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

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Abstract

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 having a respiratory disturbance index (RDI) of more than 30.

Patients and Methods: A prospective study was undertaken at the Ramathibodi Hospital. Patients with diagnosed OSA (N = 82) were recruited and separated into two groups: Group 1 (RDI of ≤30, N = 36) and Group 2 (RDI of >30, N = 46). Both groups were scanned by low-dose volumetric CT while they were i) breathing quietly, ii) at the end of inspiration, and iii) at the end of expiration. Values for CT variables were obtained from linear measurements in lateral scout images during quiet breathing, and from upper airway area and volume measurements in axial cross-sections during different phases of respiration. All CT variables were compared between study groups. A logistic regression model was constructed to calculate an individual's likelihood of having an RDI of >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 (cut-off point of ≤0.33 cm^2) was the most predictive variable for identification of patients likely to have an RDI of >30 [adjusted odds ratio (OR) = 5.50, 95% confidence interval (CI) = 1.76–17.20] with sensitivity 74% and specificity 72%, followed by the MCA measured at the end of expiration (cut-off point of ≤0.21 cm^2) [adjusted OR = 3.28, 95% CI = 1.05–10.24] with sensitivity 70% and specificity 68%.

Conclusion: CT scanning at the ends of both inspiration and expiration helped identify patients with RDI of >30 based on measurement of MCA. Low-dose volumetric CT can be a useful tool to help the clinician rapidly identify patients with severe OSA and decide upon the urgency to obtain a full-night PSG study and to start treatment.

Introduction

Obstructive sleep apnea (OSA) syndrome is characterized by repetitive episodes of cessation of breathing during sleep and reduction in blood oxygen saturation with certain sleep-related symptoms, namely, daytime sleepiness, loud snoring, morning headaches, and dry mouth upon 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 potentially would benefit from treatment [3]. 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 ≥15 in the absence of sleep-related symptoms, or ≥5 RDI in the presence of sleep-related symptoms, is adequate for the diagnosis of OSA. OSA severity is defined as mild (RDI more than or equal to 5 and less than 15), moderate (RDI more than or equal to 15 and less than or equal to 30), or severe (RDI more than 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 both 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) scanning have been utilized for assessing the upper airways of patients with OSA. MRI has been used to evaluate abnormal pharyngeal tissues in these patients while they are both awake and asleep [19-22]. Although MRI provides high resolution images that reveal the upper airway soft tissues, it is slow and costly. Several CT scanning techniques have been applied widely for determining pharyngeal narrowing in OSA patients during wakefulness [12, 23-30]. In our previous publication [31], we reported that the presence of complete obstruction and complete concentric collapse of upper airways during sleep apnea detected by CT combined with portable PSG were independently associated with severe OSA (RDI of >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 strongly correlated with the depression scale [33]. Based on our experience, although CT scanning during apneic episodes provided more informative anatomical and pathologic findings of severe OSA than did scans performed during the awake state [31], scanning while awake (with no need for asleep tracking system) may help clinicians to rapidly decide the urgency of obtaining a full-night PSG study and of treatment. We 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 significantly at the end of expiration in the patients with OSA, while 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 = 0.0036) and retroglossal region (P = 0.027) observed at the end of expiration were predictive of RDI (R^2 = 0.286) while 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 (i.e. quiet breathing, at the end of inspiration, and at the end of expiration) were predictive for identifying the OSA patients likely to have severe disease as defined by an RDI of >30.

Methods

Recruitment of subjects

We designed and implemented a prospective study. Subjects were recruited from among patients with diagnosed OSA at the Otolaryngology Outpatient Department, Faculty of Medicine, Ramathibodi Hospital, Bangkok, Thailand, during the period August 2011 through November 2016. The diagnosis of OSA was based on standard, overnight in-laboratory PSG using a Sandman Elite (Nellcor Puritan Bennett, Pleasanton, CA, USA) which recorded the following electrophysiologic variables: electroencephalogram (EEG), electrocardiogram (ECG), electrooculogram (EOG), chin electromyogram, nasal/oral airflow, thoracic and abdominal effort, and oxygen saturation at the Ramathibodi Sleep

Disorders Center. These patients' RDIs were determined by physicians using ProFusion 3 software version 3.2 (Compumedics, Abbotsford, Victoria, 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 screened by an otolaryngologist using clinical and physical examinations. All patients gave written informed consent prior to 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, Faculty of Medicine, Ramathibodi Hospital, Mahidol University. [Protocol number: ID 08-53-15]. The participants were classified into two study groups using an RDI cut-off point of 30, namely, Group 1 (RDI of ≤30) and Group 2 (RDI of >30).

Acquisition of CT data

CT scanning

A low-dose, volumetric axial scan without contrast agent [using 80 kVp and 20 mAs (500 msec, 40 mA) and causing only 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, Ramathibodi Hospital, Bangkok, Thailand. The low-exposure technique was sufficient for generating quality images of 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 both 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 awake state in different phases of respiration (i.e. during quiet breathing, at the end of inspiration, and at the end of expiration). Note that there are two phases of breathing in pulmonary physiology, i.e. inspiration and expiration. Quiet breathing is not technically a phase of breathing. In the present study, upper airway assessment during quiet breathing provided baselines for comparisons of findings during the two phases of respiration.

Image-based upper airway analysis

In the logistic regression analyses, prediction of the probability of the outcome (subject having an RDI of >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 in 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 [dashed line; 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) [i.e., MP is a plane constructed from the gnathion (Gn, most inferior point on the mandibular symphysis) through the gonion (Go, point of the jaw angle defined by intersection of the angle between the ramal and mandibular lines)]; L_{ua} is the length of upper airway (i.e., the distance from the PNS to the lower border of the hyoid bone); W_{uv} is the maximum soft palate width.

The cross-sectional area of the upper airway was measured using the analyze tool in Image-J 1.44p Software (National Institutes of Health, USA) (Fig. 2). The minimum cross-sectional areas (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 measure stack plugin (OptiNav, USA) during quiet breathing (V_w), at the end of inspiration (V_{in}), and at the end of expiration (V_{ex}). The ratios of these states for both MCAs and volumes (i.e., $MCA_{in/w,}$ $MCA_{ex/w}$, $V_{in/w,}$ and $V_{ex/w}$) were then calculated. All image-based upper airway analyses were performed by a single radiologist to avoid inter-operator variability.

Statistical analysis

The commercial statistics software package SPSS, version 18.0 (SPSS, IBM, Chicago, IL, USA) was used for statistical analyses. Normal distribution was checked using a Kolmogorov–Smirnov test. For comparisons of CT variables between the two 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 an individual belongs to one or other of the two groups, bivariate analysis of each CT variable studied was performed using an independent sample *t*-test or nonparametric Mann–Whitney U test. A *P* value of <0.05 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 cut-off points for each variable

to maximize diagnostic yield. The statistical program was designed to select the best models with *P* values of <0.05 for entering a CT variable by a forward, stepwise selection method.

Results

Eighty-three OSA patients were recruited into this study. One patient who had an infiltrative lesion was excluded. Thus, eighty-two patients were included in this analysis. They were categorized into either of two study groups, namely Group 1 (RDI ≤30, n=36) and Group 2 (RDI >30, n=46). Patient characteristics [i.e. age, body-mass index (BMI), neck circumference (NC), and waist circumference (WC)] of each subject group were compared and presented with *P* values in Table 1. There were no differences of patient characteristics between the study groups (Table 1). A 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 cut-off point of 30.

Table 2 presents the mean/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 two study groups. Table 3 shows the levels of correlation between CT variables and RDI. This set of CT variables was included in a bivariate logistic regression model. To convert quantitative to qualitative variables, cut-off points were determined that best distinguished between the data of study Groups 1 and 2. CT variables were selected as being significant from ROC curves which had areas under the curve ranging from 0.651 to 0.750. The final model revealed that an MCA_{in} of ≤0.33 cm^2 was the predictive variable which best identified patients as likely to have RDIs of >30 (sensitivity 73.9% and specificity 72.0%), followed by an MCA_{ex} of ≤0.21 cm^2 (sensitivity 69.6% and specificity 68.0%) (Table 4). The adjusted odds ratios (ORs) and the corresponding 95% CIs were 5.50 (1.76 to 17.20) and 3.28 (1.05 to 10.24), respectively (Table 4).

Discussion

This study assesses the use of awake CT scanning during different phases of respiration as indicators of severe OSA (defined as an RDI of >30). We found that measurements of minimum cross-sectional areas in axial images of upper airways at the ends of inspiration and expiration provided predictors

(MCA_{in} ≤ 0.33 cm^2 and 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 significantly at the end of expiration in the patients with OSA and remained constant during inspiration and enlarged in early expiration, while 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 one in both Groups 1 and 2 meaning that most of MCAs measured at the end of inspiration and expiration were less than those measured during quiet breathing (Table 2). Li *et al* [35] reported that MCAs of the retropalatal region (P = 0.004) and retroglossal region (P = 0.027) observed at the end of expiration were predictive of RDI (R^2 = 0.286) and thus agreed with our 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 our experience, using CT (combined with portable PSG) for scanning upper airways of patients during apneic episodes provides better anatomic- and pathologic-related OSA images than do scans performed during awake state [31]. However, CT scanning during awake state does not require utilizing an embedded sleep-tracking system, which may be useful for deciding on the urgency to confirm with a full-night PSG and to initiate a fast treatment, e.g. CPAP, to those patients likely to have severe OSA.

This study had a few limitations. First, patient radiation dose may be of concern with regard to this approach. A low-dose technique (e.g., 80 kVp, 20 mAs per scan time, causing only 0.07 mSv per scan time) without contrast agent was utilized to generate high-contrast resolution images for the CT variable measurements. In practice, the total effective dose for scanning three phases of respiration per individual to achieve the predictive CT variables was 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, Ramathibodi Hospital (120 kVp, 120 mAs affected dose length product of 734.9 mGy.cm or effective dose of 2.28 mSv). Second, while a single radiologist performed the image-based upper airway analyses to reduce inter-operator variability, multiple physicians determined the participants' RDI (all used the American Academy of Sleep Medicine diagnostic criteria) which may have led to inter-reporter variability based on assessments of PSGs.

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

Conclusion

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

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Table 1. Comparison of patient characteristics and PSG data between study groups

Characteristics	**Group 1 (RDI ≤30)**	**Group 2 (RDI >30)**	***P* value**
	N=36	**N=46**	
Age (Years)	56.0 (24.0-68.0)	53.0 (21.0-76.0)	0.840
BMI (kg/m^2)	26.47±4.30	28.10±5.75	0.220
NC (cm)	37.00±4.25	38.64±4.28	0.126
WC (cm)	89.96±12.76	94.97±13.62	0.135
AHI	14.6 (1.5-27.3)	49.2(2.0-112.9)	<0.001*
RDI	22.20 (5.5-28.3)	53.35 (33.7-113.4)	<0.001*

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

BMI = Body-mass index. NC = Neck circumference. WC = Waist circumference. AHI = Apnea-hypopnea index. RDI = Respiratory disturbance index. *P <0.05.

Table 2. Comparison of CT 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)	0.895
MP-H (cm)	1.20±0.74	1.55±0.55	0.025*
L_{ua} (cm)	7.07±0.94	7.46±0.81	0.065
W_{uv} (cm)	0.89 (0.73-1.35)	0.96 (0.63-1.56)	0.988
MCA_w (cm^2)	0.73±0.38	0.53±0.28	0.017*
MCA_{in} (cm^2)	0.44 (0.00-1.31)	0.12 (0.00-1.18)	<0.001*
MCA_{ex} (cm^2)	0.25 (0.00-1.86)	0.10 (0.00-0.86)	0.003*
$MCA_{in/w}$	0.71 (0.00-1.85)	0.28 (0.00-3.56)	0.012*
$MCA_{ex/w}$	0.35 (0.00-1.70)	0.17 (0.00-3.36)	0.029*
$MCA_{in/ex}$	1.30 (0.00-6.00)	0.41 (0.00-10.33)	0.033*
V_w (cm^3)	11.06 (5.83-36.91)	13.43 (4.88-24.76)	0.523
V_{in} (cm^3)	10.84 (4.75-41.45)	9.13 (1.92-23.15)	0.109
V_{ex} (cm^3)	8.64 (3.85-30.56)	8.31 (2.06-17.65)	0.563
$V_{in/w}$	0.90 (0.47-2.73)	0.69 (0.23-1.78)	0.023*
$V_{ex/w}$	0.70 (0.35-1.58)	0.63 (0.18-1.25)	0.150
$V_{in/ex}$	1.41 (0.40-2.52)	1.07 (0.48-2.35)	0.054

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

RDI = Respiratory disturbance index. L_{uv} = Length of soft palate and uvula (cm). MP-H = Distance from the mandibular plane to the hyoid bone (cm). L_{ua} = Length of upper airway (cm). W_{uv} = Maximum soft palate width (cm). MCA_w = MCA during quiet-breathing (cm^2). MCA_{in} = MCA at the end of inspiration

(cm^2). MCA_{ex} = MCA at the end of expiration (cm^2). $MCA_{in/w}$ = MCA_{in}/MCA_w. $MCA_{ex/w}$ = MCA_{ex}/MCA_w. $MCA_{in/ex}$ = MCA_{in}/MCA_{ex}. V_w = Volume during quiet-breathing (cm^3). V_{in} = Volume at the end of inspiration (cm^2). V_{ex} = Volume at the end of expiration (cm^2). $V_{in/w}$ = V_{in}/V_w. $V_{ex/w}$ = V_{ex}/V_w. $V_{in/ex}$ = V_{in}/V_{ex}. *P <0.05.

Table 3. Correlations between selected CT variables and RDI

Variables	RDI	
	r	*P* value
MP-H (cm)	0.470[ǂ]	0.001*
MCA_w (cm^2)	-0.426[ǂ]	0.005*
MCA_{in} (cm^2)	-0.583[‡]	<0.001*
MCA_{ex} (cm^2)	-0.540[‡]	0.003*
$MCA_{in/w}$	-0.454[‡]	0.002*
$MCA_{ex/w}$	-0.427[‡]	0.005*
$MCA_{in/ex}$	-0.412[‡]	0.008*
$V_{in/w}$	-0.419[‡]	0.007*

RDI = Respiratory disturbance index. MP-H = Distance from the mandibular plane to the hyoid bone (cm). MCA_w = MCA during quiet-breathing (cm^2). MCA_{in} = MCA at the end of inspiration (cm^2). MCA_{ex} = MCA at the end of expiration (cm^2). $MCA_{in/w}$ = MCA_{in}/MCA_w. $MCA_{ex/w}$ = MCA_{ex}/MCA_w. $MCA_{in/ex}$ = MCA_{in}/MCA_{ex}. V_w = Volume during quiet-breathing (cm^3). V_{in} = Volume at the end of inspiration (cm^2). $V_{in/w}$ = V_{in}/V_w. r = correlation coefficient. [ǂ]Pearson's correlation. [‡]Spearman's correlation. * P <0.05.

Table 4. Forward stepwise, multivariate logistic regression model for prediction using an RDI cut-off of 30.

Variables	No. (%)		Crude OR (95% CI)	Adjusted OR (95% CI)	*P* value
	Group 1 (RDI ≤30) N = 36	Group 2 (RDI >30) N = 46			
MCA_{in}					
≤ 0.33 cm^2	10 (28.0%)	34 (73.9%)	7.29 (2.44-21.74)	5.50 (1.76-17.20)	0.003
> 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)	0.041
> 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%)			

RDI = Respiratory disturbance index. OR = Odds ratio. CI = Confidence interval. MCA_{in} = MCA at the end of inspiration (cm^2). MCA_{ex} = MCA at the end of expiration (cm^2). MCA_w = MCA during quiet-breathing (cm^2). $MCA_{in/w} = MCA_{in}/MCA_w$. $MCA_{in/ex} = MCA_{in}/MCA_{ex}$. V_{in} = Volume at the end of inspiration (cm^2). V_w = Volume during quiet-breathing (cm^3). $V_{in/w} = V_{in}/V_w$.

Fig.1 Linear measurements on a lateral scout image.

Fig. 2 Cross-sectional area (CSA) measurement of the upper airway in an axial CT image by selecting ROI using polygon selections.