Upper Airway Areas, Volumes, and Linear Measurements Determined on Computed Tomography During Different Phases of Respiration Predict the Presence of Severe Obstructive Sleep Apnea

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Purpose: The objective of this study was to analyze the potential of using low-dose volumetric computed tomography (CT) during different phases of respiration for identifying patients likely to have severe obstructive sleep apnea (OSA), defined as a respiratory disturbance index (RDI) higher than 30.

Patients and Methods: A prospective study was undertaken at the Ramathibodi Hospital (Bangkok, Thailand). Patients with diagnosed OSA (N = 82) were recruited and separated into group 1 (RDI, ≤30; n = 36) and group 2 (RDI, >30; n = 46). The 2 groups were scanned by low-dose volumetric CT while they were *1)* breathing quietly, *2)* at the end of inspiration, and *3)* at the end of expiration. Values for CT variables were obtained from linear measurements on lateral scout images during quiet breathing and from the upper airway area and volume measurements were obtained on axial cross-sections during different phases of respiration. All CT variables were compared between study groups. A logistic regression model was constructed to calculate a patient's likelihood of having an RDI higher than 30 and the predictive value of each variable and of the final model.

Results: The minimum cross-sectional area (MCA) measured at the end of inspiration (cutoff point, ≤0.33 cm^2) was the most predictive variable for the identification of patients likely to have an RDI higher than 30 (adjusted odds ratio [OR] = 5.50; 95% confidence interval [CI], 1.76-17.20; sensitivity, 74%; specificity, 72%,), followed by the MCA measured at the end of expiration (cutoff point, ≤0.21 cm^2; adjusted OR = 3.28; 95% CI, 1.05-10.24; sensitivity, 70%; specificity, 68%).

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Conclusion: CT scanning at the ends of inspiration and expiration helped identify patients with an RDI higher than 30 based on measurement of the MCA. Low-dose volumetric CT can be a useful tool to help the clinician rapidly identify patients with severe OSA and decide on the urgency to obtain a full-night polysomnographic study and to start treatment.
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Obstructive sleep apnea (OSA) syndrome is characterized by repetitive episodes of cessation of breathing during sleep and a decrease in blood oxygen saturation with certain sleep-related symptoms, namely daytime sleepiness, loud snoring, morning headaches, and dry mouth at awakening.[1] OSA affects at least 2 to 4% of the adult population.[2] Of this large number of adults with OSA, many are likely to be undiagnosed and could benefit from treatment.[3] The respiratory disturbance index (RDI) is defined as the average number of episodes of apnea, hypopnea, and respiratory effort-related arousals per hour of sleep.[2] The presence of an RDI of at least 15 in the absence of sleep-related symptoms or an RDI of at least 5 in the presence of sleep-related symptoms is adequate for the diagnosis of OSA. OSA severity is defined as mild (RDI, ≥5 to <15), moderate (RDI, ≥15 to ≤30), or severe (RDI, >30).[4]

The standard for diagnosis of OSA has been full-night polysomnography (PSG), but this requires an overnight hospital stay with trained specialists who monitor and interpret complicated physiologic data throughout the night. This process is labor and resource intensive and time consuming, leading to a limited number of available appointment slots in most hospitals. Because of these limitations, various alternative diagnostic techniques (such as the Mueller maneuver,[5,6] x-ray cephalometry,[7-12] upper airway endoscopy during sleep and sedated sleep) have been proposed as alternatives.[13-17] The potential benefits of these methods over simple clinical assessment remain under discussion.[18]

Advanced imaging techniques such as magnetic resonance imaging (MRI) and computed tomography (CT) have been used for assessing the upper airways of patients with OSA. MRI has been used to evaluate abnormal pharyngeal tissues in these patients while they are awake and asleep.[19-22] Although MRI provides high-resolution images that visualize the upper airway soft tissues, it is slow and costly. Several CT techniques have been applied widely for determining pharyngeal narrowing in patients with OSA during wakefulness.[12,23-30] In their previous publication,[31] the authors reported that the presence of complete obstruction and complete concentric collapse of the upper airways during sleep apnea detected by CT combined with portable PSG were independently associated with severe OSA (RDI, >30).

It has been reported that moderate-to-severe OSA is an independent risk factor for higher all-cause mortality.[32] Furthermore, the quality of life of patients with severe OSA is decreased compared with normal control subjects and is strongly correlated with the depression scale.[33] Based on the authors' experience, although CT scanning during apneic episodes provided more informative anatomic and pathologic findings of severe OSA than did scans performed during the awake state,[31] scanning while awake (with no need for an asleep tracking system) can help clinicians to rapidly decide the urgency of obtaining a full-night PSG study and of treatment. The authors hypothesized that CT scanning while awake might identify variables with values predictive of severe OSA. Using CT for upper airway scanning during different phases of breathing of patients with OSA remains controversial. Schwab et al[34] reported that the upper airway narrowed substantially at the end of expiration in patients with OSA, whereas the upper airway diameter remained relatively constant during inspiration and enlarged in early expiration. Li et al[35] reported that minimum cross-sectional areas (MCAs) of the retropalatal region (P = .0036) and retroglossal region (P = .027) observed at the end of expiration were predictive of RDI (R^2 = 0.286), whereas Tang et al[36] reported that MCAs of the retropalatal region at the end of deep inspiration were smaller than those during quiet breathing. Thus, the purpose of this study was to determine which CT variables obtained during different phases of respiration (ie, quiet breathing, at the end of inspiration, and at the end of expiration) were predictive for identifying patients likely to have severe OSA as defined by an RDI higher than 30.

Patients and Methods

RECRUITMENT OF PATIENTS

The authors designed and implemented a prospective study. Subjects were recruited from among patients with diagnosed OSA at the Otolaryngology Outpatient Department of the Faculty of Medicine at the Ramathibodi Hospital (Bangkok, Thailand) from August 2011 through November 2016. The diagnosis of OSA was based on standard overnight in-laboratory PSG at the Ramathibodi Sleep Disorders Center using a Sandman Elite (Nellcor Puritan Bennett, Pleasanton, CA), which recorded the following

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electrophysiologic variables: electroencephalogram, electrocardiogram, electrooculogram, chin electromyogram, nasal and oral airflow, thoracic and abdominal effort, and oxygen saturation. These patients' RDIs were determined by physicians using ProFusion 3 3.2 software (Compumedics, Abbotsford, VIC, Australia) based on the American Academy of Sleep Medicine diagnostic criteria.[1] Patients were excluded as study subjects if they were found to have an infiltrative lesion in the upper airway as screened by an otolaryngologist using clinical and physical examinations. All patients gave written informed consent before participating in this research. The study was performed in accordance with the Declaration of Helsinki and was approved by the committee on human rights related to research involving human volunteers at the Faculty of Medicine of the Ramathibodi Hospital and Mahidol University (protocol number ID 08-53-15). The participants were classified into 2 study groups using an RDI cutoff point of 30: group 1 (RDI, ≤30) and group 2 (RDI, >30).

ACQUISITION OF CT DATA

CT Scanning

A low-dose volumetric axial scan without contrast agent (80 kVp and 20 mAs [500 ms, 40 mA], 0.07 mSv per scan) was performed with a 320-slice CT scanner (Aquilion ONE; Toshiba Medical Systems, Nasu, Japan) in the Advanced Diagnostic Imaging Center of the Ramathibodi Hospital. The low-exposure technique was sufficient for generating quality images of the airway regions of all participants. CT image resolution was 512 × 512 pixels (0.39 × 0.39 mm^2) and slice thickness was 1 mm. All participants were asked to lie down on the CT table in a supine position. To determine the scanning area, scout images were generated in anterior and lateral views. The scanning areas (16 cm in length) covered the region from the upper wall of the nasal cavity to the hyoid bone. The upper airways were scanned during the awake state in different phases of respiration (ie, during quiet breathing, at the end of inspiration, and at the end of expiration). Note that there are 2 phases of breathing in pulmonary physiology, namely inspiration and expiration. Quiet breathing is not technically a phase of breathing. In the present study, upper airway assessment during quiet breathing provided baseline values for comparisons of findings during the 2 phases of respiration.

Image-Based Upper Airway Analysis

In logistic regression analyses, prediction of the probability of the outcome (patient with RDI >30) occurring used CT upper airway measures as the predictor variables. CT variables were measured from lateral scout images and axial cross-sectional images. Figure 1 shows the linear measurements on a lateral scout image during quiet breathing (L_{uv}, MP-H, L_{ua}, and W_{uv}). L_{uv} is the length of the soft palate and uvula (distance from the posterior nasal spine [PNS] to the tip of the uvula using a freehand tool measurement); MP-H is the distance from the mandibular plane (MP) to the hyoid bone (H; ie, the MP is constructed from the gnathion [most inferior point on the mandibular symphysis] through the gonion [point of the jaw angle defined by intersection of the angle between the ramal and mandibular lines]); L_{ua} is the length of the upper airway (ie, the distance from the PNS to the lower border of the hyoid bone); and W_{uv} is the maximum soft palate width.

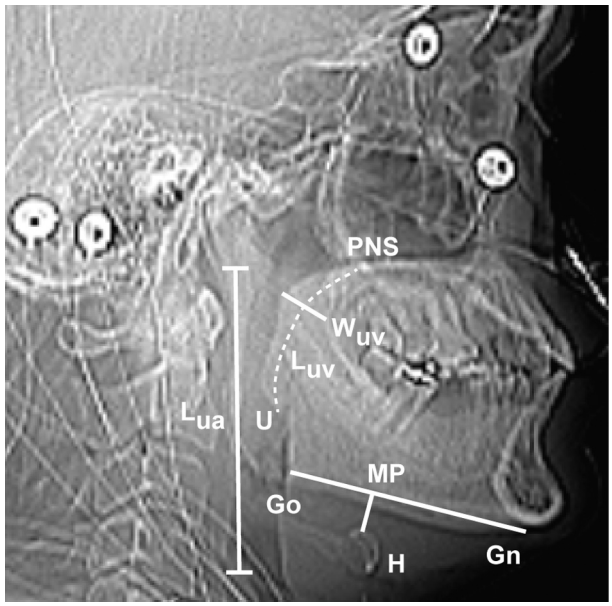

FIGURE 1. Linear measurements on a lateral scout image. Gn, gnathion (most inferior point on the mandibular symphysis); Go, gonion (point of the jaw angle defined by the intersection of the angle between the ramal and mandibular lines); H, hyoid bone; L_{ua}, length of upper airway (distance from posterior nasal spine to lower border of the hyoid bone); L_{uv}, length of soft palate and uvula (*dashed line*; distance from posterior nasal spine to tip of the uvula); MP, mandibular plane (from the gnathion through the gonion); PNS, posterior nasal spine; u, uvula; W_{uv}, maximum soft palate width.

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The cross-sectional area of the upper airway was measured using the analyze tool in ImageJ 1.44p software (National Institutes of Health, Bethesda, MD; Fig 2). The MCAs of the upper airways were measured during quiet breathing (MCA_w), at the end of inspiration (MCA_{in}), and at the end of expiration (MCA_{ex}). The volume of the upper airway (namely, the airway volume from the PNS to the lower border of the hyoid bone) was measured using a measure stack plugin (OptiNav, Bellevue, WA) during quiet breathing (V_w), at the end of inspiration (V_{in}), and at the end of

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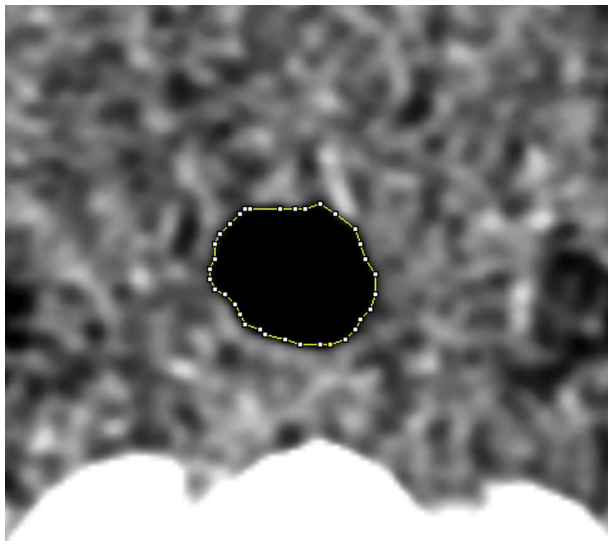

FIGURE 2. Cross-sectional area measurement of the upper airway on an axial computed tomogram by selecting the region of interest using polygon selections.

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expiration (V_{ex}). Then, the ratios of these states for MCAs and volumes (ie, $MCA_{in/w}$, $MCA_{ex/w}$, $V_{in/w}$, and $V_{ex/w}$) were calculated. All image-based upper airway analyses were performed by a single radiologist to avoid inter-operator variability.

Statistical Analysis

IBM SPSS 18.0 (IBM Corp, Armonk, NY) was used for statistical analyses. Normal distribution was checked using a Kolmogorov-Smirnov test. For comparisons of CT variables between the 2 study groups, the independent-sample *t* test was used for comparisons of the means of variables with normal distributions, whereas the nonparametric Mann-Whitney *U* test was used for comparisons of the medians of variables with asymmetric distributions.

To select CT variables for a logistic regression model of the likelihood that a patient would belong to either group, bivariate analysis of each CT variable studied was performed using an independent-sample *t* test or nonparametric Mann-Whitney *U* test. A *P* value less than .05 was defined as denoting a significant difference in between-group comparisons. Once the initial CT variables had been identified, quantitative terms were converted to qualitative ones by constructing curves of diagnostic yield (receiver operating characteristic [ROC] curves) to determine the optimal cutoff points for each variable to maximize diagnostic yield. The statistical program was designed to select the best models with *P* values less than .05 for entering a CT variable by a forward stepwise selection method.

Results

Eighty-three patients with OSA were recruited into this study. One patient who had an infiltrative lesion was excluded. Thus, 82 patients were included in this analysis. They were categorized to group 1 (RDI, ≤30; n = 36) or group 2 (RDI >30; n = 46). Patient characteristics (ie, age, body mass index, neck circumference, and waist circumference) of each group were compared and are presented with *P* values in Table 1. There were no differences in patient characteristics between study groups (Table 1). Low-dose volumetric CT was used to generate and evaluate the upper airway measurements during quite breathing, at the end of inspiration, and at the end of expiration and to determine the best CT predictors relative to an RDI cutoff point of 30.

Table 2 presents the mean and median values of MP-H, MCA_w, MCA_{in}, MCA_{ex}, $MCA_{in/w}$, $MCA_{ex/w}$, $MCA_{in/ex}$, and $V_{in/w}$, and the *P* values for comparisons between the 2 study groups. Table 3 presents the levels of correlation between CT variables and RDI. This set of CT variables was included in a bivariate logistic regression

Table 1. COMPARISON OF PATIENT CHARACTERISTICS AND POLYSOMNOGRAPHIC DATA BETWEEN STUDY GROUPS

Characteristics	Group 1 (RDI, ≤30; n = 36)	Group 2 (RDI, >30; n = 46)	*P* Value
Age (yr)	56.0 (24.0-68.0)	53.0 (21.0-76.0)	.840
BMI (kg/m^2)	26.47 ± 4.30	28.10 ± 5.75	.220
NC (cm)	37.00 ± 4.25	38.64 ± 4.28	.126
WC (cm)	89.96 ± 12.76	94.97 ± 13.62	.135
AHI	14.6 (1.5-27.3)	49.2 (2.0-112.9)	<.001*
RDI	22.20 (5.5-28.3)	53.35 (33.7-113.4)	<.001*

Note: Data are presented as the mean ± SD or median (minimum to maximum).

Abbreviations: AHI, apnea-hypopnea index; BMI, body mass index; NC, neck circumference; RDI, respiratory disturbance index; WC, waist circumference.

* $P < .05$.

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Table 2. COMPARISON OF COMPUTED TOMOGRAPHIC VARIABLES BETWEEN STUDY GROUPS

Variables	Group 1 (RDI ≤30; n = 36)	Group 2 (RDI, >30; n = 46)	*P* Value
L_{uv} (cm)	3.88 (2.96-4.86)	3.67 (2.80-5.88)	.895
MP-H (cm)	1.20 ± 0.74	1.55 ± 0.55	.025*
L_{ua} (cm)	7.07 ± 0.94	7.46 ± 0.81	.065
W_{uv} (cm)	0.89 (0.73-1.35)	0.96 (0.63-1.56)	.988
MCA_w (cm^2)	0.73 ± 0.38	0.53 ± 0.28	.017*
MCA_{in} (cm^2)	0.44 (0.00-1.31)	0.12 (0.00-1.18)	<.001*
MCA_{ex} (cm^2)	0.25 (0.00-1.86)	0.10 (0.00-0.86)	.003*
$MCA_{in/w}$	0.71 (0.00-1.85)	0.28 (0.00-3.56)	.012*
$MCA_{ex/w}$	0.35 (0.00-1.70)	0.17 (0.00-3.36)	.029*
$MCA_{in/ex}$	1.30 (0.00-6.00)	0.41 (0.00-10.33)	.033*
V_w (cm^3)	11.06 (5.83-36.91)	13.43 (4.88-24.76)	.523
V_{in} (cm^3)	10.84 (4.75-41.45)	9.13 (1.92-23.15)	.109
V_{ex} (cm^3)	8.64 (3.85-30.56)	8.31 (2.06-17.65)	.563
$V_{in/w}$	0.90 (0.47-2.73)	0.69 (0.23-1.78)	.023*
$V_{ex/w}$	0.70 (0.35-1.58)	0.63 (0.18-1.25)	.150
$V_{in/ex}$	1.41 (0.40-2.52)	1.07 (0.48-2.35)	.054

Note: Data are presented as mean ± standard deviation or median (minimum to maximum).

Abbreviations: L_{ua}, length of upper airway; L_{uv}, length of soft palate and uvula; MCA_{ex}, minimum cross-sectional area at end of expiration; $MCA_{ex/w}$, ratio of minimum cross-sectional area at end of expiration to minimum cross-sectional area during quiet breathing; MCA_{in}, minimum cross-sectional area at end of inspiration; $MCA_{in/ex}$, ratio of minimum cross-sectional area at end of inspiration to minimum cross-sectional area at end of expiration; $MCA_{in/w}$, ratio of minimum cross-sectional area at end of inspiration to minimum cross-sectional area during quiet breathing; MCA_w, minimum cross-sectional area during quiet breathing; MP-H, distance from mandibular plane to hyoid bone; RDI, respiratory disturbance index; V_{ex}, volume at end of expiration; $V_{ex/w}$, ratio of volume at end of expiration to volume during quiet breathing; V_{in}, volume at end of inspiration; $V_{in/ex}$, ratio of volume at end of inspiration to volume at end of expiration; $V_{in/w}$, ratio of volume at end of inspiration to volume during quiet breathing; V_w, volume during quiet breathing; W_{uv}, maximum soft palate width.

* $P < .05$.

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model. To convert quantitative to qualitative variables, cutoff points were determined that best distinguished between the data of groups 1 and 2. CT variables were selected as relevant from ROC curves that had areas under the curve ranging from 0.651 to 0.750. The final model showed that an MCA_{in} no larger than 0.33 cm^2 was the predictive variable that best identified patients as likely to have RDIs higher than 30 (sensitivity, 73.9%; specificity, 72.0%), followed by an MCA_{ex} no larger than 0.21 cm^2 (sensitivity, 69.6%; specificity, 68.0%; Table 4). The adjusted odds ratios (95% confidence intervals) were 5.50 (1.76-17.20) and 3.28 (1.05-10.24), respectively (Table 4).

Discussion

This study assessed the use of awake CT scanning during different phases of respiration as indicators of severe OSA (RDI, >30). Measurements of MCAs on axial images of the upper airways at the ends of inspiration and expiration provided predictors (MCA_{in}, ≤0.33 cm^2; MCA_{ex}, ≤0.21 cm^2) for identifying patients with severe OSA with 74 and 70% sensitivities and 72 and 68% specificities, respectively. Schwab et al[34] reported that the upper airway narrowed considerably at the end of expiration in patients with OSA and remained constant during inspiration and enlarged in early expiration, whereas Tang et al[36] reported that MCAs of the retropalatal region at the end of deep inspiration were smaller than those during quiet breathing. In the present study, we found that the ratios $MCA_{in/w}$, $MCA_{ex/w}$, $V_{in/w}$, and $V_{ex/w}$ were each less than 1 in groups 1 and 2, meaning that most MCAs measured at the end of inspiration and expiration were smaller than those measured during quiet breathing (Table 2). Li et al[35] reported that MCAs of the retropalatal region ($P = .004$) and retroglossal region ($P = .027$) observed at the end of expiration were predictive of RDI ($R^2 = 0.286$) and thus agreed with the present findings.

Continuous positive airway pressure (CPAP) is the standard treatment for moderate to severe OSA and is an optional therapeutic method for mild OSA.[37] In the authors' experience, using CT (combined with portable PSG) for scanning the upper airways of patients during apneic episodes provides better anatomic- and pathologic-related OSA images than do scans performed during the awake state.[31] However, CT scanning during the awake state does not require an embedded sleep-tracking system, which could be

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Table 3. CORRELATIONS BETWEEN SELECTED COMPUTED TOMOGRAPHIC VARIABLES AND RDI

	RDI	
Variables	*r*	*P* Value
MP-H (cm)	0.470†	.001*
MCA_w (cm^2)	−0.426†	.005*
MCA_{in} (cm^2)	−0.583‡	<.001*
MCA_{ex} (cm^2)	−0.540‡	.003*
$MCA_{in/w}$	−0.454‡	.002*
$MCA_{ex/w}$	−0.427‡	.005*
$MCA_{in/ex}$	−0.412‡	.008*
$V_{in/w}$	−0.419‡	.007*

Abbreviations: MCA_{ex}, minimum cross-sectional area at end of expiration; $MCA_{ex/w}$, ratio of minimum cross-sectional area at end of expiration to minimum cross-sectional area during quiet breathing; MCA_{in}, minimum cross-sectional area at end of inspiration; $MCA_{in/ex}$, ratio of minimum cross-sectional area at end of inspiration to minimum cross-sectional area at end of expiration; $MCA_{in/w}$, ratio of minimum cross-sectional area at end of inspiration to minimum cross-sectional area during quiet breathing; MCA_w, minimum cross-sectional area during quiet breathing; MP-H, distance from mandibular plane to hyoid bone; *r*, correlation coefficient; RDI, respiratory disturbance index; $V_{in/w}$, ratio of volume at end of inspiration to volume during quiet breathing.

* $P < .05$.

† Pearson correlation.

‡ Spearman correlation.

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useful for deciding on the urgency with which to confirm the severity of OSA with full-night PSG and to initiate fast treatment (eg, CPAP) to those patients likely to have severe OSA.

This study had a few limitations. First, radiation dose to the patient could be a concern with this approach. A low-dose technique (eg, 80 kVp, 20 mAs per scan time, producing only 0.07 mSv per scan time) without

Table 4. FORWARD STEPWISE MULTIVARIATE LOGISTIC REGRESSION MODEL FOR PREDICTION USING AN RDI CUTOFF OF 30

	n (%)				
Variables	Group 1 (RDI ≤30; n = 36)	Group 2 (RDI >30; n = 46)	Crude OR (95% CI)	Adjusted OR (95% CI)	*P* Value
MCA_{in}					
≤0.33 cm^2	10 (28.0)	34 (73.9)	7.29 (2.44-21.74)	5.50 (1.76-17.20)	.003
>0.33 cm^2	26 (72.0)	12 (26.1)	1		
MCA_{ex}					
≤0.21 cm^2	12 (32.0)	32 (69.6)	4.86 (1.70-13.87)	3.28 (1.05-10.24)	.041
>0.21 cm^2	24 (68.0)	14 (30.4)	1		
$MCA_{in/w}$					
≤0.47	14 (40.0)	30 (65.2)	2.81 (1.03-7.68)	—	—
>0.47	22 (60.0)	16 (34.8)	1		
$MCA_{in/ex}$					
≤1.02	14 (40.0)	28 (60.9)	2.81 (1.03-7.68)	—	—
>1.02	22 (60.0)	18 (39.1)	1		
$V_{in/w}$					
≤0.79	13 (36.0)	29 (63.0)	3.03 (1.10-8.35)	—	—
>0.79	23 (64.0)	14 (37.0)			

Abbreviations: CI, confidence interval; MCA_{ex}, minimum cross-sectional area at end of expiration; MCA_{in}, minimum cross-sectional area at end of inspiration; $MCA_{in/ex}$, ratio of minimum cross-sectional area at end of inspiration to minimum cross-sectional area at end of expiration; $MCA_{in/w}$, ratio of minimum cross-sectional area at end of inspiration to minimum cross-sectional area during quiet breathing; MCA_w, minimum cross-sectional area during quiet breathing; OR, odds ratio; RDI, respiratory disturbance index; $V_{in/w}$, ratio of volume at end of inspiration to volume during quiet breathing.

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contrast agent was used to generate high-contrast resolution images for the CT variable measurements. In practice, the total effective dose for scanning 3 phases of respiration per individual to achieve the predictive CT variables is approximately 0.21 mSv, which is 11-fold less than that of a normal CT neck scan performed using the same scanner in the Advanced Imaging Center of the Ramathibodi Hospital (120 kVp, 120 mAs affected by the dose-by-length product of 734.9 mGy/cm or an effective dose of 2.28 mSv). Second, although a single radiologist performed the image-based upper airway analyses to decrease inter-operator variability, multiple physicians determined participants' RDI (all used the American Academy of Sleep Medicine diagnostic criteria), which could have led to inter-reporter variability based on assessments of PSGs.

The importance of the present study is not in diagnosing OSA. In practice, use of multiple CT scans to diagnose OSA when various at-home PSG tests are available is not likely to occur. Rather, the benefit of CT scanning in patients with OSA is as a noninvasive and fast procedure providing predictors of severe OSA. CT can visualize anatomic upper airway abnormalities related to the RDI that might help clinicians rapidly choose which patients require confirmation by the full-night PSG study and whether and how to treat. This information could be usable in predicting outcomes from various treatment modalities for OSA. Further research should include a proof-of-concept study that can be applied to patients undergoing surgical and nonsurgical treatments to determine whether imaging can be used to predict the appropriate fit of procedure to patient.

CT scanning at the ends of inspiration and expiration helped to identify patients with severe OSA (RDI, >30). The CT measurements that were most predictive were the MCA at the end of inspiration (cutoff point, ≤ 0.33 cm^2) followed by the MCA at the end of expiration (cutoff point, ≤ 0.21 cm^2). Such CT data could help clinicians to decide on the urgency to obtain a full-night PSG study and of treatment.

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