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2 Predicting upper airway collapse sites found in drug-induced sleep endoscopy from clinical data and snoring sounds in obstructive sleep apnea patients

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ABSTRACT

Study objectives: The primary aim was to predict upper airway collapse sites found in drug-induced sleep endoscopy (DISE) from demographic, anthropometric, clinical examination, sleep study, and snoring sound parameters in obstructive sleep apnea (OSA) patients. The secondary aim was to identify the above-mentioned parameters that are associated with complete concentric collapse of the soft palate (CCCp).

Methods: All OSA patients who underwent DISE and simultaneous snoring sound recording were enrolled in this study. Demographic, anthropometric, clinical examination (viz., modified Mallampati classification and Friedman tonsil classification), and sleep study parameters were extracted from the polysomnography (PSG) report and DISE report. Snoring sound parameters during DISE were calculated.

Results: One hundred and nineteen OSA patients (79.8% men; age = 48.1 ± 12.4 yrs) were included. Increased body mass index (BMI) was found to be associated with higher probability of oropharyngeal collapse ($P < 0.01$; OR = 1.29). Patients with a high Friedman tonsil score were less likely to have tongue base collapse ($P < 0.01$; OR = 0.12) and epiglottic collapse ($P = 0.01$; OR = 0.20) than those with a low score. A longer duration of snoring events ($P = 0.05$; OR = 2.99) was associated with a higher probability of CCCp.

Conclusions: Within the current patient profile and approach, given that only a limited number of predictors were identified, it does not seem feasible to predict upper airway collapse sites found in DISE from demographic, anthropometric, clinical examination, sleep study, and snoring sound parameters in OSA patients.

Keywords: obstructive sleep apnea, snoring sound, drug-induced sleep endoscopy, upper airway, acoustic analysis, clinical data

INTRODUCTION

Obstructive sleep apnea (OSA) is a common sleep-related breathing disorder. The reported prevalence of OSA in the general adult population ranges from 9% to 38%[1]. OSA is characterized by repetitive partial or complete collapse of the upper airway during sleep, which may consequently lead to hypoxemia, respiratory arousals, and non-restorative sleep[2]. Due to the serious nature of patients' complaints and potential health risks (e.g., metabolic and cardiovascular disorders[2]), more attention has been given to the diagnosis and management of OSA[3].

Identification of level, degree, and configuration of the collapse has been reported to be essential in treatment selection in OSA patients[4], when continuous positive airway pressure (CPAP), the gold standard therapy of OSA, fails or is not tolerated. Nowadays, several modalities (e.g., Müller's maneuver, dynamic magnetic resonance imaging [MRI], drug-induced sleep endoscopy [DISE]) are generally used to investigate the collapse site of the upper airway, but all these modalities have drawbacks. For example, Müller's maneuver enables the observation of the upper airway using a flexible endoscope[5], but it is performed in awake subjects and the findings show poor agreement with the results observed during sleep[6]. Dynamic MRI creates noise that may keep patients awake, is costly, and may cause claustrophobic effects[7]. DISE is a unique and dynamic technique. During drug-induced sleep, the upper airway is observed using a flexible endoscope, and the information on collapse sites can be obtained[8]. However, drug selection has been found to have influence on DISE findings[9] and there is potential inaccuracy of DISE results due to the difference between natural sleep and drug-induced sleep[10]. Therefore, there is a continuous search for more accurate and feasible methods to identify the level, degree, and configuration of upper airway collapse.

As one of the most frequently reported symptoms of OSA[11], snoring is characterized by audible vibrations of the upper airway during respiration in sleep[11]. Previous studies demonstrated the informative nature of snoring sound in predicting the presence/severity of OSA[12]. Similar to speech, the anatomy of the upper airway was found to have significant influence on the acoustic characteristics of snoring sound, which is known as the "source-filter theory"[13]. It was therefore hypothesized that snoring sound parameters may be potential predictors of the collapse site of the upper airway[14].

Recent studies built prediction models of collapse sites based on snoring sound parameters, with a reported accuracy ranging from 60.4% to 92.2%[15,16]. It needs to be noted that these studies only focused on snoring sound parameters. Other factors, such as gender, height, body mass index (BMI), and apnea-hypopnea index (AHI), were also reported to be associated with the presence of collapse[17] but were not included in the prediction models. In addition, importantly, previous studies only included patients whose collapse site was also the site where the snoring sound was generated (i.e., the excitation site of snoring sound). This means that the snoring sound and the collapse/excitation site are considered to have a direct association. However, it is a clinical reality that the majority of OSA patients, especially those with moderate to severe OSA, have multilevel collapse[18-20]. In that case, only one or two of the collapse sites generate snoring sound while the other collapse sites do not produce any sound. However, the presence of other collapse sites does have an impact on the acoustic characteristics of snoring sound. As a consequence, the association between the snoring sound and the collapse sites should in fact be regarded as indirect and complicated. Taken together, the above-mentioned evidence suggests that the clinical relevance of exploring the possibility to predict the presence of collapse in OSA patients based on demographic, anthropometric, clinical, and acoustic parameters should be performed at each level (viz., velum, oropharynx, tongue base, and epiglottis) of the upper airway. Therefore, the primary aim of the present study was to predict the presence of collapse at each level of the upper airway observed during DISE based on demographic, anthropometric, clinical examination, and sleep study parameters and acoustic parameters of the snoring sound during DISE in OSA patients. As mentioned above, we hypothesized that, in addition to snoring sound parameters, parameters like AHI and BMI may also be predictive of the presence of collapse.

In addition to the primary aim, previous studies found that the finding of complete concentric collapse of the soft palate (CCCp) during DISE was associated with poor response to treatment options like mandibular advancement device (MAD) and upper airway stimulation[3,4]. However, maxillomandibular advancement (MMA) surgery was reported to be a promising solution to CCCp[21]. Hence, being aware of whether the soft palate collapse is CCCp can help clinicians to select appropriate treatment. To the best of the authors' knowledge, no previous study has identified associated factors of CCCp among demographic, anthropometric, clinical, and acoustic parameters. Therefore, the secondary aim of this study was to identify demographic, anthropometric, clinical, and acoustic parameters associated with CCCp in OSA patients during DISE. We hypothesized that results from soft palate-related clinical examinations like Mallampati classification can be used to predict CCCp during DISE.

METHODS

Participants

This prospective study included adult patients who were diagnosed with OSA by polysomnography (PSG) and underwent DISE at the Department of Otolaryngology, Head and Neck Surgery of the OLVG (Amsterdam, The Netherlands) between June 2020 and May 2021. All adult patients who underwent DISE were approached for this study and patients were included if they were willing to provide written informed consent. This study was approved by the medical ethics committee of the OLVG (file number: WO 20.056).

Polysomnography

Ambulatory PSG recordings (SOMNOscreen Plus, Randersacker, Germany) were performed in accordance with the hospital's protocol. The PSG recordings included electrooculogram (EOG); electroencephalogram (EEG); electrocardiogram (ECG); electromyogram (EMG) of chin, jaw, and leg muscles; oronasal airflow; tracheal sound; thoraco-abdominal movement; oxygen saturation (SPO2); pulse; and position monitoring. All PSG recordings were manually scored according to the standard criteria (AASM, version 2.6, 2020)[22] by an experienced sleep technician who was not involved in this study. Apnea was defined as a reduction of ≥ 90% in the nasal airflow pressure signal lasting for ≥ 10 s. Hypopnea was defined as a reduction of ≥ 30% in the nasal airflow pressure signal lasting for ≥ 10 s, associated with an oxygen desaturation ≥ 3%. Subjects with an AHI ≥ 5 events/hr were identified as OSA patients.

Drug-induced sleep endoscopy

According to the hospital protocol[23], DISE is generally performed before considering surgical treatment for OSA, which is mainly considered for OSA patients with a BMI < 32 kg/m^2 and an AHI < 30 events/hr. For those with an AHI ≥ 30 events/hr, CPAP is recommended first, and surgical treatment is considered when patients have CPAP failure or intolerance. Before DISE, every patient received routine clinical examinations, which included Friedman tonsil classification[24], modified Mallampati classification[25], and the presence of soft palatal webbing (viz., redundant posterior palatal pillar mucosa). DISE was performed by an experienced clinician (PB) in an outpatient endoscopy room with dimmed lights and standard anesthetic equipment. Proper sedation was achieved using target-controlled infusion (TCI) of propofol in accordance with the method described by Schnider et al[26]. A trained nurse anesthetist controlled the sedation and monitored blood pressure, electrocardiogram, and oxygen levels. Patients were asleep for about 15 minutes. The VOTE (Velum, Oropharynx, Tongue base, and Epiglottis) classification[27] was used to document DISE findings, which incorporated the collapse patterns (antero-posterior [AP], lateral, and concentric) and the collapse degrees (0: no collapse, 1: partial collapse [collapse between 50 and 75%], and 2: complete collapse [collapse more than 75%]) of the most common levels and structures contributing to collapse (velum [V], oropharynx [O], tongue base [T], and epiglottis [E]; Figure 1). Given the impact of body position on snoring sound[28], only snoring sounds generated when patients were in supine position without any maneuver (e.g., jaw thrusting) were extracted and analyzed.

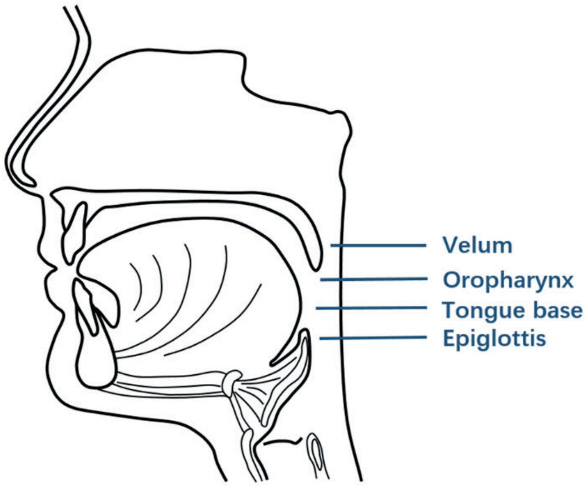

Figure 1-Schematic visualization of the upper airway. According to the VOTE classification, velum, oropharynx, tongue base, and epiglottis are four anatomical levels that are commonly involved in upper airway collapse, either individually or in every possible combination.

Snoring sound recording

A non-contact microphone (20-20k Hz; ZOOM H5, Zoom Corporation, New York, USA) was used to record snoring sounds. Before recording, the recording chain was calibrated using a sound calibrator (Testo 0554.0452, Testo Ltd, Alton Hampshire, UK), which produced a reference sound pressure level (94 dB [0 dB = 20 μPa], 1 kHz sine wave). The microphone was hung about 50 cm above the patient's mouth to record snoring sounds during DISE. A snoring event was identified when the vibration of soft tissue was observed in the endoscopic video recording and the snoring sound was heard. When a snoring event was identified, the time point on the sound recorder was manually recorded so that the snoring event could be extracted afterwards. It needs to be noted that, when a patient was in supine position and presented with a stable collapse pattern during DISE, multiple snoring events can be recorded.

Data extraction

Patients' demographic data (viz., age and gender), anthropometric data (viz., height and BMI), and sleep study data (viz., AHI and AHI in supine position [AHIS]) were extracted from PSG reports. Snoring-related complaint (viz., the presence and position of snoring in natural sleep; see results), Friedman tonsil classification, modified Mallampati classification, and the presence of soft palatal webbing, were extracted from DISE reports. As for the acoustic parameters, the acoustic analysis of snoring events consisted of two parts, viz., extraction of snoring events in Audacity (Dominic Mazzoni, Fremont, USA) and data analysis in R (Vienna University of Economics and Business, Vienna, Austria). Audacity is a digital audio editor and R is a programming language, by which data analysis and statistical computing can be performed. In the present study, the original recordings with a sampling frequency of 44.1 kHz were used for snoring sound analysis. According to the time points that were manually recorded during DISE, all snoring events were extracted from the recordings in Audacity. To avoid bias in the result caused by the high weight of a single patient's snoring events in the database, only the first five snoring events were extracted if more than five snoring events were identified in a snoring sound recording. After that, the extracted snoring events were input into R and 12 snoring sound parameters were calculated. Among the 12 parameters, nine conventional snoring sound parameters, viz., crest factor (the peak amplitude of the waveform divided by the root mean square [RMS] value of the waveform)29, dominant frequency (DF; the frequency that carries the most energy)30, duration of snoring event, fundamental frequency (FF; the lowest frequency of a waveform)31, the first three formants (F1, F2, F3; three specific frequencies of snoring sound that are amplified by resonating in the upper airway)31, and sound pressure level (max, mean; sound intensity), were extracted from each of the snoring event using the "seewave" package of R32 and the codes written by the authors (ZH and AH). It needs to be noted that the above-mentioned frequency components, viz., DF, FF, F1, F2, and F3, are relatively low frequency components. To extract the information in high frequency range, i.e., higher than F3, three frequencies with the highest energy were extracted as well.

Sample size

Since no similar study has been performed, the calculation of the sample size of this study cannot be based on previous findings. In the present study, 22 independent variables were included in the regression models and we followed the rule that a minimum of 15 snoring events are required for each independent variable to ensure sufficient statistical power33. This suggested a minimum sample size of 330 snoring events for this study.

Statistics

Descriptive statistics included demographic parameters, anthropometric parameters, clinical parameters, and acoustic parameters. In addition, the descriptive statistics of the dependent variables (for the primary aim: the presence of collapse at each of the V, O, T, and E levels; for the secondary aim: the presence of CCCp) were included as well. Ratio and interval data were presented as mean ± SD; nominal and ordinal data were presented as percentages.

For the primary aim, logistic regression models were built to evaluate the associations between the dependent variables (viz., the presence of collapse at each of the V, O, T, and E levels) and the independent variables (demographic parameters, anthropometric parameters, clinical parameters, and snoring sound parameters). Because multiple snoring events can be extracted from the recording of a participant, a multilevel dataset was obtained, i.e., snoring event-level variables (level 1; snoring sound parameters) were nested within participant-level variables (level 2; demographic parameters, anthropometric parameters, and clinical parameters). Therefore, a multilevel binary logistic regression model was built for each collapse level. As the first step, univariable logistic regression models were built to assess the associations between the presence of collapse at each of the V, O, T, and E levels on the one hand and all demographic parameters, anthropometric parameters, clinical parameters, and snoring sound parameters on the other hand. Snoring event-level variables and individual-level variables that showed at least a weak association ($P < 0.1$) with each collapse level were entered in the corresponding multilevel logistic regression model. To adjust for the fact that multiple snoring events from one participant were not independent of each other, generalized estimating equations (GEE) was used to build multilevel logistic regression models as to assess the adjusted associations between snoring event-level variables and individual-level variables on the one hand and the presence of collapse at each of the V, O, T, and E levels on the other hand. Independent variables with a P value of < 0.05 in the multilevel models were considered to be significantly associated with the presence of collapse. For the secondary aim, the univariable and multilevel logistic regression models were also built to identify the associated factor(s) of CCCp among demographic parameters, anthropometric parameters, clinical parameters, and snoring sound parameters. Given that patients who received previous upper airway surgeries were also included in the present study, the above-mentioned logistic regression analyses were performed twice, viz., analyses with and without patients who received previous upper airway surgeries, in case including these patients might affect the results.

For the ordinal variables (viz., modified Mallampati classification and Friedman tonsil classification), initial analyses were based on the full range of the response options, and linearity of their effect on the dependent variable was checked by inspection of the regression coefficients. Linearity was considered present if the regression coefficients consistently increased or decreased. In case of a nonlinear association, the variable was dichotomized. Independent variables in each multilevel logistic regression model were checked for multicollinearity, using tolerance value <0.1 or variance inflation factor (VIF) >1034. To ensure the validity of the logistic regression model, no analysis was performed in cases where events per variable (EPV) was less than 15. Analyses were conducted using the IBM SPSS Statistics 27 software package (IBM Corp, Chicago, USA).

RESULTS

In total, 312 patients received DISE at the Department of Otolaryngology, Head, and Neck Surgery of the OLVG between June 2020 and May 2021. Of the 312 patients, 278 patients provided informed consent; 31 primary snorers were excluded as this study focused on OSA patients; and three patients declined to provide written informed consent as they were not willing to participate in this study. Of the 278 patients who provided informed consent, 191 (68.7%) patients snored in supine position during DISE, but snoring sounds from 72 patients were too light to be recorded and analyzed. As a consequence, only 119 (42.8%) snoring OSA patients were included in this study. It needs to be noted that there was no significant difference between included and excluded OSA patients in age, gender, BMI, AHI, prevalence of CCCp, and prevalence of collapse at each of the V, O, T, and E levels (Table S1 in the supplemental material). All the included 119 participants were inspiratory snorers; the participant characteristics are shown in Table 1. It is worth noting that 27 (22.7%) of the 119 participants received previous upper airway surgeries (viz., 23 had tonsillectomy [TE], three had uvulopalatopharyngoplasty [UPPP], and one had expansion sphincter pharyngoplasty [ESP]) and therefore presented with a Friedman tonsil classification of zero. However, 19 of these 27 participants still had oropharyngeal collapse. The collapse patterns and sites that were observed during DISE are shown in Table 2.

Table 1-Participant characteristics

Characteristics	
Demographic parameters	
Age (y, mean ± SD)	48.1 ± 12.4
Male gender (N, %)	95 (79.8%)
Anthropometric parameters	
Height (cm, mean ± SD)	177.4 ± 11.4
BMI (kg/m2, mean ± SD)	27.9 ± 3.1
Clinical parameters	
AHI (events/hr, mean ± SD)	29.8 ± 20.2
AHIS (events/hr, mean ± SD)	44.9 ± 28.9
Patient's complaint	
- Snoring is not a main complaint (N, %)	13 (10.9%)
- Snoring position unknown (N, %)	37 (30.3%)
- Snoring in every position (N, %)	53 (45.4%)
- Snoring in supine position (N, %)	16 (13.4%)
Friedman tonsil classification	
- Class 0 (N, %)	31 (26.1%)
• Without intervention	4 (3.4%)
• After surgery	27 (22.7%)
➢ Tonsillectomy	23 (19.3%)
➢ UPPP	3 (2.5%)
➢ ESP	1 (0.8%)
- Class 1 (N, %)	36 (30.3%)
- Class 2 (N, %)	37 (31.1%)
- Class 3 (N, %)	11 (9.2%)
- Class 4 (N, %)	1 (0.8%)
Mallampati classification	
- Class 0 (N, %)	2 (1.7%)
- Class 1 (N, %)	9 (7.6%)
- Class 2 (N, %)	66 (55.5%)
- Class 3 (N, %)	37 (31.1%)
- Class 4 (N, %)	3 (2.5%)
Webbing (N, %)	49 (41.2%)

Acoustic parameters	
Duration of snoring event (s, mean ± SD)	1.1 ± 0.3
Crest factor	6.0 ± 2.5
Max dB (dB, mean ± SD)	72.9 ± 6.7
Mean dB (dB, mean ± SD)	55.3 ± 4.6
FF (Hz, mean ± SD)	291.2 ± 14.0
DF (Hz, mean ± SD)	254.5 ± 238.8
F1 (Hz, mean ± SD)	1417.2 ± 787.4
F2 (Hz, mean ± SD)	3155.9 ± 1961.6
F3 (Hz, mean ± SD)	4914.6 ± 2417.3
High Frequency component 1 (Hz, mean ± SD)	6743.3 ± 2101.4
High Frequency component 2 (Hz, mean ± SD)	7187.5 ± 2199.9
High Frequency component 3 (Hz, mean ± SD)	7560.4 ± 2257.4

AHI = apnea-hypopnea index; AHIS = AHI in supine position; BMI = body mass index; dB = decibel; DF = dominant frequency; ESP = expansion sphincter pharyngoplasty; F1 = the first formant; F2 = the second formant; F3 = the second formant; FF = fundamental frequency; Hz = hertz; SD = standard deviation; UPPP = uvulopalatopharyngoplasty

A total of 384 snoring events were extracted from the recordings of the 119 participants. As 379 of the 384 snoring events corresponded to the presence of velum collapse, logistic regression models could not be built for velum collapse. Another point to be noted that the Class 4 of Friedman tonsil classification was merged into Class 3 for the feasibility of statistical analysis, since only one participant was classified as Class 4. In addition, the Class 4 of modified Mallampati classification was merged into Class 3, since only two participants were classified as Class 4. For oropharyngeal collapse, logistic regression models with (Table 3) and without (Table 4) patients who received previous upper airway surgeries showed different results.

In the model with patients who received previous upper airway surgeries, patients with Class 1 Friedman tonsil classification were less likely to have oropharyngeal collapse than those with Class 0 (P = 0.04; OR = 0.17 [0.03 – 0.88]). However, this association disappeared, and increased BMI was found to be associated with higher probability of oropharyngeal collapse ($P < 0.01$; OR = 1.29 [1.07 – 1.55]) in the model without patients who received previous upper airway surgeries. It needs to be noted that, for tongue base collapse, epiglottic collapse, and CCCp, there was no difference in identified associated factors between logistic regression models with (Table 5, 6, and 7, respectively) and without (Table S2-4 in the supplemental

Table 2-Collapse patterns and sites observed during DISE in supine position and corresponding participants and snoring events

Collapse pattern	
Multilevel collapse	
- Participants (N, %)	110 (92.4%)
- Snoring events (N, %)	357 (93.0%)
Single-level collapse	
- Participants (N, %)	9 (7.6%)
• solitary velum collapse (N, %)	7 (5.9%)
• solitary oropharyngeal collapse (N, %)	2 (1.7%)
- Snoring events (N, %)	27 (7.0%)
• solitary velum collapse (N, %)	22 (5.7%)
• solitary oropharyngeal collapse (N, %)	5 (1.3%)
Collapse site	
Velum collapse	
- Participants (N, %)	117 (98.3%)
• CCCp (N, %)	21 (17.9%)
• non-CCCp (N, %)	96 (82.1%)
➢ Partial concentric (N, %)	2 (1.8%)
➢ AP (N, %)	61 (52.1%)
➢ Lateral (N, %)	33 (28.2%)
- Snoring events (N, %)	379 (98.7%)
• CCCp (N, %)	71 (18.7%)
• non-CCCp (N, %)	308 (81.3%)
➢ Partial concentric (N, %)	3 (0.8%)
➢ AP (N, %)	207 (54.6%)
➢ Lateral (N, %)	98 (25.9%)
Oropharyngeal collapse	
- Participants (N, %)	82 (68.9%)
- Snoring events (N, %)	243 (63.3%)
Tongue base collapse	
- Participants (N, %)	72 (60.5%)
- Snoring events (N, %)	236 (61.5%)
Epiglottic collapse	
- Participants (N, %)	78 (65.5%)
• Secondary to tongue base collapse	58 (74.4%)
- Snoring events (N, %)	253 (65.9%)

AP = anterior-posterior; CCCp = complete concentric collapse of the soft palate; SD = standard deviation

Table 3-Logistic regression models for oropharyngeal collapse (with patients who received previous upper airway surgeries)

	Univariable logistic regression model		Multilevel logistic regression model	
Independent variable	*P* value	OR (95% CI)	*P* value	OR (95% CI)
Age (y)	0.51	0.99 (0.96 – 1.02)		
Gender				
- Female		Reference		
- Male	0.79	1.14 (0.44 – 2.96)		
Height (cm)	0.74	0.99 (0.96 – 1.03)		
BMI (kg/m2)	0.12	1.11 (0.97 – 1.26)		
AHI (events/hr)	0.23	1.01 (0.99 – 1.04)		
AHIS (events/hr)	0.09	1.01 (1.00 – 1.03)	0.07	
Patient's complaint				
- Snoring is not a main complaint		Reference		
- Snoring position unknown	0.26	2.19 (0.56 – 8.57)		
- Snoring in every position	0.73	1.25 (0.36 – 4.37)		
- Snoring in supine position	0.96	1.04 (0.23 – 4.70)		
Friedman tonsil classification				
- Class 0		Reference		Reference
- Class 1	0.05	0.37 (0.13 – 1.01)	0.04	0.17 (0.03 – 0.88)
- Class 2	0.21	2.11 (0.66 – 6.80)	0.19	
- Class 3	0.18	4.50 (0.50 – 40.17)	0.22	
Mallampati classification				
- Class 1		Reference		
- Class 2	0.69	1.31 (0.35 – 5.00)		
- Class 3	0.69	1.33 (0.33 – 5.42)		
Webbing				
- No		Reference		
- Yes	0.13	1.95 (0.83 – 4.63)		
Duration of snoring event (s)	0.63	0.86 (0.47 – 1.57)		
Crest factor	0.29	0.96 (0.88 – 1.04)		
Max dB (dB)	0.51	1.01 (0.98 – 1.04)		
Mean dB (dB)	0.05	1.05 (1.00 – 1.10)	0.53	
FF (Hz)	0.13	0.99 (0.97 – 1.00)		
DF (Hz)	0.63	1.00 (1.00 – 1.00)		
F1 (Hz)	0.54	1.00 (1.00 – 1.00)		
F2 (Hz)	0.30	1.00 (1.00 – 1.00)		
F3 (Hz)	0.80	1.00 (1.00 – 1.00)		
High Frequency component 1 (Hz)	0.44	1.00 (1.00 – 1.00)		
High Frequency component 2 (Hz)	0.35	1.00 (1.00 – 1.00)		
High Frequency component 3 (Hz)	0.67	1.00 (1.00 – 1.00)		

AHI = apnea-hypopnea index; AHIS = AHI in supine position; BMI = body mass index; CI = confidence interval; dB = decibel; DF = dominant frequency; F1 = the first formant; F2 = the second formant; F3 = the second formant; FF = fundamental frequency; Hz = hertz; OR = odds ratio

Table 4-Logistic regression models for oropharyngeal collapse (without patients who received previous upper airway surgeries)

	Univariable logistic regression model		Multilevel logistic regression model	
Independent variable	*P* value	OR (95% CI)	*P* value	OR (95% CI)
Age (y)	0.40	0.99 (0.95 – 1.02)		
Gender				
- Female		Reference		
- Male	0.19	2.02 (0.70 – 5.82)		
Height (cm)	0.87	1.00 (0.97 – 1.04)		
BMI (kg/m2)	0.04	1.18 (1.01 – 1.37)	<0.01	1.29 (1.07 – 1.55)
AHI (events/hr)	0.23	1.01 (0.99 – 1.04)		
AHIS (events/hr)	0.29	1.01 (0.99 – 1.02)		
Patient's complaint				
- Snoring is not a main complaint		Reference		
- Snoring position unknown	0.05	5.63 (1.02 – 30.90)	0.16	
- Snoring in every position	0.16	2.86 (0.67 – 12.27)		
- Snoring in supine position	0.46	1.88 (0.35 – 9.98)		
Friedman tonsil classification				
- Class 0		Reference		
- Class 1	0.31	0.30 (0.03 – 1.01)		
- Class 2	0.66	1.72 (0.15 – 19.49)		
- Class 3	0.40	3.67 (0.17 – 77.55)		
Mallampati classification				
- Class 1		Reference		
- Class 2	0.88	1.13 (0.25 – 5.07)		
- Class 3	0.90	1.11 (0.23 – 5.47)		
Webbing				
- No		Reference		
- Yes	0.22	1.76 (0.71 – 4.36)		
Duration of snoring event (s)	0.88	1.08 (0.41 – 2.84)		
Crest factor	0.41	0.95 (0.83 – 1.08)		
Max dB (dB)	0.47	1.02 (0.96 – 1.09)		
Mean dB (dB)	0.07	1.09 (0.99 – 1.20)	0.13	
FF (Hz)	0.08	0.98 (0.96 – 1.00)	0.18	
DF (Hz)	0.58	1.00 (1.00 – 1.00)		
F1 (Hz)	0.44	1.00 (1.00 – 1.00)		
F2 (Hz)	0.27	1.00 (1.00 – 1.00)		
F3 (Hz)	0.86	1.00 (1.00 – 1.00)		
High Frequency component 1 (Hz)	0.31	1.00 (1.00 – 1.00)		
High Frequency component 2 (Hz)	0.20	1.00 (1.00 – 1.00)		
High Frequency component 3 (Hz)	0.61	1.00 (1.00 – 1.00)		

AHI = apnea-hypopnea index; AHIS = AHI in supine position; BMI = body mass index; CI = confidence interval; dB = decibel; DF = dominant frequency; F1 = the first formant; F2 = the second formant; F3 = the second formant; FF = fundamental frequency; Hz = hertz; OR = odds ratio

Table 5-Logistic regression models for tongue base collapse

	Univariable logistic regression model		Multilevel logistic regression model	
Independent variable	*P* value	OR (95% CI)	*P* value	OR (95% CI)
Age (y)	0.05	1.03 (1.00 – 1.06)	0.34	
Gender				
- Female		Reference		
- Male	0.11	0.45 (0.16 – 1.20)		
Height (cm)	0.81	1.00 (0.97 – 1.04)		
BMI (kg/m2)	0.02	0.86 (0.76 – 0.98)	0.06	
AHI (events/hr)	0.57	1.01 (0.99 – 1.02)		
AHIS (events/hr)	0.95	1.00 (0.99 – 1.01)		
Patient's complaint				
- Snoring is not a main complaint		Reference		
- Snoring position unknown	0.49	0.62 (0.16 – 2.40)	0.85	
- Snoring in every position	0.96	0.97 (0.26 – 3.59)	0.46	
- Snoring in supine position	0.05	0.20 (0.04 – 0.98)	0.13	
Friedman tonsil classification				
- Low score		Reference		Reference
- High score	< 0.01	0.28 (0.13 – 0.60)	< 0.01	0.12 (0.04 – 0.44)
Mallampati classification				
- Class 1		Reference		
- Class 2	0.71	1.28 (0.36 – 4.64)		
- Class 3	0.63	1.39 (0.36 – 5.35)		
Webbing				
- No		Reference		
- Yes	0.77	0.89 (0.41 – 1.94)		
Duration of snoring event (s)	0.14	1.59 (0.86 – 2.93)		
Crest factor	0.80	1.01 (0.93 – 1.10)		
Max dB (dB)	0.69	0.99 (0.94 – 1.02)		
Mean dB (dB)	0.41	0.98 (0.94 – 1.03)		
FF (Hz)	0.26	1.01 (0.99 – 1.02)		
DF (Hz)	0.39	1.00 (1.00 – 1.00)		
F1 (Hz)	0.18	1.00 (1.00 – 1.00)		
F2 (Hz)	0.38	1.00 (1.00 – 1.00)		
F3 (Hz)	0.62	1.00 (1.00 – 1.00)		
High Frequency component 1 (Hz)	0.39	1.00 (1.00 – 1.00)		
High Frequency component 2 (Hz)	0.21	1.00 (1.00 – 1.00)		
High Frequency component 3 (Hz)	0.47	1.00 (1.00 – 1.00)		

AHI = apnea-hypopnea index; AHIS = AHI in supine position; BMI = body mass index; CI = confidence interval; dB = decibel; DF = dominant frequency; F1 = the first formant; F2 = the second formant; F3 = the second formant; FF = fundamental frequency; Hz = hertz; OR =

odds ratio
Table 6-Logistic regression models for epiglottic collapse

	Univariable logistic regression model		Multilevel logistic regression model	
Independent variable	*P* value	OR (95% CI)	*P* value	OR (95% CI)
Age (y)	0.08	1.03 (1.00 – 1.06)	0.30	
Gender				
- Female		Reference		
- Male	0.12	0.43 (0.15 – 1.26)		
Height (cm)	0.42	1.01 (0.98 – 1.05)		
BMI (kg/m2)	0.03	0.86 (0.76 – 0.99)	0.06	
AHI (events/hr)	0.65	1.00 (0.98 – 1.01)		
AHIS (events/hr)	0.39	0.99 (0.98 – 1.01)		
Patient's complaint				
- Snoring is not a main complaint		Reference		
- Snoring position unknown	0.49	0.60 (0.14 – 2.60)	0.59	
- Snoring in every position	0.55	0.65 (0.16 – 2.68)	0.83	
- Snoring in supine position	0.08	0.23 (0.05 – 1.19)	0.16	
Friedman tonsil classification				
- Low score		Reference		Reference
- High score	0.01	0.35 (0.16 – 0.78)	0.01	0.20 (0.06 – 0.72)
Mallampati classification				
- Class 1		Reference		
- Class 2	0.50	0.62 (0.15 – 2.54)		
- Class 3	0.74	0.78 (0.18 – 3.43)		
Webbing				
- No		Reference		
- Yes	0.18	0.58 (0.26 – 1.28)		
Duration of snoring event (s)	0.23	1.47 (0.79 – 2.74)		
Crest factor	0.58	1.02 (0.94 – 1.12)		
Max dB (dB)	0.39	0.99 (0.96 – 1.02)		
Mean dB (dB)	0.19	0.97 (0.93 – 1.02)		
FF (Hz)	0.69	1.00 (0.99 – 1.02)		
DF (Hz)	0.58	1.00 (1.00 – 1.00)		
F1 (Hz)	0.65	1.00 (1.00 – 1.00)		
F2 (Hz)	0.29	1.00 (1.00 – 1.00)		
F3 (Hz)	0.58	1.00 (1.00 – 1.00)		
High Frequency component 1 (Hz)	0.17	1.00 (1.00 – 1.00)		
High Frequency component 2 (Hz)	0.16	1.00 (1.00 – 1.00)		
High Frequency component 3 (Hz)	0.71	1.00 (1.00 – 1.00)		

AHI = apnea-hypopnea index; AHIS = AHI in supine position; BMI = body mass index; CI = confidence interval; dB = decibel; DF = dominant frequency; F1 = the first formant; F2 = the second formant; F3 = the second formant; FF = fundamental frequency; Hz = hertz; OR = odds ratio

Table 7-Logistic regression models for complete concentric collapse of the soft palate (CCCp)

	Univariable logistic regression model		Multilevel logistic regression model	
Independent variable	*P* value	OR (95% CI)	*P* value	OR (95% CI)
Age (y)	0.77	0.99 (0.96 – 1.03)		
Gender				
- Female		Reference		
- Male	0.68	0.79 (0.26 – 2.43)		
Height (cm)	0.43	1.02 (0.98 – 1.06)		
BMI (kg/m2)	0.13	1.13 (0.96 – 1.34)		
AHI (events/hr)	0.38	1.01 (0.99 – 1.03)		
AHIS (events/hr)	0.13	1.01 (1.00 – 1.03)		
Patient's complaint				
- Snoring is not a main complaint		Reference		
- Snoring position unknown	0.19	0.31 (0.05 – 1.80)		
- Snoring in every position	0.94	1.06 (0.25 – 4.43)		
- Snoring in supine position	0.51	0.51 (0.07 – 3.68)		
Friedman tonsil classification				
- Low score		Reference		
- High score	0.68	0.82 (0.31 – 2.16)		
Mallampati classification				
- Class 1		Reference		
- Class 2	0.46	2.26 (0.26 – 19.42)		
- Class 3	0.40	2.58 (0.29 – 23.24)		
Webbing				
- No		Reference		
- Yes	0.57	1.32 (0.51 – 3.41)		
Duration of snoring event (s)	< 0.01	3.95 (1.91 – 8.16)	0.05	2.99 (1.01 – 8.84)
Crest factor	0.07	0.89 (0.78 – 1.01)	0.11	
Max dB (dB)	0.53	0.99 (0.95 – 1.03)		
Mean dB (dB)	0.78	1.01 (0.95 – 1.07)		
FF (Hz)	0.28	1.01 (0.99 – 1.03)		
DF (Hz)	0.16	1.00 (1.00 – 1.00)		
F1 (Hz)	0.54	1.00 (1.00 – 1.00)		
F2 (Hz)	0.30	1.00 (1.00 – 1.00)		
F3 (Hz)	0.80	1.00 (1.00 – 1.00)		
High Frequency component 1 (Hz)	0.44	1.00 (1.00 – 1.00)		
High Frequency component 2 (Hz)	0.35	1.00 (1.00 – 1.00)		
High Frequency component 3 (Hz)	0.67	1.00 (1.00 – 1.00)		

AHI = apnea-hypopnea index; AHIS = AHI in supine position; BMI = body mass index; CI = confidence interval; dB = decibel; DF = dominant frequency; F1 = the first formant; F2 = the second formant; F3 = the second formant; FF = fundamental frequency; Hz = hertz; OR = odds ratio

material) patients who received previous upper airway surgeries. For tongue base collapse, the full range of the response options of the Friedman tonsil classification showed non-linear association with the presence of collapse and was therefore dichotomized (low score = Class 0 and Class 1; high score = Class 2 and Class 3). In the multilevel logistic regression model, an interesting finding was that patients with a high Friedman tonsil score were less likely to have tongue base collapse than those with a low score ($P < 0.01$; OR = 0.12 [0.04 – 0.44]). In addition, a high Friedman tonsil score ($P = 0.01$; OR = 0.20 [0.06 – 0.72]) was also found to be associated with lower probability of epiglottic collapse. For CCCp, it was found that the duration of snoring event ($P = 0.05$; OR = 2.99 [1.01 – 8.84]) was the only associated factor of CCCp, viz., the longer the duration of a snoring event, the higher the probability of CCCp.

DISCUSSION

In the present study, the logistic regression model with patients who received previous upper airway surgeries showed that patients with Class 1 Friedman tonsil classification were less likely to have oropharyngeal collapse than those with Class 0. However, in the model without patients who received previous upper airway surgeries, increased BMI was found to be associated with higher probability of oropharyngeal collapse. In addition, it was found that patients with a high Friedman tonsil score were less likely to have tongue base collapse and epiglottic collapse than those with a low score. For CCCp, the probability of CCCp increases with the increase of the duration of snoring events.

In the present study, only 68.7% of OSA patients snored in supine position during DISE and only 42.8% of OSA patients generated analyzable snoring sounds in supine position during DISE, while previous studies reported that 82% - 100%[35,36] OSA patients snored during DISE. A possible explanation to this discrepancy is that we only included patients who snored in supine position in the present study. It is a clinical reality that some OSA patients only snored in lateral position, but not in supine position. Another possible reason is that only TCI was used during DISE as to obtain a medium-sedation level status (viz., loss of response to verbal stimulation at a normal volume[37]), but EEG-derived index like bispectral index (BIS) was not used to monitor the depth of sedation. A previous study found that the mean infusion rate was significantly higher in patients receiving TCI of propofol without monitoring

BIS than in those who received TCI of propofol with monitoring BIS38. This suggests the possibility that some snoring OSA patients might have been excluded due to relatively high sedative dose, which may lead to excessive muscle relaxation, more severe obstructive breathing, and consequent absence of snoring.

It was found that including patients who received previous upper airway surgeries affected the analysis for oropharyngeal collapse, but not those for tongue base collapse, epiglottic collapse, and CCCp. A possible explanation is that these upper airway surgeries (viz., TE, UPPP, and ESP) focus on velum and oropharynx, but have no effect on tongue base and epiglottis. In addition, CCCp was found to be associated with decreased success rate of upper airway surgeries21. As a consequence, only analysis for oropharyngeal collapse was affected. In the model without patients who received previous upper airway surgeries, increased BMI was found to be associated with higher probability of oropharyngeal collapse. Previous studies reported same results39,40 and explained that obesity was associated with anatomic factors (e.g., lateral pharyngeal muscle thickness and fat volume39) that may cause the narrowing of the oropharynx. Taken together, the above-mentioned evidence suggests that the presence of oropharyngeal collapse is affected by obesity.

An interesting finding is that high score (viz., Class 2 and Class 3) of the Friedman tonsil classification was associated with lower probability of tongue base collapse during DISE in supine position. We hypothesize that large tonsils may act as airway stents to create space for the retroglossal area, thereby reducing the degree of tongue base collapse during sleep. To the best of the authors' knowledge, only two previous studies41,42 proposed the same hypothesis. In addition, two other previous studies found that larger tonsils are associated with higher success rate of surgery for tongue base collapse43,44, even though these two studies did not discuss the potential supporting role of tonsils in tongue base collapse. Tonsils, as a common cause of oropharyngeal collapse39, are generally removed during upper airway surgery. However, due to the collapse of other anatomical structures, such as the lateral pharyngeal wall, oropharyngeal collapse may remain after tonsillectomy. This situation was also observed in the present study, viz., 19 participants presented with a postoperative Friedman tonsil classification of zero but still had oropharyngeal collapse. Hence, futures studies are needed to investigate the role of tonsils in tongue base collapse. In addition, otolaryngologist-head and neck surgeons need to comprehensively consider the potential postoperative changes in the upper airway of OSA patients, evaluating the necessity of tonsillectomy.

Another finding is that the results of the logistic regression models (both the identified associated factors and the directions of associated factors) for tongue base collapse and epiglottic collapse are basically the same. A possible reason of the similarity is that a majority of the epiglottic collapse cases (74.4%; Table 2) were secondary to tongue base collapse (viz., a bulky tongue base pushes the epiglottis backwards and causes collapse45). It is a clinical reality that, compared with primary epiglottic collapse (e.g., floppy epiglottis45), secondary epiglottic collapse is more common45,46. It is also possible that the above-mentioned stent role of tonsils also applies to epiglottic area, but future studies are needed to test this hypothesis.

As for velum collapse, it is consistent with previous studies that velum is the most frequently observed collapse site in the upper airway (98.3% in the present study)8 and the prevalence of CCCp ranges from 10% - 32% (17.9% in the present study)4. As for the associated factor of CCCp, a longer duration of snoring event was found to be associated with higher probability of CCCp. Long duration of a snoring event means long inspiratory time and small inspiratory volume per unit time. Given that CCCp is associated with high upper airway collapsibility (viz., small cross-sectional area and limited airflow)33,44, it is reasonable that snoring events from patients with CCCp had longer duration than those from patients without CCCp. The positive association between the duration of snoring event and the probability of CCCp during DISE in supine position may be applicable to snoring sounds during natural sleep to predict the presence of CCCp. But before that, given the potential difference between natural sleep and drug-induced sleep47, this finding needs to be confirmed in a representative OSA population during natural sleep, and the cut-off value(s) for the duration of CCCp snoring sound or/and the proportion of the duration of CCCp snoring sound in a respiratory cycle (inspiration and expiration) needs to be determined in further studies.

In previous studies15,16, snoring sound parameters, especially those in frequency domain, e.g., DF, FF, F1-3, were found to be applicable to distinguish between snoring sounds that were generated from different levels in the upper airway. However, in the present study, only the duration of snoring event was identified as an associated factor of CCCp and no snoring sound parameter was found to be associated with the collapse at the levels of oropharynx, tongue base, and epiglottis. This may be due to the fact that, compared with single-level collapse (viz., the collapse site is also the excitation site of snoring sound), the association between snoring sound parameters and multi-level collapse is relatively indirect. As a consequence, it is difficult to identify the associated factors of the presence of collapse at each level of the upper airway, especially for conventional statistical methods like logistic regression models. Nowadays, as a branch of artificial intelligence, machine learning plays an increasingly important role in making predictions, including for acoustic analysis15,16. According to the “source-filter” theory13, it is theoretically feasible to predict the presence of collapse at each level of the upper airway based on snoring sound parameters, but, in future studies, more intelligent techniques like machine learning are needed for the task.

The present study inevitably has some limitations. Firstly, as an intrinsic limitation, acoustic analysis of snoring sound only applies to snoring OSA patients. For non-snoring OSA patients, acoustic analysis is not applicable. In addition, although there is no difference in age, gender, BMI, AHI, and collapse site between included and excluded OSA patients, the generalizability of the results was limited by the inclusion of only patients who generated analyzable snoring sounds in supine position during DISE. DISE is generally prescribed when upper airway surgery is considered and upper airway surgery is only considered for OSA patients with a BMI < 32 kg/m2 and an AHI < 30 events/hr, and when patients have CPAP failure or intolerance. In other words, a lot of OSA patients with high BMI and AHI were excluded from this study and the study results may be limited to the current patient profile. Secondly, as mentioned above, some snoring OSA patients might have been excluded because only TCI was used during DISE. Thirdly, previous studies also reported the impact of the degree and configuration of collapse on snoring sounds48. However, as to keep this study focused, the degree of collapse and the configuration of collapse at oropharynx, tongue base, and epiglottis levels were not taken into consideration.

CONCLUSION

Within the current patient profile and approach, given that only a limited number of predictors were identified, it does not seem feasible to predict upper airway collapse sites found in DISE from demographic, anthropometric, clinical examination, sleep study, and snoring sound parameters in OSA patients.

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