CHEST

Official publication of the American College of Chest Physicians

Anatomic Determinants of Sleep-Disordered Breathing Across the Spectrum of Clinical and Nonclinical Male Subjects*

Jerome A. Dempsey, James B. Skatrud, Anthony J. Jacques, Stanley J. Ewanowski, B. Tucker Woodson, Pamela R. Hanson and Brian Goodman

Chest 2002;122;840-851
DOI 10.1378/chest.122.3.840

ISSN:0012-3692

Anatomic Determinants of Sleep-Disordered Breathing Across the Spectrum of Clinical and Nonclinical Male Subjects*

Jerome A. Dempsey, PhD; James B. Skatrud, MD; Anthony J. Jacques, BS; Stanley J. Ewanowski, PhD; B. Tucker Woodson, MD; Pamela R. Hanson, DDS, MS; and Brian Goodman, PhD

Objectives: **We wished to determine the independent contribution of craniofacial dimensions of the upper airway to sleep-disordered breathing (SDB) in subjects who spanned the entire continuum of SDB. We also determined the interactive effects of body mass index (BMI) and age on the relationship between airway dimensions and SDB.**

Design and subjects: **We studied 142 nonclinical male subjects in a working community population (average age, 47 years; average BMI, 29; average ± SD apnea/hypopnea index [AHI], 20 ± 20/h), and 62 patients with obstructive sleep apnea (average age, 47 years; average BMI, 32; average ± SD AHI, 48 ± 35/h. We determined the AHI from overnight polysomnography and the number of oxygen desaturations (≥ 2%) per hour of sleep. We used lateral facial cephalometric radiographs to measure 41 anatomic landmarks and 55 dimensions in the upper airway.**

Setting: **A university hospital and a sleep-disorders clinic.**

Data analysis: **We used stepwise regression analysis to determine the independent contributions of measured variables to SDB.**

Measurements and results: **In the entire study population (n = 204), variations in BMI and six measures of craniofacial morphology accounted equally for one half of the total variance in AHI, and their interactive effects accounted for an additional 15%. Membership in the clinical or nonclinical group *per se* had no significant influence on these relationships. The single most important cephalometric variable in predicting AHI severity was the horizontal dimension of the maxilla (*ie*, porion vertical to supradentale [PV-A] distance). When the PV-A distance was relatively narrow (< 97 mm) the probability of having mild (AHI, 15 to 30/h) to severe (AHI > 30/h) SDB increased fivefold to sevenfold in nonobese subjects and threefold in obese subjects. Thus, in nonobese subjects (average BMI, 25 ± 2) and in subjects with narrow upper airway dimensions, four cephalometric dimensions were the dominant predictors of AHI, accounting for 50% of the variance. However, in subjects with a large anteroposterior facial dimension, BMI was the major predictor of AHI and a BMI > 28 increased the probability of moderate-to-severe sleep apnea by approximately fivefold. Finally, the combination of cephalometric dimensions and BMI accounted for an increasing amount of the variance in AHI as the severity of AHI increased.**

Conclusions: **Across the population spectrum of SDB, four cephalometric dimensions of the upper airway in combination with BMI accounted independently for up to two thirds of the variation in AHI; and the relative contribution of these two sets of determinants of AHI varied depending on airway size, obesity, and the amount of SDB.** ***(CHEST 2002; 122:840–851)***

Key words: cephalometry; obesity; sleep-disordered breathing

Abbreviations: AHI = apnea/hypopnea index; ANOVA = analysis of variance; ANS = anterior nasal spine; BMI = body mass index; CI = confidence interval; Co-ANS = condylion to anterior nasal spine; CPAP = continuous positive airway pressure; FH = Frankfurt horizontal; MnAI = mandibular anterior dental point; MP = mandibular plane; MxAI = maxillary anterior dental point; NV = nasion vertical; PAS_1 = midpoint of the velum to the pharyngeal wall parallel to the Frankfurt horizontal; PAS_2 = velum tip to the pharyngeal wall parallel to the Frankfurt horizontal; PCA = principal components analysis; PNS = posterior nasal spine; PV = porion vertical; PV-A = porion vertical to supradentale; ROC = receiver operating characteristic; Sao_2 = arterial oxygen saturation; SDB = sleep-disordered breathing; SE = spheno-ethmoidal point; SO = spheno-occipital point

Sleep-disordered breathing (SDB) has many potential causes. The occurrence of upper airway narrowing or closure in sleep occurs as a result of anatomic and functional abnormalities of upper airway regulation. Anatomic susceptibility to sleep apnea is determined by the relationship between the fixed dimensions of the craniofacial skeleton and volume and distribution of soft-tissue structures and adipose tissue that reside in the skeletal compartment. Superimposed on this anatomic substrate are complex neurophysiologic mechanisms that regulate the patency of the upper airway during sleep.

For editorial comment see page 765

Several previous studies[1–8] have addressed the problem of anatomic determinants of SDB in patients with a diagnosis of sleep apnea or those referred to a sleep laboratory for symptoms suggestive of sleep apnea. Referrals to a sleep laboratory tend to cluster into groups of patients with predominantly craniofacial abnormalities, or predominantly obese, or a combination of craniofacial abnormalities and obesity. The use of these biased study populations limits the spectrum of severity of sleep apnea under examination and does not consider the disease as a continuum consisting of normal subjects, snorers, and asymptomatic and symptomatic patients with sleep apnea. Thus, the relative contributions of craniofacial structures and obesity to SDB across this continuum has not been well defined.

Our goal was to identify independent anatomic predictors of SDB across the entire spectrum of severity of the disorder. More specifically, we wished to determine the relative contributions of craniofacial structure and obesity and their interactions in predicting the severity of SDB. To this end, we used cephalometry to determine the craniofacial dimensions of the upper airway and overnight polysomnography to quantify SDB. We combined two types of subpopulations that represent the entire continuum of SDB. These included a subsample from the Wisconsin Sleep Cohort study (a random sample of working adults representing a wide range of SDB[9]) and a clinical population of subjects referred specifically for symptoms of sleep apnea.

*From the Departments of Population Health Sciences (Dr. Dempsey and Mr. Jacques) and Medicine (Drs. Skatrud and Ewanowski), University of Wisconsin, Madison; the Departments of Otolaryngology and Communication Sciences (Dr. Woodson) and Oral and Maxillofacial Surgery (Dr. Hanson), Medical College of Wisconsin, Milwaukee; and the W. S. Middleton Veteran's Administration Hospital (Dr. Goodman), Madison, WI.
This work was supported by National Heart, Lung, and Blood Institute grants 42242, 62686, and 03899.
Manuscript received August 14, 2001; revision accepted March 18, 2002.
Correspondence to: Jerome A. Dempsey, PhD, John Rankin Laboratory of Pulmonary Medicine, Department of Population Health Sciences, 504 N. Walnut St, Madison, WI 53705-2368; e-mail: jdempsey@facstaff.wisc.edu

Materials and Methods

Subjects

The study population was selected to obtain a broad spectrum of severity of SDB ranging from normal subjects to patients with severe sleep apnea syndrome. To make our study population more representative of the general population, we selected subjects from a working population who had not sought medical attention (nonclinical group) rather than from a group of subjects who had sufficient symptoms to cause them to seek medical advice in a sleep clinic. However, this working population alone did not provide a sufficient number of subjects with severe disease. Therefore, we included a group of patients with sleep apnea severe enough to require treatment (clinical group). By combining these two groups, we were able to study a continuum of SDB and craniofacial dimensions ranging from healthy, asymptomatic, normal subjects through patients with severe, symptomatic sleep apnea who required treatment. As reported in the "Results" section, we justified the two groups of subjects by showing statistically that membership in the clinical or nonclinical groups *per se* did not contribute significantly to the effects of airway dimensions, obesity, and age on the apnea/hypopnea index (AHI). Our study was approved by the University of Wisconsin Committee on Human Research. All subjects gave informed consent.

The nonclinical subjects were selected from the Wisconsin Sleep Cohort Study.[9] This cohort represented a random sample of state employees in Wisconsin. A two-staged sampling technique was used to enrich the cohort with subjects with self-reported habitual snoring who had a greater likelihood of demonstrating some degree of SDB. First, all employees 30 to 60 years old who worked for three large state agencies were surveyed about their sleep habits with a questionnaire. Secondly, subjects were classified as habitual snorers if they reported snoring on most nights. In order to obtain a cohort that represented a sufficient range of SDB, all of the habitual snorers and 25% of a random sample of subjects who were not habitual snorers were invited to undergo nocturnal polysomnography. Subjects were excluded due to pregnancy, unstable or decompensated cardiopulmonary disease, airway cancers, recent upper airway surgery, and tracheostomy.

For 28 months, lateral cephalograms were added to the overnight polysomnographic studies. Technically adequate measurements were obtained in 142 white men. The average age was 46.3 ± 7.5 years (± SD). The average body mass index (BMI) was 29.1 ± 4.6. These 142 subjects were comparable to male patients in the sleep cohort as a whole in terms of age and BMI. AHI for a given range of values for age and BMI was almost identical for our subgroup and the cohort. Symptomatically, the cohort subgroup was also comparable in the prevalence of complaints of not feeling rested during the day and excessive daytime sleepiness (17% vs 18%). Smoking history in both past smokers (42% vs 45%) and current smokers (14% vs 18%) was also comparable. The number of self-reported habitual male snorers was slightly higher in the cephalometric study group (7%) compared to the entire cohort (4%).

The clinical group was derived from 72 consecutive patients who were referred to the sleep clinic of the Medical College of Wisconsin for management of sleep apnea. The reason for referral included 43 patients who had received diagnoses but had

not yet been treated, and 29 patients in whom continuous positive airway pressure (CPAP) had been unsuccessful, or who did not want to continue CPAP, and/or who wanted a second opinion. All patients had undergone nocturnal polysomnography and cephalometry. None of these patients manifested comorbid exclusionary conditions, including neuromuscular disorders, craniofacial syndromes, nasopharyngeal stenosis, major maxillofacial trauma, or previous pharyngeal surgery. Technically adequate measurements were obtained for 62 men. No difference in demographics was noted in the patients who had technically inadequate cephalometric findings. The average age was 47 ± 9 years. The average BMI was 32.5 ± 6.4.

Collection of Data

Polysomnography consisted of continuous polygraphic recording (model 78; Grass Instruments; Quincy, MA) of the EEG (leads C4/A1 and O1/A2) electro-oculogram, ECG, and electromyogram (chin and right leg), and from noninvasive sensors for nasal airflow (thermocouples), oral airflow by end-tidal carbon dioxide gauge (Ohmeda; Englewood, CO), tracheal sounds (microphone), thoracic and abdominal respiratory effort by inductance plethysmography (Respitrace; Ambulatory Monitoring; Ardsley, NY), and arterial oxygen saturation (SaO_2) by finger pulse oximetry (model 3740; Ohmeda). The transducers and lead wires permitted normal positional changes during sleep. Data were recorded on paper and digitized using custom software.[9]

Cephalometric Analysis

Lateral cephalometric radiographs were obtained with the subjects in both upright and supine positions. A conventional cephalometric head-holding device was modified to enable the subject's head, while she or he was in the supine position, to be restrained in a manner comparable to what it was when in the upright position. For the upright cephalogram, the subject was seated with her or his head in a neutral position, with the gaze horizontal and the teeth in neutral occlusion. For the supine cephalogram, the subject reposed on a gurney with her or his head again in a neutral position, with the gaze upward and the teeth in neutral occlusion. The radiograph film holder was placed next to the left side of the head, and the cone of the radiograph unit was 1.5 m from the subject. Two exposures were obtained with the subjects in upright and supine positions. Thermoluscent dosimeters were placed on the skin in the following locations: at the corner of the eye, on the cheek adjacent to the malar area, and on the lateral aspect of the thyroid. These dosimeters were used to measure skin radiation exposure. Mean radiation dosages to the three sites was 0.068 R with a range of 0.06 to 0.08 R.

Lateral cephalometric dimensions were traced on matte acetate paper with a lead pencil by the same investigator and verified by a second investigator. Landmarks were digitized on a digitizing tablet (model 2210; Numonics Corporation; Montgomeryville, PA) using Sigma Scan software (SPSS; Chicago, IL). Linear and angular measurements were computed using custom software.

Forty-one anatomic landmark measurements are shown in Figure 1. Five reference lines were constructed: Frankfurt horizontal (FH), the line through orbitale and porion; porion vertical (PV), the line from porion perpendicular to the FH; nasion vertical (NV), the line from nasion perpendicular to the FH; mandibular plane (MP), the line through gonion and gnathion; and occlusal plane, the line through the anterior-interdental point to the posterior-interdental point.

Forty distances between the landmarks were calculated: anterior nasal spine (ANS) and posterior nasal spine (PNS), gonion and gnathion, condylion and gonion, condylion and pogonion,

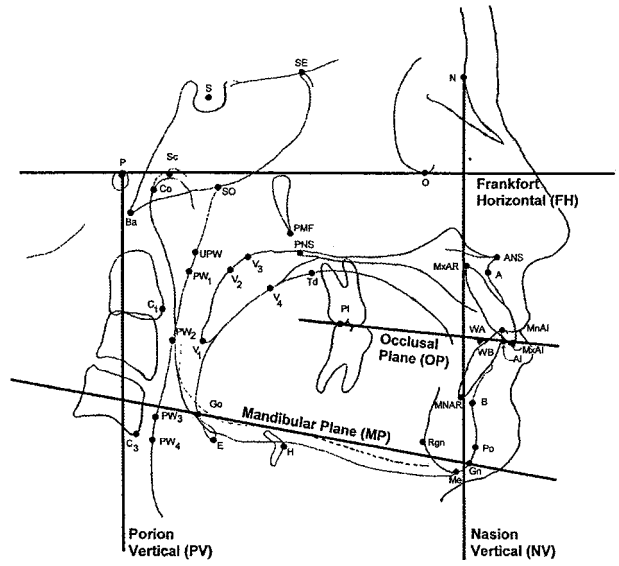

FIGURE 1. Diagrammatic representation of anatomic points used to identify craniofacial and soft-tissue parameters on cephalometric radiographs. S = sella; Ba = basion; UPW = upper pharyngeal wall; AI = anterior-interdental point; A = supradentale; B = infradentale; Po = pogonion; WA = Wits point A; WB = Wits point B; Gn = gnathion; Me = menton; E = epiglottis base; Rgn = retrognathion; O = orbitale, N = nasion; P = porion; Sc = super condylion; Co = condylion; Td = tongue dorsum; PI = posterior interdental point; MNAR = mandibular anterior dental point; MxAR = maxillary anterior dental point; PMF = ptergomaxillary fissure, interior point; PW_1 to PW_4 = points on the pharyngeal wall corresponding to distances PAS_1 to PAS_4; C_1 = most anterior and inferior points on the first vertebra; C_3 = most anterior and inferior points on the third vertebra; V_1 = velum tip; V_2 = midpoint of the velum; V_3 and V_4 = widest points of the velum; H = hyoid; Go = gonion.

condylion and ANS, nasion and sella, nasion and supradentale, nasion and infradentale, Wits A point and Wits B point, hyoid perpendicular to MP, and hyoid perpendicular to the retrognathion-C_3 line.

Distances measured parallel to the FH include the following: NV to supradentale, NV to infradentale, PV to PNS, PV to pogonion, PV to supradentale, PV to infradentale, PNS to C_1, NV to ANS, PNS to spheno-occipital point (SO), hyoid to C_3, hyoid to PV, and maxillary anterior dental point (MxAI) to mandibular anterior dental point (MnAI). Distances parallel to the PV were as follows: nasion to menton, ANS to menton, PNS to sphenoethmoidal point (SE), hyoid to PNS, hyoid to FH, hyoid to SO, hyoid to SE, hyoid to sella, PNS to sella, and MxAI to MnAI.

The following soft-tissue variables were measured: the midpoint of the velum to the pharyngeal wall parallel to the FH (PAS_1); velum tip to the pharyngeal wall parallel to the FH (PAS_2); gonion to the pharyngeal wall parallel to the FH (PAS_3); epiglottis base to the pharyngeal wall parallel to the FH (PAS_4); maximum tongue height, distance from tongue dorsum on a line perpendicular to the retrognathion-hyoid line; length of velum, distance from velum tip to the PNS; and thickness of the velum.

Fifteen angles were measured: basion-sella-nasion, cranial base; sella-nasion-supradentale, maxillary prognathism; sella-nasion-infradentale, mandibular prognathism; supradentale-nasion-infradentale, difference in anterior position of maxilla and mandible; basion-SE-PNS, difference in posterior position of maxilla and mandible relative to posterior cranial base; basion-

SE-gonion, posterior position of mandible relative to posterior cranial base; gonion-SE-PNS; basion-SO-PNS; basion-SO-gonion; gonion-SO-PNS; sella-nasion line to occlusal plane; sella-nasion line to MP, facial divergence; condylion-gonion-gnathion, ramus angle; maxillary anterior dental point-MxAI line to the nasion-supradentale line, maxillary incisor angle; and MnAI-mandibular anterior dental point line to the nasion-infradentale line, mandibular incisor angle.

Data Analysis

For all subjects, polysomnographic records were manually scored for sleep stage in 30-s epochs according to the system of Rechtschaffen and Kales.[10] SDB events were detected manually and defined as a minimum 2% oxygen desaturation combined with a reduction or cessation of airflow that lasted ≥ 10 s. In the cohort subjects, oxygen desaturations were also determined by computer algorithm.[11] The manual and computerized estimates of AHI were highly correlated ($r = 0.94$; $p < 0.01$), and average values of the two methods differed by less than two events per hour across the spectrum of AHI. This computerized detection method was also previously verified against human scoring of Sao_2 and other measures of ventilatory output.[11] Consequently for both clinical and nonclinical subjects, the AHI was calculated as the average number of computer-scored SDB oxygen desaturation events per hour of sleep.

Statistical Analysis

We used a one-way analysis of variance (ANOVA) to test for statistically significant differences in the mean values of our dependent and independent variables among different subgroupings of our subjects. Stepwise regression was used to remove and/or add variables, for the purpose of identifying a significant subset of multiple linear regression predictors. The procedure we used adds or subtracts a variable, one at a time. The criteria for inclusion (or exclusion) of a variable is based on whether the regression results in a significant decrease in the standard error of the estimate of the regression model residuals and a significant increase in the fraction of explained variance (R^2) of the regression model fit.[12] These calculations are done both before and after a variable is removed or entered into the regression model equation. All variables not included in the model, at any given iteration, are always considered in the next iteration, and the iterations continue until no more predictors are removed or entered. To test for the possibility of systematic biases between our clinical and nonclinical subject populations, we included a "clinical/nonclinical" bias term in all of our stepwise regression models.

To insure that the condition of normality of error distribution was met in our regression model residuals, we performed a residual analysis.[13] We used a χ^2-based Kolmogorov-Smirnov goodness-of-fit test for normality.

Coherent patterns of variation among the 55 individual cephalometric measures were identified using principal components analysis (PCA). PCA is a multivariate technique to determine a smaller number of uncorrelated variables for a data set by accounting for any multicollinearity among a set of variables.[12] When variables are measured by different scales, it is appropriate to standardize the variables by computing the associated eigenvectors and eigenvalues from the correlation matrix. By definition, the associated eigenvector calculations always generate as many principal component patterns as there are variables. These components are ranked from highest to lowest degree of pattern communality. Communality is defined as the amount of total variance explained by an individual component among the entire set of cephalometric measures. In general, all of the different methods consider a principal component to be statistically significant when it explains > 5% of the total observed variance. For this study a scree plot[14] was used, which is based on the individual principal component eigenvalues and identification of their respective "white noise" background random error contribution. All PCA calculations were performed using the procedures found in MINITAB Release 12 for Windows (Minitab; State College, PA).

In order to determine the relative contributions of airway dimensions and BMI to AHI, we computed the area under receiver operating characteristic (ROC) curves for a wide range of potential threshold values for a selected airway dimension (PV to supradentale [PV-A]) that varied from 94 to 101 mm in 1-mm incremental steps (see "Results" section). This analysis allowed us to determine a specific PV-A threshold value that discriminated subjects into two categories with a maximum AHI sensitivity and specificity coincident with a minimum BMI sensitivity and specificity. ROC calculations were done using the SPSS statistical package (SPSS Release 10.0; SPSS, Inc; Chicago, IL).

Results

Relative Contributions of Airway Dimensions, Body Mass, and Age to Variation in AHI in All Subjects (n = 204)

Stepwise regression was applied to build an additive model to predict AHI, drawing from all cephalometric dimensions, BMI, and age (Table 1). Our

Table 1—*Regression Models (n = 204)

Variables	AHI Explained Variance: Sequential R^2, %	p Value
AHI vs cephalometric measures and BMI, excluding BMI interactions		
Constant		0.000
BMI	26.3	0.000
PV-A	14.0	0.000
PAS_1	3.2	0.000
S-N-B	2.3	0.003
Gonion-SE-PNS	2.0	0.001
H-(Rgn-C_3)	1.6	0.014
PNS-SO	1.1	0.016
Total R^2	**50.5**	
AHI vs cephalometric measures, BMI, and age, including BMI interactions		
Constant		0.009
BMI	26.3	0.000
BMI vs (PV-A)	15.7	0.000
BMI vs (PAS_1)	3.1	0.000
Age	2.0	0.010
BMI vs (S-N-B)	1.9	0.001
BMI vs (H-MP)	1.7	0.006
BMI vs age	1.3	0.020
BMI vs (PNS-SO)	1.3	0.001
Gonion-SE-PNS	1.2	0.000
BMI vs (H-[Rgn-C_3])	0.11	0.015
Total R^2	**65.5**	

*S-N-B = angle between sella, nasion, and basion; H-MP = anterior-superior hyoid point to mandibular plane; H-(Rgn-C_3) = anterior-superior hyoid point to line joining the retrognathion and the anterior inferior point on C_3.

best-fit model accounted for approximately 50% of the variance in AHI, with half being attributed to BMI and the other half to a subset of six cephalometric dimensions. The horizontal dimension from the PV-A was the key variable accounting for greater than half of the variance explained by the subset of six significant cephalometric dimensions (Figs 2, 3).

Variations in BMI interacted with those in cephalometric dimensions in predicting AHI. This was shown when we redid the stepwise regression and included significant interactive terms of BMI with cephalometric dimensions (Table 1). The important predictors of AHI were similar to the additive model in terms of BMI and cephalometric measurements, except that the interaction of BMI with five of the six cephalometric measurements accounted for a greater fraction of the variance in AHI than each of these cephalometric dimensions by themselves. The increase in the explained variance in AHI was an additional 15% (to a total of 65% of total variance in AHI) when these interactions were included.

Relative Contributions of Airway Dimensions and BMI to AHI in Obese (BMI > 28; n = 123) vs Nonobese (BMI < 28; n = 81) Subjects

The group means in these two groups are compared in Table 2 by ANOVA, and their regression analysis is shown in Tables 3, 4. The ANOVA showed that the group mean AHI was about double (17/h vs 36/h) in the obese group vs the nonobese group (mean BMI, 33 vs 25) with no difference in age (45 years vs 47 years, respectively). Almost all airway dimensions were similar between the two BMI groups. The only major cephalometric difference between the groups was for PAS_2, a measure of soft-tissue dimension.

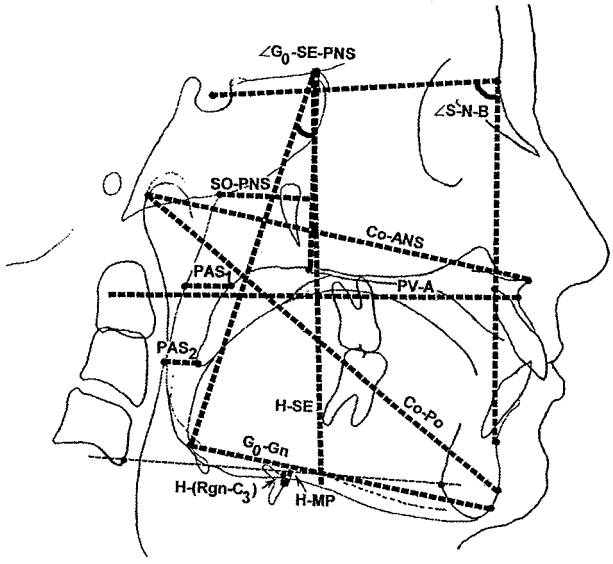

FIGURE 2. Cephalometric dimensions that made significant contributions to the variance in AHI. Dimension PV-A (parallel to FH) was the single airway dimension that contributed most significantly to variations in AHI within the study population. Go-SE-PNS = gonion-SE-PNS; Co-Po = condylion-pogonion; Go-Gn = gonion-gnathion. See Table 1 for expansion of other abbreviations.

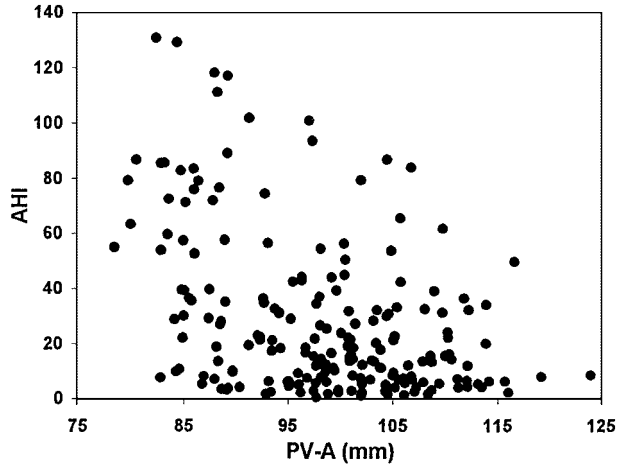

FIGURE 3. Relationship of PV-A cephalometric dimension to AHI in all subjects.

The regression analysis in the nonobese and obese groups is shown in Tables 3 and 4, respectively. For the obese group (BMI > 28), the contributions to AHI variance were similar to those for the whole group (Table 1). That is, a total of 50% of the variance was accounted for with a combination of BMI and six cephalometric measurements. BMI accounted for about half of this total variance, and cephalometric measurements (principally PV-A distance) accounted for the remaining half of the total variance. Interactive effects between BMI and cephalometric dimensions did not add significantly to the total variance in AHI accounted for independently by these measures.

Within the nonobese group (BMI < 28), BMI bore no significant relationship to AHI, whereas four cephalometric measurements and age accounted for 41% of the variance in AHI. Again, the anteroposterior maxillary dimension (condylion to ANS [Co-ANS]) was the major contributor to AHI. A similar measurement of anteroposterior maxillary dimension (PV-A) was the greatest cephalometric contributor to AHI for the group as a whole (Table 1).

Relative Contributions of Airway Dimensions and BMI to AHI in Subjects With Large vs Small Airway Dimensions

To address this question, we selected the most prominent cephalometric measurement in our re-

Table 2—*Comparison of Mean Values Between Groups with BMI > 28 vs BMI ≤ 28

Cephalometric Measures	One-Way ANOVA		
	BMI ≤ 28	BMI > 28	p Value
Patients, No.	81	123	
AHI	17.34	35.85	0.000
SD	20.31	30.74	
BMI	25.259	33.314	0.000
SD	1.973	4.555	
Age	47.130	45.432	0.149
SD	7.321	8.701	
Co-ANS	97.086	98.124	0.384
SD	8.563	8.149	
PV-A	98.04	98.28	0.858
SD	9.87	9.08	
H-MP	− 20.820	− 22.209	0.162
SD	6.679	7.061	
H-(Rgn-C_3)	12.908	14.204	0.135
SD	6.015	6.059	
PNS-SO	24.449	24.590	0.909
SD	8.585	8.743	
PAS_1	10.486	10.185	0.582
SD	3.761	3.835	
PAS_2	8.992	10.394	0.003
SD	3.164	3.285	
S-N-B	78.089	78.751	0.306
SD	4.848	4.270	
Gonion-SE-PNS	13.774	13.116	0.200
SD	3.202	3.803	

*H-MP = anterior-superior hyoid point to the MP. See Table 1 for expansion of other abbreviations.

gression analysis of the entire group, PV-A, and classified the groups based on this measurement. We determined a threshold value for the PV-A distance of 97 mm based on our ROC analysis (see "Materials and Methods" section). We then stratified the population based on the PV-A dimensions > 97 mm and < 97 mm as an indication of a large vs small craniofacial dimension. The differences in group mean values between those with large vs small upper airway dimensions and the multiple regression analysis in each of these groups is shown in Table 5.

Table 3—*Regression Model of AHI vs Cephalometric Measures, BMI, and Age for BMI ≤ 28, Excluding BMI Interactions (n = 123)

Variables	AHI Explained Variance	
	Sequential R^2, %	p Value
Constant		0.000
Co-ANS	29.0	0.000
H-(Rgn-C_3)	4.0	0.085
PAS_1	3.3	0.058
Age	2.8	0.066
PNS-SO	1.5	0.119
Total R^2	**40.6**	

*See Table 1 for expansion of abbreviation.

Table 4—*Regression Model of AHI vs Cephalometric Measures, BMI, and Age for BMI > 28, Excluding BMI Interactions (n = 81)

Variables	AHI Explained Variance	
	Sequential R^2, %	p Value
Constant		0.003
BMI	24.6	0.000
PV-A	12.3	0.000
PAS_1	4.3	0.002
H-MP	2.5	0.044
Gonion-SE-PNS	2.2	0.002
PAS_2	2.2	0.039
S-N-B	1.5	0.063
Total R^2	**49.6**	

*See Tables 1, 2 for expansion of abbreviations.

The groups differed significantly with respect to AHI (39/h vs 19/h) and to a significant but relatively small extent in BMI (31 vs 29, respectively). Of the six key cephalometric measurements (as selected from the regression analysis), PV-A (by definition), Co-ANS, and PNS-SO were significantly different between the groups.

The step-wise regression (Table 6) showed that in the group with the narrower upper airways, BMI, and four cephalometric dimensions accounted almost equally for a total of 61% of the total variance in AHI. There were no significant interactive effects

Table 5—*Comparison Between Group Mean Values for PV-A Distance ≤ 97 mm vs PV-A Distance > 97 mm in the AHI Multiple Regression Models

Cephalometric Measures	One-Way ANOVA		
	PV-A ≤ 97 mm	PV-A > 97 mm	p Value
Patients, No.	51	120	
AHI	40.19	20.31	0.000
SD	33.89	20.53	
BMI	31.09	29.43	0.031
SD	6.32	4.64	
Age	47.04	46.05	0.4
SD	8.73	7.83	
PV-A	88.96	104.65	0.000
SD	5.06	5.47	
H-PV	29.44	44.98	0.000
SD	8.47	10.91	
H-SO	93.75	102.56	0.000
SD	8.58	8.27	
PAS_1	10.47	10.19	0.611
SD	3.91	3.73	
(MnAR-MnAI)-(N-B)	35.17	37.30	0.710
SD	36.32	40.42	

*(MnAR-MnAI)-(N-B) = the mandibular incisor angle; H-PV = hyoid to porion vertical parallel to FH; H-SO = hyoid to the SO parallel to porion vertical.

Table 6—*Regression Models

Variables	AHI Explained Variance: Sequential R^2, %	p Value
AHI vs cephalometric measures, BMI, and age for PV-A distance ≤ 97 mm, excluding BMI interactions (n = 51)		
Constant		0.002
BMI	23.9	0.000
PAS_1	17.8	0.000
H-PV	10.0	0.003
PV-A	5.6	0.032
Total R^2	**57.3**	
AHI vs cephalometric measures, BMI, and age for PV-A distance > 97 mm, excluding BMI interactions (n = 153)		
Constant		0.661
BMI	17.9	0.000
H-SO	6.2	0.007
PV-A	4.6	0.016
(MnAR-MnAI)-(N-B)	3.8	0.026
Total R^2	**32.5**	

*See Table 5 for expansion of abbreviations.

of BMI with cephalometric dimensions. However, among subjects with a larger upper airway dimension (Table 6), cephalometric measurements accounted for a total of only 5% of the variation in AHI, whereas BMI and age accounted for 31% of the variance in AHI.

Contribution of BMI and Airway Dimensions to AHI Variability in Subjects With Large (AHI > 15/h) vs Small (AHI < 15/h) Amounts of SDB

We stratified the subjects into groups of AHI > 15/h and AHI < 15/h. As shown in Table 7, the group with greater AHI averaged more than six times the number of oxygen desaturation events, had greater BMI, were 5 years older, and had a significantly smaller PV-A dimension.

In the > 15/h AHI group, BMI and cephalometric measurements accounted for a total of 38% of the variance in AHI, with six cephalometric measures accounting for two thirds and BMI for one third of this total variance (Table 8). Variations in the PV-A dimension was the major contributor of the six cephalometric measurements to the variation in AHI. Interactive effects of BMI with the PV-A dimension accounted for an additional 5% of the variance in AHI (data not shown). In the < 15/h AHI group, the BMI plus a single airway dimension accounted for only 22% of the total variance in AHI with BMI, rather than cephalometric dimensions providing the major contribution (Table 8). Thus, the greater the AHI, the more the variation in AHI was accounted for by cephalometric dimensions; whereas with lesser amounts of AHI, the total variance in

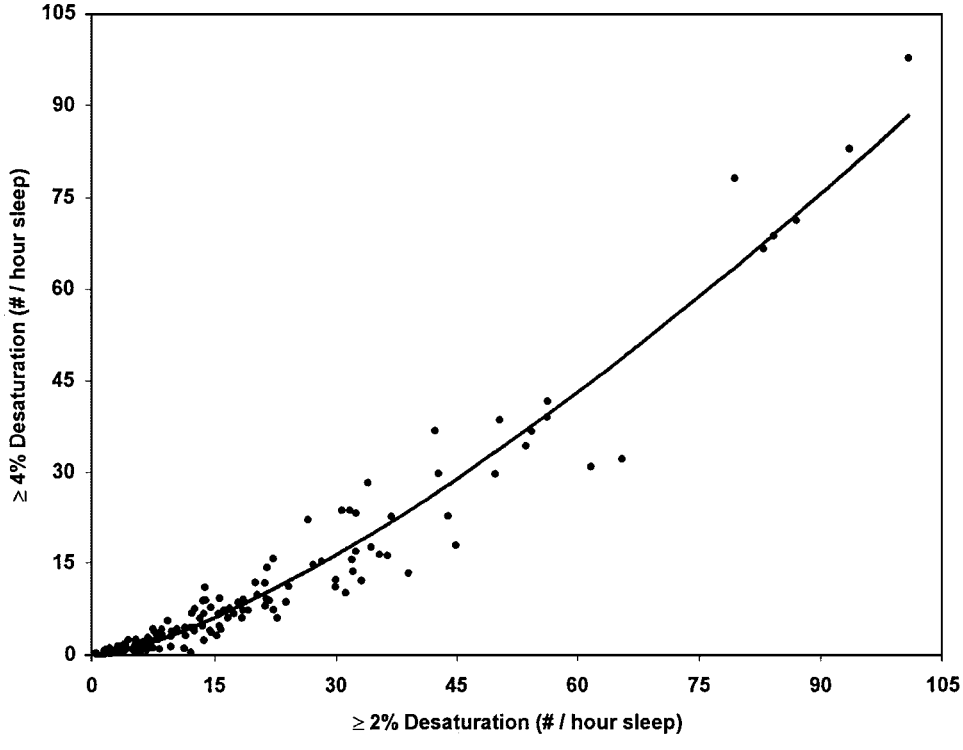

FIGURE 4. Relationship of SDB events with 2% oxygen desaturation to subjects with 4% oxygen desaturation (nonclinical subjects only, n = 142).

Table 7—*Comparison of Group Mean Values Between AHI < 15 vs AHI ≥ 15*

Cephalometric Measures	One-Way ANOVA AHI < 15	AHI ≥ 15	p Value
Patients, No.	90	114	
AHI	7.07	45.42	0.000
SD	3.91	28.17	
BMI	27.482	32.194	0.000
SD	3.623	5.743	
Age	43.444	48.833	0.000
SD	7.721	7.813	
PV-A	101.44	95.63	0.000
SD	8.32	9.41	
PNS-SO	23.400	25.437	0.096
SD	8.351	8.830	
PAS_1	10.881	9.853	0.055
SD	4.047	3.548	
Gonion-gnathion	75.584	70.816	0.000
SD	6.856	8.237	
Gonion-SE-PNS	13.981	12.899	0.032
SD	3.294	3.741	

AHI accounted for by BMI and airway dimensions was substantially less and was accounted for, to a greater extent, by BMI compared to cephalometric measurements.

Clinical and Nonclinical Group Membership

The group mean values for selected measures in clinical and nonclinical subjects are shown in Table 9. Note that the clinical group subjects had greater AHI and BMI, and were similar in age to the nonclinical group. Several, but not all, of the selected airway dimensions that contributed significantly to variations in AHI (Tables 1–8) were significantly different between the two groups.

Table 8—*Regression Models**

Variables	AHI Explained Variance Sequential R^2, %	p Value
AHI vs cephalometric measures, BMI, and age for AHI < 15, excluding BMI interactions (n = 90)		
Constant		0.016
BMI	15.8	0.000
PNS-SO	6.1	0.011
Total R^2	**21.9**	
AHI vs cephalometric measures, BMI, and age for AHI ≥ 15, excluding BMI interactions (n = 114)		
Constant		0.686
PV-A	15.9	0.000
BMI	12.5	0.000
S-N-B	3.5	0.009
Gonion-gnathion	3.2	0.057
PAS_1	2.7	0.021
Total R^2	**37.8**	

*See Table 1 for expansion of abbreviation.

Table 9—*Comparison of Selected Mean Values Between Clinical and Nonclinical Subgroups**

Measures	One-Way ANOVA Nonclinical	Clinical	p Value
Patients, No.	142	62	
AHI	20	48	0.00
SD	20	35	
BMI	29.1	32.5	0.00
SD	4.6	6.4	
Age	46.3	46.8	0.7
SD	7.5	9.7	
PV-A	102.5	88.2	0.00
SD	7.8	5.6	
PAS_1	10.1	10.7	0.4
SD	3.7	4.0	
PAS_2	9.3	11.2	0.00
SD	3.2	3.2	
PNS-SO	22.6	29.0	0.00
SD	8.4	7.7	
S-N-B	78.9	77.6	0.07
SD	4.6	4.2	
Gonion-SE-PNS	13.2	13.7	0.4
SD	3.6	3.4	
Co-ANS	101.2	89.7	0.00
SD	6.6	6.0	
Condylion to pogonion	132.3	113.1	0.00
SD	9.9	7.1	

*See Table 1 for expansion of abbreviation.

We determined whether simple membership in the clinical or nonclinical group had an effect on the distribution of residuals from the regression analysis of AHI vs BMI, age, and cephalometric dimensions (see "Materials and Methods" section). The analysis revealed no significant effects of group membership ($p > 0.4$). Thus, membership in the clinical or nonclinical group *per se* had no significant influence on the relative contributions of BMI and cephalometric airway measures and their interaction to the variance in AHI established across the continuum of clinical and nonclinical subjects.

Odds Ratios for AHI Using Cutoff Values for BMI and Airway Dimension

We determined the influence of a narrowed horizontal airway PV-A dimension on the likelihood of having mild or severe SDB. To determine odds ratios, we used logistic regression equations that incorporated BMI, the single most important airway dimension (PV-A), and their interaction (Tables 1, 2, 5).

Mild SDB (AHI of 15 to 30/h): In nonobese subjects (BMI < 28) the odds of having mild SDB

increased 5.2-fold on average (confidence interval [CI], 1.9 to 14.1) when PV-A distance was < 97 mm ($p < 0.01$). In obese subjects, the influence of a small PV-A distance increased the odds of an AHI > 15/h by 2.8-fold (CI, 1.2 to 6.6; $p < 0.02$).

Moderate-to-Severe SDB (AHI > 30/h): In nonobese subjects, when PV-A distance was < 97 mm the odds of having moderate-to-severe SDB increased an average of 7.5-fold (CI, 1.9 to 29.6; $p < 0.01$). In the obese, the influence of a small PV-A distance increased the odds of an AHI > 30/h by 2.7-fold (CI, 1.3 to 5.7; $p < 0.01$).

Discussion

Summary of Findings

We performed overnight polysomnography and 55 cephalometric measurements of the upper airway in a large group of clinical and nonclinical subjects in order to determine the independent contributions of obesity and craniofacial structures to SDB. First, over the entire spectrum of AHI, the magnitude of independent contributions from craniofacial morphology to AHI was comparable to that observed for obesity. A single horizontal airway dimension (PV-A distance) accounted for more than one half the variance in AHI attributable to all 55 cephalometric measurements. The odds of having moderate-to-severe SDB (AHI > 30/h) increased threefold to sevenfold when this horizontal airway dimension was narrow. Secondly, taken together, both craniofacial morphology and BMI accounted for approximately one half of the total variance in AHI, and together with their interactive effects accounted for a total of 65% of total AHI variance. This total variance in AHI accounted for by BMI and especially cephalometric dimensions in this population representing the entire continuum of SDB substantially exceeded that previously found in groups of clinical patients alone.[1–8] Thirdly, simply membership in a clinical or nonclinical group *per se* did not influence the relationship of cephalometric dimensions, BMI, and age to AHI. Fourthly, in nonobese subjects, cephalometric dimensions rather than BMI were the predominant predictors of AHI; whereas in obese subjects, cephalometric dimensions and BMI both contributed to the magnitude of AHI. Further, BMI was a relatively more important predictor of AHI in subjects with a larger anteroposterior facial dimension compared to subjects with a small anteroposterior facial dimension. Finally, the combination of craniofacial morphology and obesity was more important in predicting AHI in subjects who had higher levels of AHI compared to subjects with less severe SDB.

Limitations

Our study of anatomic determinants of SDB has several limitations, including the use of lateral cephalometry to quantify upper airway morphology, the characteristics of our study population, and our methods for quantifying SDB.

Cephalometry reduces the description of a complex, three-dimensional structure to single lateral dimensions. Cephalometrics are inadequate to measure important soft-tissue structures, such as the lateral pharyngeal wall thickness that was found to be increased in patients with sleep apnea.[15] Volumetric measurement of the upper airway is not available. Soft-tissue measurements, such as the soft palate or posterior pharyngeal wall, are sometimes poorly defined, making measurements of these important structures subject to great degrees of variability. So our limited measures of craniofacial morphology may underestimate the actual contributions when other anatomic measures are considered. Furthermore, it might also be argued that our cephalometric measurements were obtained in the upright position during wakefulness, which may have limited relevance to the sleeping state. However, we also measured cephalograms in the supine position in all nonclinical subjects (data not shown). Our consideration of these supine measures or of differences in airway dimensions between the upright and supine positions did not add significantly to our ability to predict severity of SDB in obese or nonobese subjects in the nonclinical group. These supine cephalometric data agree with previous reports.[1,5]

Our study population consisted of a sampling of working adults who were enriched by emphasizing recruitment of snorers (based on questionnaire data),[9] combined with patients referred specifically for the evaluation of clinically apparent sleep apnea syndrome. This combination of clinical and nonclinical subjects allowed us to represent the variance over the entire spectrum of SDB with sufficient power in the group of subjects with mild levels of breathing instability. This analysis was further enhanced by our use of stepwise multivariate regression techniques to identify independent correlations of AHI in the entire group and within groups of obese and nonobese, severe and mild SDB, and small and large airway dimensions. It was especially advantageous that our subject population provided normal distributions of values across the entire spectrum of measured variables. However, our subject population had no women, no racial diversity, and the upper age range was < 65 years. Accordingly, we were unable to determine the importance of extremes in aging as an interactive influence on the relationship between anatomic dimensions and AHI. Nor could

we test for an anatomic basis to the protective effect of female gender on sleep apnea.[9]

Quantifying SDB

All of our clinical and nonclinical subjects underwent overnight polysomnography in order to quantify SDB events. We chose to define an event as a reduction in $Sa_{O_2} \geq 2\%$ below baseline, with specific constraints on the duration and rate of fall and rise in Sa_{O_2}. The desaturation events had been previously shown to coincide with reductions or cessations of ventilation, as estimated from inductance plethysmography.[11] Although our definition is considerably more sensitive than the usual requirement of a 4% desaturation, we think it was important to document these milder forms of SDB because significant physiologic responses such as EEG arousal and substantial increases in BP and heart rate do occur in response to many of these events.[16] In addition, limited data have indicated that CPAP treatment in patients with relatively small amounts of SDB does improve daytime sleepiness.[17] Nevertheless, studies of this type are not yet sufficient in number to provide a precise definition of a clinically significant level of apnea and hypopnea in terms of the number and/or severity of events.

Accordingly, in order to compare our more liberal estimates of SDB with the usual more severe criteria, we contrasted the occurrence of 2% vs 4% desaturation events in the nonclinical cohort subjects (Fig 4). We found a tight curvilinear correlation of 2% desaturation events with 4% events ($r^2 = 95\%$). These data also showed that at the lower AHI (AHI < 30/h), the number of 4% desaturation events was about one half that of the 2% desaturation events for a given subject; and that as the number of 2% AHI events increased to > 30/h, the fraction of 4% events increased to two thirds or more of the total events. So, these tight correlations indicate that the number of milder desaturation events is predictive of the relative severity of more conventionally defined SDB events in a large population of subjects.

Finally, our analysis did not allow us to distinguish between the "causes" of desaturation by distinguishing events caused primarily by high airway resistance or airway obstruction from so-called "central" sleep apneas or hypopneas. Although it is often very difficult to distinguish these events, and especially hypopneic events, when only noninvasive measures are used in sleeping subjects, it would be of significant value to know which type of SDB events are best predicted by cephalometric dimensions and their interactions with BMI.

Role of Craniofacial Structure and Obesity in Predicting AHI

The effect of obesity on SDB may be mediated by at least two independent mechanisms. First, independent of any abnormality in craniofacial structure, obesity alone can compromise upper airway function and result in breathing instability and apnea during sleep. However, our observation that only 26% of the total variance in AHI is attributable to obesity, indicates that other influences such as craniofacial anatomy and neural control of upper airway muscle function and ventilation regulation may also contribute to breathing instability. The contribution of variance in BMI to variance of AHI in the present study is very similar to that reported in previous investigations[1,5] that studied primarily clinical populations. The importance of obesity alone was demonstrated when subjects were grouped according to normal and high BMI (Tables 2, 3). Despite AHI values in the obese that averaged twice that in the nonobese, major differences in craniofacial structure were not observed between the two groups. The only significant difference in cephalometric measurements was the larger posterior airspace in the obese at the level of the tip of the soft palate. This larger posterior airway during wakefulness in obese compared to nonobese subjects has also been reported in previous studies.[6,7]

The importance of craniofacial structure alone is demonstrated by the significant independent correlation of AHI with cephalometric measurements that represented four characteristics of the craniofacial skeleton and soft tissue. Significant predictive contributions to the AHI were made by the maxillary projection from the skull base, the posterior airway space, the mandibular protrusion, the relationship of the hard palate to the base of the skull, and the position of the hyoid bone (Fig 2). Our data indicate that 24% of the variance of AHI was accounted for by these cephalometric dimensions, and that the probability of having moderate-to-severe SDB was enhanced threefold to sevenfold by a narrowed maxillary projection from the skull base.

It is noteworthy that the most prominent cephalometric variable (PV-A distance) reflects the projection of the maxilla from the skull base. It is the maxilla that determines the effective horizontal dimension of the pharynx, and in particular the upper pharynx. A constricted maxilla places the upper pharynx (pharyngeal isthmus) at increased risk of collapse with loss of muscle tone. The efficacy of mandibular advancement with either oral appliance[18] or surgery[19] does not refute the primary importance of the maxilla in determining upper airway dimensions. Rather, mandibular advance-

ment has a major effect on both the nasopharyngeal and retropalatal airways, which are both determined by the maxillary dimension.[18,19] These findings challenge previous reports that a deficient mandible is the primary bony structural abnormality in obstructive sleep apnea.[20,21]

The second contribution of obesity to SDB is via its interaction with craniofacial structure as measured by the cephalometrics. When this interaction is considered, an additional 15% of variance in AHI (total, 66%) is explained in the entire group. This interaction is further illustrated by determining the explained variance in AHI in subjects with a lower anteroposterior dimension of the face (PV-A distance) compared to subjects with a greater anteroposterior dimension. In subjects with a reduced PV-A distance, 61% of the variance in AHI can be explained by a combination of BMI and cephalometrics, compared to only 36% in subjects with a large PV-A distance. Accordingly, we would predict that patients with a reduced anteroposterior facial dimension would be susceptible to exacerbate their SDB with even modest increases in body fat, as is common with aging. For example, epidemiologic longitudinal data from the Wisconsin Sleep Cohort obtained at 4-year intervals showed that increases in BMI with aging are associated with increasing AHI, but there was marked interindividual variability in changes in AHI for any given change in BMI.[22] According to present findings, individual differences in upper airway skeletal morphology may well explain these differences in individual susceptibility of AHI to weight gain. In contrast, patients with a large craniofacial structure (larger PV-A distance) are less constrained by skeletal and soft-tissue anatomy; thus, apnea and hypopnea in these persons may be more susceptible to functional abnormalities related to neural control of upper airway muscle function and ventilatory instability.[23–26]

Relative Contributions of Craniofacial Structure and Obesity in Predicting AHI in Subjects With Mild vs Moderate Sleep Apnea

The relative contribution of obesity and craniofacial structure to predicting the variance in AHI was dependent on the severity of the underlying SDB. Subjects who showed a mild degree of sleep apnea (AHI $<$ 15/h) showed a prominent component of BMI and a minimal component of craniofacial structure in predicting their variance in AHI. In contrast, subjects with more severe sleep apnea (AHI $>$ 15/h) showed a much more prominent contribution of craniofacial abnormality. Thus, in the more severe AHI group, the combination of obesity and craniofacial abnormality resulted in SDB. In the mild group, obesity alone was the predominant influence in causing the abnormal events. This difference is not surprising since obesity can predispose to oxygen desaturations, which formed the basis of our definition of hypopneas. First, the baseline Sa_{O_2} was likely to be lower in obese subjects because of ventilation-perfusion inequality. This in turn would place the Sa_{O_2} closer to the steep part of the oxygen-hemoglobin dissociation curve and cause a greater amount of oxygen desaturation for a given reduction in Pa_{O_2}. Second, obese subjects have poorer sleep quality independent of OSA, which causes periodic fluctuation of ventilation and, in turn, Sa_{O_2}. Third, low functional residual capacity and low oxygen stores provide less buffering against transient falls in oxygen saturation. Some authors have suggested that these findings indicate a different pathogenesis of disease in patients with mild vs severe sleep apnea. An alternative interpretation is that the spectrum of severity of disease represents a continuum based on the relative contributions of craniofacial abnormality and obesity. The strong interaction between these two determinants is further evidence of a combined effect on pathogenesis.

Summary

We have demonstrated, over a wide spectrum of clinical and nonclinical subjects with SDB, that the variance in AHI is determined to an almost equal degree by obesity and craniofacial structure. Subgroups of patients can be identified in whom skeletal structure or obesity play a more or less prominent role in the association with sleep apnea. The likelihood of having severe SDB in the presence of a narrowed horizontal dimension of the maxilla was increased threefold and sevenfold in obese and nonobese subjects, respectively. These findings also indicate that although obesity and craniofacial structure and their interactions play a major role in accounting for the variance in AHI, at least one third of the variance is unexplained by these variables and may be related to structural or functional abnormalities that were not measured in our study.

ACKNOWLEDGMENT: The authors thank Linda Evans for technical assistance, Terry Young for permission to study Wisconsin Cohort subjects, and Ron Leder and his staff in the University of Wisconsin sleep Cohort Laboratory.

References

1 Brander PE, Mortimore IL, Douglas NJ. Effect of obesity and erect/supine posture on lateral cephalometry: relationship to sleep-disordered breathing. Eur Respir J 1999; 13:398–402

2 Ferguson KA, Ono T, Lowe AA, et al. The relationship between obesity and craniofacial structure in obstructive sleep apnea. Chest 1995; 108:375–381

3 Tsuchiya M, Lowe AA, Pae EK, et al. Obstructive sleep apnea subtypes by cluster analysis. Am J Orthod Dentofacial Orthop 1992; 101:533–542
4 Sakakibara H, Tong M, Matsushita K, et al. Cephalometric abnormalities in non-obese and obese patients with obstructive sleep apnoea. Eur Respir J 1999; 13:403–410
5 Lowe AA, Ozbek MM, Miyamoto K, et al. Cephalometric and demographic characteristics of obstructive sleep apnea: an evaluation with partial least squares analysis. Angle Orthod 1997; 67:143–153
6 Partinen M, Guilleminault C, Quera-Salva MA, et al. Obstructive sleep apnea and cephalometric roentgenograms: the role of anatomic upper airway abnormalities in the definition of abnormal breathing during sleep. Chest 1988; 93:1199–1205
7 Hierl T, Humpfner-Hierl H, Frerich B, et al. Obstructive sleep apnoea syndrome: results and conclusions of a principal component analysis. J Craniomaxillofac Surg 1997; 25:181–185
8 Sforza E, Bacon W, Weiss T. Upper airway collapsibility and cephalometric variables in patients with obstructive sleep apnea. Am J Respir Crit Care Med 2000; 161(2 pt 1):347–352
9 Young T, Palta M, Dempsey J, et al. The occurrence of sleep-disordered breathing among middle-aged adults. N Engl J Med 1993; 29; 328:1230–1235
10 Rechtschaffen A, Kales A. A manual of standardized terminology, techniques and scoring systems for sleep stages of human subjects. Bethesda, MD: US Government Printing Office, 1968
11 Taha BH, Dempsey JA, Weber SM, et al. Automated detection and classification of sleep-disordered breathing from conventional polysomnography data. Sleep 1997; 20:991–1001
12 Johnson R, Wichern D. Applied multivariate statistical methods. 2nd ed. New York, NY: Prentice-Hall, 1988
13 Cook RD, Weisberg S. Residuals and influence in regression. New York, NY: Chapman and Hall, 1982
14 Cattell RB. The basis of recognition and interpretation of factors. Educ Psychol Meas 1962; 22:667–697
15 Schwab RJ, Gupta KB, Gefter WB, et al. Upper airway and soft tissue anatomy in normal subjects and patients with sleep-disordered breathing: significance of the lateral pharyngeal walls. Am J Respir Crit Care Med 1995; 152(5 pt 1):1673–1689
16 Morgan BJ, Demsey JA, Pegelow DF, et al. Blood pressure perturbations caused by subclinical sleep-disordered breathing. Sleep 1998; 21:737–746
17 Engleman HM, Kingshott RN, Wraith PK, et al. Randomized placebo-controlled crossover trial of continuous positive airway pressure for mild sleep apnea/hypopnea syndrome. Am J Respir Crit Care Med 1999; 159:461–467
18 Kato J, Isono S, Tanaka A, et al. Dose-dependent effects of mandibular advancement on pharyngeal mechanics and nocturnal oxygenation in patients with sleep-disordered breathing. Chest 2000; 117:1065–1072
19 Isono S, Tanaka A, Sho Y, et al. Advancement of the mandible improves velopharyngeal airway patency. J Appl Physiol 1995; 79:2132–2138
20 DeBerry-Borowiecki B, Kukwa A, Blanks RH. Cephalometric analysis for diagnosis and treatment of obstructive sleep apnea. Laryngoscope 1988; 98:226–234
21 Tangugusorn V, Skatvedt O, Krogstad O, et al. Obstructive sleep apnoea: a cephalometric study; Part 1. Cervico-craniofacial skeletal morphology. Eur J Orthod 1995; 17:45–56
22 Peppard PE, Young T, Palta M, et al. Longitudinal study of moderate weight change and sleep-disordered breathing. JAMA 2000; 284:3015–3021
23 Horner RL. Motor control of the pharyngeal musculature and implications for the pathogenesis of obstructive sleep apnea. Sleep 1996; 19:827–853
24 Hudgel DW, Gordon EA, Thanakitcharu S, et al. Instability of ventilatory control in patients with obstructive sleep apnea. Am J Respir Crit Care Med 1998; 158:1142–1149
25 Onal E, Burrows DL, Hart RH, et al. Induction of periodic breathing during sleep causes upper airway obstruction in humans. J Appl Physiol 1986; 61:1438–1443
26 Warner G, Skatrud JB, Dempsey JA. Effect of hypoxia-induced periodic breathing on upper airway obstruction during sleep. J Appl Physiol 1987; 62:2201–2211