Influence of gender on upper airway mechanics: upper airway resistance and Pcrit

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Rowley, James A., Xusong Zhou, Isabelle Vergine, Mahdi A. Shkoukani, and M. Safwan Badr. Influence of gender on upper airway mechanics: upper airway resistance and Pcrit. J Appl Physiol 91: 2248–2254, 2001.—It has been proposed that the difference in sleep apnea prevalence is related to gender differences in upper airway anatomy and physiology. To explain the prevalence difference, we hypothesized that men would have an increased upper airway resistance and increased critical closing pressure (Pcrit) compared with women. In protocol 1, resistance at two points, fixed flow of 0.2 l/s (RL) and peak flow (Rpk), was measured in 33 men and 27 women without significant sleep-disordered breathing. We found no difference in either RL (–6.9 ± 5.9 vs. –8.6 ± 8.2 cmH2O) or Rpk (–9.3 ± 6.8 vs. –10.0 ± 11.9 cmH2O) between the men and women. A multiple linear regression to correct for the effects of age and body mass index confirmed that gender had no effect on resistance. In protocol 2, Pcrit was measured in eight men and eight women without sleep-disordered breathing. We found no difference in Pcrit (–10.4 ± 3.1 vs. –8.8 ± 2.7 cmH2O) between men and women. We conclude that there are no significant differences in collapsibility between men and women. We present an unifying hypothesis to explain the divergent findings of gender differences in upper airway physiology.

The obstructive sleep apnea syndrome (OSAS) is a common disorder characterized by recurrent upper airway collapse and obstruction. Upper airway structure and function are believed to be primary determinants of the degree of upper airway collapsibility. Gender differences in upper airway structure and function are believed to explain the clear male predominance of OSAS in the general population (11, 27). Upper airway collapsibility can be measured in several ways. Most researchers have focused on pharyngeal resistance, an indirect measure of upper airway caliber. During eupneic breathing, Trinder et al. (24) showed that there was no difference in pharyngeal resistance between men and women until the onset of slow-wave sleep, at which time men had a larger pharyngeal resistance than women (25). Recently, Pillar et al. (9) demonstrated that men had larger increases in pharyngeal resistance during inspiratory resistance loading than women. Both these studies suggest that the upper airway of men is more susceptible to closure during normal sleep especially if there is an added inspiratory load during sleep compared with women.

Another measure of upper airway collapsibility is critical closing pressure (Pcrit). The concept of Pcrit arises from modeling the upper airway as a simple collapsible tube (6). In this model, Pcrit is the level of nasal pressure below which the pharynx collapses. The advantage of this model is that it gives a global measure of upper airway collapsibility that includes both the structural and neuromuscular factors that determine upper airway collapsibility (12, 14). Although Pcrit has been compared between subjects with and without sleep apnea (5), there have been no reports on differences in Pcrit with gender.

Therefore, to gain further insight into the mechanisms that may explain the gender difference in sleep-disordered breathing, we examined the effect of gender on two measures of upper airway mechanics that have been previously shown to characterize upper airway mechanics and function: pharyngeal resistance and Pcrit. In particular, we hypothesized that 1) pharyngeal resistance during sleep would be larger in men and 2) Pcrit would be higher (airway more susceptible to collapse) in men compared with women.

METHODS

The experimental protocols described below were 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

For both resistance and Pcrit protocols, the following parameters were measured in all subjects. Standard sleep pa-
rameters were recorded (model 7-B, Grass) by using the international 10–20 system of electrode placement. Airflow was measured by a pneumotachometer (model 3700A, Hans Rudolph) attached to a nasal mask. Tidal volume was obtained from the integrated airflow signal. Supraglottic airway pressures were measured with a pressure-tipped catheter (model TC-500XG, Millar) threaded through the mask and positioned in the oropharynx just below the base of the tongue. Correct placement was verified by visually inspecting the catheter’s position in the oropharynx.

Protocol 1: Measurement of Upper Airway Resistance

Data analysis. Measurements of upper airway resistance (Rua) were collected from studies performed on 33 men and 27 women. These subjects had either no sleep complaints or mild snoring on history. Studies in which apneas and hypopneas were demonstrated were excluded from analysis. In the majority of subjects (85%), breaths for analysis were chosen from a 5-min segment of stable stage 2 sleep. For the remaining subjects, a total of 5 min of stable stage 2 sleep was chosen from multiple segments. Airflow and supraglottic pressure were recorded with Biobench data acquisition software (National Instruments, Austin, TX) on a separate computer. For each breath, a pressure-flow loop was generated, from which resistance was measured at two points. Resistance at a fixed flow of 0.2 l/s (RL) was computed as a numeric representation of the linear part of the pressure-flow loop. Resistance at peak airflow (Rpk) was computed at maximal airflow in non-flow-limited breaths or maximal flow in flow-limited breaths. Each loop was also analyzed for the presence of inspiratory flow limitation (IFL) (Fig. 1). 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 was calculated as the number of IFL breaths divided by total breaths. Approximately 50–100 breaths were analyzed per subject.

Statistical analysis. A simple \( t \)-test was used to compare men and women for age, body mass index (BMI), neck circumference (NC), Rt, and Rpk. Multiple linear regression was utilized to determine whether gender, age, BMI, or NC predicted the Rt and Rpk during non-rapid eye movement (NREM) sleep. Because neither Rt nor Rpk was normally distributed, we first transformed the values to the natural logarithm. We used multiple logistic regression analysis to determine whether gender, age, BMI, NC, or Rt predicted whether a subject had >10% of the analyzed breaths showing flow limitation.

Protocol 2: Measurement of Pcrit

Measurement of Pcrit was performed in eight men and eight women recruited from the general population. The subjects were free of any sleep complaints, including snoring. If, during the course of the study, the subject demonstrated sleep-disordered breathing, the study was terminated because we were interested in studying only normal subjects. An additional 10 subjects were studied but either did not achieve the study requirements of more than five negative-pressure trials and complete airway occlusion (8 subjects) or had technical problems precluding the analysis of data (2 subjects). In addition to the above measurements, pressure was also monitored at the nasal mask (Pn) in each subject. Pcrit measurements were performed in a manner similar to a previously published report on this measurement (18).

Experimental setup. The pneumotachometer was attached to a Y-shaped circuit with two balloon valves. The first balloon valve, when open, allowed the subject to breathe room air (Pn = 0 cmH₂O). The other was connected to a negative-pressure generator (modified REM-Star, Respironics, Murrysville, PA). When this valve was opened, a subatmospheric pressure was generated in the upper airway as indicated by a decrease in Pn. The level of subatmospheric pressure generated could be preset on the modified REM-Star unit. This system allowed investigators to manually switch between atmospheric pressure and negative pressure. In all trials, negative pressure was applied and terminated at the end of expiration. The dead space of the mask and

Fig. 1. Pressure-flow loops illustrating a non-flow-limited (A) and a flow-limited (B) breath.
pneumotachometer when the patient was breathing at atmospheric pressure was 165 ml.

Protocol. All patients were monitored in the supine position and used a U-shaped pillow to maintain head and neck position. Patients were allowed to fall asleep breathing at atmospheric pressure. During periods of stable stage 2 sleep, Pn was abruptly reduced by the application of negative pressure at the end of expiration, maintained for two breaths, and then raised back to atmospheric. The first reduction in Pn was to −4 cmH₂O; Pn was subsequently reduced from atmospheric in 0.5-cmH₂O decrements at 1- to 2-min intervals (with a return to atmospheric after 2 breaths) until airflow ceased. Complete airway collapse was achieved in all subjects. Figure 2A illustrates a section of polysomnogram in which the reduction in Pn resulted in decreased flow, whereas Fig. 2B illustrates a section in which the reduction in Pn resulted in an apnea. It should be noted that, whereas previous investigators have decreased Pn for three breaths (18), in preliminary studies we found that subjects were aroused by the third breath during negative pressure. The major difference between the two studies was the type of subjects studied: the subjects in the Schwartz et al. (18) paper all had moderate to severe obstructive sleep apnea (OSA), whereas our patients had no sleep-disordered breathing. We found we could prevent these arousals by limiting the application of negative pressure to two breaths. However, if there was still an arousal from sleep secondary to the negative-pressure application, subjects were allowed to return to stable 2 sleep for several minutes before Pn was again reduced.

Data analysis. For each reduction in Pn, the second breath was analyzed. Pcrit was defined as the first measured Pn at which flow was zero (see Fig. 3). If there was more than one Pn at which flow was zero, the largest (most positive) Pn was used as the Pcrit value for the subject. In addition, analysis of the relationship between Pn and maximal inspiratory airflow (VImax) was performed as previously described (18). For these breaths, VImax was determined as the plateau in inspiratory flow as supraglottic pressure continued to fall (see arrow, Fig. 2A). For each subject, the relationship between VImax and Pn was determined, as illustrated for a representative woman (A) and man (B) in Fig. 3. The nasal resistance (Rn) was defined as the reciprocal of the slope of the relationship between VImax and Pn.

Statistical analysis. Simple t-tests were used to compare age, BMI, NC, Pcrit, and Rn between men and women. Our sample size of 16 subjects (8 men and 8 women) was chosen to detect a gender difference in Pcrit of 4–5 cmH₂O. The difference of 4–5 cmH₂O was chosen because this is the approximate difference in Pcrit between subjects with the different types of sleep-disordered breathing that make up the clinical spectrum of OSA (i.e., normal vs. snoring subjects) (5).
RESULTS

R\text{ua}

We analyzed studies from 33 men and 27 women. The men and women did not differ significantly by age (30.1 ± 7.2 vs. 28.5 ± 6.6 yr) or BMI (26.3 ± 4.0 vs. 25.7 ± 6.0 kg/m\(^2\)). However, the men had a larger NC (39.6 ± 2.3 vs. 33.6 ± 3.5 cmH\(_2\)O; \(P < 0.001\)). With the use of a \(t\)-test for comparison, \(R_t\) was not different between men and women (\(-6.9 \pm 5.9 \text{ vs. } -8.6 \pm 8.2 \text{ cmH}_2\text{O}\cdot\text{l}^{-1}\cdot\text{s}, P = \text{not significant (NS)}\) nor was \(R_{pk}\) (\(-9.3 \pm 6.8 \text{ vs. } -10.0 \pm 11.9 \text{ cmH}_2\text{O}\cdot\text{l}^{-1}\cdot\text{s}; P = \text{NS}).

The results of the multiple linear regression are presented in Table 1. In both analyses, there was significant collinearity between gender and NC; because we were most interested in the effect of gender, NC was dropped from the regression analyses. Neither gender nor BMI was significant independent predictors of \(R_t\) or \(R_{pk}\). Increasing age was a predictor of both increased \(R_t\) (\(P = 0.002\)) and \(R_{pk}\) (\(P = 0.055\)). Both analyses had sufficient power to detect meaningful relationships (0.95 for \(R_t\), 0.80 for \(R_{pk}\)). However, whereas both were statistically significant regressions, the variance was low for both (\(R_t\): overall \(P = 0.006, R^2 = 0.2; R_{pk}\): overall \(P = 0.055, R^2 = 0.12\)).

We used multiple logistic regression analysis to determine whether gender, age, BMI, and \(R_t\) were independent predictors of a subject having >10% of analyzed breaths flow limited. NC was not included because of the collinearity with gender. Results are presented in Table 2. For our subjects, the presence of >10% flow-limited breaths was best predicted by the BMI and \(R_t\). Results indicate that, for each 1 kg/m\(^2\) increase in BMI, there is a 20% increase in the odds of having >10% flow-limited breathing during sleep (\(P = 0.015\)). For \(R_t\), each 1 cmH\(_2\)O l\(^{-1}\) s increase is associated with a 18% decrease in the odds of having >10% flow-limited breaths during sleep (\(P = 0.011\)).

\(P_{crit}\)

For the men and women, there were no significant differences for age (26.9 ± 6.2 vs. 24.5 ± 3.4 yr; \(P = \text{NS}\)) or BMI (26.3 ± 6.2 vs. 23.8 ± 4.9 kg/m\(^2\); \(P = \text{NS}\)). The mean group NC for men (38.5 ± 2.7 cmH\(_2\)O) was larger than in the group mean NC for women (31.9 ± 2.9 cmH\(_2\)O; \(P < 0.001\)). The comparison of \(P_{crit}\) and \(R_n\) between women and men is presented in Fig. 4. With the use of simple \(t\)-tests, there was no difference between men and women for \(P_{crit}\) (\(-10.4 ± 3.1 \text{ vs. } -8.8 ± 2.7 \text{ cmH}_2\text{O}; P = \text{NS}) or \(R_n\) (25.8 ± 9.4 vs. 20.6 ± 9.5 cmH\(_2\)O l\(^{-1}\) s; \(P = \text{NS}\)).

DISCUSSION

The aim of the present study was to investigate the influence of gender on \(R_{ua}\) and \(P_{crit}\). The important findings from this study were that 1) there was no effect of gender on \(R_{ua}\) and \(P_{crit}\), in two groups of young subjects without OSA and 2) the percentage of flow-limited breaths was best predicted by the BMI and \(R_t\). These findings indicate that the gender difference in OSA prevalence is not explained by gender differences in upper airway structure or collapsibility.

Influence of Gender on Upper Airway Structure and Function

Our study showed no gender difference in upper airway resistance during stable stage 2 NREM sleep. Our findings corroborate recent work demonstrating no gender difference in the changes in R\(_{ua}\) between the awake state and NREM sleep (22). Our data are in agreement with previous work demonstrating no gen-

Table 1. Multiple linear regression analysis of \(R_t\) and \(R_{pk}\)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Correlation Coefficient</th>
<th>SE</th>
<th>95% CI</th>
<th>(P) Value</th>
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<td>(R_t)</td>
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<td></td>
<td></td>
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<td>-0.17–0.67</td>
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<tr>
<td>(R_{pk})</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
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<td>0.021</td>
<td>-0.021–0.044</td>
<td>0.324</td>
</tr>
</tbody>
</table>

\(R_t\), resistance at flow of 0.2 l/s; \(R_{pk}\), resistance at peak flow; BMI, body mass index; 95% CI, 95% confidence intervals.

Fig. 4. Effect of gender on \(P_{crit}\) (top) and \(R_n\) (bottom). There was no significant difference between men and women for either \(P_{crit}\) or \(R_n\).
nder difference in Rua during stage 2 NREM sleep (24). This previous work also found an increased resistance in men during slow-wave sleep; however, our study does not address slow-wave sleep because some subjects did not reach slow-wave sleep during their studies. Given that resistance measured on the linear portion of the inspiratory flow-volume loop is reflective of upper airway caliber, these data would indicate that there is no gender difference in upper airway caliber during NREM sleep. This also corroborates our laboratory’s recent finding that retropalatal airway cross-sectional area (using a fiber-optic bronchoscope) was not different between women and men in either the awake state or NREM sleep (J. A. Rowley, C. S. Sanders, B. K. Zahn, and M. S. Badr, unpublished observations) and is consistent with other imaging studies performed during the awake state (4, 7).

We also found no gender difference in Pcrit, which suggests that the upper airway of men is not more prone to collapse than that of women. Our data on Pcrit as a measure of collapsibility contrast with recently published work in which changes in airway mechanics were measured by changes in pharyngeal pressure during inspiratory resistance loading (9). In this study, maximum Rua increased more in men relative to women when inspiratory resistive loading was applied; the authors concluded that the pharyngeal airway is more collapsible in men, who were also more likely to develop inspiratory flow limitation in response to resistive loading. Methodological differences may contribute to the difference in findings. First, some of the mechanical changes in upper airway function may be related to differences in lung volume changes rather than intrinsic differences in upper airway structure and function. An alternative explanation of the results would be that immediate load compensation is less impaired in women relative to men, leading to a larger reduction in lung volume in men, decreasing caudal traction and increasing pharyngeal collapsibility in men relative to women (12, 23). Second, collapsibility in the Pillar et al. (9) paper was inferred from changes in Rpk. However, upper airway caliber is best reflected by resistance measured on the linear portion of the pressure-flow curve. Linear resistance was not different between the genders in the work of Pillar et al., suggesting that the degree of upper airway narrowing was similar in the men and women. We believe that this previous finding of no difference in resistance at fixed flow is consistent with our data on Pcrit and Rn (which is a measure of airway narrowing above the collapsible segment).

The absence of a gender difference in the Pcrit can also be contrasted with our laboratory’s recent work demonstrating higher retropalatal compliance in normal men relative to women during NREM eupneic breathing; despite similar baseline cross-sectional areas (J. A. Rowley, C. S. Sanders, B. K. Zahn, and M. S. Badr, unpublished observations). The disparate findings indicate that different aspects of upper airway function are being measured by different methodologies and may provide insight into the different neuromuscular and nonneuromuscular factors influencing upper airway patency. For instance, our laboratory has previously concluded that nonneuromuscular properties of the upper airway are major determinants of both retropalatal and retroglossal compliance. This conclusion was made on the basis of our laboratory’s finding that retropalatal and retroglossal compliance during rapid eye movement sleep are not increased despite reduced neuromuscular activity (13, 15). Therefore, we believe that gender comparisons of compliance indicate differences in the nonneuromuscular properties of the upper airway.

Pcrit, on the other hand, is determined by both neuromuscular and nonneuromuscular properties. In the animal model, Pcrit has been shown to decrease with increases in tracheal and tongue tension (12), hypercapnia, and vagotomy (21). In humans, Pcrit has been shown to decrease after uvulopalatoplasty (which changes upper airway structure) (19) and has been shown to be influenced by nonneuromuscular structures when studied in a hypotonic state (18). Therefore, Pcrit should be influenced by both nonneuromuscular properties and the neuromuscular activity of the upper airway. Given the differences in upper airway structure between men and women (25), we would then have expected Pcrit to be more negative in women. We believe that our results differ because we determined Pcrit by abruptly exposing the upper airway to negative pressure. Rapid application of negative pressure results in reflex activation of the genioglossus. This electromyographic phenomenon has been hitherto void of mechanical consequence. We speculate that the application of negative pressure in our model challenges the upper airway by activating the negative-pressure reflex and that Pcrit in our model is primarily determined by the neuromuscular response to this challenge. If true, we believe that the lack of a gender difference in Pcrit measured by the rapid application of negative pressure could indicate that the reflex response to negative pressure is similar in men and women. Although the influence of gender on the negative-pressure reflex has not been systematically studied, there is anecdotal evidence to support the lack of difference between the genders (D. P. White, personal communication). This is also consistent with the data from Pillar et al. (9) that showed no gender difference in genioglossus response with inspiratory loading.

In summary, we propose a putative unifying hypothesis to explain the divergent findings regarding upper airway patency in men and women. Different factors may predominate under different conditions. First, nonneuromuscular factors, primarily pharyngeal wall structures and properties, are the likely dominant factor to explain within-breath changes in patency during breathing. We postulate that the anatomy of the male upper airway renders it more susceptible to within-breath narrowing under eupneic conditions. This postulate is supported by the findings that men have higher nasopharyngeal compliance compared with women during eupneic breathing (J. A. Rowley, C. S. Sanders, B. K. Zahn, and M. S. Badr, unpublished observations).
resistance measurement. However, there may be other determinants of upper airway obstruction. We avoided this limitation by measuring resistance in two points, both are on the linear part of the pressure-flow relationship; no measurements were taken from a point after flow limitation develops. Our measurements represent the slope of the linear part of the pressure-flow plot and hence, in fundamental differences between various methodologies used to measure collapsibility and the implications of the differences for sleep-disordered breathing are indicated. Because it has also been shown that men are more susceptible to hypopnic hypopneas than women (28), further investigations in how the neurochemical control of ventilation interplays with mechanical and structural factors could be helpful in determining potential mechanisms for the gender prevalence difference in OSA.

Limitations of the Study

Several limitations need to be addressed for proper interpretation of our data. First, we did not control for the specific phase of the menstrual cycle in either protocol. However, the consistency of the results regardless of the phase of the menstrual cycle, and between men and women, argues against a significant role for the menstrual phase. In addition, there is no evidence that nonneuromuscular properties of the upper airway are influenced by the menstrual cycle. Finally, evidence from our laboratory suggests that there is no significant difference at the apneic threshold or Rua in women between the luteal and follicular phase (28). Therefore, we consider the results in the women as representative of upper airway mechanics independent of the phase of the menstrual cycle.

Second, we used Rua to reflect upper airway caliber. However, resistance computations are invalid once flow limitation develops because pressure and flow become dissociated. We avoided this limitation by measuring resistance in two points, both are on the linear part of the pressure-flow relationship; no measurements were taken from a point after flow limitation had developed. Our measurements represent the slope of the linear part of the pressure-flow plot and hence, in our opinion, are an acceptable surrogate for caliber. However, there may be other determinants of upper airway caliber, such as the transmural pressure of the upper airway, that are not taken into account by the resistance measurement.

Finally, the validity of our findings depends on the validity of our method of applying the negative Pn to determine Pcrit. Pcrit is an extensively studied measure of upper airway function in both human and animal models and reflects the total upper airway, including both nasopharyngeal and oropharyngeal structures. Furthermore, Pcrit correlates with the clinical spectrum of sleep-disordered breathing and indicates the propensity of a subject’s airway to naturally collapse (or not collapse) during sleep (5, 6, 20). For these reasons, we believe that Pcrit is a valid measurement to make a comparison of upper airway collapsibility between genders. However, there are two methods to determine Pcrit: slow, sustained decreases in pressure (5, 20) or abrupt, nonsustained changes in pressure (8, 18). We chose the abrupt application method to eliminate the effects of sustained loading, including the recruitment of abdominal muscles (2), changes in arterial PCO2 (26), and reductions in lung volume (1). Clearly, the choice of method could have affected our results. There is evidence in awake subjects that the genioglossus response to sustained loading is different between men and women (10); therefore, it is possible that, if we had measured Pcrit by slow, sustained decreases in pressure, there would have been a gender difference in Pcrit. However, there is no evidence of a gender effect on the genioglossus during sustained loading during sleep, nor it is clear, given the other effects of sustained loading, that the genioglossus effect would be the predominant influence on the determination of Pcrit.

Conclusion

The gender difference in OSA prevalence could be secondary to differences in upper airway structure, function, or the neurochemical control of breathing. The evidence suggests there is no gender difference in upper airway size, whether measured directly by imaging methodologies or indirectly by Rua. Evidence also suggests that the degree of airway narrowing secondary to interventions such as negative pressure or resistance loading is not different between the genders. However, there remains a fundamental difference between the upper airway of men and women as evidenced by the increased susceptibility to the development of flow limitation and increased upper airway compliance in men compared with women. We believe that different methodological approaches to upper airway function are measuring different aspects of upper airway function. Further research to explore the fundamental differences between various methodologies used to measure collapsibility and the implications of the differences for sleep-disordered breathing are indicated. Because it has also been shown that men are more susceptible to hypopnic hypopneas than women (28), further investigations in how the neurochemical control of ventilation interplays with mechanical and structural factors could be helpful in determining potential mechanisms for the gender prevalence difference in OSA.
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