM Cua between the genders (\( P = 0.15 \)).

Because we were unable to correct for the effect of gender on Cua for NC by either ANCOVA, we performed an additional analysis. We regrouped the subjects based on NC instead of gender. We chose a NC of 37 cm to divide the groups because it has been shown that a NC above this value is associated with an increased risk of OSAS in both men and women (35). In this analysis, which included only those subjects with a NC measurement, nine subjects (1 man, 8 women) had a NC <37 cm; the mean Cua for these subjects was 2.5 ± 0.8 mm\(^2\)/cmH\(_2\)O in wakefulness and 3.2 ± 1.7 mm\(^2\)/cmH\(_2\)O during NREM sleep. There were 17 subjects with a NC >37 cm (13 men and 4 women); the

<table>
<thead>
<tr>
<th>Variable</th>
<th>Wake</th>
<th>NREM</th>
</tr>
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<tbody>
<tr>
<td>V( \text{I}, \text{l/min} )</td>
<td>7.5±0.8</td>
<td>7.5±0.9</td>
</tr>
<tr>
<td>V( \text{T}, \text{liters} )</td>
<td>0.39±0.02</td>
<td>0.48±0.005</td>
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<tr>
<td>f, l/s</td>
<td>17.1±1.1</td>
<td>16.4±1.4</td>
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<tr>
<td>T( \text{I}, \text{s} )</td>
<td>1.5±0.1</td>
<td>1.8±0.2</td>
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<tr>
<td>T( \text{TOT}, \text{s} )</td>
<td>3.5±0.2</td>
<td>4.2±0.4</td>
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Values are means ± SE. NREM, non-rapid eye movement; V\( \text{I} \), minute ventilation; V\( \text{T} \), tidal volume; f, breathing frequency; T\( \text{I} \), inspiratory time; T\( \text{TOT} \), total breath time. *\( P < 0.001 \) wake vs. NREM sleep.
mean Cua for these subjects was 6.5 ± 1.5 m²/cmH₂O in wakefulness and 11.9 ± 3.0 mm²/cmH₂O in NREM sleep. A repeated measures two-factor (NC and sleep stage) ANOVA found a significant effect of NC (P = 0.04) but not of sleep stage (P = NS).

DISCUSSION

The aim of the present study was to investigate the effect of gender on two measures of retropalatal structure and function: CSA and Cua. The important findings from this study were the following: 1) there was no difference in retropalatal CSA after correction of the CSA for body surface area; 2) retropalatal Cua was larger in men than women in during sleep, but this difference in Cua during sleep was not observed after correction for the larger NC in men; and 3) retropalatal Cua was higher in subjects with large NC. These findings indicate that a gender difference in Cua could contribute to the gender difference in OSAS prevalence. However, the gender difference in Cua may be more appropriately attributed to gender differences in NC and may not be an effect of gender per se.

Upper airway CSA and Cua. It has been hypothesized that a smaller upper airway would predispose the upper airway increased airway collapsibility (5). Our findings are similar to those of a previous investigation that showed that men had larger pharyngeal area during wakefulness but that this difference was not apparent after correction for body surface area (3). Other investigators have also shown no difference in CSA (11, 25). Our data extend these findings by showing no differences in CSA after correction for body surface area during NREM sleep. The weight of evidence indicates that there is not a gender difference in upper airway size during wakefulness or NREM sleep that explains the gender difference in sleep-disordered breathing.

Cua is a frequently discussed measure of upper airway function (1). A highly “compliant” upper airway is more likely to collapse, making the subject more prone to the development of sleep-disordered breathing. Previous studies have shown that the static Cua (calculated by measuring CSA over a wide range of externally applied pressure) is increased in subjects with sleep apnea compared with normal controls (7). In this study, we measured the changes in CSA over the range of Pph values seen in eupneic breathing. Using this methodology, we previously showed that retropalatal Cua increases during NREM sleep, a result that has been confirmed with the present data (22). In this work, we showed that Cua of the retropalatal airway is higher in men than in women in NREM sleep. However, the difference in Cua was not observed after correction for NC. Furthermore, after separation of the subjects into two groups based on a NC previously associated with the sleep-disordered breathing (37 cm)
NC has been shown to be an important determinant of OSA prevalence and severity (4, 28). In particular, in the Wisconsin Cohort Study, models of OSAS determinants that included NC showed no difference in OSAS prevalence between the genders and suggested that women would be more likely to have OSAS for similar NC (34, 35). If NC is an important marker for airway collapsibility, it is likely to be a surrogate measurement for the nonneuromuscular properties of the upper airway. Nonneuromuscular determinants of Cua could include the intrinsic properties of the muscles, connective tissue, bony structures, and fat. We and others have previously concluded that the nonneuromuscular properties of the upper airway are important determinants of retropalatal Cua (15, 21, 22). It has recently been shown, with the use of magnetic resonance imaging, that men had a larger degree of fat deposition at the level of the palate (32). Although NC was not correlated with pharyngeal soft tissue volume in this study, NC was larger in the male group. We believe that NC could be a surrogate marker for pharyngeal soft tissue and fat. It could also be a marker for other craniofacial characteristics of the airway, some of which have been shown to be different between the genders (10, 13, 24). Therefore, we speculate that differences in Cua could be secondary to differences in soft tissue density and craniofacial structure, as measured by NC, not gender.

A mechanism that explains how increased NC results in increased Cua cannot be elucidated by our data. However, there are potential explanations for the findings. The importance of the lateral pharyngeal walls in the pathogenesis of upper airway narrowing and obstruction has been emphasized (26). In particular, it has been suggested that the lateral walls are more compliant than other structures in the upper airway and that thicker walls are more compliant than thinner walls (27). Increased NC could indicate thicker lateral walls and, therefore, a more compliant airway. Second, because our methodology does not allow us to separate the relative contributions of the pressure intrinsic to the airway wall and the pressure surrounding the airway (see Limitations of the study), it is possible that an increased Cua may be due to an increase in the surrounding pressure of the upper airway. The increased NC, as a surrogate for increased soft tissue and fat, could indicate an increased pressure surrounding the upper airway and therefore increased compliance as measured by our methodology.

Our NC findings have important implications for the interpretation of gender-based studies. NC has been found to be larger in men compared with women in an epidemiological study (34), clinic-based populations (4, 19), and normal volunteers (23, 32). These studies provide evidence of an independent effect of gender on NC because NC was shown to be larger in men even after correction for BMI in one study (11) and found to be smaller in women despite a larger BMI in another (19). The evidence suggests that NC cannot be matched between genders, which has important implications for studies in upper airway physiology. Differences in NC will confound interpretation of results if there are differences between the genders, because the differences may be related to differences in the properties of the upper airway measured by NC and not gender per se. In other words, differences between genders may not be apparent if the genders could be matched for NC (34). Therefore, we believe that gender-comparison studies must be interpreted cautiously if there is no matching for NC between the two groups.

Limitations of the study. Fiber-optic endoscopy has several limitations that need to be considered when interpreting the findings (14, 22). The extensive instrumentation could effect upper airway mechanics because the nasal passages are blocked by the endoscope and pressure catheter. This could preferentially limit flow in smaller nostrils, presumably in women. However, we found no difference in the range of Pph values during eupneic breathing between either of the two groups used in the analysis (data not shown). Also, we provided upper airway anesthesia to ease the passage of the endoscope. However, we used short-acting lidocaine with a duration of action <20 min; data collection was not started until after this time.

Another major consideration is the ability to accurately and reproducibly detect the edge of the airway lumen. Although this process is operator dependent, we believe that the edge can be visualized with reasonable precision. To ensure this, only images in which the airway lumen was clearly visible were analyzed. In addition, only 12–15 images were analyzed per stage of sleep. Reasons for the limited number of breathing included the need to manually outline the pharyngeal lumen of each image and poor visualization of the pharyngeal lumen. Despite the small numbers, we believe that the images analyzed are representative because of the similarity of findings between the subjects and because the values for CSA are similar to those in the literature for the nasopharynx (7, 25).

The measurement of pharyngeal Cua requires several assumptions. First, we are not measuring true pharyngeal Cua because measurement of pharyngeal volume in sleeping, spontaneously breathing subjects is not feasible. We believe that pharyngeal CSA is a reasonable substitute, as have others who have measured Cua (7, 8). Second, an accurate Cua measurement using area requires that the pressure measured be at the same level as the changes in area, as we have done in this study. Third, the measurement of Cua assumes that the pressure being measured is a transmural pressure as the extraluminal pressure is assumed to be constant (8).

In addition, there are limitations to the interpretation of the results. First, the relative contributions to the transmural pressure (20), such as the pressure intrinsic to the airway wall (attributed mostly to the upper airway muscles) 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. Therefore, increased Cua may be due to a true increase in the compliance of the pharyngeal wall or to an increase in the surrounding pressure (33). Second, we cannot ascertain the relative contributions of neuromuscular activity and nonneuromuscular properties of the upper airway. Therefore, we cannot be certain that the differences in Cua are not secondary to differences in neuromuscular activity between the groups analyzed. Finally, our method makes assumptions regarding the relationship between inspiratory flow, CSA, and Cua, but the exact relationships between these variables are not known and cannot be ascertained in our model. In particular, the method assumes that the starting CSA of each breath does not influence the measured Cua; in other words, that a larger CSA is not associated with a larger Cua. We do not believe this to be the case, because tube law would predict that a larger CSA is associated with a smaller static Cua, which has been confirmed experimentally (7, 9).

It must be noted that we made pharyngeal compliance measurements over a small range of Pph values ($\sim 4–5$ cmH$_2$O) because we were specifically interested in studying the effect of sleep on Cua during eupneic breathing. Thus the compliance measurements may be different from those made by experimentally manipulating the Pph with externally applied pressure over a larger range of pressures ($\sim 10–20$ cmH$_2$O) (6–8). By measuring Cua in this fashion in the static upper airway, it has been observed that the pharyngeal Cua changes with the pharyngeal CSA (6–8). 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.

Although the men and women were similar in age and BMI, we did not specifically match the subjects for these parameters during our selection process. In addition, it should be noted that the mean BMI in both groups is borderline normal at 25 kg/m$^2$. It could be argued that subjects with this BMI are not normal; however, we note that no subject had symptoms of sleep-disordered breathing, nor were signs of sleep-disordered breathing noted on baseline polysomnography in any subject. We did not study the women during a specific phase of the menstrual cycle. This is in contrast to most previous investigators, who have generally studied women during the follicular stage of the menstrual cycle. We chose not to study women at a particular phase of the menstrual cycle for several reasons. First, there is no evidence that the phase of the menstrual cycle influences upper airway structure or size. Second, recent data from our laboratory indicated no menstrual phase difference in the development of central apneas in response to a hypocapnic stimulus (37). Finally, there is increasing evidence that the differences between men and women with regard to ventilation and sleep-disordered breathing is due to the influence of testosterone, not progesterone (12, 31, 37). For these reasons, we do not believe that there would have been a different result if we had systematically studied our female subjects during a specific phase of the menstrual cycle.

Finally, our results cannot be generalized to the population as a whole for two reasons. First, the subjects were self-selected volunteers because of the invasive nature of the testing. Second, the sample size is relatively small (30 subjects total). Although the sample size is consistent with others in the field who have studied gender differences (15, 16, 23), caution is recommended in interpreting our findings, because the data may not be representative of the whole population.

In summary, we have shown that the upper airway of men is more compliant than that of women with no difference in upper airway size after correction for body surface area. These results are consistent with other studies comparing men and women and support the hypothesis that differences in upper airway function contribute to the different prevalence of OSAS in men and women. However, we also found that there was no difference between men and women after correction for differences in NC. We speculate that Cua differs between genders because of gender differences in the nonneuromuscular properties of the upper airway, specifically differences in soft tissue volume and fat distribution, that are indirectly measured by NC. Future studies should be directed at further elucidating the mechanisms for the difference in collapsibility between men and women, with cautious interpretation of positive findings given that it will likely be difficult to match the genders for NC.

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