Physical Findings and the Risk for Obstructive Sleep Apnea

The Importance of Oropharyngeal Structures

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In this study, we hypothesized that anatomic abnormalities of the oropharynx, particularly narrowing of the airway by the lateral pharyngeal walls, tonsils, and tongue, would be associated with an increased likelihood for obstructive apnea among patients presenting to a sleep disorders center. To test this hypothesis, we used data from a cohort of 420 patients presenting to the Penn Center for Sleep Disorders. Associations between individual variables in the clinical evaluation model and sleep apnea as defined by a re-spiratory disturbance index greater than or equal to 15 events per hour were characterized by odds ratios (ORs) with 95% confidence intervals (CIs). Multivariable logistic regression was used to simultaneously estimate ORs for multiple variables and to control for other relevant patient characteristics. Results showed that narrowing of the airway by the lateral pharyngeal walls (OR = 2.5; 95% CI, 1.6–3.9) had the highest association with obstructive sleep apnea (OSA) followed by tonsillar enlargement (OR = 2.0; 95% CI, 1.0–3.8), enlargement of the uvula (OR = 1.9; 95% CI, 1.2–2.9), and tongue enlargement (OR = 1.8; 95% CI, 1.0–3.1). Low-lying palate, retrognathia, and overjet were not found to be significantly associated with OSA. Controlling for BMI and neck circumference, only lateral narrowing and enlargement of the tonsils maintained their significant (OR = 2.0 and 2.6, respectively). A subgroup analysis examining differences between male and female subjects showed that no oropharyngeal risk factor achieved significance in women while lateral narrowing was the sole independent risk factor in men. These findings suggest that enlargement of the oropharyngeal soft tissue structures, particularly the lateral pharyngeal walls, is associated with an increased likelihood of OSA among patients presenting to sleep disorders centers.

Obstructive sleep apnea (OSA) is a disease characterized by collapse of the pharyngeal airway resulting in repeated episodes of airflow cessation, oxygen desaturation, and sleep disruption (1). Upper airway anatomic factors are thought to play a critical role in the pathogenesis of airway closure in OSA (2–4). Individual patients with sleep apnea may have occlusion at different points along the upper airway, with the retropalatal region and retroglossal regions being implicated most frequently (5–7). Airway narrowing in these different anatomic regions is dependent on the surrounding craniofacial and soft tissue structures (3, 8).

There are a number of important anatomic risk factors for sleep-disordered breathing, and these factors directly relate to changes in the upper airway craniofacial and soft tissue structures. Morphologic changes in upper airway structure, neck circumference (NC), and obesity contribute to such factors. The soft tissues of the pharynx that are important in mediating airway size include the tonsils, soft palate, uvula, tongue, and the lateral pharyngeal walls (8). The major craniofacial bony structures that determine airway size are the mandible (9) and position of the hyoid bone (10). Abnormalities in any of these upper airway structures may adversely affect airway size, leading to obstructive apneas. Obesity is thought to affect airway size through deposition of fat within the soft tissue regions of the neck (11, 12) and perhaps by changing resistive loading on the upper airway to promote airway collapsibility (13). NC is a well-known risk factor for OSA (14) and may be a surrogate marker of regional fat distribution within the neck (15). We believe the interaction between these anatomic factors is important in mediating airway size and may have a strong impact on the development of OSA.

To date, little attention has been given to incorporating the examination and quantification of both craniofacial bony and soft tissue structures in the assessment of the risk for OSA despite the fact that these structures are intimately involved in the pathogenesis of the disease. A predictive model designed by Kushida and coworkers combined oral cavity measurements with measurements of body mass index (BMI) and NC to predict the presence of sleep apnea (as defined by an apnea–hypopnea index greater than 5 events per hour). Although this model appeared to have a high degree of sensitivity, most of its explanatory power arose from large differences in BMI among individuals with OSA (mean BMI = 33.6 kg/m^2) and controls (mean BMI = 23.2 kg/m^2) (16). Moreover, this model did not include upper airway soft tissue structures.

In addition, no study has examined the differences in anatomic risk factors that may affect the development of OSA in women as compared with men. Previous studies have described the increase in prevalence of OSA in men as compared with women (17) and previous work by our group identified sex as an independent risk factor for OSA (18). However, an analysis of the differences in the relative contribution of morphologic features of obesity and oropharyngeal structures between women and men has not been performed.

The purpose of this study is to identify the upper airway bony and soft tissue structural abnormalities determined by physical examination that are associated with an increased risk for OSA. We hypothesize that enlargement of the lateral pharyngeal walls, macroglassia, and tonsillar hypertrophy will be the primary structural risk factors for OSA because of their known effect on pharyngeal airway narrowing (19, 20). In addition, we hypothesize that evaluation of these variables will have additional predictive value over measurement of BMI and NC alone. The use of a logistic regression analysis that includes BMI and NC will allow us to determine the relative importance of the clinical variables in this study. Moreover, it may provide further insight into the relationship between obesity and oro-pharyngeal structures as they relate to the risk of developing OSA. The final purpose of this study is to deter-

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mine if there are significant differences in the anatomic risk factors for OSA (oropharyngeal structures) between male and female subjects. A subgroup analysis using the same logistic regression model will be applied to each sex group separately.

METHODS

Study Design

The patient population consisted of 420 patients referred for evaluation of a suspected sleep disorder. All patients were evaluated by a single physician at a regional university sleep center.

This study is a secondary historical cohort analysis of data obtained from the Clinical Research Support Data Base maintained by the Human Assessment and Biostatistics Core of the Special Center of Research in the Neurobiology of Sleep and Sleep Apnea (HL-60287-01) (Philadelphia, PA). It was prospective in that the population represented a sequential group of patients presenting to a sleep disorders center who underwent clinical evaluation and subsequent overnight polysomnography (PSG). However, the data were reviewed historically once all of the subject information (clinical features and polysomnography) was completed and entered into the database. Data were either collected on standardized forms or electronically obtained (PSG). Correlation was made between respiratory disturbance index (RDI) and clinical observations of upper airway soft tissue and craniofacial structures made at the time of initial evaluation. The demographic characteristics of the subjects with apnea (RDI $\geq$ 15) and subjects without apnea (RDI $<$ 15) are presented in Table 1.

Clinical Evaluation

Each patient's age, sex, height, and weight were recorded. BMI was calculated from the patient's height and weight in standard units of kilograms per meter-squared. NC was measured at the level of the thyroid cartilage.

During the morphometric evaluation, upper airway soft tissue structures were evaluated in the supine position whereas craniofacial bony structures were evaluated in the upright position. During these measurements, the patient's head was placed with the Frankfurt plane (defined by a line extending from the tragus of the ear to the inferior edge of the ipsilateral orbit) parallel to the floor in the upright position and perpendicular to the floor in the supine position. A single examiner performed all measurements. The mouth was opened maximally during the examination. The tongue remained in the mouth in a relaxed position during the soft tissue examination. The posterior pharynx was directly visualized with the aid of tongue blade, and phonation was initiated only to assess the full size of the uvula, soft palate, and lateral peritonsillar tissue when not fully visible without phonation. Tonsillar enlargement was defined as the presence of lateral impingement of greater than 50% of the posterior pharyngeal airspace (clinical grade 2+ or greater). The uvula was considered enlarged if it was more than 1.5 cm in length or $>$ 1.0 cm in width. The soft palate was considered low-lying if greater than one-third of the uvula extended below the level of the mandibular occlusal plane. Lateral peritonsillar narrowing was defined as impingement of greater than 25% of the pharyngeal space by the peritonsillar tissues, excluding the tonsils, which were evaluated independently as described above (*see* Figure 1). The tongue was considered enlarged if it was above the level of the mandibular occlusal plane (*see* Figure 2). Overjet was noted if there were greater than a 3-mm anterior–posterior distance between the upper and lower incisors during occlusion (*see* Figure 3). Retrognathia was defined as a $>$ 0.5-cm retroposition of the gnathion (the most inferior point in the contour of the chin) relative to the plane of the nasion (the deepest point of the superior aspect of the nasal bone) and subspinale (the deepest point on the premaxillary outer contour) (*see* Figure 4).

TABLE 1

SUBJECT DEMOGRAPHICS

Measurement	Subjects with Apnea (RDI $\geq$ 15) (*n = 158*)	Subjects without Apnea (RDI $\geq$ 15) (*n = 262*)	p Value
RDI, events per hour	39.3 $\pm$ 23.9	4.6 $\pm$ 4.4	$<$ 0.001
Age, yr	50.5 $\pm$ 13.9	49.0 $\pm$ 14.0	0.28
BMI, kg/m^2	35.9 $\pm$ 9.3	32.2 $\pm$ 9.0	$<$ 0.001
Neck size, in.	17.0 $\pm$ 1.6	15.7 $\pm$ 1.6	$<$ 0.001
Percent male	78.4	63.0	$<$ 0.001

Definition of abbreviations: BMI = body mass index; RDI = respiratory disturbance index.

Polysomnography

All patients underwent overnight polysomnography in the sleep center, using a model EEG 4418 A/K polygraph (Nihon Kohden, Tokyo, Japan) or Sandman (Mallinckrodt/Nellcor-Puritan-Bennet, Ottawa, ON, Canada) in standard fashion with a test time of 7 to 8 h. During the study, standard parameters were monitored including central, occipital, and frontal electroencephalograms, right and left electrooculograms, chin electromyogram, right and left anterior tibialis electromyograms, nasal and oral airflow via thermistor (single-port nasal thermistors; Nihon Kohden America, Irvine, CA), chest and abdominal wall motion (RESP-EZ belt; EPM Systems, Midlothian, VA), oxygen saturation (Biox 3700 pulse oximeter; Ohmeda, Boulder, CO), and electrocardiogram. Snoring was measured with a microphone (from Radio Shack; Tandy Corporation, Fort Worth, TX) attached to the lateral surface of the thyroid cartilage. Polysomnography records were scored by registered sleep technologists and reviewed by certified sleep physicians using the standard criteria of Rechtschaffen and Kales (21). Apneas were defined as cessation of oronasal airflow for at least 10 s, associated with oxygen desaturation of at least 4%. Hypopneas were defined as a greater than 50% reduction in oronasal airflow for at least 10 s. Apneas and hypopneas were designated as obstructive, mixed, or central according to the presence or absence of breathing efforts recorded during episodes. The RDI was calculated as the number of apneas and hypopneas per hour. An RDI $\geq$ 15 events per hour was used to define the presence of OSA in order to achieve separation between subject groups.

Statistical Analysis

The relative magnitudes of the association between individual variables and the likelihood of having an RDI $\geq$ 15 were compared by crude odds ratios (ORs). The precision of the estimated ORs was assessed by 95% confidence intervals (CIs). An OR of greater than 1 suggests an increased likelihood of having an RDI $\geq$ 15 relative to baseline prevalence. The association between specific morphometric characteristics and sleep apnea was considered significant when the lower bound of the 95% CI excluded 1.

The second step in the analysis involved estimating a multivariable logistic regression model containing all candidate variables. This model was used to examine the independent contribution of each morphometric variable while controlling for all variables and resulted in an adjusted OR and calculated 95% CI. A backward stepwise procedure was then used to eliminate morphometric variables one at a time by identifying those variables that did not independently contribute to the prediction of sleep apnea. As a final step, the backward stepwise algorithm was repeated except that first BMI, and then NC were forced into the regression model. This was done to determine if the morphometric variables retained their independent contribution to predicting sleep apnea after controlling for overall obesity (BMI) and a surrogate measure of neck fat distribution, NC. These analyses were then repeated stratified by sex. The statistics program used for the analysis was *SAS/STAT User's Guide Version 6*, 4th ed. (SAS Institute, Cary, NC).

RESULTS

The demographic characteristics of the apneic and nonapneic subjects are shown in Table 1. While the two groups were similar in age, the subjects with apnea had an increased BMI, increased NC, and higher percentage of males as compared with subjects without apnea. These findings are consistent with previous information on prevalence and risk factors in subjects with apnea (22).

The results of the logistic regression analyses are presented in Tables 2, 3, and 4. Table 2 displays (*1*) the number of patients

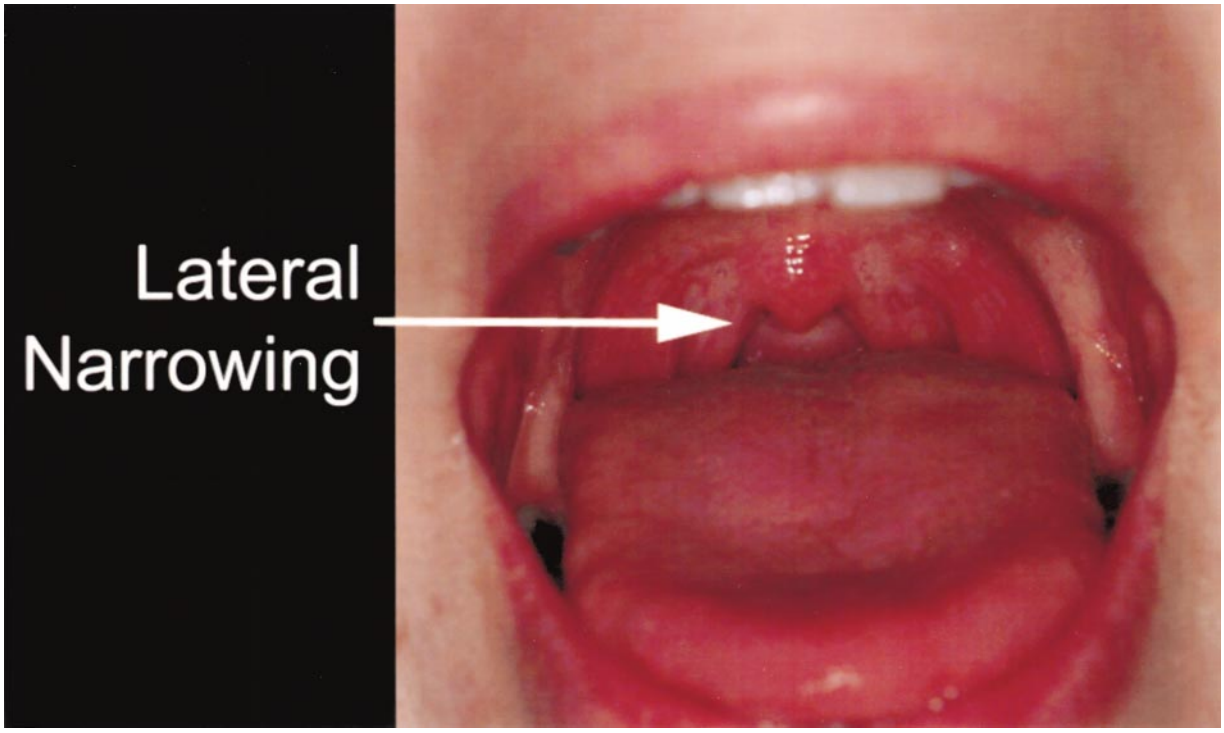

Figure 1. A view of the posterior pharynx demonstrating lateral narrowing. Lateral narrowing is defined by the presence of bands of tissue impinging into the observable posterior pharyngeal space.

found to have the structural risk factor, as well as the percentage having an RDI $\geq$ 15, (*2*) the crude (i.e., unadjusted) OR and 95% CI for each structural feature, (*3*) the adjusted OR for each structural risk factor when adjusted for all variables in the model, and (*4*) the adjusted ORs from reduced models with and without controlling for BMI and NC. Tables 3 and 4 display the results of the same analyses when considering female subjects (Table 3) and male subjects (Table 4) separately.

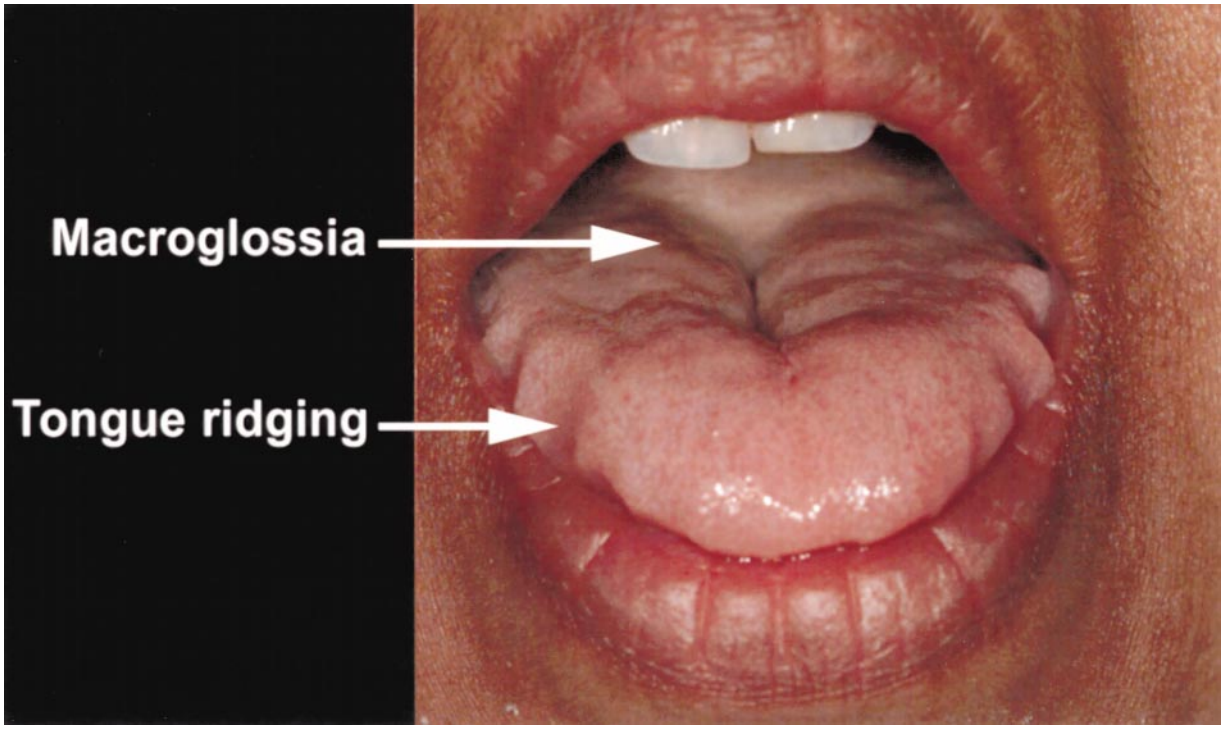

Figure 2. A view of the tongue during a maximal mouth opening/tongue extrusion (Mallampati) maneuver. The tongue is enlarged with its superior aspect well above the level of the mandibular occlusal plane, nearly filling the observable pharyngeal space. Tongue ridging, a common associated finding in macroglassia, is also demonstrated.

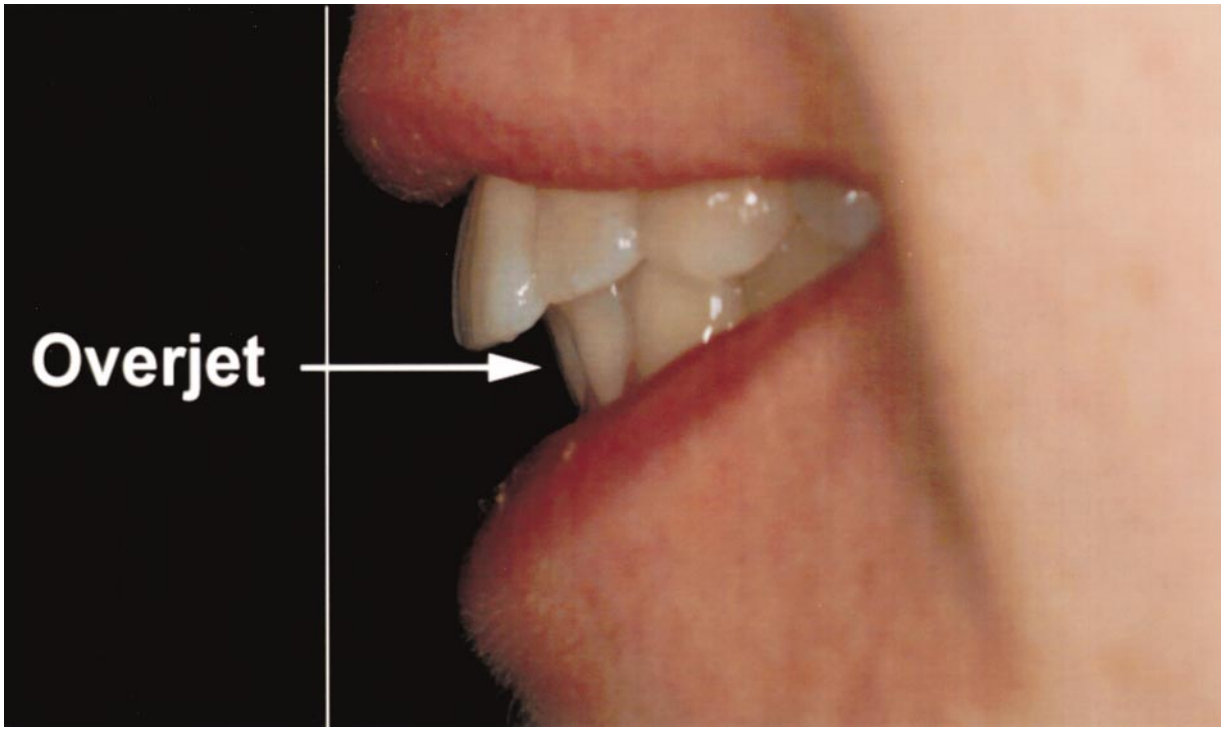

Figure 3. A view of the lateral profile of the jaw demonstrating a 3-mm overjet. Overjet is seen as the maxilla extrudes forward as compared with the mandible.

These results demonstrate that lateral narrowing as defined by a 25% or greater occlusion of the posterior pharyngeal space by the lateral peritonsillar tissue is a significant independent risk factor for the development of OSA with an adjusted OR of 2.6 (95% CI = 1.7–5.0). It remained significant even after controlling for BMI and NC with an OR of 2.0 (95% CI = 1.3–3.3).

Of the remaining soft tissue structures evaluated in this

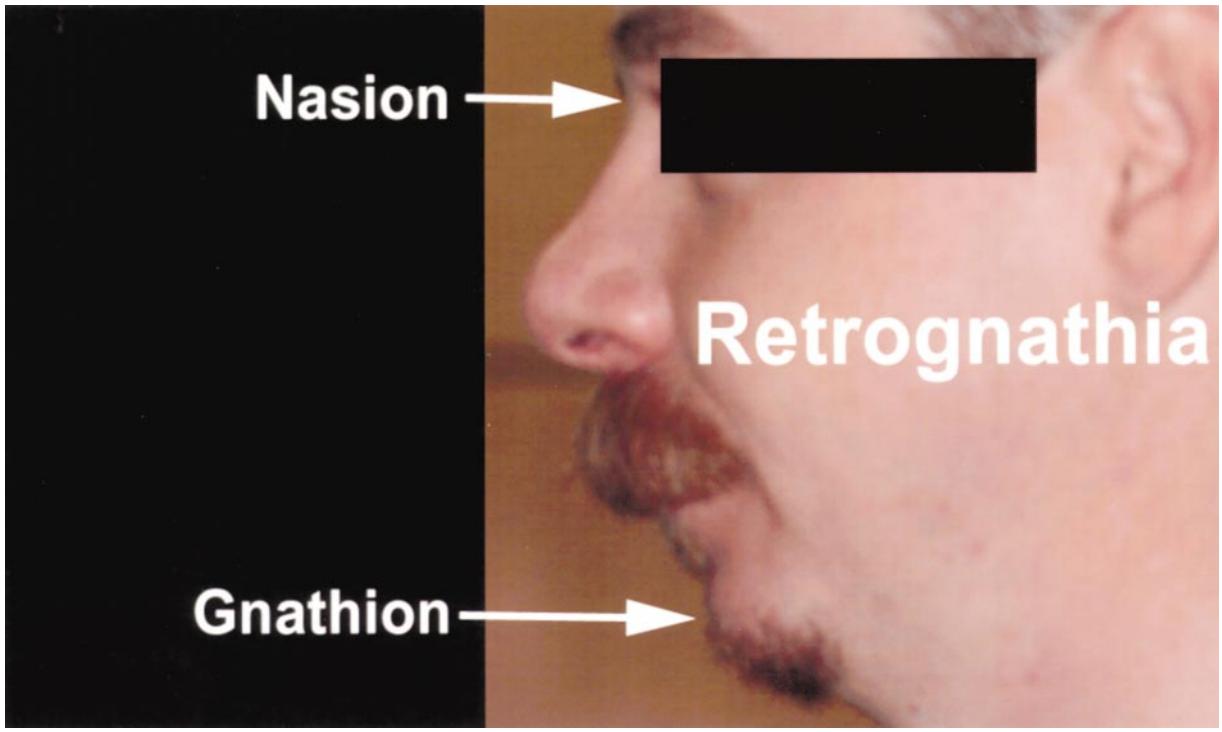

Figure 4. A lateral profile of the entire face demonstrating retrognathia. Retrognathia is observed as the position of the gnathion is posteriorly displaced as compared with the nasion.

TABLE 2

CRUDE AND ADJUSTED ASSOCIATIONS BETWEEN MORPHOMETRIC VARIABLES AND OBSTRUCTIVE SLEEP APNEA*

Structure	n (420 total)	Percent RDI ⩾ 15	Crude OR (95% CI)	Adjusted OR (95% CI)	Backward Regression OR (95% CI)	Backward Regression OR Adjusted for BMI and NC (95% CI)
Lateral narrowing						
Present	224	50.0	3.3	2.6	2.5	2.0
Absent	196	23.5	(2.1–5.0)	(1.7–4.1)	(1.6–3.9)	(1.3–3.3)
Tonsils enlarged						
Present	50	60.0	2.8	2.1	2.0	2.6
Absent	370	34.6	(1.6–5.2)	(1.1–4.2)	(1.0–3.8)	(1.3–5.2)
Tongue enlarged						
Present	330	41.2	2.2	2.0	1.8	NS
Absent	90	24.4	(1.3–3.7)	(1.1–3.6)	(1.0–3.1)	
Uvula enlarged						
Present	164	50.6	2.5	1.9	1.9	NS
Absent	256	29.3	(1.6–3.7)	(1.2–2.9)	(1.2–2.9)	
Low-lying palate						
Present	259	39.4	1.2	1.1	NS	NS
Absent	161	34.8	(0.8–1.8)	(0.7–1.8)		
Retrognathia						
Present	161	42.2	1.4	1.3	NS	NS
Absent	259	34.8	(0.9–2.1)	(0.8–2.1)		
Overjet						
Present	47	44.7	1.4	1.6	NS	NS
Absent	373	36.7	(0.8–2.6)	(0.8–3.3)		

Definition of abbreviations: BMI = body mass index; CI = confidence interval; NC = neck circumference; NS = not significant; OR = odds ratio; RDI = respiratory disturbance index.

* Results pooling males and females. For each morphometric variable, the number of subjects with the structural feature present or absent is displayed, as well as the percentage of patients in each group (present versus absent) with an RDI ⩾ 15. For example, for the variable lateral narrowing 224 of 420 subjects had the structural finding on examination and 50% of these (or 112 subjects) had an RDI ⩾ 15. Crude OR, adjusted OR (which estimates the independent contribution of each variable in the model), backward regression OR (a parsimonious morphometric model retaining only variables that are simultaneously significant), and adjusted backward regression OR controlling for BMI and NC are all displayed along with their corresponding 95% CIs.

model, enlargement of the tonsils, tongue, and uvula were each found to be associated with OSA. However, the magnitudes of these adjusted associations with OSA were not as large as that demonstrated for lateral narrowing. Enlargement of the tonsils as defined by 50% or greater occlusion of the posterior pharyngeal space by the tonsils was found to be a significant risk factor for OSA (adjusted OR = 2.0) even when adjusted for BMI and NC (OR = 2.6). Enlargement of the tongue as defined by the tongue extending about the level of the mandibular occlusal plane was associated with an increased risk for OSA when controlled for other variables within the model (adjusted OR = 2.0) but was not significant after controlling for BMI and NC. Enlargement of the uvula as defined by a uvula greater than 1.5 cm in length or greater than 1.0 cm in width was associated with an increased risk for sleep apnea when controlled for other variables in the model (adjusted OR = 1.9) and but not after adjusting for BMI and NC.

Interestingly, the bony structures that were assessed in this study were not found to be associated with a significant increase in risk for sleep apnea. This finding was consistent when adjusted for all variables within the model, as well as when adjusted for BMI and NC.

The subgroup analyses examining the oropharyngeal risk factors for sleep apnea in women as compared with men are presented in Tables 3 and 4, respectively. In women, no single factor achieved significance as an independent risk factor for OSA. When only men were considered, lateral narrowing and enlargement of the uvula achieved significance as independent risk factors for sleep apnea when adjusted for all oropharyngeal variables within the model. However, only lateral narrowing remained significant when adjusted for both BMI and NC, using the backward stepwise regression algorithm.

DISCUSSION

Findings of Current Study

Previous studies correlating anatomic risk factors with OSA have focused mainly on obesity as defined by BMI or NC. Although obesity is intimately involved in the pathogenesis of disease, the anatomic structures that form the upper airway are also important. Moreover, obesity may narrow the upper airway caliber by increasing the size or configuration of these upper airway soft tissue structures (8). Our data indicate that oropharyngeal soft tissue structures independent of obesity and neck size are important in the assessment of a patient presenting with signs or symptoms of obstructive sleep since they increase the risk for sleep-disordered breathing. However, the effect of obesity on upper airway morphology is important since controlling for BMI and NC in the logistic regression model eliminated the significance of many of the oropharyngeal variables.

In our study, the upper airway anatomic feature associated with the highest risk for OSA was enlargement of the lateral peritonsillar tissues. The lateral pharyngeal walls are complex structures composed of numerous pharyngeal muscle groups. These muscles include the hyoglossus, styloglossus, stylohyoid, stylopharyngeus, palatoglossus, palato-pharyngeus, and the pharyngeal constrictors (23). Previous studies by our group have demonstrated that the lateral pharyngeal walls are responsible for changes in upper airway caliber in subjects with and without apnea during wakefulness, sleep, respiration, and with the application of continuous positive airway pressure (CPAP) (3, 4, 6, 8, 19, 23). Thickening of the lateral walls was shown to be the predominant factor resulting in airway narrowing in subjects with apnea (8). Enlargement of the lateral walls is also thought to

TABLE 3

CRUDE AND ADJUSTED ASSOCIATIONS BETWEEN MORPHOMETRIC VARIABLES AND OBSTRUCTIVE SLEEP APNEA: FEMALES*

Structure	n (131 Total)	Percent RDI ⩾ 15	Crude OR (95% CI)	Adjusted OR (95% CI)	Backward Regression OR (95% CI)	Backward Regression OR Adjusted for BMI and NC (95% CI)
Lateral narrowing						
Present	67	31.3	1.8	1.4	NS	NS
Absent	64	20.3	(0.8–4.0)	(0.6–3.2)		
Uvula enlarged						
Present	28	32.1	1.5	0.9	NS	NS
Absent	103	24.3	(0.6–3.7)	(0.3–2.7)		
Tonsils enlarged						
Present	16	43.7	2.5	3.4	NS	NS
Absent	115	23.5	(0.9–7.4)	(0.9–12.5)		
Tongue enlarged						
Present	102	28.4	1.9	1.7	NS	NS
Absent	29	17.2	(0.7–5.5)	(0.5–5.5)		
Low-lying palate						
Present	80	28.7	1.5	1.5	NS	NS
Absent	51	21.6	(0.6–3.3)	(0.6–3.9)		
Retrognathia						
Present	39	33.3	1.7	1.6	NS	NS
Absent	92	22.8	(0.7–3.9)	(0.6–4.0)		
Overjet						
Present	12	41.7	2.2	1.9	NS	NS
Absent	119	24.4	(0.7–7.5)	(0.4–6.8)		

Definition of abbreviations: BMI = body mass index; CI = confidence interval; NC = neck circumference; NS = not significant; OR = odds ratio.

* Data for females only. For each morphometric variable, the number of subjects with the structural feature present or absent is displayed, as well as the percentage of patients in each group (present versus absent) with an RDI ⩾ 15. For example, for the variable lateral narrowing, 67 of 131 subjects had the structural finding on examination, and 31.3% of these (or 21 subjects) had an RDI ⩾ 15. Crude ORs, adjusted ORs controlling for all variables in the model (which estimates the independent contribution of each variable in the model), backward regression ORs (a parsimonious morphometric model retaining only variables that are simultaneously significant), and adjusted backward regression ORs (controlling for BMI and NC are all displayed along with their corresponding 95% CIs).

be responsible for the differences in the airway configuration observed in subjects without apnea (greater lateral dimension) as compared with subjects with apnea (greater anteroposterior dimension) (8, 19). This conformational change may be responsible for the increased collapsibility of the apneic airway during sleep (24). In addition, electromyographic studies have shown that activity of these muscle groups is reduced during sleep, which may predispose these structures to collapse during sleep (25). Our data support the importance of the lateral pharyngeal walls by demonstrating that they are a primary risk factor for the development of OSA independent of obesity, NC, and other craniofacial anomalies (e.g., retrognathia).

Other soft tissues that are important inmediating airway size include the tonsils, soft palate, uvula, and tongue. Our results demonstrate that tonsillar enlargement is associated with an increased risk for OSA even when BMI and NC were forced into the regression model. It is known that enlargement of the palatine tonsils can lead to airway obstruction by decreasing airway caliber (26). In addition, tonsil and adenoid hypertrophy is the most common risk factor for sleep-disordered breathing in children (27) and can be pathogenic in adults with OSA (28). Although the finding of enlarged tonsils was infrequent in our study population, this finding was strongly correlated with the presence of disease. Our study also demonstrates that enlargement of the uvula is associated with an increased risk for OSA except when BMI and NC were forced into the regression model. Pathologic studies have demonstrated thickening, fibrosis, and fat deposition in the uvula and soft palate of patients with OSA (29). Other studies have shown an increase in the amount of muscular tissue, number of lymphocytes, and thickness of the lamina propria in the uvulas of patients with OSA as compared with normal subjects (30, 31). Tongue enlargement was found to be associated with an increased risk for sleep apnea, but this association lost significance when adjusted for BMI and NC. Cephalometric evaluation and computerized tomagraphy (CT) studies have also shown that patients with OSA have enlarged tongues as compared with control subjects (20, 32). The significance of macroglossia in OSA is demonstrated by the strong prevalence of OSA in patients with macroglossia as a primary or secondary condition (e.g., in hypothyroidism, acromegaly, amyloidosis, and Down syndrome) (33).

Etiology of Changes in Upper Airway Morphology

Why are these upper airway soft tissue structures enlarged in subjects with apnea? Why did several of the risk factors identified in this study lose significance when controlled for BMI and NC? We believe that there are several important determinants of the upper airway anatomic structures. These include genetic determinants of airway anatomic structures, environmental factors that may affect the form and function of airway structures including sleep apnea itself, and the effects of obesity on the soft tissues that comprise the upper airway.

It has long been recognized that obesity is a major risk factor for OSA (18, 34). However, not all obese individuals suffer from OSA and conversely not all individuals with sleep apnea are obese. It has been suggested that subjects with apnea fall into three general categories—obese individuals with minimal upper airway structural risk factors, obese individuals with coexisting upper airway risk factors, and nonobese individuals with a high incidence of upper airway structure abnormalities (35, 36). Several of the oropharyngeal risk factors discussed in

TABLE 4

CRUDE AND ADJUSTED ASSOCIATIONS BETWEEN MORPHOMETRIC VARIABLES AND OBSTRUCTIVE SLEEP APNEA: MALES*

Structure	n (289 Total)	Percent RDI ⩾ 15	Crude OR (95% CI)	Adusted OR (95% CI)	Backward Regression OR (95% CI)	Backward Regression OR Adjusted for BMI and NC (95% CI)
Lateral narrowing						
Present	157	58.0	4.1	3.3	3.7	2.7
Absent	132	25.0	(2.5–6.9)	(1.9–5.7)	(2.2–6.1)	(1.6–4.8)
Uvula enlarged						
Present	136	54.4	2.5	1.8	2.0	NS
Absent	153	32.7	(1.5–4.0)	(1.1–3.0)	(1.2–3.3)	
Tonsils enlarged						
Present	34	67.7	3.2	2.3	NS	NS
Absent	255	39.6	(1.5–6.8)	(1.0–5.3)		
Tongue enlarged						
Present	228	47.0	2.3	2.4	NS	NS
Absent	61	27.9	(1.2–4.2)	(1.2–4.8)		
Low-lying palate						
Present	179	44.1	1.1	1.1	NS	NS
Absent	110	40.9	(0.7–1.8)	(0.6–1.9)		
Retrognathia						
Present	122	45.1	1.2	1.1	NS	NS
Absent	167	41.3	(0.7–1.9)	(0.6–1.9)		
Overjet						
Present	35	45.7	1.1	1.8	NS	NS
Absent	254	42.5	(0.6–2.3)	(0.6–4.2)		

Definition of abbreviations: BMI = body mass index; CI = confidence interval; NC = neck circumference; NS = not significant; OR = odds ratio; RDI = respiratory disturbance index.

* Data for males. For each morphometric variable, the number of subjects with the structural feature present or absent is displayed, as well as the percentage of patients in each group (present versus absent) with an RDI ⩽ 15. For example, for the variable lateral narrowing, 157 of 289 subjects had the structrual finding on examination, and 58% of these (or 91 subjects) had an RDI ⩽ 15. Crude ORs, adjusted ORs controlling for all variables in the model (which estimates the independent contribution of each variable in the model), backward regression ORs (a parsimonious morphometric model retaining only variables that are simultaneously significant), and adjusted backward regression ORs (controlling for BMI and NC are all displayed along with their corresponding 95% CIs).

this article may be directly related to obesity, whereas others may be associated with different factors such as genetic predisposition or environmental exposures. For example, tongue enlargement in obese subjects may occur secondary to fat deposition within the tongue. This increased fat deposition within the tongue has been described by magnetic resonance imaging (MRI) of the upper airway in patients with OSA (12). The same phenomenon of fat deposition within oropharyngeal soft tissues may contribute to enlargement of the uvula as described in pathologic specimens of postuvulopalatopharyngoplasty patients (29). In addition, obesity can result in deposition of fat within the parapharyngeal space (37) and may lead to enlargement of the surrounding soft tissue structures (23). Increases in muscle mass associated with weight gain may also explain the increase in size of the tongue, the soft palate, and the lateral pharyngeal walls (8).

In addition to obesity, genetic factors may be important mediators of the size and conformation of upper airway bony and soft tissue structures. In particular, retrognathia likely has a strong genetic determinant as demonstrated by the familial craniofacial disorders associated with OSA such as Treacher Collins syndrome (38). Macroglossia is a common feature in individuals with Down syndrome and is likely to be a major factor in the increased prevalence of obstructive sleep apnea observed in this patient population (39). The size of the tongue, soft palate, lateral walls, and mandible may be determined by genetic factors and subsequently affected by environmental factors.

Environmental factors and underlying medical conditions may also be important in determining the properties of the upper airway structures. Immunologic disturbances, allergic rhinitis, chronic sinusitis, recurrent pharyngeal infections, and malignancy can all result in enlargement of the tonsils. Macroglassia can occur as a result of systemic diseases such as amyloidosis, hypothyroidism, acromegaly, and nutritional deficiencies (33). Finally, morphometric changes in the soft tissue structures of the upper airway may be influenced by sleep apnea itself. Recurrent apneic episodes may be traumatic to the soft tissue structures of the upper airway, resulting in inflammation and edema of the tongue, soft palate, uvula, and lateral pharyngeal walls (40). It is most probable that environmental influences on upper airway structures, genetically determined structural features of the upper airway, and changes in airway structure and function secondary to obesity all interact to determine airway size and the likelihood for developing OSA. The same forces that lead to enlargement of the uvula (fat deposition, inflammation from repeated apneic episodes, etc.) may concurrently lead to enlargement of the soft palate, lateral walls, or the tongue. It is possible that some of the clinical variables in this study lost significance when analyzed in the logistic regression model because of their interdependence.

Effect of Sex on Upper Airway Morphology

The influence of sex on the morphometric features of the upper airway is also important to discuss. The fact that in women no oropharyngeal structure achieved significance may be a reflection of the diminished sample size of women in this study. However, other factors relating to sex differences in apneic subjects may have contributed to this result. It is possible that sleep apnea in women is less associated with pharyngeal anatomic risk factors than in men. For instance, the prevalence of OSA is less in women than in men (22) despite the observa-

tion that pharyngeal airway size has been described as smaller in women as compared with men (41, 42). Another possibility is that the distribution of obesity is different in men as compared with women. Generalized obesity may not be as important in the development of OSA as is regional fat deposition. Truncal or central obesity (male pattern) may be more closely associated with OSA (43) as it is with other disease processes such as type II diabetes mellitus (44), hypertension (45), and coronary artery disease (46). Overweight females tend to have fat distribution in the gluteofemoral region, whereas males tend to have a predisposition toward abdominal fat deposition (47). Because of this, overweight women with a "gynoid" peripheral pattern of fat distribution may be relatively protected from OSA as compared with overweight men with "android" central fat distribution. This different type of fat distribution in men compared with women may affect the size and configuration of the upper airway anatomic structures. A study by Whittle and coworkers demonstrated that women have a decreased proportion of parapharyngeal fat and soft tissue volume in the neck as compared with BMI-matched men despite having an increased percentage of body fat (48). The importance of regional fat distribution in the development of OSA warrants further study.

Another potential explanation for the sex difference in oropharyngeal risk factors we observed is that alterations in airway tone may be relatively more important in mediating sleep apnea in women than anatomic factors alone. There is evidence to suggest that women have increased pharyngeal dilator muscle activity (49) as compared with men and may have less upper airway collapsibility than men (42). It is possible that hormonal factors are responsible for these differences (50), although the data to support this are limited. The effects of obesity and hormonal factors on the development of sleep apnea in women may have important ramifications in the accurate diagnosis and treatment of this disorder in women, who likely represent an underrecognized and undertreated population (51).

Study Design and Limitations

One limitation of this study was that this evaluation was performed on awake subjects. Changes in airway muscle tone associated with the sleeping state are known to be significant in the pathogenesis of sleep apnea and may not be appreciated in the evaluation of an awake patient. However, the purpose of this study was to identify clinically observable findings that can help to identify a patient at increased risk for OSA. The relationship between abnormal anatomic findings and airway function during sleep is an important issue that requires methods that are impractical in the routine assessment of patients in the outpatient setting. Another limitation of our study is the use of a single observer to assess the physical features described in this article. The criteria used to evaluate patients, however, were rigorously standardized as described in METHODS. Although the investigator is an experienced clinician who evaluates hundreds of patients referred for the evaluation of sleep disorders annually, interrelater validity and test–retest reliability were not assessed in this study. In the future, a comprehensive morphometric predictive model that includes the evaluation of the soft tissue structures of the oropharynx will need to incorporate these key elements.

Another limitation of this investigation is that it studied a population at increased risk for sleep apnea, those presenting to sleep center for evaluation. For this reason, the generalizability of the results cannot be adequately assessed without further population-based studies. Finally, the qualitative nature of the clinical assessment in this study may limit its diagnostic utility. The position of the soft tissue structures of the pharynx in the awake patient is affected by body position (upright versus supine), the use of instruments such as tongue blades to visualize structures, and phonation. Future studies will benefit from correlating the clinical assessment of the oropharynx with more objective anatomic or physiologic measurements of upper airway structure such as MRI, digital photography, or CT.

Summary and Future Directions

In summary, soft tissue structures of the oropharynx are important determinants of OSA. Enlargement of the lateral pharyngeal walls is intimately involved in the pathogenesis of this disease and has been shown in this study to be an independent risk factor for OSA even when controlling for BMI and NC. Patients with symptoms of sleep-disordered breathing who have enlargement of the lateral pharyngeal walls are at increased risk for the development of OSA. The relationship between the various soft tissue structures of the oropharynx with the bony structures of the face and the effects of regional obesity warrants further investigation. Clinical assessment of the oropharyngeal soft tissues in patients being evaluated for suspected sleep-disordered breathing may allow for better risk stratification of these patients and may provide insight into the best means of treating affected patients on the basis of their individual anatomic risk factors. Further research efforts examining differences in the risk factors for OSA between men and women is also indicated.

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