ORIGINAL ARTICLE

Dynamic Upper Airway Imaging during Wakefulness in Obese Subjects with and without Sleep Apnea

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Abstract

Rationale: Obesity is a major risk factor for obstructive sleep apnea. Although greater dimensional changes in the upper airway during wake respiration have been noted in patients with apnea compared with control subjects, whether these differences remain in the presence of obesity is unknown.

Objectives: To evaluate upper airway anatomic characteristics and airway compliance (distensibility) in obese subjects with obstructive sleep apnea compared with obese control subjects.

Methods: Dynamic magnetic resonance imaging was performed in 157 obese subjects with apnea and 46 obese control subjects during wakefulness in the midsagittal and three axial upper airway regions (retropalatal, retroglossal, epiglottal). Differences in measurements between subjects with apnea and control subjects, and correlations with apnea–hypopnea index among subjects with apnea, were examined.

Measurements and Main Results: Measurements included airway areas and linear dimensions. Subject-specific coefficients of variation were calculated to examine variability in airway size. Controlling for covariates, the retropalatal area during respiration was significantly smaller in subjects with apnea than control subjects, based on the average ($P = 0.003$), maximum ($P = 0.004$), and minimum ($P = 0.001$) airway area. Airway narrowing was observed in anteroposterior and lateral dimensions (adjusted $P < 0.05$). Results were similar in an age, sex, and body mass index–matched subsample. There were significant correlations between apnea–hypopnea index and dynamic measures of airway caliber in the retropalatal and retroglossal regions among subjects with apnea.

Conclusions: Upper airway caliber during respiration was significantly narrower in obese subjects with apnea than obese control subjects in the retropalatal region. These findings provide further evidence that retropalatal airway narrowing plays an important role in the pathogenesis of obstructive sleep apnea in obese subjects.

Keywords: dynamic upper airway; obesity; obstructive sleep apnea; magnetic resonance imaging; respiration

Obstructive sleep apnea (OSA) is a common disorder characterized primarily by recurrent upper airway (UA) collapse during sleep (1). The structural narrowing of the UA combined with inadequate compensation for a decrease in UA neuromuscular tone is thought to play the key role in the pathogenesis of OSA (2). Imaging techniques, including cine computerized tomography and dynamic magnetic resonance imaging (MRI), can study the anatomic structure and dynamic function of the UA during wake and sleep (3–6). Such data have provided important insights into understanding UA obstruction in subjects with apnea (3–6).

Although UA collapse or closure in patients with OSA only occurs during sleep, studies using static or dynamic computerized tomography/MRI have shown UA narrowing in patients with OSA compared with control subjects during wakefulness (7, 8). Our previous study using cine computerized tomography found

(Received in original form November 3, 2017; accepted in final form July 24, 2018)

Supported by the NIH (R01HL089447 and P01HL094307) and China Scholarship Council (201508440455).

Author Contributions: Conception and design, Y.F., B.T.K., A.I.P., and R.J.S. Analysis and interpretation, Y.F., B.T.K., S.W., A.W., and R.J.S. Drafting of the manuscript, Y.F., B.T.K., and R.J.S. Critical revision, B.T.K., S.L., A.W., and R.J.S. Final approval of the version to be published, Y.F., B.T.K., S.W., S.L., A.I.P., and R.J.S.

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This article has an online supplement, which is accessible from this issue's table of contents at www.atsjournals.org.

Am J Respir Crit Care Med Vol 198, Iss 11, pp 1435–1443, Dec 1, 2018

Originally Published in Press as DOI: 10.1164/rccm.201711-2171OC on July 24, 2018
Internet address: www.atsjournals.org

At a Glance Commentary

Scientific Knowledge on the Subject: Obesity is a major risk factor for obstructive sleep apnea. However, most published data examining upper airway anatomy and dimensional changes have compared overweight or obese patients with apnea with control subjects without obesity or lean snorers. Our study addresses dynamic upper airway changes at multiple airway regions and airway compliance (distensibility) in obese subjects with and without obstructive sleep apnea.

What This Study Adds to the Field: Unlike static imaging, dynamic magnetic resonance imaging enables one to study the respiratory-related changes to the upper airway. We found that the retropalatal region of the upper airway was significantly narrower in obese subjects with apnea than obese control subjects during respiration. These findings provide further evidence that retropalatal airway narrowing plays an important role in the pathogenesis of obstructive sleep apnea in obese subjects.

greater dimensional changes in patients with OSA compared with control subjects during wake respiration, suggesting that UA compliance was greater in OSA subjects than control subjects (4). In addition, multiple studies by Badr and colleagues (9–11) have shown that UA compliance is increased in subjects with sleep apnea compared with normal control subjects in both wakefulness and sleep.

Obesity is present in most patients with OSA and is the major risk factor for the development and progression of sleep apnea (12). UA fat deposition in the parapharyngeal fat pads and tongue is thought to narrow the UA (7, 13, 14). UA collapsibility is also related to obesity (12). Pharyngeal critical closing pressure, a measure of airway collapsibility, was found to be associated with obesity measurements (body mass index [BMI], waist, neck circumference) in a cross-sectional study (15). Moreover, reduction in the UA critical closing pressure was observed in OSA subjects after weight loss, but not in weight stable subjects with apnea (16). These findings indicate that obesity directly affects the anatomy and functional physiology of the UA in OSA.

Because of the prevalence of obesity in patients with OSA, most published data examining UA structures and dimensional changes have compared overweight or obese subjects with apnea with control subjects without obesity or lean snorers (3, 4, 7, 14). Prior studies have not addressed dynamic UA changes in obese subjects with and without OSA, especially in relation to anatomy and airway compliance at multiple UA regions.

In the current study, we performed dynamic MRI in sagittal and three axial regions of the UA among obese subjects with apnea and obese control subjects during wake respiration. Based on previous findings (4), we hypothesized that, compared with obese control subjects, obese subjects with apnea would show smaller UA caliber in all UA regions and increased UA compliance (distensibility).

Methods

Participants

The present study used a case-control design in primarily obese patients with OSA and obese control subjects, with 97% of patients having a BMI $\geq$30 kg/m^2. The protocol was approved by the institutional review board of the University of Pennsylvania (Philadelphia, PA) and written informed consent was obtained from each subject. Obese cases were required to have an apnea–hypopnea index (AHI) $\geq$15 events/h and recruited primarily from the Center for Sleep and Circadian Neurobiology (Philadelphia, PA) outpatient practice. Obese control subjects were required to have an AHI $\leq$5 events/h and recruited in the Philadelphia region. Subjects with AHI $>$5 and $<$15 events/h were considered indeterminate and excluded.

Sleep Study

In-laboratory polysomnograms were performed using standard recording montages (13, 17) and scored using the alternative scoring criteria from the American Academy of Sleep Medicine (18), as previously described (19). Briefly, both thermal sensor and nasal pressure monitors were used in all subjects to measure airflow. Apneas were defined as a $\geq$90% drop in the thermal sensor excursion lasting $\geq$10 seconds; hypopneas were defined as a 50% reduction in nasal pressure airflow for $\geq$10 seconds and associated with $\geq$4% desaturation and/or an arousal. An event was called central when there was no associated chest wall or abdominal movement or obstructive or mixed if there was associated chest wall and abdominal movement. The AHI was calculated as the mean number of apnea and hypopnea events per hour of sleep.

Dynamic UA MRI Acquisition

UA imaging was performed in the supine position during wakefulness using a 1.5-T MAGENETO Espree Scanner (Siemens Medical Systems). Subjects were instructed to breathe through the nose with mouth closed and refrain from swallowing and moving their head during scanning. Patients were talked to before and after each scanning sequence to ensure that they were awake.

Rapid dynamic imaging was performed using an ultrafast gradient echo sequence at the following pulse sequence parameters: TR (repetition time) of 490–535 ms; TE (echo time) of 1.46 ms; flip angle of 26°; 930-Hz bandwidth; 192 $\times$ 192 matrix; signal-to-noise ratio of 1; number of excitations = 1; field-of-view of 250 mm; slice thickness of 5.0 mm; and acquisition time of 54 seconds in sagittal region and 49 seconds in each axial region. One sagittal and three axial sets of 100 slices were obtained from the midsagittal, mid–soft palate (retropalatal), midtongue (retroglossal), and midepiglottis (epiglottal) regions (Figure 1). The axial images were all perpendicular to the scanner bed. The sagittal localizer was used to make sure there was no neck flexion or extension.

UA Analysis and Measurements

MRIs of the UA were manually examined at the Pulmonary/Sleep Imaging laboratory using Amira version 5.4.1 (Visage Imaging). The ultrafast MRIs were analyzed in four regions, each with 100 slices. MRIs where the subject was coughing, swallowing, opening their mouth, or making any other UA movements that were not related to normal respiration were excluded from the analysis. We were able to exclude these images because the airway would suddenly be blocked or become blurred because of motion. Images measured immediately

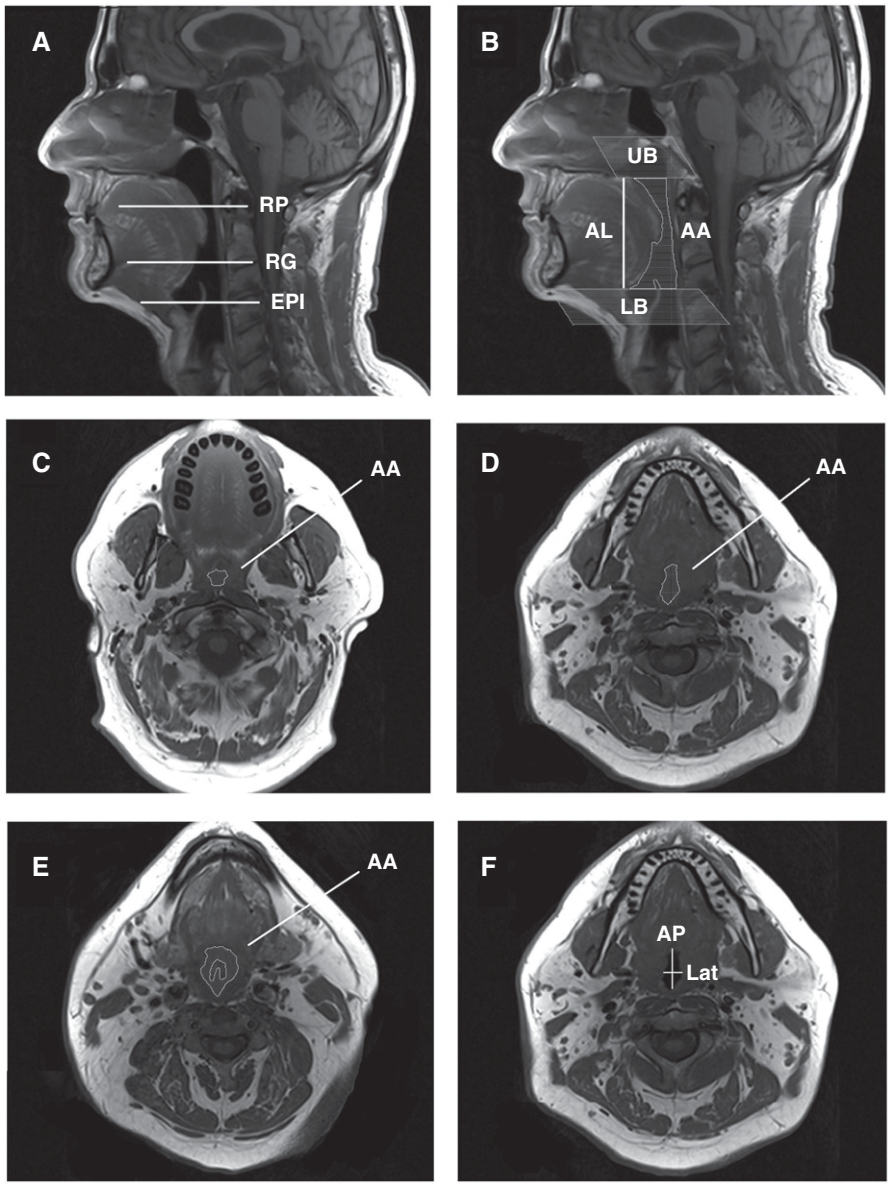

Figure 1. Upper airway imaging and measurements (two-dimensional areas and linear dimensions are measured in both sagittal and axial images). (*A*) Midsagittal image showing the location of the axial images (RP, RG, and Epi). (*B*) Midsagittal image showing the upper boundary set through the top of the hard palate and lower boundary through the bottom of C4; the airway between these two boundaries represents the midsagittal airway area and the perpendicular distance between two boundaries is the length of airway. (*C–E*) Examples of images in the three axial regions: retropalatal (*C*), retroglossal (*D*), and epiglottal (*E*). (*F*) Example of the method used to measure airway lateral and anteroposterior dimensions. The lateral and anteroposterior dimensions are measured in the three axial regions. AA = airway area; AL = airway length; AP = anterposterior; EPI = epiglottal; LAT = lateral; LB = lower boundary; RG = retroglossal; RP = retropalatal; UB = upper boundary.

before and after such nonrespiratory "events" were also excluded.

Measurements included maximum, minimum, and average airway areas in each of the axial regions (retropalatal, retroglossal, epiglottal) and on the midsagittal image during wake respiration. Linear dimensions (anteroposterior [AP] [9] and lateral dimensions in axial images and airway length in midsagittal scans) were obtained on the images showing the maximum and minimum area of each region. Within the midsagittal region, maximum and minimum airway areas were corrected for airway length on the corresponding image, because airway length is thought to be greater in subjects with apnea than control subjects and is greater in men than women (20, 21). Airway length was defined as the perpendicular distance between the hard palate and bottom of the C4 vertebra. AP distance was determined across the midpoint of the airway and lateral distance was defined as the distance from the left to the right margins of the airway through the airway midpoint (Figure 1). To examine variability in airway size (a marker of airway compliance, distensibility), subject-specific coefficients of variation (CV) were calculated in each region as the ratio of the standard deviation to the mean across airway area measures. One technician performed the image analysis and was blinded to subject group.

Reproducibility and Reliability

To assess reliability and reproducibility of measurements, we examined baseline and repeated dynamic MRI at a 6-month follow-up visit within 14 weight-stable individuals (defined as $<2.5\%$ change in body weight). To test the reliability of the image analysis, baseline MRIs in the same 14 participants were analyzed twice by the same examiner, 4 months apart. Reliability of the measurements was assessed using intraclass correlation coefficients (ICCs) and quantified based on definitions provided by Landis and Koch (22) as: poor (ICC <0.00), slight (0.00–0.20), fair (0.21–0.40), moderate (0.41–0.60), substantial (0.61–0.80), or almost perfect (0.81–1.00).

Statistical Analysis

The online supplement provides complete statistical analysis. Briefly, differences in dynamic MRI measurements between subjects with apnea and control subjects were assessed using linear regression models. For each UA measure, we fit a linear regression model with apnea status as an independent variable and report the model-derived β-estimate and 95% confidence interval, which is equal to the estimated mean difference for subjects with apnea compared with control subjects. In addition to comparing differences between subjects with apnea and control subjects, we examined whether there were associations between AHI and dynamic MRI measures among subjects with apnea only. Analyses were performed using unadjusted and partial (e.g., adjusted) Pearson correlation

coefficients. All analyses in the full sample were performed unadjusted and controlling for primary covariates of age, BMI, sex, and race. In addition to primary analyses in the entire study population, to further reduce bias caused by differences in clinical covariates, we performed complementary analyses within a subsample of apneic–control pairs matched with respect to age (within 5 yr), BMI (within 2.5 kg/m^2), and sex. Using these criteria, a total of 36 pairs were selected for inclusion in this subsample.

Results

Demographic Characteristics and OSA Status

A total of 157 subjects with apnea (AHI ⩾15 events/h) and 46 control subjects (AHI ⩽5 events/h) were studied. The population was obese (37.8 ± 7.5 kg/m^2) and middle-aged (48.9 ± 11.6 yr) on average; 44.8% were male and 53.2% African American. Demographic characteristics stratified by OSA status are shown in Table 1. Mean AHI was 42.4 ± 27.3 events/h in subjects with apnea compared with 2.7 ± 1.4 events/h in control subjects. Subjects with apnea were older ($P < 0.0001$) and had greater BMI (38.7 ± 7.8 kg/m^2) than control subjects ($P < 0.0001$), although the control subjects were also obese (BMI of 34.6 kg/m^2). There were no differences in sex ($P = 0.222$) or race ($P = 0.927$) between subjects with apnea and control subjects.

Table E1 in the online supplement shows the characteristics of apneic–control pairs matched on age, BMI, and sex. In the overall matched sample, there were no differences in age ($P = 0.844$), race ($P > 0.999$), or BMI ($P = 0.682$); the sample was matched for sex. Average AHI was 3.0 ± 1.4 events/h among control subjects and 32.3 ± 20.7 events/h among subjects with apnea. When examining within-pair differences, subjects with apnea tended to be slightly heavier (+0.49 kg/m^2; $P = 0.006$), although this difference is not clinically significant.

Reproducibility and Reliability of the Airway Measurements

Reliability analyses of repeated dynamic airway measurements from images taken 6 months apart in a subset of weight-stable patients are shown in Table E2. Results suggest that most of the measurements obtained through dynamic UA imaging are at least moderately reproducible (ICC >0.40), except within the epiglottal region, where results were less reliable. Specifically, using criteria of Landis and Koch (22) described in the Methods, all measurements in the midsagittal region had good reliability, with ICC statistics ranging from moderate (ICC, 0.55) to almost perfect (0.88). Within the retropalatal region, the maximum (0.57) and minimum (0.58) airway areas were moderately reliable, the average airway area (0.62) and AP distance at maximum area (0.62) were substantially reliable, and the AP distance at maximum (0.90) showed almost perfect reliability. The remaining three measures in the retropalatal region had only slight/fair reliability (ICCs between 0.19 and 0.37). Within the retroglossal region, all measurements except the lateral distance at maximum area (0.24) showed at least moderate reliability, with ICCs ranging from 0.52 to 0.91. In the epiglottal area, measurements showed the lowest reliability over time, with moderate reliability for only the CV of airway area (0.58) and AP distances at maximum (0.52) and minimum areas (0.48). The remaining measures in the epiglottal region showed slight or fair reliability, with lateral distance at the minimum in the poor range.

Intraexaminer reproducibility estimates for repeated analysis of the same dynamic MRI are also shown in Table E2. All measures of airway size, length, AP distance, and lateral distance, as well as CV in the midsagittal, retropalatal, and retroglossal regions, had ICC ⩾0.89 when repeating the analysis using the same dynamic image, whereas the CV in the epiglottis was moderately reliability (ICC, 0.61). Thus, the analysis technique showed almost perfect reliability.

Dynamic Airway Measurements Comparison with OSA in the Four UA Regions

Table 2 shows unadjusted comparisons between subjects with apnea and control subjects in different airway regions. Airway area was significantly larger in the midsagittal region in subjects with apnea, specifically for the average ($P = 0.0019$) and maximum corrected for airway length ($P = 0.0032$). Airway lengths in both the maximum ($P = 0.0066$) and minimum ($P = 0.0088$) midsagittal area were significantly longer in subjects with apnea. The larger midsagittal airway length explains part of the increased airway area in subjects with apnea. However, the significantly larger maximum airway area after controlling for airway length in subjects with apnea suggests that the width of the midsagittal airway was also greater. This was not true for the minimum airway corrected for length. There were no differences in the CV of the sagittal airway area.

Although the airway area was greater in subjects with apnea in the midsagittal region, the opposite was true in the retropalatal region. All three measures of retropalatal airway area (Table 2) were significantly or nominally smaller in subjects with apnea compared with control subjects, including the average ($P = 0.0030$), maximum ($P = 0.0183$), and minimum ($P = 0.0004$) areas. Smaller retropalatal airway measurements were observed in subjects with apnea for both AP distance at the maximum ($P = 0.0371$) and minimum ($P = 0.0010$) and lateral

Table 1. Demographic Characteristics of the Study Sample

Measure	Overall	AHI ⩽5 Events/h	AHI ⩾15 Events/h	*P* Value*
n	203	46	157	—
Age, yr	**48.9 ± 11.6**	**42.7 ± 13.1**	**50.7 ± 10.5**	**<0.0001**
Male, %	44.8	37.0	47.1	0.222
Race, %				0.927
White	43.4	43.5	43.3	
African American	53.2	52.2	53.5	
Other	3.5	4.4	3.2	
BMI, kg/m^2	**37.8 ± 7.5**	**34.6 ± 4.9**	**38.7 ± 7.8**	**<0.0001**
AHI, events/h	**33.4 ± 29.2**	**2.7 ± 1.4**	**42.4 ± 27.3**	**<0.0001**

Definition of abbreviations: AHI = apnea–hypopnea index; BMI = body mass index.
Data are shown as mean ± SD unless otherwise indicated. Significant ($P < 0.05$) differences are shown in bold.
*P value from Student's t test or chi-square test comparing obstructive sleep apnea with control subjects for continuous or categorical variables, respectively.

Table 2. Dynamic Airway Measurements in Subjects with Apnea and Control Subjects

Measurement	AHI ⩽5 Events/h		AHI ⩾15 Events/h		*P* Value*
	n	Mean ± SD	*n*	Mean ± SD	
Midsagittal					
Average airway area, mm^2	**42**	**733.3 ± 275.8**	**149**	**895.4 ± 299.9**	**0.0019**
CV of airway area, %	42	6.8 ± 4.0	149	7.9 ± 4.7	0.2037
Airway length in slice with maximum area, mm	**42**	**74.6 ± 11.1**	**149**	**80.1 ± 11.7**	**0.0066**
Airway length in slice with minimum area, mm	**42**	**74.4 ± 10.8**	**149**	**79.8 ± 11.9**	**0.0088**
Maximum airway area corrected for length, mm	**42**	**11.2 ± 2.8**	**149**	**12.9 ± 3.4**	**0.0032**
Minimum airway area corrected for length, mm	42	8.3 ± 2.5	149	9.1 ± 2.6	0.0907
Middle soft palate (retropalatal)					
Average airway area, mm^2	**45**	**227.0 ± 118.4**	**149**	**168.8 ± 112.1**	**0.0030**
CV of airway area, %	**45**	**11.0 ± 12.3**	**149**	**16.5 ± 13.2**	**0.0138**
Maximum airway area, mm^2	**45**	**275.9 ± 143.9**	**149**	**221.1 ± 132.7**	**0.0183**
Minimum airway area, mm^2	**45**	**188.0 ± 107.4**	**149**	**125.0 ± 101.8**	**0.0004**
Lateral distance at maximum area, mm	45	14.9 ± 5.1	149	14.0 ± 5.1	0.2844
Lateral distance at minimum area, mm	**45**	**12.3 ± 5.2**	**149**	**10.2 ± 5.3**	**0.0205**
AP distance at maximum area, mm	**45**	**19.8 ± 6.8**	**149**	**17.6 ± 5.9**	**0.0371**
AP distance at minimum area, mm	**45**	**17.6 ± 7.2**	**149**	**14.0 ± 6.2**	**0.0010**
Middle tongue (retroglossal)					
Average airway area, mm^2	45	173.4 ± 89.8	153	190.6 ± 101.7	0.3086
CV of airway area, %	**45**	**11.2 ± 7.1**	**153**	**16.5 ± 12.5**	**0.0005**
Maximum airway area, mm^2	45	225.9 ± 122.8	153	262.9 ± 160.7	0.1023
Minimum airway area, mm^2	45	135.4 ± 73.4	153	130.9 ± 83.9	0.7441
Lateral distance at maximum area, mm	45	18.7 ± 7.6	153	18.6 ± 8.6	0.9459
Lateral distance at minimum area, mm	**45**	**14.7 ± 5.7**	**153**	**12.5 ± 6.2**	**0.0377**
AP distance at maximum area, mm	**45**	**14.9 ± 4.2**	**153**	**17.3 ± 4.6**	**0.0019**
AP distance at minimum area, mm	45	12.6 ± 3.5	153	13.3 ± 4.6	0.2335
Middle epiglottis (epiglottal)					
Average airway area, mm^2	45	321.0 ± 143.0	154	361.0 ± 151.3	0.1155
CV of airway area, %	**45**	**7.7 ± 4.9**	**154**	**11.3 ± 6.8**	**0.0002**
Maximum airway area, mm^2	**45**	**385.2 ± 187.5**	**154**	**461.2 ± 206.1**	**0.0277**
Minimum airway area, mm^2	45	264.6 ± 115.4	154	277.5 ± 129.4	0.5477
Lateral distance at maximum area, mm	45	24.7 ± 6.8	154	26.1 ± 7.0	0.2349
Lateral distance at minimum area, mm	45	21.2 ± 5.2	154	21.1 ± 6.0	0.9010
AP distance at maximum area, mm	**45**	**19.1 ± 4.9**	**154**	**22.3 ± 5.2**	**0.0004**
AP distance at minimum area, mm	**45**	**16.7 ± 4.2**	**154**	**18.7 ± 4.7**	**0.0101**

Definition of abbreviations: AHI = apnea–hypopnea index; AP = anteroposterior; CV = coefficient of variation.
Significant or suggestive ($P < 0.05$) differences are shown in bold.
*P value from Student's t test comparing dynamic measure between subjects with apnea and control subjects.

distance at the minimum ($P = 0.0205$), but not maximum ($P = 0.2844$), airway area. There were no differences in airway areas in the retroglossal and epiglottal regions, except for a nominally larger maximum area ($P = 0.0277$) in the epiglottal region of subjects with apnea. Significantly larger AP distances of the maximum airway were observed in subjects with apnea in the retroglossal ($P = 0.0019$) and epiglottal ($P = 0.0004$) regions. In all three axial regions, CVs of airway area were significantly larger in these unadjusted analyses, suggesting increased airway compliance (distensibility) in subjects with apnea.

After controlling for age, sex, BMI, and race (Table 3), area measures in retropalatal region remained significantly different between subjects with apnea and control subjects, including the average ($P = 0.0025$), maximum ($P = 0.0038$), and minimum ($P = 0.0013$). Similarly, in the retropalatal region there were statistically significant differences in AP distance ($P = 0.0033$) and lateral distance ($P = 0.0108$) at the minimum area, and nominally significant differences in AP ($P = 0.0223$) and lateral ($P = 0.0400$) distances at the maximum area. There were no differences in airway measurements in either the midsagittal or the other two axial regions in adjusted analyses, suggesting that results in these regions observed in unadjusted analyses may be caused by differences in demographic factors. Thus, data indicate that after covariate adjustments, respiratory-related differences in obese subjects with apnea and control subjects were related to narrowing in retropalatal region, but not the other UA regions. The CV for the axial airway areas showed no statistical significance after adjustment, although trends were similar to unadjusted analyses.

Results in the matched subsample were similar to adjusted analyses in the full dataset, suggesting that remaining covariate imbalance is not driving associations (Tables E3 and E4). In unadjusted analyses within matched pairs, we see differences in the retropalatal region, but not in the midsagittal, retroglossal, or epiglottal regions. Subjects with apnea had smaller airway areas in the retropalatal region compared with matched control subjects when examining the average (163.1 vs. 237.8 mm^2; $P = 0.023$), maximum (208.0 vs. 292.2; $P = 0.038$), or minimum (122.0 vs. 195.4; $P = 0.010$). There was also evidence for a smaller lateral distance in subjects with apnea at both the maximum

Table 3. Differences in Dynamic Measurements between Subjects with Apnea and Control Subjects

Measurement	Unadjusted		Adjusted*	
	β (95% CI)†	*P* Value	β (95% CI)†	*P* Value
Midsagittal				
Average airway area, mm^2	**162.0 (60.4 to 263.6)**	**0.0019**	46.8 (−46.3 to 140.0)	0.3226
CV of airway area, %	1.02 (−0.56 to 2.60)	0.2037	0.60 (−1.15 to 2.35)	0.4989
Airway length in slice with maximum area, mm	**5.67 (1.57 to 9.58)**	**0.0066**	2.93 (−0.51 to 6.37)	0.0943
Airway length in slice with minimum area, mm	**5.40 (1.38 to 9.43)**	**0.0088**	2.85 (−0.58 to 6.27)	0.1026
Maximum airway area corrected for length, mm	**1.71 (0.58 to 2.83)**	**0.0032**	0.51 (−0.62 to 1.64)	0.3753
Minimum airway area corrected for length, mm	0.76 (−0.12 to 1.64)	0.0907	0.01 (−0.89 to 0.90)	0.9865
Middle soft palate (retropalatal)				
Average airway area, mm^2	**−58.2 (−96.3 to −20.1)**	**0.0030**	**−66.6 (−109.4 to −23.8)**	**0.0025**
CV of airway area, %	**5.49 (1.13 to 9.85)**	**0.0138**	3.69 (−1.20 to 8.58)	0.1381
Maximum airway area, mm^2	**−54.8 (−100.2 to −9.4)**	**0.0183**	**−75.4 (−126.1 to −24.6)**	**0.0038**
Minimum airway area, mm^2	**−63.0 (−97.6 to −28.4)**	**0.0004**	**−64.6 (−103.6 to −25.6)**	**0.0013**
Lateral distance at maximum area, mm	−0.93 (−2.65 to 0.78)	0.2844	**−1.96 (−3.84 to −0.09)**	**0.0400**
Lateral distance at minimum area, mm	**−2.09 (−3.86 to −0.33)**	**0.0205**	**−2.57 (−4.53 to −0.60)**	**0.0108**
AP distance at maximum area, mm	**−2.18 (−4.23 to −0.13)**	**0.0371**	**−2.69 (−4.99 to −0.39)**	**0.0223**
AP distance at minimum area, mm	**−3.66 (−5.82 to −1.51)**	**0.0010**	**−3.71 (−6.17 to −1.25)**	**0.0033**
Middle tongue (retroglossal)				
Average airway area, mm^2	17.2 (−16.0 to 50.3)	0.3086	−8.8 (−45.2 to 27.6)	0.6344
CV of airway area, %	**5.26 (1.41 to 9.11)**	**0.0077**	3.41 (−0.93 to 7.75)	0.1229
Maximum airway area, mm^2	37.0 (−14.1 to 88.2)	0.1549	−10.4 (−66.3 to 45.5)	0.7136
Minimum airway area, mm^2	−4.5 (−31.8 to 22.8)	0.7441	−18.0 (−48.5 to 12.4)	0.2448
Lateral distance at maximum area, mm	−0.10 (−2.92 to 2.72)	0.9459	−1.59 (−4.61 to 1.44)	0.3028
Lateral distance at minimum area, mm	**−2.16 (−4.20 to −0.13)**	**0.0377**	−2.01 (−4.24 to 0.21)	0.0761
AP distance at maximum area, mm	**2.43 (0.91 to 3.95)**	**0.0019**	1.16 (−0.38 to 2.71)	0.1382
AP distance at minimum area, mm	0.77 (−0.70 to 2.24)	0.3043	−0.13 (−1.73 to 1.48)	0.8746
Middle epiglottis (epiglottal)				
Average airway area, mm^2	40.0 (−9.9 to 90.0)	0.1155	2.83 (−50.7 to 56.3)	0.9171
CV of airway area, %	**3.56 (1.42 to 5.70)**	**0.0012**	2.38 (0.00 to 4.76)	0.0504
Maximum airway area, mm^2	**76.0 (8.4 to 143.5)**	**0.0277**	21.6 (−50.1 to 93.4)	0.5529
Minimum airway area, mm^2	12.9 (−29.3 to 55.1)	0.5477	−9.1 (−55.3 to 37.2)	0.6994
Lateral distance at maximum area, mm	1.41 (−0.92 to 3.74)	0.2349	0.67 (−1.84 to 3.18)	0.5993
Lateral distance at minimum area, mm	−0.12 (−2.07 to 1.82)	0.9010	−0.44 (−2.57 to 1.69)	0.6867
AP distance at maximum area, mm	**3.14 (1.42 to 4.87)**	**0.0004**	1.30 (−0.49 to 3.09)	0.1524
AP distance at minimum area, mm	**2.00 (0.48 to 3.53)**	**0.0101**	0.77 (−0.87 to 2.40)	0.3555

Definition of abbreviations: AP = anteroposterior; CI = confidence interval; CV = coefficient of variation.
Significant or suggestive ($P < 0.05$) differences are shown in bold.
*Model adjusted for age, body mass index, sex, and race.
†β coefficient and 95% CI from linear regression model representing the estimated mean difference in indicated measure between subjects with apnea and control subjects (calculated as apneic value – control value).

(12.6 vs. 16.2 mm; $P = 0.016$) and minimum (9.8 vs. 13.3; $P = 0.019$) areas. Although not significant in this reduced sample, associations for AP distances and CV of airway area were similar to those in adjusted analyses from the full sample. Differences between matched subjects with apnea and control subjects were similar, or in some cases larger, when adding additional adjustment for residual differences in age, BMI, and race, although differences were no longer statistically significant (Table E4).

Correlations of OSA Severity with Dynamic Imaging Phenotypes

The correlations between dynamic airway measures and AHI among subjects with apnea are shown in Table 4. Results suggest significant associations between several dynamic measures and more severe OSA, particularly in the retropalatal and retroglossal regions.

Within the midsagittal region, we observed significant unadjusted correlations between OSA severity and both the maximum ($P = 0.0020$) and minimum ($P = 0.0022$) airway length in unadjusted analyses among subjects with apnea; longer airway length was associated with more severe OSA. However, these correlations were no longer significant controlling for covariates. A nominally significant correlation between smaller minimum airway area and more severe OSA did emerge when controlling for covariates ($P = 0.0481$).

Several variables in the retropalatal and retroglossal regions were associated with higher AHI among subjects with apnea in both unadjusted and adjusted analyses. For unadjusted analyses in the retropalatal region, a larger CV of airway area was significantly associated with OSA severity ($P = 0.0095$). Moreover, smaller average ($P = 0.0498$) and minimum ($P = 0.0177$) areas and AP ($P = 0.0390$) and lateral ($P = 0.0246$) distances at the minimum area were nominally associated with more severe OSA. Results for these measures were similar when controlling for covariates; lateral distance at the minimum area became statistically, rather than nominally, significant ($P = 0.0097$). Additionally, both smaller maximum airway area ($P = 0.0444$) and smaller AP distance at the maximum

Table 4. Pearson Correlation of OSA Severity (AHI) with Dynamic Imaging Phenotypes in Subjects with Apnea*

Measurement	*n*	Unadjusted		Adjusted†	
		Rho	*P* Value	Rho	*P* Value
Midsagittal					
Average airway area, mm^2	149	0.17	0.0414	−0.11	0.1721
CV of airway area, %	149	0.12	0.1415	0.15	0.0753
Airway length in slice with maximum area, mm	149	**0.25**	**0.0020**	0.03	0.7411
Airway length in slice with minimum area, mm	149	**0.25**	**0.0022**	0.02	0.8389
Maximum airway area corrected for length, mm	149	0.13	0.1222	−0.07	0.3971
Minimum airway area corrected for length, mm	149	0.05	0.5262	**−0.17**	**0.0481**
Middle soft palate (retropalatal)					
Average airway area, mm^2	149	**−0.16**	**0.0498**	**−0.18**	**0.0301**
CV of airway area, %	149	**0.21**	**0.0095**	**0.22**	**0.0076**
Maximum airway area, mm^2	149	−0.13	0.1131	**−0.17**	**0.0444**
Minimum airway area, mm^2	149	**−0.19**	**0.0177**	**−0.20**	**0.0183**
Lateral distance at maximum area, mm	149	−0.05	0.5704	−0.12	0.1548
Lateral distance at minimum area, mm	149	**−0.17**	**0.0390**	**−0.21**	**0.0097**
AP distance at maximum area, mm	149	−0.15	0.0735	**−0.18**	**0.0294**
AP distance at minimum area, mm	149	**−0.18**	**0.0246**	**−0.21**	**0.0130**
Middle tongue (retroglossal)					
Average airway area, mm^2	153	−0.05	0.5686	−0.16	0.0507
CV of airway area, %	153	**0.26**	**0.0014**	**0.24**	**0.0034**
Maximum airway area, mm^2	153	−0.02	0.8330	−0.13	0.1108
Minimum airway area, mm^2	153	−0.13	0.1102	**−0.21**	**0.0103**
Lateral distance at maximum area, mm	153	−0.10	0.2047	−0.10	0.2052
Lateral distance at minimum area, mm	153	**−0.21**	**0.0109**	**−0.19**	**0.0177**
AP distance at maximum area, mm	153	**0.19**	**0.0191**	0.00	0.9943
AP distance at minimum area, mm	153	**−0.16**	**0.0455**	**−0.29**	**0.0003**
Middle epiglottis (epiglottal)					
Average airway area, mm^2	154	0.09	0.2867	−0.03	0.7497
CV of airway area, %	154	**0.18**	**0.0299**	0.11	0.2010
Maximum airway area, mm^2	154	0.12	0.1242	0.01	0.9390
Minimum airway area, mm^2	154	0.03	0.7562	−0.05	0.5074
Lateral distance at maximum area, mm	154	0.10	0.2316	0.07	0.3867
Lateral distance at minimum area, mm	154	0.02	0.8292	0.03	0.7328
AP distance at maximum area, mm	154	0.14	0.0732	−0.01	0.8863
AP distance at minimum area, mm	154	0.10	0.2358	−0.02	0.7741

Definition of abbreviations: AHI = apnea–hypopnea index; AP = anteroposterior; BMI = body mass index; CV = coefficient of variation; OSA = obstructive sleep apnea.
Significant or suggestive ($P < 0.0125$) differences are shown in bold.
*Sample restricted to subjects with apnea.
†Model adjusted for age, BMI, sex, and race.

area ($P = 0.0294$) became nominally significant after adjustment. This suggests that correlations in the retropalatal region are not driven by known clinical risk factors.

Similarly, in the retroglossal region there were significant unadjusted correlations between severity of OSA and larger CV of airway area ($P = 0.0014$) and smaller lateral distance at the minimum area ($P = 0.0109$), and nominal correlations between AHI severity and larger AP distance at the maximum ($P = 0.0191$) and smaller AP distance at the minimum ($P = 0.0455$). Correlations between larger CV ($P = 0.0034$) and smaller AP distance at the minimum ($P = 0.0003$) remained or became statistically significant, respectively, after adjustment, whereas the negative correlation with lateral distance at the minimum became nominally significant ($P = 0.0177$). A smaller minimum airway area also became significantly correlated with more severe OSA ($P = 0.0103$) after controlling for covariates in the retroglossal region.

In the epiglottal region, only the CV showed an unadjusted correlation with OSA severity ($P = 0.0299$). There were no significant correlations in adjusted analyses.

Discussion

We studied the dynamic behavior of UA with MRI during wake respiration in obese subjects with apnea and obese control subjects. The main findings of the study include: *1*) most dynamic airway measures are at least moderately reproducible within a weight stable population; *2*) the analysis technique showed high reliability in repeated analyses; *3*) airway area in the retropalatal region was significantly smaller in obese subjects with apnea compared with obese control subjects, independent of age, sex, BMI, and race; *4*) airway narrowing in subjects with apnea was observed in both AP and lateral dimensions in the retropalatal region; and *5*) there were strong correlations between AHI and many of the dynamic measures in the retropalatal and retroglossal regions.

Although we found larger CV in airway area among subjects with apnea in unadjusted analyses, suggesting more compliant airways, these results did not remain significant in adjusted analyses. Results in the retropalatal region were supported by analyses within a subsample of subjects with apnea and control subjects matched for age, BMI, and sex. Our findings suggest that dynamic airway changes in the retropalatal region, as opposed to airway changes in the retroglossal, epiglottal, or midsagittal regions, are strongly associated with OSA in obese subjects. In addition, dynamic respiratory-related airway changes may provide a unique phenotype for personalized treatments and precision medicine approaches for the diagnosis and management of OSA. Dynamic imaging may be similar to other recently identified physiologic traits including airway collapsibility (P_{crit}), loop gain, pharyngeal muscle responsiveness, and arousal threshold, which have been shown to be important in the pathogenesis and treatment of OSA (23, 24).

UA Narrowing and Obesity

Obstruction of the UA in subjects with apnea is thought to occur at all levels, from the nasopharynx to the laryngopharynx (25). Among those regions, the retropalatal region of the pharynx has been consistently shown to be smaller in subjects with apnea than control subjects with static and dynamic

UA imaging (7, 14, 26). However, these studies did not specifically compare obese control subjects with obese subjects with apnea. Our results provide new data, showing that obese subjects with apnea have greater retropalatal airway narrowing during wake respiration compared with obese control subjects. The other UA regions (retroglossal, epiglottal, and midsagittal) did not show differences in dynamic respiratory-related characteristics after covariate adjustments. There were also strong correlations between the dynamic respiratory-related retropalatal airway characteristics and OSA severity among subjects with apnea.

Overall, these findings suggest that airway narrowing in the retropalatal region plays the key role in the pathogenesis of sleep apnea in obese subjects. Furthermore, our data indicate that dynamic airway narrowing of the retropalatal region in obese subjects with apnea occurs not only in the lateral dimension, but also in the AP dimension. This is in contrast to our previous findings predominantly showing lateral airway narrowing in subjects with apnea compared with control subjects (7). The lateral airway narrowing during dynamic imaging is likely associated with respiratory-related movement of the lateral pharyngeal walls, whereas the AP airway narrowing is likely caused by respiratory-related movement of the soft palate and tongue.

Our data showing that the dynamic behavior of the airway in the retropalatal region is more important in distinguishing obese subjects with apnea from obese control subjects than airway measures in the other regions may relate to the regional effect of obesity on the UA. Obesity can increase sleep apnea susceptibility by increasing mechanical loads. Fat surrounding the UA can narrow the airway by being deposited in the tongue, soft palate, and parapharyngeal fat pads (7, 13). Increased fat deposition specifically in the soft palate and parapharyngeal fat pads would directly affect the retropalatal region, but not the retroglossal or epiglottal regions. In the retropalatal region, which is the smallest region of the UA, even small increases in the mechanical load could make airway narrowing much more prominent. Moreover, fat deposits have been observed in the soft palate of subjects with apnea, but not control subjects (27).

UA Compliance (Distensibility) in Obese OSA Population

Unlike static imaging, dynamic MRI can examine the compliance (distensibility) of the airway during respiration. The current findings indicate that among obese individuals, subjects with apnea may have greater UA compliance (distensibility) than control subjects, although these findings did not remain significant after covariate adjustments. The increased UA compliance (distensibility) may, therefore, have been secondary to covariate differences between subjects with apnea and control subjects. Previous studies (4, 9–11, 28) have shown that subjects with apnea have a more compliant (distensible) UA than control subjects. Greater UA compliance (distensibility) might be attributed to increases in tissue pressure by excessive UA soft tissue sizes (16) or to the decreased lung volume secondary to increased visceral abdominal fat (29, 30).

Study Limitations and Strengths

Strengths of this study include the large sample size, the evaluation of reproducibility and reliability of the dynamic airway measurements, the assessment of obese subjects with apnea and obese control subjects, and providing further evidence that the retropalatal region is important in OSA pathogenesis.

There are also limitations. First, although most dynamic measurements were at least moderately reproducible with repeated measurement in a small, BMI-stable population, several measures (particularly in the epiglottal region) showed only slight or fair reproducibility. Potential unreliability in these measurements could have affected the ability to find significant associations. Next, subjects with apnea and control subjects were not well-matched for age or BMI, with an 8-year difference in age and, despite both groups being obese, a 4 kg/m^2 higher BMI in subjects with apnea. We controlled for these covariates in all analyses and results were consistent in a smaller subgroup matched for age, BMI, and sex, although statistical significance was lost for some measures because of the smaller sample size. Moreover, studies suggest that age-related airway changes predominantly occur during childhood and early adulthood (31), not in middle-aged adults (32), suggesting the age differences in our sample should not have significantly affected airway measurements.

Additionally, the timing of inspiration/expiration was not measured during the MRI scans; thus, dynamic images were not stratified by inspiration and expiration in this analysis. However, our specific study phenotypes (average, minimum, and maximum airway size and CV) would not have been affected by examining inspiration/expiration. Moreover, our previous research has already shown that the minimum airway area occurs at the end of expiration, whereas the maximum occurs in early expiration (33). Future studies should further examine the relationship between respiration and UA measurements with dynamic MRI during wakefulness and sleep. Although unlikely because we talked to the patients to make sure they were awake and no patient reported falling asleep during each scanning sequence, we did not measure EEG during the scans so it is possible that the patients fell asleep during the scan acquisition. Finally, we did not examine the effect of folding of the airway wall (34) on the dynamic images but it should not have affected the midsagittal image, although it could have affected the cross-sectional area measurement on the axial images.

Conclusions

Our results demonstrate that the UA during respiration is significantly narrower in the retropalatal region in obese subjects with apnea compared with obese control subjects. Thus, in obese subjects, retropalatal airway narrowing in both AP and lateral dimensions, and reduced airway area, seem to play an important role in determining OSA status, independent of demographic factors, such as age, BMI, sex, or race. Further studies should be performed to replicate these results and investigate the dynamic UA narrowing and collapsibility during different stages of sleep. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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