Factors Associated with Postoperative Exacerbation of Sleep-disordered Breathing

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ABSTRACT

Introduction: The knowledge on the mechanism of the postoperative exacerbation of sleep-disordered breathing may direct the perioperative management of patients with obstructive sleep apnea. The objective of this study is to investigate the factors associated with postoperative severity of sleep-disordered breathing.

Methods: After obtaining approvals from Institutional Review Boards, consenting patients underwent portable polysomnography preoperatively, and on postoperative nights 1 and 3 in hospital or at home. The primary outcomes were polysomnography parameters measuring the sleep-disordered breathing. They were treated as repeated measurement variables and analyzed for associated factors by mixed models.

Results: Three hundred seventy-six patients, 168 men and 208 women, completed polysomnography on preoperative and postoperative night 1. Age was 59 ± 12 yr (mean ± SD). Preoperative apnea–hypopnea index (AHI) was 12 (4, 26) (median [25th, 75th percentile]) events per hour. Thirty-five patients had minor surgeries, 292 intermediate surgeries, and 49 major surgeries, with 210 general anesthesia and 166 regional anesthesia. The 72-h opioid dose was 55 (14, 85) mg intravenous morphine-equivalent dose. Preoperative AHI, age, and 72-h opioid dose were associated with postoperative AHI. Preoperative central apnea index, male sex, and general anesthesia were associated with postoperative central apnea index. Slow wave sleep percentage was inversely associated with postoperative AHI and central apnea index.

Conclusions: Patients with a higher preoperative AHI were predicted to have a higher postoperative AHI. Preoperative AHI, age, and 72-h opioid dose were positively associated with postoperative AHI. Preoperative central apnea index, male sex, and general anesthesia were associated with postoperative central apnea index. (Anesthesiology 2014; 120:299-311)

OBSTRUCTIVE sleep apnea (OSA) is a common comorbidity in surgical patients.1–3 It has been shown to be associated with an increased incidence of postoperative adverse events.2,4–9 Sleep-disordered breathing was exacerbated with peak worsening on postoperative night 3 and recovered to preoperative level on postoperative night 7.10 The postoperative exacerbation of sleep-disordered breathing may be related to the increased incidence of postoperative complications in patients with OSA. The knowledge on the mechanism of the postoperative exacerbation of sleep-disordered breathing may help to direct the perioperative management of patients with OSA. To date, the published evidence in this area is scarce.11,12 Rosenberg et al.11 reported that postoperative rebound of nocturnal rapid eye movement (REM) sleep might contribute to the development of sleep-disordered breathing and nocturnal episodic hypoxemia. Isono et al.12 found that postoperative hypoxemia is highly correlated with preoperative hypoxemia and witnessed apnea. To our knowledge, no other study focused on the issue has been published. The objective of this study is to investigate the association between postoperative exacerbations of sleep-disordered breathing with the clinical factors, such as age, sex, preoperative apnea–hypopnea index (AHI), type of anesthesia, the invasiveness of surgical procedure, and opioid dose. We hypothesized that preoperative AHI is a major factor associated with the exacerbations of postoperative AHI.

Materials and Methods

This study was closely related to the previous report.10 Both studies followed the same protocol. The objective of the first report10 was to document the postoperative evolution in sleep architecture and sleep-disordered breathing up to postoperative night 7. The current report is to investigate the
factors associated with the exacerbation of sleep-disordered breathing on postoperative nights 1 and 3. In this study, all patients who completed preoperative, postoperative night 1, and/or postoperative night 3 polysomnography were analyzed, including the patients in the previous report.10

**Study Design**

This is a prospective observational study. There was no intervention. The primary outcomes were polysomnography parameters measuring the sleep-disordered breathing. The secondary outcomes were polysomnography parameters measuring the sleep architecture.

**Study Subjects**

Approvals from Institutional Review Boards were obtained from Toronto Western Hospital and Mount Sinai Hospital at Toronto. All patients of 18 yr or older, who were of American Society of Anesthesiologists physical status I–IV and were scheduled for elective surgical procedures, were approached by the study coordinators for written informed consent. Patients who were unwilling or unable to give an informed consent or patients who were expected to have abnormal electroencephalographic findings (e.g., brain tumor, epilepsy surgery, patients with deep brain stimulator) were excluded. If a patient used continuous positive airway pressure (CPAP) therapy on any perioperative night with polysomnography, he or she was excluded from the final analysis. The patients were recruited from November 2007 to December 2009. The quality of the portable polysomnography recordings of 41 patients was reported in a previous method article.13

**Sleep Studies and Follow-up**

The recruited patients underwent sleep studies with a 10-channel portable polysomnography device (Emblettta X100; Embla, Broomfield, CO) preoperatively at home and on postoperative night 1, and 3 in hospitals or at home. Emblettta X100 is a level 2 diagnostic tool for OSA and has been validated against laboratory polysomnography.13

The polysomnography recording montage consisted of two electroencephalographic channels (C3 and C4), left or right electrooculogram, chin muscle electromyogram, nasal cannula (pressure), thoracic and abdominal respiratory effort bands, body-position sensor, and pulse oximetry.

A full night sleep study with Emblettta X100 was carried out as previously described.13 At bedtime, the portable polysomnography device was connected to the patients by a polysomnography technician in hospital or at their home. The overnight recording itself was unattended. The patients were taught how to disconnect the device, which was picked up by the same sleep technician the following morning. The patients were asked to keep a sleep diary. The sleep technician picking up the device ensured that the sleep diary was completed.

The recordings from the portable polysomnography were scored by a certified polysomnography technologist and reviewed by a sleep physician. Somnologia Studio 5.0 (Embla) was the platform used for scoring polysomnography recordings. The polysomnography recordings were manually scored epoch by epoch by the polysomnography technologist, according to the manual published by American Academy of Sleep Medicine in 2007. Apnea was defined as at least 90% drop in air flow from baseline, which lasted at least 10 s. Apneic episodes were further classified as obstructive if respiratory effort was present or central if respiratory effort was absent during the event. Mixed apnea was apnea episodes with characteristics of both obstructive and central apnea. Apnea index was the average number of apnea episodes per hour. Hypopnea was defined as at least 50% reduction in air flow, which lasted at least 10 s and was associated with at least 3% decrease in arterial oxyhemoglobin saturation or associated with arousal. Hypopnea index was the average number of hypopnea episodes per hour. AHI was the average number of apnea and hypopnea episodes per hour. In this study, all polysomnography recordings were scored after the patients were discharged from the hospitals. The anesthesiologists and the surgeons caring for the study patients were blinded to the results of the polysomnography recordings. During the study period, the healthcare team provided routine care to these patients. The perioperative care team made the clinical decision of oxygen therapy or CPAP therapy for patients. According to the institution protocol, if SpO2 on oximeter monitoring is less than 94%, oxygen therapy will be provided. If they suspected a patient who might be suffering from OSA, they could refer the patient for further evaluation and provide the patient with CPAP treatment. The patients with an AHI greater than five events per hour on the preoperative home polysomnography were defined as OSA patients. Their family physicians were notified after surgery so that the patients could be referred to sleep physicians for further clinical management. The patients with an AHI of five events or less per hour on the preoperative home polysomnography were defined as non-OSA patients.

**Anesthesia and Postoperative Pain Control**

A balanced anesthetic technique was used in all patients. In general anesthesia (GA), patients received an induction dose of propofol, a narcotic, an inhalational agent, and a muscle relaxant. The muscle relaxant was reversed with neostigmine and atropine. In regional anesthesia (RA), patients received epimorph and a propofol infusion. Both groups received narcotic in the postoperative period.

All patients were reviewed twice daily by the Acute Pain Service team, as per our institutional standard of care. Pain was evaluated on a score of 0–10, with 0 as no pain and 10 as the most excruciating pain. Intravenous morphine through patient-controlled analgesia was initiated when the verbal pain score was 4 or higher. The Acute Pain Service team increased the immediate-release oxycodone dose and/or added controlled-release oxycodone to achieve a verbal pain score of 4 or less for pain.
Data Analysis and Statistics

Data were entered into a specifically designed Microsoft Access database (Microsoft Corporation, Redmond, WA) and checked for possible errors, SAS 9.2 for Windows (SAS Institute, Cary, NC) was used for data analysis. The invasiveness of surgical procedure was classified as major, moderate, and minor following the criteria proposed by Donati et al.16 Regional and spinal anesthesia were combined as RA.

The demographic data and summary of data from polysomnography were presented with descriptive statistics. Categorical data were presented as frequency with percentage and the statistical significance was checked by chi-square test or Fisher exact test. The mean ± SD was used for continuous data with normal distribution. The median (25th, 75th percentile) was used for continuous data with skewed distribution.

Mixed models with polysomnography parameters as outcome and preoperative OSA status and the night of polysomnography as predictors were used to analyze the difference between the different perioperative nights in OSA and non-OSA patients. Preoperative OSA status and the night of polysomnography were treated as fixed effect and subject was treated as random effect. The postoperative values of parameters were compared with the preoperative baseline, respectively.

The Holm–Bonferroni method was used to adjust P value for multiple comparisons. All the statistical tests were two-tailed, and P less than 0.05 or adjusted P less than 0.05 was accepted as statistically significant. The relation between AHI, central apnea index and preoperative severity of OSA, type of anesthesia, and sex were shown in box plots. Then the factors that might contribute to postoperative AHI and central apnea index were first assessed with univariate analysis and followed by multivariate analysis. Generalized linear mixed models were used to explore the factors that may be associated with postoperative AHI and central apnea index. The evaluated factors included preoperative baseline (AHI or central apnea index), age, sex, body mass index, neck circumference, the type of anesthesia, the invasiveness of surgical procedure, postoperative REM sleep percentage, postoperative slow wave sleep percentage, and supine sleep percentage. Because AHI and central apnea index were close to normal distribution after log transformation, log normal was selected as distribution in the modelling.

Sleep efficiency and REM sleep percentage on postoperative night 1 were assessed by generalized linear models with preoperative baseline (sleep efficiency or REM sleep percentage), preoperative AHI, age, sex, body mass index, neck circumference, the type of anesthesia, the invasiveness of surgical procedure, and opioid dose as the independent variables. Log transformation was used for analysis of REM sleep percentage.

Results

Patient recruitment and study implementation are shown in figure 1. Six hundred sixty-one patients completed preoperative polysomnography. Of them, 69 patients were wearing CPAP while undergoing polysomnography. Three hundred seventy-six patients did polysomnography on preoperative and postoperative night 1, and 242 patients completed polysomnography on preoperative and postoperative nights 1 and 3 without wearing CPAP during polysomnography. Two hundred thirty, 144, and 78 patients withdrew from study before preoperative, postoperative night 1 and night 3 polysomnography, respectively. Reasons for withdrawal were anxiety, discomfort, pain, nausea, and vomiting in the postoperative period. The demographic data between 376 patients who did preoperative and postoperative polysomnography and 216 patients who did not have postoperative polysomnography were not significantly different (data not shown).

Basic Clinical Data

The baseline information of the three study populations, 592 patients who completed preoperative polysomnography, 376 patients who did 2 nights of polysomnography (preoperative and postoperative night 1), and a subgroup of 242 patients who completed 3 nights of polysomnography (preoperative and postoperative night 1 and 3) were summarized in table 1. The demographic data, the American Society of Anesthesiologists physical status, the prevalence of preexisting medical conditions, type of anesthesia, and the invasiveness of surgical procedure were similar in the three populations. Two hundred twenty-two patients (59.3%) and 18 patients (7.4%) received oxygen therapy on postoperative nights 1 and 3, respectively. Preoperative AHI, the frequency distribution of the severity of OSA, 72-h opioid dose, and the percentage of supine sleep were also similar in the patients who completed preoperative and postoperative
Factors Associated with Postoperative Sleep Apnea

Table 1. Demographic Data

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<tr>
<th></th>
<th>Preop PSG</th>
<th>Preop, Postop Night 1</th>
<th>Preop, Postop Night 1, 3</th>
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<tr>
<td>n</td>
<td>592</td>
<td>376</td>
<td>242</td>
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<tr>
<td>Sex, women/men*</td>
<td>332/260</td>
<td>208/168</td>
<td>133/109</td>
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<tr>
<td>Age, yr†</td>
<td>59.2 ± 12.2</td>
<td>59.4 ± 11.5</td>
<td>59.4 ± 11.4</td>
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<td>Body mass index, kg/m²‡</td>
<td>29.4 (25.7, 33.5)</td>
<td>29.4 (25.8, 32.8)</td>
<td>29.5 (25.3, 33.4)</td>
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<tr>
<td>Neck circumference, cm‡</td>
<td>38.1 (36.0, 41.0)</td>
<td>38.1 (36.0, 41.0)</td>
<td>38.1 (36.0, 41.9)</td>
</tr>
</tbody>
</table>

Invasiveness of surgical procedures
- Minor: 161 (27.3) vs 35 (9.4) vs 18 (7.4)
- Moderate: 365 (61.6) vs 292 (77.6) vs 203 (83.7)
- Major: 66 (11.2) vs 49 (18.0) vs 21 (8.9)

Type of anesthesia*
- General: 357 (60.3) vs 210 (55.9) vs 114 (47.1)
- Spinal/regional: 235 (39.8) vs 166 (44.1) vs 128 (52.9)

ASA physical status*
- I: 15 (2.5) vs 8 (2.1) vs 4 (1.7)
- II: 320 (54.0) vs 207 (55.1) vs 131 (54.1)
- III: 245 (41.5) vs 156 (41.5) vs 106 (43.8)
- IV: 12 (2.0) vs 5 (1.3) vs 1 (0.4)

Comorbidities*
- Hypertension: 284 (48.1) vs 186 (49.5) vs 125 (51.7)
- Diabetes: 98 (16.6) vs 66 (17.6) vs 35 (14.5)
- GERD: 145 (24.5) vs 92 (24.5) vs 59 (24.4)
- Smoker: 115 (19.5) vs 80 (21.3) vs 48 (19.8)
- Asthma: 74 (12.5) vs 47 (12.5) vs 31 (12.8)
- COPD: 19 (3.2) vs 12 (3.2) vs 8 (3.3)
- CAD: 35 (5.9) vs 22 (5.9) vs 15 (6.2)
- Stroke: 24 (4.1) vs 16 (4.3) vs 9 (3.7)
- Hypothyroidism: 94 (15.9) vs 59 (15.7) vs 32 (13.2)

* Data presented as frequency (%). † Data presented as mean ± SD. ‡ Data presented as median (25th, 75th percentile).

ASA = American Society of Anesthesiologists; CAD = coronary arterial disease; COPD = chronic obstructive pulmonary disease; GERD = gastroesophageal reflux disease; Preop = preoperative; Postop = postoperative; PSG = polysomnography.

The relationship between the preoperative severity of OSA and postoperative AH and central apnea index

The postoperative change of AH and central apnea index in patients with non-OSA or mild, moderate, or severe OSA is shown in figure 3A and B. AHI was significantly increased on postoperative nights 1 and 3 in patients having non-OSA, mild, moderate OSA (all adjusted \( P < 0.05 \)). In non-OSA patients, median AHI was increased from 9.6 events per hour preoperatively to 10.6 events per hour on postoperative night 1 (adjusted \( P = 0.004 \)) and 17.4 events per hour on postoperative night 3 (adjusted \( P < 0.001 \)). For moderate OSA patients, median AHI was increased from 21.9 events per hour preoperatively to 22.2 events per hour on postoperative night 1 (adjusted \( P = 0.001 \)) and 30.6 events per hour on postoperative night 3 (adjusted \( P < 0.001 \)). In patients with severe OSA, median AHI was decreased from 45 events per hour preoperatively to 40.4 events per hour on postoperative night 1 (adjusted \( P = 0.017 \)) and subsequently was increased to 65.5 events per hour on postoperative night 3 (adjusted \( P = 0.007 \) vs preoperative baseline and adjusted \( P < 0.001 \) vs postoperative night 1).

The preoperative central apnea index was low in this study population (fig. 3B). The median of central apnea index was 0 in all patient groups with non-OSA, mild, moderate, or severe OSA on all 3 observed nights. It was increased postoperatively in patients with non-OSA or mild, moderate, or severe OSA, especially on postoperative night 1. However, the increase was not statistically significant (all adjusted \( P > 0.05 \); fig. 3B).

The relationship between type of anesthesia and postoperative AH and central apnea index

The relation between type of anesthesia, preoperative AH and central apnea index is shown in figure 4, A and B. In...
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non-OSA patients receiving GA, median AHI was increased from 1.8 events per hour preoperatively to 3.7 events per hour on postoperative night 1 (adjusted $P < 0.001$) and 7.1 events per hour on postoperative night 3 (adjusted $P = 0.002$). In non-OSA patients receiving RA, a significant AHI increase was only observed on postoperative night 3 versus preoperative baseline (adjusted $P = 0.012$; fig. 4A).

In OSA patients, a significant AHI increase was observed in both patients receiving GA and RA on postoperative night 3. For GA, median AHI was increased from preoperative 17.4 to 28.4 events per hour on postoperative night 3 (adjusted $P < 0.001$ vs. preoperative baseline and adjusted $P = 0.003$ vs. postoperative night 1) and for RA, from preoperative 19.3–30.8 events per hour on postoperative night 3 ($P < 0.001$ vs. preoperative baseline and $P < 0.001$ vs. postoperative night 1; fig. 4A). Essentially, the exacerbations in AHI occurred equally in patients receiving GA or RA. No significant difference in AHI between the two types of anesthesia was found (fig. 4A).

Compared with preoperative baseline, a significant increase in central apnea index was observed on postoperative night 1 in both non-OSA and OSA patients receiving GA (adjusted $P = 0.002$ for non-OSA and $P = 0.001$ for OSA; fig. 4B). Compared with patients receiving RA,
the OSA patients with GA had a significantly higher central apnea index on postoperative night 1 (adjusted \( P = 0.004 \); fig. 4B). The difference in central apnea index between non-OSA patients receiving GA and RA was not statistically significant on postoperative night 3 (adjusted \( P = 0.060 \)).

Relation between Sex and Postoperative Sleep-disordered Breathing

Compared with the female OSA patients, the male OSA patients had a higher median AHI at preoperative baseline (adjusted \( P < 0.001 \)), on postoperative night 1 (adjusted \( P = 0.007 \)) and night 3 (adjusted \( P = 0.073 \); fig. 5A). On postoperative night 1, median AHI in male OSA patients was twofold higher than that of the female OSA patients (27.7 vs. 13.5 events per hour). In non-OSA patients, compared with the preoperative baseline, AHI was significantly increased in both male and female patients with no difference between sex (fig. 5A).

Compared with preoperative baseline, a significant increase of central apnea index was observed on postoperative night 1 in female non-OSA patients (adjusted...
The male OSA patients had a significantly higher central apnea index on postoperative night 1 versus female OSA patients (adjusted $P = 0.015$; fig. 5B). No difference between sex was observed in non-OSA patients. There was no difference in the invasiveness of surgery and the type of anesthesia between the male and female patients (data not shown).

Relationship between the Sleep Position and Postoperative Sleep-disordered Breathing

The percentage of supine sleep was increased in both OSA and non-OSA patients postoperatively (fig. 6A). The increase was significant on postoperative night 1 in non-OSA patients by 39% (adjusted $P < 0.001$) and mild OSA patients by 24% (adjusted $P = 0.003$). On postoperative night 3, the percentage of supine sleep was increased by 28% for mild OSA patients (adjusted $P = 0.002$) and 49% in severe OSA patients (adjusted $P = 0.005$; fig. 6A).

AHI during supine sleep was significantly higher than that in nonsupine sleep on preoperative, postoperative nights 1 and 3. The median AHI in the supine sleep was three folds higher than that during the nonsupine sleep preoperatively (adjusted $P < 0.001$), fourfold higher on both postoperative nights 1 and 3 (adjusted $P < 0.001$ for both postoperative night 1 and 3; fig. 6B).

Factors Associated with the Postoperative AHI and Central Apnea Index

Generalized linear mixed models were used to assess the factors associated with the postoperative severity of sleep-disordered breathing. The postoperative AHI and central apnea index on postoperative night 1 and 3 were treated as repeated measurements and evaluated respectively as the dependent variable. The independent variables included preoperative baseline AHI or central apnea index, 72-h opioid dose, age, sex, body mass index, neck circumference, type of anesthesia, invasiveness of surgical procedures, oxygen therapy, slow wave sleep percentage, and REM sleep percentage. The results of univariate and multivariate analysis of postoperative AHI are summarized in table 3.

Preoperative baseline AHI, age, and 72-h opioid dose were found to be positively associated with postoperative AHI on postoperative nights 1 and 3 ($P < 0.05$). Slow-wave sleep percentage and major surgical procedure were found to be inversely associated with postoperative AHI ($P < 0.05$). The association between male sex and postoperative AHI did not reach a statistically significant level ($P = 0.085$).

The results of univariate and multivariate analysis of postoperative central apnea index are summarized in table 4. Preoperative baseline central apnea index, male sex, and GA were found to be positively associated with postoperative central apnea index on postoperative nights 1 and 3 ($P < 0.05$). Slow wave sleep percentage and major surgical procedure were found to be inversely associated with postoperative AHI ($P < 0.05$). The association between oxygen therapy and 72-h opioid dose with postoperative central apnea index was not statistically significant ($P = 0.085$).

The results of univariate and multivariate analysis of postoperative central apnea index are summarized in table 4. Preoperative baseline central apnea index, male sex, and GA were found to be positively associated with postoperative central apnea index on postoperative nights 1 and 3 ($P < 0.05$). Slow wave sleep percentage and major surgical procedure were found to be inversely associated with postoperative central apnea index ($P = 0.026$). The association between oxygen therapy and 72-h opioid dose with postoperative central apnea index was not statistically significant, $P = 0.093$ and 0.094, respectively.

Factors Associated with Sleep Efficiency and REM Sleep on Postoperative Night 1

The factors associated with postoperative sleep efficiency and REM sleep percentage on postoperative night 1 was assessed.
Factors Associated with Postoperative Sleep Apnea

with generalized linear models. The sleep efficiency and log transformed REM sleep percentage were outcome variables respectively. The independent variables included preoperative baseline (sleep efficiency and REM sleep percentage), preoperative AHI, age, sex, body mass index, neck circumference, the type of anesthesia, the invasiveness of surgical procedure, oxygen therapy, and first 24-h opioid dose. Preoperative AHI was found to be positively associated with sleep efficiency ($P = 0.018$). Major surgical procedures ($P = 0.012$) and age ($P = 0.011$) were inversely associated with sleep efficiency (table 5). Moderate procedures, major procedures, and first 24-h opioid dose were inversely associated with REM sleep percentage, but the association was not statistically significant, with a $P$ value from 0.055 to 0.062 (table 5).

Table 3. Factors Associated with Postoperative AHI

<table>
<thead>
<tr>
<th>Dependent Variable</th>
<th>Independent Variable</th>
<th>Comparison</th>
<th>Univariate Analysis*</th>
<th>Multivariate Analysis*</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Estimate (95% CI)</td>
<td>$P$ Value</td>
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<tr>
<td>AHI (events per hour)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Age, yr</td>
<td>+1</td>
<td>Demographic</td>
<td>0.023 (0.010–0.035)</td>
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<td>Sex</td>
<td>Male vs. female</td>
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<td>0.578 (0.297–0.861)</td>
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<td>Body mass index, kg/m²</td>
<td>+1</td>
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<td>0.022 (−0.002 to 0.045)</td>
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<td>Neck circumference, cm</td>
<td>+1</td>
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<td>0.065 (0.030–0.102)</td>
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<td>Procedure invasiveness</td>
<td>Moderate vs. minor</td>
<td>Perioperative factor</td>
<td>−0.049 (−0.399 to 0.302)</td>
<td>0.456</td>
</tr>
<tr>
<td>Anesthesia type</td>
<td>GA vs. RA</td>
<td></td>
<td>−0.242 (−0.744 to 0.302)</td>
<td>0.785</td>
</tr>
<tr>
<td>Oxygen therapy</td>
<td>Yes vs. no</td>
<td></td>
<td>−0.288 (−0.557 to 0.212)</td>
<td>0.069</td>
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<td>72h opioid dose, mg</td>
<td>+1</td>
<td></td>
<td>0.053 (−0.200 to 0.307)</td>
<td>0.679</td>
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<tr>
<td>Preop baseline AHI</td>
<td>+1</td>
<td>Polysomnographic</td>
<td>0.005 (0.002–0.007)</td>
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<tr>
<td>Supine sleep, %</td>
<td>+1</td>
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<td>0.001 (−0.003 to 0.008)</td>
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<td>REM, %</td>
<td>+1</td>
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<td>0.003 (−0.014 to 0.010)</td>
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<td>SWS, %</td>
<td>+1</td>
<td></td>
<td>−0.021 (−0.034 to −0.009)</td>
<td>0.001</td>
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* Estimates were from generalized linear mixed model analysis with log transformation of dependent variable.

AHI = apnea–hypopnea index; Apnea index = average hourly number of apnea episodes; GA = general anesthesia; Preop = preoperative; RA = regional/spinal anesthesia; REM percentage = percentage of rapid eye movement sleep in total sleep time; SWS = slow wave sleep (stage 3 and 4).
Discussion

This study showed that AHI was increased in non-OSA, mild, and moderate OSA patients on postoperative night 1, and in all patient groups on postoperative night 3 regardless of the severity of OSA. The central apnea index was increased on postoperative night 1 in non-OSA and OSA patients receiving GA. No difference in postoperative AHI was found between patients receiving GA or RA. Compared with female OSA patients, male OSA patients had a significantly higher AHI on both postoperative night 1 and 3.

The preoperative AHI, age, and 72-h opioid dose were associated with high postoperative AHI, whereas slow wave sleep percentage and major surgical procedures were inversely associated with postoperative AHI. The preoperative central apnea index, GA and male sex were associated with postoperative central apnea index. Slow wave sleep percentage was inversely associated with postoperative central apnea index.

At present, the mechanism for the postoperative exacerbation of sleep-disordered breathing is not fully understood. It may be related to genetics, sex, age, opioid dose, the preoperative severity of OSA, change in sleep architecture, sleep position, the type of anesthesia and the invasiveness of the surgical procedures.

Because the OSA patients are prone to pharyngeal collapsibility, they may have an increased postoperative AHI. However, it was unexpected that a subset of non-OSA patients had a significantly increased postoperative AHI. There are several possible explanations. Due to the night-to-night variability in the frequency of sleep apnea and hypopnea, and first night effect, some OSA patients may not be recognized preoperatively by a single night of polysomnography. Genetic variations may make some patients especially sensitive to opioids. Patients with small maxillomandible enclosure are particularly vulnerable to the postoperative decrease in lung volume. Further investigations are needed to identify "non-OSA" patients who may experience a significant postoperative exacerbation of sleep-disordered breathing.

Male sex was found to be associated with high postoperative central apnea index and tended to be associated with AHI ($P = 0.085$). It may be related to the difference in the fat distribution, upper airway anatomy, breathing control, and hormonal influence. The correlation between the size of the upper airway and the severity of OSA is only found in men. Compared with women, men have a larger but more collapsible airway during mandibular movement. Estrogen is shown to have a substantial beneficial effect on the measures of sleep-disordered breathing in the postmenopausal women whereas testosterone may predispose to sleep-disordered breathing.

Our finding that the higher the slow wave sleep percentage, the lower postoperative AHI and central apnea index were consistent with the results of a recent retrospective study in nonsurgical patients. AHI during slow wave sleep was significantly lower than AHI during REM and other non-REM sleep. During slow wave sleep, single motor unit activity of genioglossus is increased.

<table>
<thead>
<tr>
<th>Table 4. Factors Associated with Postoperative CAI</th>
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<tr>
<td><strong>Dependent Variable</strong></td>
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<tr>
<td>CAI (events per hour)</td>
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</table>

* Estimates were from generalized linear mixed model analysis with log transformation of dependent variables (CAI).

CAI = central apnea index; GA = general anesthesia; Preop = preoperative; RA = regional/spinal anesthesia; REM percentage = percentage of rapid eye movement sleep in total sleep time; SWS = slow wave sleep (stage 3 and 4).
which makes the upper airway more stable and resistant to collapse throughout the respiratory cycle. Women are found to have a significantly higher slow wave sleep percentage with lower AHI, which may contribute to the sex effect on AHI.

Our data showed that the supine AHI was significantly higher than that during the non-supine sleep, and the percentage of supine sleep was increased postoperatively on both postoperative night 1 and 3. The increased duration of supine sleep position might have contributed to the increase of postoperative AHI. The shape of the upper airway was changed from a circular shape in the lateral recumbent posture to an elliptical shape when supine. The change in body posture from the lateral to supine position significantly increases the passive pharyngeal collapsibility. Lateral position structurally improves the maintenance of the passive pharyngeal airway in patients with OSA.

The central apnea index was low in our study population. A significant increase of central apnea index was found in female non-OSA patients and male OSA patients on postoperative night 1 (adjusted $P = 0.003$). The postoperative central apnea index was associated with preoperative baseline central apnea index, male sex, and GA.

Our finding that the amount of opioids used was associated with postoperative AHI and central apnea index is consistent with the results from a previous study. Morphine dose was predictive of central apneas for both OSA and non-OSA patients. Opioids can induce central respiratory depression through $\mu$- and $\kappa$-opioid receptors. The evidence also supports that opioids inhibit central tonic outflow to the primary upper airway dilator, genioglossus muscle. Due to the facts that opioids induce central respiratory depression, inhibit central tonic flow to upper airway dilator muscle, and that OSA patients are more sensitive to opioids, special caution should be taken with administration of opioids and sedatives to OSA patients. Using multimodal analgesia with the goal of reducing opioid consumption will decrease postoperative sleep-disordered breathing. Risk-reduction strategy, such as perioperative CPAP, may prevent postoperative increase of AHI and have long-term health benefits.

### Table 5. Factors Associated with Sleep Efficiency and REM Sleep on Postoperative Night 1

<table>
<thead>
<tr>
<th>Dependent Variable</th>
<th>Independent Variable</th>
<th>Comparison</th>
<th>Multivariate Estimate (95% CI)</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep efficiency</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Age, yr</strong></td>
<td>Demographic</td>
<td>−0.421 (−0.675 to −0.168)</td>
<td>0.011</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sex</td>
<td>Male vs. female 1.075 (−4.861 to 7.012)</td>
<td>0.723</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.172 (−0.288 to 0.632)</td>
<td>0.464</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.085 (−0.598 to 0.769)</td>
<td>0.807</td>
</tr>
<tr>
<td></td>
<td><strong>Procedure invasiveness</strong></td>
<td></td>
<td>−4.554 (−11.172 to 2.065)</td>
<td>0.178</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Major vs. minor</td>
<td>−12.093 (−21.552 to −2.634)</td>
<td>0.012</td>
</tr>
<tr>
<td></td>
<td></td>
<td>GA vs. RA</td>
<td>−3.479 (−9.044 to 2.086)</td>
<td>0.221</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Yes vs. no</td>
<td>0.021 (−5.144 to 5.186)</td>
<td>0.994</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Preop polysomnographic</td>
<td>−0.032 (−0.115 to 0.050)</td>
<td>0.442</td>
</tr>
<tr>
<td></td>
<td><strong>AHI, events per hour</strong></td>
<td></td>
<td>0.171 (0.029−0.312)</td>
<td>0.018</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.035 (−0.144 to 0.215)</td>
<td>0.700</td>
</tr>
<tr>
<td>REM sleep percentage</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Age, yr</strong></td>
<td>Demographic</td>
<td>0.002 (−0.009 to 0.013)</td>
<td>0.782</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sex</td>
<td>Male vs. female 0.006 (−0.276 to 0.287)</td>
<td>0.969</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>−0.007 (−0.041 to 0.027)</td>
<td>0.495</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>−0.007 (−0.041 to 0.027)</td>
<td>0.681</td>
</tr>
<tr>
<td></td>
<td><strong>Procedure invasiveness</strong></td>
<td></td>
<td>−0.287 (−0.580 to 0.006)</td>
<td>0.055</td>
</tr>
<tr>
<td></td>
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<td>Major vs. minor</td>
<td>−0.406 (−0.833 to 0.021)</td>
<td>0.062</td>
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<tr>
<td></td>
<td></td>
<td>GA vs. RA</td>
<td>0.118 (−0.139 to 0.374)</td>
<td>0.368</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Yes vs. no</td>
<td>0.097 (0.041−0.027)</td>
<td>0.681</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Preop polysomnographic</td>
<td>−0.004 (−0.007 to 0.002)</td>
<td>0.062</td>
</tr>
<tr>
<td></td>
<td><strong>AHI, events per hour</strong></td>
<td></td>
<td>−0.005 (−0.011 to 0.001)</td>
<td>0.121</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>0.009 (−0.005 to 0.023)</td>
<td>0.198</td>
</tr>
</tbody>
</table>

* Multivariate estimates for REM sleep percentage were from generalized linear model analysis with log transformation of REM sleep percentage; original data were used for sleep efficiency analysis.

AHI = apnea–hypopnea index; GA = general anesthesia; Preop = preoperative; RA = regional/spinal anesthesia; REM = percentage of rapid eye movement sleep in total sleep time; sleep efficiency = percentage of total sleep time in sleep period.
Although a recent study shows that patients with OSA undergoing their procedures with neuraxial anesthesia had significantly lower rates of major complications than those with OSA who received GA,\textsuperscript{43} we did not find any different effects of GA and RA on AHI. Our study is observational. The patients receiving RA mainly had orthopedic surgery and the patients receiving GA had a combination of other surgeries. The difference in type of surgery might be related to higher opioid dose in patients receiving RA. Although the patients receiving RA used more opioids, they did not demonstrate a higher AHI or central apnea index. On contrary, a significantly higher central apnea index on postoperative night 1 was found in patients receiving GA. This suggests that the higher central apnea index might possibly be related to the other perioperative medications used in GA.

The impact of postoperative exacerbation of sleep-disordered breathing is still not clear. Gögenur et al.\textsuperscript{45} demonstrated that postoperative nocturnal hypoxemia was associated with tachycardia and myocardial ischemia. In a retrospective study of 206 OSA patients undergoing ambulatory surgery with RA, Liu et al.\textsuperscript{44} showed that OSA-related postoperative hypoxemia in ambulatory orthopedic surgical patients was not associated with increased adverse events and unplanned hospital admission. More evidence needs to be accumulated on this issue.

Our results showed that sleep efficiency on postoperative night 1 was associated with preoperative AHI and inversely associated with the major surgical procedures and age. This is consistent with our results from 58 patients who completed 4–5 nights of polysomnography.\textsuperscript{10} Compared with non-OSA patients, sleep efficiency was affected less postoperatively in OSA patients.\textsuperscript{19} Essentially on postoperative night 1, sleep efficiency was better in OSA patients whereas it decreased in elderly patients and those undergoing major surgery.

Besides preoperative AHI, sleep efficiency and REM sleep may be affected by the postoperative severity of sleep-disordered breathing. The patients with high postoperative AHI may have more frequently fragmented sleep, lower sleep efficiency and lower REM sleep percentage. Our results showed that compared to non-OSA patients, OSA patients actually had less severe interruption in sleep efficiency. This may be due to the suppression of arousal episodes in OSA patients by postoperative medications or opioids.

Regardless of OSA severity, the greater the invasiveness of the surgical procedures, the lower was the percentage of REM sleep on postoperative night 1. Also, the higher the first 24-h opioid dose, the lower was the percentage of REM sleep on postoperative night 1. Our data are consistent with the results from the previous studies.\textsuperscript{45,46} Knill et al. found a severe sleep disruption in patients undergoing upper abdominal surgery. Gögenur et al.\textsuperscript{46} found that the sleep disruption was less pronounced after laparoscopic cholecystectomy versus open abdominal surgery.

Opioids were shown to significantly reduce deep sleep and inhibited REM sleep.\textsuperscript{47–50} However, postoperative patients still suffered a profound sleep disturbance even when opioids were avoided and pain was well controlled.\textsuperscript{51} This suggests that factors other than opioids may play an important role in postoperative sleep disturbance.

There are some limitations in this study. First, the patients were only monitored during night and the diurnal changes in sleep–wake activity or sleep-disordered breathing were not measured. A previous study showed that patients experienced significantly increased REM sleep, light sleep, and reduced time awake during the daytime period after surgery.\textsuperscript{52} Because this was an observational study, we did not control the type of surgery, perioperative medications such as opioids and oxygen therapy. This may have increased the difficulty in data interpretation. Another limitation of the study was the high withdrawal rate. Due to the generalized discomfort of patients during postoperative period and the attachment of multiple channels for polysomnography, a large number of patients withdrew from study on postoperative night 1 or 3. The high drop-out rate may affect our results.

In conclusion, the patients with a higher preoperative AHI were predicted to have a higher postoperative AHI. Increased preoperative baseline AHI, age, and 72-h opioid dose were associated with an increased postoperative AHI. A larger slow wave sleep percentage was associated with a lower postoperative AHI. Higher preoperative central apnea index, male sex, and GA were associated with an increased postoperative central apnea index. Risk-reduction strategy in patients with higher preoperative AHI may reduce postoperative increase of AHI.

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**Competing Interests**

The authors declare no competing interests.
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