A novel algorithm to predict oxygen desaturation in sedated patients with obstructive sleep apnea utilizing polysomnography

A STROBE-compliant article

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Abstract

This retrospective study aimed at identifying the predictors of oxygen desaturation (OD) (i.e., SpO2 < 95%) in patients with obstructive sleep apnea (OSA) requiring deep sedation and developing an algorithm to predict OD.

We studied 66 OSA patients undergoing propofol-induced deep sedation for drug-induced sleep endoscopy (DISE). The patients were divided into prediction (n = 35) and validation (n = 31) groups. Patient characteristics and polysomnographic parameters were analyzed with receiver operating characteristic curve and Chi-squared test to identify significant predictors of OD for developing an algorithm in the prediction group. The predictive accuracy, sensitivity, positive predictive value, and negative predictive value of the algorithm were determined in the validation group.

Six polysomnographic predictors of OD were identified, including Apnea-Hypopnea Index of total sleep time (AHI-TST), AHI at the stage of rapid eye movement (AHI-REM), percentage of time with oxygen saturation < 90% (mO2 < 90%), average SpO2, lowest SpO2, and desaturation index. Stepwise multiple logistic regression analysis demonstrated that low average SpO2 (< 95.05%) and high AHI-REM (> 16.5 events/h) were independent predictors of OD. The algorithm thus developed showed that patients with an average SpO2 < 95.05% and those with an average SpO2 ≥ 95.05% together with an AHI-REM > 16.5 events/h would be at risk of OD under sedation. The predictive accuracy, sensitivity, positive predictive value, and negative predictive value were 84%, 100%, 83%, 100%, respectively.

For patients with OSA, average SpO2 and AHI-REM may enable clinicians to predict the occurrence of oxygen desaturation under deep sedation. Future large-scale studies are needed to validate the findings.

Abbreviations: AHI = Apnea-Hypopnea Index, AHI-TST = Apnea-Hypopnea Index of total sleep time, AHI-REM = Apnea-Hypopnea Index of rapid eye movement, AHI-NREM = Apnea-Hypopnea Index of non-rapid eye movement, AUC = area under the curve, BMI = body mass index, BIS = bispectral index score, EES = electroencephalographic, mO2 < 90% = percentage of time with oxygen saturation < 90%, OSA = obstructive sleep apnea, OD = oxygen desaturation, RSS = Ramsay sedation scale, REM = rapid eye movement, ROC = receiver operating characteristic.

Keywords: deep sedation, obstructive sleep apnea, oxygen desaturation, polysomnogram, propofol
1. Introduction

Obstructive sleep apnea (OSA) is a clinical condition characterized by frequent upper airway collapses and hypoxia during sleep. Unfavorable upper airway anatomy and sleep-related decrease in muscle activity, reduced pharyngeal caliber, elevated upper airway resistance, increased upper airway compliance lead to pharyngeal airway obstruction. Its prevalence ranges from 9% to 24% in men and from 4% to 9% in women, and it is believed that 80% of patients with OSA are undetected. Of all patients who are required to undergo surgery with anesthesia, 24.5% are estimated to be at a high risk of OSA. The perioperative risk of patients with OSA depends on the severity of OSA, surgery and anesthesia types, and the need for postoperative opioids. Patients with OSA exhibit a higher risk of post-anesthesia adverse events, such as oxygen desaturation (OD), reintubation, respiratory-related intensive care unit stays, delirium, and cardiovascular events compared to those without.

Although a previous practice guideline suggested that patients with OSA may have an increased risk of respiratory adverse events during moderate to deep sedation, a simple method which can reliably predict the occurrence of sedation-related OD among patients with OSA is still unavailable. Taking into account that moderate-to-deep sedation is often necessary for various surgeries and procedures, development of an algorithm that allows the clinician to identify sedation-related OD among patients with OSA may be useful. However, there were still limited data for anesthesiologists to predict respiratory events during sedation for OSA patients. Taking into consideration that polysomnography is commonly used for diagnosing and classifying OSA severity in clinical practice, we hypothesized that polysomnographic parameters may enable the clinician to effectively predict the occurrence of sedation-related OD. Hence, the primary aim of this study was to investigate the potential predictors of sedation-related OD among OSA patients, while the secondary outcome was to develop a predictive algorithm for OD and to validate its accuracy.

2. Methods

2.1. Study population and design

After obtaining approval from the Institutional Review Board of Chang Gung Memorial Hospital (approval number: 101-4101B), medical records of patients with OSA who received drug-induced sleep endoscopy (DISE) to guide subsequent surgical interventions for OSA between January 2010 and February 2012 were reviewed. The inclusion criteria included adult patients (i.e., ≥18 years) with documented OSA based on polysomnography and the use of target-controlled infusion pump with propofol for deep sedation during DISE. Exclusion criteria included patients with previous oral or head surgery, American Society of Anesthesiologists (ASA) classification III or higher, chronic obstructive pulmonary disease, chronic use of sedatives, history of allergy to propofol, and unavailability of key information (e.g., polysomnogram or intraoperative parameters). In addition, patients who exhibited abnormal electroencephalographic (EEG) activity (e.g., epilepsy, an abnormal brain lesion, or a cerebrovascular accident) were also excluded. Informed consent was waived because of the retrospective nature of the study.

Based on the purpose of the current study, OSA patients were divided into 2 groups (i.e., prediction group and validation group) and a 2-step process was conducted. In the first step, polysomnographic parameters or patient characteristics were used to determine the predictors of OD in the prediction group. In the second step, an algorithm for prediction of OD was developed based on the results of first step. Then the accuracy, sensitivity, and specificity of this algorithm were validated in the validation group.

2.2. Polysomnography for diagnosis of obstructive sleep apnea

A day after the definite diagnosis of OSA based on polysomnography at the sleep center, the patients were scheduled to receive DISE and surgical interventions for OSA. During examination, the results of EEG, submental electromyography, and electrocorticography were reviewed. In addition, naso/oral airflow and oxygen saturation were measured and recorded by standard techniques. All results were scored and interpreted by a certified and experienced sleep medicine physician. Sleep stage was determined and the severity of sleep-disordered breathing was assessed based on the number of apnea/hypopnea episodes. OSA and obstructive hypopnea were defined separately according to previous study, namely, the cessation of airflow for at least 10 seconds with a corresponding respiratory effort and an abnormal respiratory event accompanied by at least 30% reduction in thoracoabdominal movement or airflow when compared with the baseline, which lasts for at least 10 seconds and is associated with ≥4% oxygen desaturation. Besides, the apnea–hypopnea index (AHI) was calculated by the definition of the total number of apnea and hypopnea episodes per hour of electroencephalographic sleep, while obstructive sleep apnea/hypopnea syndrome was defined as an AHI of >5 events per hour. Respiratory events of central origin were all excluded for severity classification.

2.3. Drug-induced sleep endoscopy (DISE) and sedation technique

DISE was performed at the operating room on the same day just prior to surgery. The patients received no pre-medications (e.g., diazepam, midazolam, clonidine, and dexmedetomidine) because these medications may affect the tone of the airway and potentially cause false-positive findings, resulting in “overtreatment” of the patients during the following surgery. After the application of standard anesthetic monitors, a bispectral index (BIS) Quatro sensor (Aspect Medical Systems, Norwood, MA) was positioned on the forehead of the patient according to the manufacturer’s instructions. BIS data were calculated by the BIS module of the GE Datex-Ohmeda S/5 ADU CareStation. Supplemental oxygen (4.0L/min) was administered by a breathing circuit adjacent to the nasal openings. Using the Fresenius Orchestra Infusion Workstation (Fresenius Kabi), an anesthesiologist slowly titrated propofol until the desired effect was achieved by effect-site steering of the pharmacokinetic Schnider model. When the sedation depth was judged to be between level 4–5 on the Ramsay sedation scale (RSS) and the BIS value was <70, nasoendoscopy was performed immediately. Intravenous lidocaine (1 mg/kg) and atropine (0.5 mg) were administered before this procedure to suppress airway reflex and secretion.

If patients had a brisk limb movement during DISE, the dosage of propofol was increased according to the anesthesiologist’s experience. Sedation level 6 on the RSS or a BIS value of <40 was
considered too deep and was avoided. Blood pressure and heart rate were maintained within 25% of the baseline, and arterial oxygen saturation (SpO2) was maintained at >85% to 90%. Additional intravenous atropine (0.01 mg/kg) was administered for bradycardia, while intravenous ephedrine (4 mg) was given for patients with hypotension to maintain hemodynamic stability. If SpO2 was <90%, the mandible was tilted slightly forward. If SpO2 dropped to 85%, mask ventilation was immediately performed with transient cessation of propofol infusion. For a respiratory rate of <8/min, the dosage of propofol was reduced. After completion of DISE, additional propofol boluses (40–60 mg), alfentanil (10 μg/kg) and cis-atracurium (0.2 mg/kg) were given to facilitate tracheal intubation. General anesthesia was maintained with continuous infusion of propofol in the BIS range of 40 to 60 for surgery.

2.4. Definition, outcomes, and data collection

The primary outcome was the identification of potential predictors of OD among OSA patients under DISE. The secondary outcomes were to develop a predictive algorithm and validate its accuracy. OD was defined as SpO2 < 95% measured using pulse oximetry. All medical history, demographic data, polysomnographic results, and intraoperative parameters such as blood pressure, respiratory rate, SpO2, and BIS values were collected. The log history of propofol infusion was simultaneously recorded using the software Base Dump installed on a laptop (Ver. 1.0; Fresenius Kabi, Taipei, Taiwan) via the RS-232 interface.

2.5. Statistical analysis

As there were more than 1 primary outcome in this retrospective pilot study, sample size estimation was not performed. Two independent-sample t test was used for continuous variables, and categorical data were analyzed by Chi-squared or Fisher exact test. To predict OD, the receiver operating characteristic (ROC) curve was plotted to determine the cutoff point (maximal sum of sensitivity and specificity) according to the odds ratio of a dichotomous comparison. In univariate analysis, potential significant predictors presenting with an area under the curve (AUC) of >0.7 or P < 0.1 by Chi-squared or Fisher exact test were selected for inclusion into a multiple binary logistic regression model.

3. Results

From January 2010 to February 2012, medical records of 66 OSA patients who met the inclusion criteria were reviewed. The data from the first 35 cases (i.e., prediction group) were used to identify the predictors of OD and develop a predictive algorithm, while data from the subsequent 31 cases (i.e., validation group) were used to validate the accuracy, sensitivity, and specificity of this algorithm.

3.1. Association of patient characteristics and polysomnographic parameters with oxygen desaturation events

A total of 57.1% of cases (n = 20) in the prediction group had developed OD during DISE. The characteristics and polysomnographic data of patients with and without OD are shown in Table 1. Older patients and those with a higher body mass index (BMI) had a high risk of developing OD (both P < .05). In addition, there were significant differences in most polysomnographic parameters between patients with OD and those without, except sleep efficiency, hypopnea-longest, and snoring index (Table 1).

3.2. Propofol concentration and anesthetic depth during DISE

The propofol concentration, anesthetic depth, and limb movement in patients with OD and those without are shown in Table 2. Comparison between patients with OD and those without demonstrated no significant differences in propofol concentration (4.88 ± 1.05 vs 4.51 ± 1.12, respectively, P = .330), anesthetic depth (i.e., BIS score: 50.05 ± 7.66 vs 45.00 ± 7.20, P = .056), and limb movement (P = .686).

3.3. Predictors of oxygen desaturation during sedation and predictive algorithm

To explore whether patient characteristics or the polysomnogram-based variables can predict the occurrence of OD during...
Table 2

Propofol concentration, anesthetic depth, and limb movement in patients with oxygen desaturation and those without.

| Variable                        | Overall (n=35) | Patients with SpO2 < 95% (n=15) | Patients with SpO2 ≥ 95% (n=20) | P value |
|---------------------------------|----------------|----------------------------------|---------------------------------|--------|
| Ce propofol (µg/mL)             | 4.72 ± 1.08    | 4.51 ± 1.12                      | 4.88 ± 1.05                     | .330   |
| Bispectral index score          | 47.89 ± 7.79   | 45.00 ± 7.20                     | 50.05 ± 7.66                    | .056   |
| Limb movement (yes/no)          | 22/13          | 1/5                              | 12/8                            | .686   |

Ce propofol: propofol effect site concentration.

DISE, we assessed age, sex, BMI, and polysomnographic parameters (Table 3). Based on the definitions of significance for ROC analysis (i.e., AUC > 0.7) and Chi-squared test (i.e., P < .1), 6 potential polysomnographic predictors were identified, namely, apnea-hypopnea index of total sleep time (AHI-TST), apnea-hypopnea index of rapid eye movement (AHI-REM), percentage of time with arterial oxygen saturation <90% (mO2 < 90%), average SpO2, lowest SpO2, and the desaturation index (Table 3).

Stepwise multiple logistic regression models identified average SpO2 and AHRR-REM as independent predictors of OD (Table 4). In subgroup analysis, of the 12 OSA patients with an average SpO2 of <95.05%, the presence of high AHRR-REM (cut-off defined as 16.5 events/h) was able to predict OD (AUC = 0.714, sensitivity = 89%, and specificity = 64%). In other words, the algorithm for predicting OD among OSA patients based on the results of the present study revealed that those with an average SpO2 <95.05% and those with an average SpO2 ≥ 95.05% together with an AHRR-REM > 16.5 events/h would be at risk of developing OD under sedation (Figure 1).

3.4. Validation of the predictive algorithm

Data from a total of 31 patients (i.e., validation group) were used to validate the simple algorithm. 77.4% of OSA patients (n=24) in the validation group exhibited OD during DISE. By using this algorithm, the predictive accuracy, sensitivity, positive predictive value, and negative predictive value were 84% (26/31), 100% (24/24), 83% (24/29), and 100% (2/2), respectively.

3.5. Adverse Events during drug-induced sleep endoscopy (DISE)

All OSA patients underwent DISE smoothly without cardiovascular complications and emergent tracheal intubation. No patients reported unpleasant memories of BIS-guided DISE when questioned by a nurse anesthetist on postoperative day 1. Only 1 patient (2.9%) suffered from mild postoperative nausea and vomiting but no antiemetic treatment was required within 72 hours after surgery.

4. Discussion

DISE has become an important diagnostic examination tool to guide subsequent surgical interventions in OSA patients. During deep sedation induced by propofol using a target-controlled infusion (TCI) pump, we found that 2 polysomnographic parameters could be used effectively to predict the occurrence of sedation-related OD, namely, AHRR-REM and average SpO2. By using average SpO2 < 95.05% as the main predictive criterion and AHRR-REM > 16.5 events/h as a supplemental criterion, OD can be predicted during sedation with predictive accuracy, sensitivity, positive predictive value, and negative predictive value of 84%, 100%, 83%, and 100%, respectively.

Propofol, a common intravenous general anesthetic, induces loss of consciousness by potentiating GABA_A receptors[23] and leads to dose-dependent depression on EEG.[24] Propofol exhibits a dose-dependent inhibition of upper airway reflex and central respiratory control of upper airway muscle, which leads to the inhibition of genioglossus muscle activity and upper airway obstruction.[25] Hypoxia and hypoxemia are typical sedation-related adverse events caused by propofol.[26,27] In a large-scale

Table 3

Predictors of oxygen desaturation (SpO2 < 95%) based on ROC curve analysis and Chi-squared test during propofol-induced deep sedation.

| Variables                         | AUC  | Cutoff value | Sensitivity/Specificity (%) | Odds ratio (95% CI) | P value |
|-----------------------------------|------|--------------|-----------------------------|---------------------|--------|
| Age (yr)                          | 0.652| >42.5        | 60/80                       | 6.00 (1.27–28.25)   | .018   |
| BMI (kg/m2)                       | 0.485| >26.15       | 95/53                       | 1.40 (0.36–5.39)    | .625   |
| ESS                               | 0.538| >10.5        | 70/27                       | 0.85 (0.19–3.77)    | 1.000  |
| AHI-TST (events/h)                | 0.712| >24.25       | 80/53                       | 4.57 (1.03–20.35)   | .04    |
| AHRR-REM (events/h)               | 0.728| >16.5        | 85/60                       | 8.50 (1.71–42.28)   | .006   |
| AHRR-NREM (events/h)              | 0.667| >22.35       | 78/50                       | 3.50 (0.79–15.58)   | .144   |
| Apnea-longest (seconds)           | 0.579| >34.75       | 80/43                       | 2.67 (0.59–12.02)   | .266   |
| Hypopnea-longest (seconds)        | 0.485| >45.95       | 75/33                       | 1.50 (0.34–6.56)    | .712   |
| mO2 < 90% (%)                     | 0.743| >3.05        | 70/73                       | 6.42 (1.44–28.51)   | .011   |
| Average SpO2                      | 0.733| >95.05       | 93/55                       | 17.11 (8.7–156.26)  | .003   |
| Lowest SpO2                       | 0.732| <7.95        | 73/40                       | 4.13 (0.97–17.63)   | .050   |
| Desaturation index (events/h)     | 0.717| >14.2        | 70/60                       | 3.50 (0.86–14.30)   | .076   |
| Arousal index (events/h)          | 0.665| >27.4        | 60/67                       | 3.00 (0.74–12.13)   | .118   |
| Snoring index (events/h)          | 0.527| >136.05      | 65/40                       | 1.24 (0.31–4.93)    | .762   |

mO2 < 90% = percentage of time with oxygen saturation < 90%.

AHI-TST = Apnea-Hypopnea Index of total sleep time, AUC = area under curve, BMI = body mass index, CI = confidence interval, ESS = Epworth sleepiness scale, NREM = non-rapid eye movement, REM = rapid eye movement.
study with 2574 patients receiving sedative gastrointestinal endoscopy under propofol, the total dose of propofol, duration of sedation, ASA classification, and patient height are significant predictors of an SpO2 below 90%.[28] In contrast, we did not find that patient characteristics (i.e., age and BMI) were predictors of OD after multiple regression analysis. The propofol concentration and sedation depth (i.e., BIS values) were also comparable in OSA patients with and without OD. This discrepancy may be attributed to the experience of the operators who perform the sedative procedures, the modes of drug administration (e.g., TCI or manual infusion), and the characteristics of patient populations.

In our patients, OD (i.e., SpO2 < 95%) occurred in 57.1% and 77.4% of OSA patients in the prediction group and validation group, respectively. The finding was consistent with that of a previous study showing a comparable incidence of OD (i.e., 59%) in OSA patients receiving propofol-induced sedation for DISE.[29] Furthermore, the occurrence of OD has been reported to be positively associated with the risk of cardiovascular complications (e.g., cardiac ischemic events) in surgical patients.[32] Therefore, the ability to preoperatively predict the risk of OD would allow clinicians to implement timely strategies to improve the safety of sedation for high risk OSA patients.

Although the STOP-BANG questionnaire is a practical screening tool to identify OSA patients,[33] the reliability of this questionnaire in predicting cardiopulmonary complications during sedative endoscopy (e.g., colonoscopy) was found to be suboptimal in a previous study.[34] Based on the STOP-BANG questionnaire, that study with a total of 243 patients showed no significant difference in the rates of hypoxia and hypertension in patients with OSA compared to the data of those without.[34] Although this finding highlighted that routine screening for identifying patients with OSA cannot directly predict their subsequent sedation-related respiratory events, the questionnaire may be adopted as a preliminary selection tool for patients to undergo polysomnographic study from which

### Table 4

| Polysomnographic Variables | Odds ratio (95% CI) | P value† |
|---------------------------|---------------------|---------|
| AHI-REM > 16.5 (events/h) | 7.45 (1.18–47.07)   | .033    |
| Average SpO2 < 95.05%     | 15.16 (1.43–160.30) | .024    |

AHI-REM = apnea-hypopnea index at the stage of rapid eye movement, CI = confidence interval.

† P < 0.05 was considered a significant difference.

P = .432 was calculated using the Hosmer–Lemeshow goodness-of-fit test.

#### Figure 1

A simple algorithm to predict oxygen desaturation in patients with obstructive sleep apnea during deep sedation. AHI-REM = Apnea–Hypopnea Index of rapid eye movement.
average SpO2 and AHI-REM could be acquired to predict their risk of OD under sedation using the present algorithm. Nevertheless, further studies are required to elucidate whether the use of this novel algorithm could reduce the incidence of respiratory-associated adverse events during moderate-to-deep sedation.

Although there are many potential predictors of OD (Table 1), multiple regression analysis only identified AHI-REM and average SpO2 as significant predictors during DISE in the current study. Previous studies have reported that the severity of OSA depends on the sleep stages [35–37]. Because the stage of REM has been found to be associated with a tendency for obstruction to extend from upper to lower parts of the upper airway [35,37], it is possible that the lower part of the upper airway tends to collapse in patients with high AHI-REM. This phenomenon may predominate during sedation, leading to a high incidence of OD in those with a high AHI-REM. Another interesting finding was that, instead of the parameter of lowest SpO2, average SpO2 was a significant predictor of sedation-related OD. The underlying mechanism for this finding remains unknown. Polysomnogram contain important data and parameters, some of which correlate well with the severity of OSA [18]. However, no previous studies have addressed their capability of predicting OD during sedation. To the best of our knowledge, our study was the first to demonstrate the association of AHI-REM and average SpO2 with sedation-related OD.

Nevertheless, there are still some limitations to this study. First, the polysomnogram may not be available in every OSA patient; therefore, our algorithm could not be applied to those whose polysomnographic data are unavailable. Second, the incidence of OD and the local obstruction pattern of airway in OSA patients may vary with the ways of drug administration (e.g., bolus vs. continuous infusion), the sedative employed, and the depth of sedation [29,38]. Our algorithm may not be generalized to other clinical scenarios when different sedative regimens or depths of sedation were applied. Third, this study focused on adult OSA patients; therefore, its efficacy in the pediatric population remains unknown. Fourth, identification of the predictors for OD was our primary outcome. As there were more than 1 primary outcome, sample size estimation was not performed. Besides, because the secondary outcome may be statistically underpowered, further large-scale studies are warranted to support our findings. Fifth, our study did not include OSA patients with lung diseases (e.g., chronic obstructive pulmonary disease); therefore, judicious use of this algorithm in this subgroup patients is advised. Lastly, the relatively small number of patients in the current study was due to the fact that DISE was relatively uncommon although surgical interventions for OSA were routine procedures at our institute during the study period.

5. Conclusions

Our results demonstrated that 2 polysomnographic parameters, namely, average SpO2 < 95.05% and AHI-REM > 16.5 events/h, could be used to develop an algorithm with high accuracy and sensitivity for the prediction of oxygen desaturation in patients with obstructive sleep apnea undergoing sedation with propofol. This novel algorithm could be used as a tool to optimize procedure safety when deep sedation is indicated in this group of patients. Further large-scale studies are warranted to validate our findings.

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