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The Site of Airway Collapse in Sleep Apnea, Its Associations with Disease Severity and Obesity, and Implications for Mechanical Interventions

To the Editor:

The upper airway is composed of various structures. The increase in volume and repetitive collapse of these structures are risk factors for obstructive sleep apnea (OSA). In patients with OSA, the structure or site of obstruction can be identified by using drug-induced sleep endoscopy (DISE), and each obstruction site is believed to increase the severity of OSA. However, some recent studies have reported a negative correlation between the specific type of anatomic obstruction and the apnea–hypopnea index (AHI) (1, 2). These results suggest that not all sites of obstruction identified on DISE influence OSA severity equally. Although the sites of obstruction are commonly considered to represent different phenotypes, no study has formally evaluated the characteristics of these phenotypes in terms of the associations with disease severity, obesity, and implications for mechanical interventions. Therefore, this study aimed to identify the clinical characteristics and expected treatment response according to phenotype labeling using DISE.

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We performed a retrospective review of 637 patients with symptoms of snoring or sleep apnea who underwent polysomnography and DISE from October 2014 to February 2019. Forty-seven patients with incomplete polysomnography or DISE data and three patients with a history of surgery were excluded. Polysomnography was conducted according to American Academy of Sleep Medicine scoring manuals. DISE was performed under propofol or dexmedetomidine while maintaining a bispectral index score between 50 and 70. In addition to supine DISE, simulated maneuvers were used to evaluate the airway status. The results of DISE were assessed on the basis of the VOTE classification (2). The Mann-Whitney *U* test and chi-square and Fisher exact tests were performed to compare the clinical characteristics of patients with and without obstruction. In addition, restricted cubic spline regressions with three knots, adjusting for age, sex, body mass index (BMI), and AHI, were performed to analyze associations between the probability of observing obstruction at each site and AHI (Figure 1). The institutional review board of the Chonnam National University Hospital approved this study protocol (institutional review board number CNUH-2020-282).

Anatomic phenotypes showed varying associations with an increased AHI or an increased BMI (Figure 1). With an increasing AHI, there was an increased probability of observing a velum ($P < 0.001$), oropharynx ($P < 0.001$), or tongue base ($P = 0.001$) obstruction but no increased probability of epiglottic obstruction. However, epiglottis collapse showed no association with the AHI ($P = 0.154$). BMI trends also varied according to the site. Velum and oropharyngeal obstructions were positively correlated with the BMI ($P = 0.024$ and $P < 0.001$), but tongue base ($P < 0.001$) and epiglottis ($P = 0.001$) obstructions were negatively correlated with the BMI.

Patients with velum obstruction showed the most clinical characteristics consistent with OSA. Velum obstruction was positively correlated with the AHI and BMI (Figure 1). In addition, compared with obstructions at other sites, velum obstruction showed male predominance (71.2% vs. 84.6%; $P = 0.001$) and an association with older age (34.7 ± 15.9 vs. 48.2 ± 14.9 ; $P < 0.001$). Considering the highest incidence of velum obstruction (79%; Table 1) in our study participants, velum obstruction may be a representative clinical characteristic of OSA.

Patients with oropharyngeal collapse showed clinical characteristics that were different from those with velum obstruction. Age and sex did not affect oropharyngeal obstruction. Most factors that affected oropharyngeal obstruction in our study were obesity-related, such as the BMI, underlying disease, and lower minimum oxygen saturation. In addition, previous studies showed that obesity was closely related to anatomic factors that cause narrowing of the oropharyngeal lateral wall (3), such as parapharyngeal fat volume (4), lateral pharyngeal muscle thickness, and lateral pharyngeal fat volume (3, 5). Therefore, our findings provide clear support for the notion that oropharyngeal (lateral wall) collapse is influenced by obesity.

In contrast, patients with tongue base obstruction and epiglottis collapse showed different clinical characteristics. The AHI was positively correlated with tongue base obstruction (Figure 1). However, patients with tongue base obstruction had a lower BMI in our study, which contradicts the notion that increased tongue volume is a risk factor for OSA (6). However, this observation is in concordance with findings from a previous study involving phenotype labeling using DISE (1). The study also showed that the patient with tongue base collapse

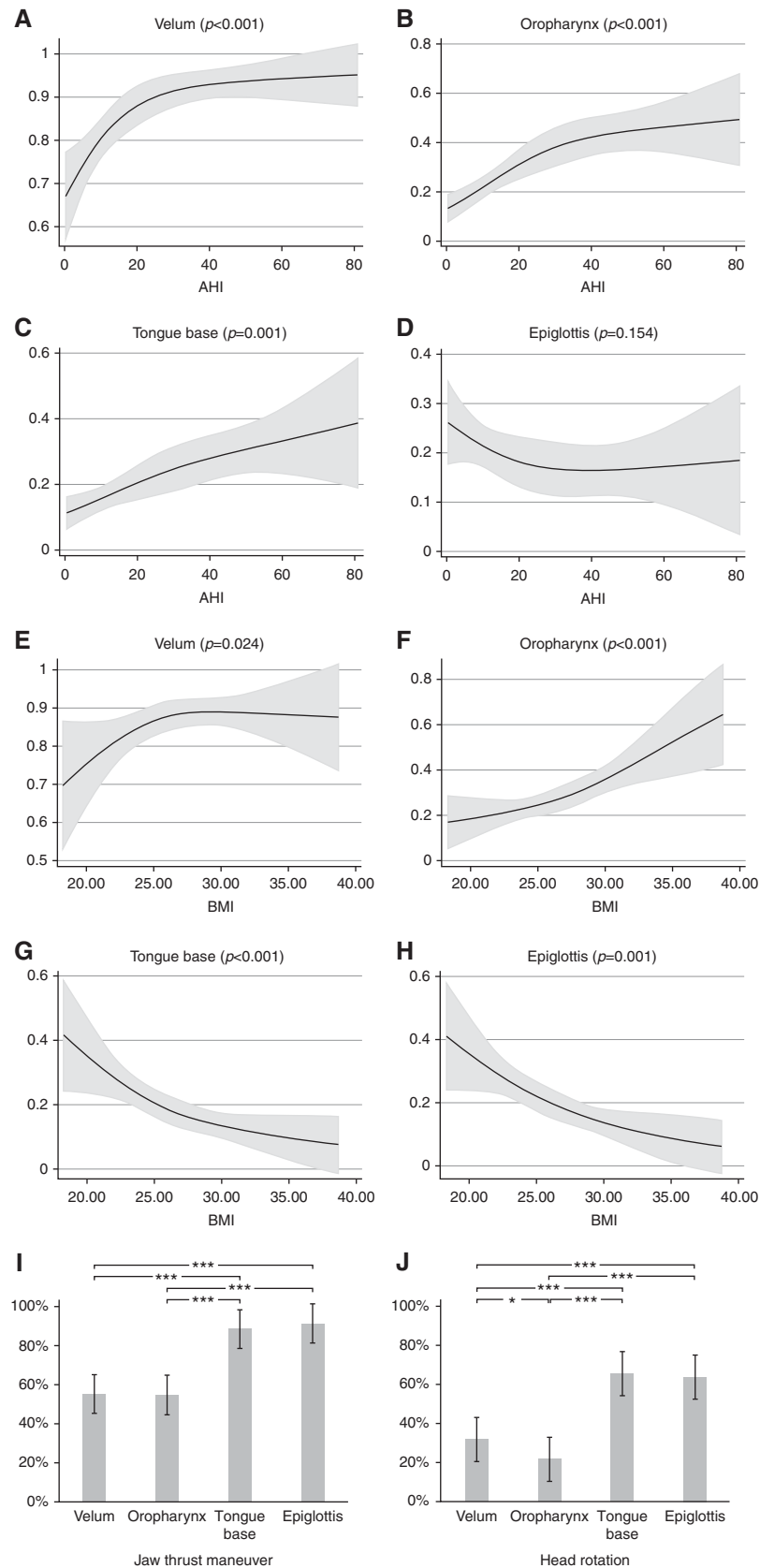


Figure 1. The association among the obstruction risk, the apnea-hypopnea index (AHI) or body mass index (BMI), and the response rate to the simulated maneuver according to phenotype labeling by using drug-induced sleep endoscopy. (A–C) The obstruction risks of the velum, oropharynx, and tongue base were positively associated with the AHI. (D) However, the obstruction risk of the epiglottis was negatively associated

Table 1. Demographics and Clinical Characteristics of the Study Population

	All Subjects
Demographic factors	
Patient number	587
Age, yr	45.3 ± 16.1
Sex, M	480 (81.8)
Hypertension	135 (23.1%)
Diabetes mellitus	48 (8.2%)
Body mass index, kg/m ²	26.4 ± 4.2
Subjective symptom scores	
Epworth Sleepiness Score	8.0 ± 4.8
Snoring visual analog scale	6.3 ± 2.6
Stanford Sleepiness Scale	3.21 ± 1.49
Physical examination	
Friedman tongue position (I/II/III/IV)	185/141/126/103
Tonsil grade (I/II/III/IV)	329/175/40/6
PSG parameters	
Apnea–hypopnea index, events/h	22.8 ± 21.5
Minimal O ₂ saturation, %	82.8 ± 9.5
DISE phenotype	
Velum obstruction	462 (79%)
Oropharynx obstruction	174 (30%)
Tongue base obstruction	119 (20%)
Epiglottis obstruction	121 (21%)

Definition of abbreviations: DISE = drug-induced sleep endoscopy;

PSG = polysomnography.

Data are expressed as the mean ± SD, median (interquartile range), or n (%).

detected by using DISE had a lower BMI. Therefore, we can assume that the increased tongue volume and collapse of the tongue base detected by using DISE are different characteristics.

Patients with epiglottis collapse also showed clinical characteristics that were different from those with obstruction at other sites. The epiglottic collapse did not correlate with the AHI (Figure 1). In addition, age, sex, and symptoms of OSA did not affect epiglottis collapse. However, the BMI remained lower in this phenotype after adjusting for the lower AHI (plus sex and age). This result is in concordance with findings from a previous study by Kim and colleagues (2).

Each simulated maneuver also had a different effect on airway obstruction. The jaw thrust maneuver improved obstructions of the velum, oropharynx, tongue base, and epiglottis in 55.6%, 53.9%, 89.0%, and 91.7% of patients, respectively. Similarly, the head rotation maneuver improved obstructions of the velum (27.1%), oropharynx (17.8%), tongue base (60.6%), and epiglottis (62.8%). Patients with obstructions of the tongue base and epiglottis responded significantly better than those with obstruction of the velum or oropharynx ($P < 0.001$ for all comparisons; Figure 1).

These results suggest that non-continuous positive airway pressure (CPAP) mechanical interventions might be more effective for tongue base or epiglottis collapse. Patients with tongue base and epiglottis collapse responded well to a non-CPAP simulated maneuver

in our study, which was consistent with previous studies (7, 8). Furthermore, the primary clinical characteristic of these patients in our study, the lower BMI, is favorable to non-CPAP mechanical interventions (9). A previous study showed that an anteroposterior collapse, such as a tongue base or epiglottis collapse, require higher CPAP (10).

However, this study has some limitations. First, this study included patients with multisite obstructions, which potentially manifest with clinical characteristics of obstruction at another site. Second, some cases of tongue base obstruction could be classified as velum obstruction because the velum could be pushed by the tongue base. Third, we analyzed the obstruction by using “all-or-none” criteria; the magnitude of obstruction might also provide additional information.

In conclusion, clinical features differ among the obstruction sites examined according to the phenotype obtained by using DISE. Our findings could be helpful for achieving precision medicine for OSA through an accurate diagnosis of the obstruction site and designing specialized treatment. ■

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Figure 1. (Continued). with the AHI. (E) Velum and (F) oropharynx obstructions were positively associated with the BMI. However, (G) tongue base and (H) epiglottic obstructions were negatively associated with the BMI. (I and J) Patients with tongue-base and epiglottis collapse responded well to the simulated maneuver. (A–H) The restricted cubic spline curve shows the model-predicted probability (solid line) and 95% confidence intervals (shaded regions) for the association of the AHI and BMI with the obstruction risk. Models were analyzed by using restricted cubic spline regression with three knots, adjusting for age, sex, BMI, and AHI. Plots were truncated at the first and 99th percentiles to minimize the influence of outlier values. (I and J) The chi-square test was performed to compare groups in terms of the response rate to the stimulated maneuver. * $P < 0.05$ and *** $P < 0.001$.

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Overnight Oximetry–derived Pulse Rate Variability Predicts Stroke Risk in Patients with Obstructive Sleep Apnea

To the Editor:

Obstructive sleep apnea (OSA) is increasingly recognized as a risk factor for stroke, the second most common cause of death and the third most

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common cause of disability-adjusted life-years worldwide (1). Given the heterogeneous OSA phenotypes and disease outcomes (2), a stroke risk biomarker would be clinically useful for implementing preventive actions. Cohort studies may help increase our understanding of OSA pathophysiology and enable extraction of novel biomarkers from sleep recordings (3). Heart rate variability (HRV) parameters have been shown to be useful biomarkers for stroke incidence (4). Our group has recently reported an association between stroke incidence and HRV indices in patients investigated for OSA (5). However, the high prevalence of OSA has led to increasing use of type 3 home sleep apnea testing, which does not include electrocardiography. Unlike electrocardiography, oximetry is easy to use in the ambulatory setting and is widely available. Pulse rate variability (PRV) derived from the oximeter's photoplethysmography (PPG) signal is an accurate estimation of HRV in subjects at rest or in nonstationary conditions as well as during sleep (6–8). We have recently demonstrated an association of PRV indices with the incidence of atrial fibrillation (6), a stroke risk factor. Within the same clinic-based cohort, we aimed to determine whether PRV indices could predict the risk of stroke in patients with OSA.

Methods

This retrospective study was conducted on the Pays de la Loire Sleep Cohort, linked with data from the French administrative healthcare database (Système National des Données de Santé) (6). We included stroke-free patients with OSA and an apnea–hypopnea index (AHI) ≥ 5 events/h on manually scored (9) PSG or home sleep apnea testing findings (recorded using the CID102L8D and CID102L devices, respectively; CIDELEC) between May 15, 2007, and December 31, 2017. As described previously (6), PRV analyses were performed on the oximeter's PPG signal as extracted from diagnostic sleep studies. Time domain analysis included the SD of normal-to-normal beat intervals and the root mean square of the successive normal-to-normal differences. Frequency domain parameters were extracted from the spectral analysis of the normal-to-normal intervals. The normalized low-frequency power (LF; from 0.04–0.15 Hz) and high-frequency power (HF; from 0.15–0.4 Hz) were calculated. The LF/HF ratio evaluates the balance between the sympathetic and parasympathetic systems.

The study endpoint was the first episode of stroke at any time between the date of the diagnostic sleep study and the end of December 2018. As previously described (5), the first occurrence of stroke was defined as the entry date of the first hospitalization with a discharge diagnosis of stroke. The association of PRV indices with stroke incidence was evaluated by using Cox proportional hazard models. Covariates that are recognized as stroke risk factors were entered in the multivariate analysis in addition to study site and the type of sleep study. Associations were considered statistically significant at a *P* value of <0.05 . All statistical analyses were performed with SAS 9.4 software (SAS Institute).

Results

The study sample included 6,075 stroke-free patients with OSA (median [interquartile range] age, 62.0 [52–71] yr; median [interquartile range] AHI, 28 [14–43] events/h; median [interquartile range] body mass index, 30 [26–34] kg/m²) who were predominantly male (65.7%) and frequently had comorbidities (hypertension, 35.0%; diabetes, 15.2%;