

# AMERICAN THORACIC SOCIETY DOCUMENTS

## Knowledge Gaps in the Perioperative Management of Adults with Obstructive Sleep Apnea and Obesity Hypoventilation Syndrome

### An Official American Thoracic Society Workshop Report

Najib T. Ayas, Cheryl R. Laratta, John M. Coleman, Anthony G. Doufas, Matthias Eikermann, Peter C. Gay, Daniel J. Gottlieb, Indira Gurubhagavatula, David R. Hillman, Roop Kaw, Atul Malhotra, Babak Mokhlesi, Timothy I. Morgenthaler, Sairam Parthasarathy, Satya Krishna Ramachandran, Kingman P. Strohl, Patrick J. Strollo, Michael J. Twery, Phyllis C. Zee, and Frances F. Chung; on behalf of the ATS Assembly on Sleep and Respiratory Neurobiology

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#### Abstract

The purpose of this workshop was to identify knowledge gaps in the perioperative management of obstructive sleep apnea (OSA) and obesity hypoventilation syndrome (OHS). A single-day meeting was held at the American Thoracic Society Conference in May, 2016, with representation from many specialties, including anesthesiology, perioperative medicine, sleep, and respiratory medicine. Further research is urgently needed as we look to improve health outcomes for these patients and reduce health care costs. There is currently insufficient evidence to guide screening and optimization of OSA and

OHS in the perioperative setting to achieve these objectives. Patients who are at greatest risk of respiratory or cardiac complications related to OSA and OHS are not well defined, and the effectiveness of monitoring and other interventions remains to be determined. Centers involved in sleep research need to develop collaborative networks to allow multicenter studies to address the knowledge gaps identified below.

**Keywords:** obstructive sleep apnea; perioperative care; obesity hypoventilation syndrome; risk assessment; postoperative complications

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#### Contents

##### Overview

###### Key Knowledge Gap

1. How can we identify patients with obstructive sleep apnea or obesity hypoventilation syndrome at highest risk of postoperative cardiopulmonary complications?
2. How do we prevent postoperative cardiopulmonary complications in patients with obstructive sleep apnea or obesity hypoventilation syndrome?

###### Introduction

##### Methods

Committee Composition  
Workshop Structure and Literature Review  
Document Development  
Perioperative Outcomes of Patients with Sleep-disordered Breathing  
Screening for Obstructive Sleep Apnea in Surgical Patients  
Obstructive Sleep Apnea Endotypes and Potential Relevance in the Perioperative Period  
Role of Algorithms in the Perioperative Management

of Obstructive Sleep Apnea and Obesity Hypoventilation Syndrome  
Perioperative Use of Positive Airway Pressure  
Obesity Hypoventilation Syndrome in the Perioperative Period  
Opioids and the Surgical Patient with Obstructive Sleep Apnea  
The Use of Administrative Databases and Patient Registries  
Patient Safety and Healthcare Management Considerations  
Conclusions

## Overview

Perioperative management of sleep-disordered breathing, such as obstructive sleep apnea (OSA) and obesity hypoventilation syndrome (OHS), is an area of patient care that requires improvement due to the risk of morbidity and mortality from sleep-disordered breathing in the perioperative period (1). Adverse perioperative outcomes of patients with OSA or OHS include anoxic brain injury or death in rare circumstances (2), and may be preventable. During the development of the Society of Anesthesia and Sleep Medicine (SASM) Guidelines on Preoperative Screening and Assessment of Adult Patients with Obstructive Sleep Apnea, hereafter referred to as the SASM guidelines, it became clear that further research was necessary to improve the quality and strength of the clinical recommendations. Further research on OSA and OHS in the perioperative setting is urgently needed as we look to improve health outcomes for these patients, and reduce health care costs that arise from postoperative monitoring, cardiopulmonary complications, increased length of stay (LOS) in intensive care, and increased LOS in hospital. There is little evidence to guide screening and treatment of sleep-disordered breathing in the perioperative setting to achieve these objectives. Patients who are at greatest risk of respiratory or cardiac complications related to OSA or OHS are not well defined, and the effectiveness of monitoring and other interventions remains to be determined. Centers involved in sleep research need to develop collaborative networks to allow multicenter studies to address the research questions identified below.

## Key Knowledge Gaps

**1. How can we identify patients with obstructive sleep apnea or obesity hypoventilation syndrome at highest risk of**

### *postoperative cardiopulmonary complications?*

- A. Can we risk stratify patients for perioperative complications related to OSA or OHS?
- B. Is there any safe threshold of opioid therapy in patients identified as high risk of having OSA or OHS?
- C. What clinical or physiologic markers (serum bicarbonate, troponin levels, preoperative inflammatory markers, etc.) predict opioid sensitivity or postoperative cardiopulmonary complications?
- D. Do particular physiologic endotypes of OSA predict opioid sensitivity or postoperative cardiopulmonary complications?
- E. Can assessments in postanesthesia care unit (PACU) provide additional value in reducing adverse outcomes upon discharge?
- F. Are polysomnography (PSG) or ambulatory studies useful in risk stratifying patients before surgery? That is, do these tests help to predict which patients may be at increased risk after surgery and help to direct management?

### **2. How do we prevent postoperative cardiopulmonary complications in patients with obstructive sleep apnea or obesity hypoventilation syndrome?**

- A. Key questions related to positive airway pressure therapy in the perioperative setting include:
  - i. Does it confer benefits beyond those of enhanced monitoring strategies?
  - ii. When does continuous positive airway pressure (CPAP) administration reduce risks: is postoperative administration sufficient, or is preoperative initiation of CPAP needed, and, if so, for how long preoperatively?
  - iii. Which ventilatory strategies would be most effective in treating postoperative OSA?

- iv. Are there nonopioid analgesic strategies (e.g., nonsteroidal antiinflammatories, peripheral/epidural use of local anesthetics) or novel strategies (e.g., respiratory stimulants) that can be employed in patients with OSA or OHS to mitigate risk?
- v. Are there patient (or family) educational tools and interventions that can be employed to improve patient outcomes?
- B. Key questions related to monitoring in the perioperative setting include:
  - i. How do we risk stratify patients with OSA to identify patients who may not require monitoring (low risk of postoperative complications)?
  - ii. What duration and components of monitoring are critical to mitigate risk?
  - iii. Once optimized detection and alarm thresholds are determined, how do we train our workforce and use our electronic health records to optimize outcomes and resource utilization?

## Introduction

The prevalence of OSA is 10%–20% in adult surgical patients (3, 4) and up to 70% before bariatric surgery (5). Postoperatively, there are physiologic changes in sleep architecture and an increase in the apnea-hypopnea index (AHI) in both patients with and without OSA (6). The most severe arterial oxygen desaturations and highest AHI occur on Night 3 postoperatively, and have been attributed in part to a gradual increase in rapid eye movement sleep and a reduction in the use of supplemental oxygen after the initial postoperative night (6). Numerous variables influence sleep-disordered breathing in the perioperative period, including the anesthetic, upper airway injury after intubation, fluid shifts, pain medications, and the administration of oxygen.

ORCID IDs: 0000-0003-0259-7464 (N.T.A.); 0000-0002-7656-0173 (C.R.L.); 0000-0003-1268-0106 (M.E.); 0000-0002-9391-2011 (P.C.G.); 0000-0001-7712-7729 (R.K.); 0000-0001-9664-4182 (A.M.); 0000-0001-8135-5433 (B.M.); 0000-0002-2614-3793 (T.I.M.); 0000-0002-1128-3005 (S.P.); 0000-0002-7176-6375 (S.K.R.); 0000-0001-7740-9013 (K.P.S.); 0000-0002-2065-9641 (P.J.S.); 0000-0001-6296-6685 (P.C.Z.); 0000-0001-9576-3606 (F.F.C.).

Correspondence and requests for reprints should be addressed to Najib T. Ayas, M.D., M.P.H., Leon Judah Blackmore Centre for Sleep Disorders UBC Hospital, Purdy Pavillion Room G34A, 2211 Wesbrook Mall Vancouver, BC, V6T 2B5 Canada. E-mail: [nayas@providencehealth.bc.ca](mailto:nayas@providencehealth.bc.ca).

Moderate-quality evidence predominantly from large cohort studies suggests that patients with OSA have a two- to three-times increased risk of cardiopulmonary complications after surgery (7, 8); the absolute risk varies between studies, in part related to variability in the definitions of OSA and postoperative outcomes. Retrospective studies that have required a preoperative diagnosis of OSA, or confirmed diagnosis of OSA by PSG, provide estimates of postoperative complications of 14%–49% versus 2.6%–31% of control subjects (7, 9, 10). Prospective or retrospective cohort studies evaluating noncardiac surgery suggest that patients with OSA have an odds ratio (OR) of 2.07 (95% confidence interval [CI] = 1.23–3.50) for cardiac events (3.76% vs. 1.69%), an OR of 2.43 (95% CI 1.34–4.39) for respiratory failure (1.96% vs. 0.70%), and a nonsignificantly higher odds of reintubation (0.92% vs. 0.63%) in the postoperative period (7). More heterogeneous data suggest an OR of 2.27 (95% CI = 1.20–4.26) for desaturation, and an OR of 2.81 (95% CI = 1.46–5.43) for intensive care unit (ICU) transfer (5.09% vs. 1.57%) (7). A retrospective cohort study suggests that the perioperative morbidity experienced by patients with unrecognized OHS is even higher than that experienced by patients with OSA (11).

Across hospitals, there is substantial variability in the management of these patients. Due to the evidence supporting physiologic worsening of OSA in the perioperative period, and the increased perioperative complication risk attributed to OSA and OHS, the perioperative management of sleep-disordered breathing is now considered an important patient safety initiative (12). A systematic analysis was recently completed creating the basis for the SASM guidelines (1). During the creation of these guidelines, numerous limitations in our knowledge on how to identify and manage OSA perioperatively were identified. An additional drive to better understand perioperative management of sleep-disordered breathing is that OSA-related perioperative complications are increasingly linked to malpractice lawsuits with severe financial penalties (2, 13). Further research in this area is urgently needed.

The purpose of this workshop was to identify knowledge gaps in the perioperative management of OSA and OHS in adult

patients. During the planning of this workshop, which was originally organized to discuss primarily OSA, it was identified that a particularly high-risk group in the perioperative period are patients with OHS, which often coexists with OSA. As a result, this was included as a specific objective to address within the workshop. Of note, the workshop did not include discussion of issues pertaining to patients undergoing elective surgeries to correct OSA (i.e., upper airway surgery).

## Methods

This single-day workshop was held on May 13, 2016 at the American Thoracic Society Conference in San Francisco, California. The workshop was chaired by N. Ayas and F. Chung, hereafter referred to as the Chairs. The structure of this workshop report was conceived as an initiative to complement the recently published SASM guidelines (1). The Chairs brought together researchers from anesthesia, sleep medicine, and respiratory to identify the limitations of the current evidence, important areas for further research, and strategies to overcome barriers to research in patients with OSA. The workshop was funded by the American Thoracic Society without additional industry or other funding. Conflict of interest statements were reviewed by the Chairs to ensure that significant bias could be avoided.

## Committee Composition

A total of 12 clinician-scientists in respiratory and nonrespiratory sleep medicine or anesthesiology were selected by the Chairs for invitation due to their expertise in the field of OSA or OHS and perioperative management. One invited clinician-scientist was unable to participate due to time constraints. In addition, a hospital administrator and a representative from the National Institutes of Health with significant research expertise were invited so that resource management and funding were considered in all discussions.

## Workshop Structure and Literature Review

A total of 10 participants were invited to review and present in their areas of expertise on a list of topics selected by the Chairs with input from the committee. Search strategies, inclusion and exclusion criteria, and areas of

discussion within each topic were performed independently by each presenter. After a short presentation, the presenter and Chairs facilitated a discussion with all workshop participants to achieve consensus regarding key limitations in knowledge within each topic. After the final presentation, the Chairs facilitated a discussion among all participants of key knowledge gaps, which resulted in the final list of knowledge gaps and recommended key questions outlined in the major conclusions.

## Document Development

The recommendations were collated by the chair after review of audiotapes and PowerPoint presentations available from all presentations and discussions. This was reviewed with workshop participants by e-mail and by two teleconferences in the fall of 2016. Questions at the end of each section were those discussed within the workshop, included in the document to provide the reader with a sense of the directions of interest. Consensus regarding key knowledge gaps outlined in the OVERVIEW was reached by all members of the workshop before submission.

## Perioperative Outcomes of Patients with Sleep-disordered Breathing

In observational and interventional studies, the evaluation of the particular perioperative outcomes to further our understanding of impact of sleep-disordered breathing is still under debate. A recent systematic review outlined some of the commonly used outcomes in the literature (8). Outcomes discussed are outlined in Table 1. Outcomes that extend beyond cardiopulmonary outcomes, such as delirium, may be important, but were not addressed.

Respiratory outcomes are an important category. OSA is a risk factor for postoperative respiratory failure rate, which is a patient safety indicator (7); the definition is based on the International Classification of Diseases codes (14). Based on this definition, approximately 1.0%–1.5% of patients will develop postoperative respiratory failure (15), with significant comorbidity in 50%, and an estimated mortality of 23% (14). The utility of desaturation as an intermediate

**Table 1.** Potential outcomes for evaluation of the impact of obstructive sleep apnea on perioperative outcomes in an observational study or clinical trial

Outcome Category	Relevant Outcomes
Pulmonary complications	Acute respiratory failure (11, 19, 21, 77, 78) Reintubation (9–11, 19, 37, 77, 78) Pneumonia (3, 21, 37, 77, 79, 80) Pulmonary embolism (3, 37, 77, 79, 80) Prolonged mechanical ventilation (11) Desaturation (9, 10, 78, 79)
Cardiac complications	Arrhythmias (including atrial fibrillation) (9, 10, 19, 21, 37, 79) Heart failure (9–11, 81) Cardiac arrest (9, 21, 37) Myocardial infarction (3, 9–11, 21, 37, 78–80)
Biomarkers	Troponin (82)
Clinical outcomes	Mortality (3, 81) Hospital length of stay (3, 19) Medical emergency team responses ICU admission (3, 10, 78) ICU length of stay (3, 78) Health care costs (19) Health care utilization (3, 21, 80)

Definition of abbreviation: ICU = intensive care unit.

outcome was debated, as this is a “characteristic” of OSA. However, severe desaturation may be a reasonable outcome measure, especially if it is associated with additional resources utilization (e.g., medical emergency team activation). However, further work is needed to identify desaturation thresholds that are relevant.

Postoperative cardiac outcomes are also important, given the association between OSA and cardiac disease (16). However, there are many comorbidities that are potential confounders, such as obesity, diabetes, dyslipidemia, coronary artery disease, and increasing age. Pulmonary edema is an important cause of postoperative respiratory failure (17, 18). Postoperative atrial fibrillation in cardiothoracic surgery is common, even up to 30 days postoperatively, and may be increased in patients with OSA (19, 20). One large national database study reported increased rates of shock and cardiac arrest postoperatively in patients with OSA when identifying patients with OSA with International Classification of Diseases data (21).

Approximately 9% of patients have asymptomatic elevations of troponin after noncardiac surgery. Even without meeting criteria for myocardial infarction (22), patients with increased postoperative troponins are at higher risk of complications (23) and 30-day mortality (24). Troponin and other cardiac biomarkers may be useful intermediate outcomes to study, especially if

they are associated with robust clinical outcomes perioperatively. That is, they may serve as a risk indicator for the infrequent clinical outcomes.

### Screening for Obstructive Sleep Apnea in Surgical Patients

Many tools have been used to detect risk of OSA, including the STOP-Bang score, perioperative sleep apnea prediction score, Berlin questionnaire, and American Society of Anesthesiologists checklist (1). A STOP-Bang score of 3 or greater has high sensitivity and modest specificity for OSA, and is associated with an increased risk of perioperative complications (1). The use of a higher STOP-Bang threshold (e.g.,  $\geq 5$ ) may be more appropriate in populations with a lower prevalence of OSA (25).

The utility of confirmatory testing in patients identified at high risk of OSA or OHS during preoperative screening is unclear. PSG is often challenging to schedule before surgery, and ambulatory technologies may be more useful, and should be studied in this context.

The objective of preoperative screening was addressed. Some argue that it is more important to identify patients at increased risk of postoperative complications rather than the presence of

OSA *per se*. As such, integrating other clinical aspects into screening tools should be considered, such as type of surgery, mode of anesthesia; requirement of opioids, and other comorbidities. In addition, it is unclear what proportion of perioperative complications is attributable to OSA or OHS as opposed to associated comorbidities (e.g., obesity, coronary artery disease). Determining the attributable risk may give an indication of what is potentially reversible with interventions. Screening questionnaires should be considered strategically for those with a moderate/high or low pretest probability of disease, depending on whether the goal is to confirm (i.e., obtain a very high posttest probability) or exclude disease (i.e., obtain a very low posttest probability).

There was substantial discussion about risk stratification of patients in the PACU. Not all patients who have clinically important OSA after surgery are identified by preoperative screening tools; in addition, some patients with no or mild OSA may develop apnea postoperatively secondary to physiologic challenges from opioids or intravenous fluids. Monitoring in the PACU has the potential to evaluate if a patient has failed an anesthetic/opioid “stress test,” and thereby may identify patients at risk of further adverse events on the ward. Gali and colleagues (26) found that recurrent PACU “events” (apnea, bradypnea, oxygen desaturation, pain sedation mismatch in two of three 30-min evaluation periods) in patients at high risk of OSA were associated with postoperative respiratory complications, such as ICU admissions for a respiratory indication, the need for respiratory therapy beyond standard postoperative clinical practice, the need for noninvasive ventilatory support, or the development of postoperative pneumonia. More research to determine how PACU monitoring could help to risk stratify and identify patients who need more intensive monitoring would be useful. Potential interventions during the initial postoperative period (e.g., during monitoring in the PACU) will have to consider the challenges inherent in increasing the use of resources in a high-acuity setting. Similarly, interventions that can only be implemented in high-acuity settings, such as an ICU, are unlikely to be available to sufficient patients to make a dramatic reduction in adverse postoperative outcomes.

## Obstructive Sleep Apnea Endotypes and Potential Relevance in the Perioperative Period

Understanding the different endotypes underlying the phenotype of OSA may result in more personalized screening, monitoring, and therapy. An endotype, in this context, is a subtype of OSA defined by a unique or distinctive function or pathophysiologic mechanism (27). There are multiple mechanistic pathways that can lead to OSA (e.g., compromised anatomy, dilator muscle dysfunction, low arousal threshold, elevated loop gain, inadequate lung volume tethering, and vascular leak) that are potentially relevant in a perioperative setting (27).

Arousal threshold is an important consideration. Arousal threshold is defined using esophageal/epiglottic pressure before electroencephalogram arousal; however, arousal threshold can be estimated using a recently validated multivariate model that uses PSG data (28). Low arousal thresholds can prevent the accumulation of respiratory stimuli, resulting in reduced activation of genioglossus postoperatively. Though highly speculative and theoretical, in these patients, increasing the arousal threshold with sedatives or allowing a low level of carbon dioxide retention postoperatively may increase the genioglossus muscle activation and decrease apneas (29, 30). However, individuals with high arousal threshold may be especially prone to adverse sedative effects of anesthetic agents and opioids if profound hypoxemia and hypercapnia were to develop before arousal.

Dilator muscle control may be possible to manipulate to improve OSA perioperatively. The genioglossus muscle is stimulated with an increased partial pressure of carbon dioxide in combination with a mechanoreceptor load (31). These combinations of stimuli can activate the genioglossus during stable sleep, and may represent a therapeutic target to stabilize breathing in predisposed individuals. Methods of percutaneous stimulation of the hypoglossal nerve are now being studied in this context as well (32).

In the discussion, the potential utility in further defining endotypes of OSA and determining whether these would predispose to postoperative opioid sensitivity and postoperative complications

was recognized. This approach would require in-depth physiological studies until endotyping can be accomplished with less time-intensive studies or through PSG. The development of noninvasive and readily available physiological studies or clinical prediction models that can characterize patients who have high-risk endotypes of OSA is an important area of research, as this strategy could then be employed by numerous health care providers to improve care if outcome data were supportive.

## Role of Algorithms in the Perioperative Management of Obstructive Sleep Apnea or Obesity Hypoventilation Syndrome

There are limited published data on algorithms of care to identify or manage patients with OSA. The protocols are often instituted as quality-improvement initiatives, and thus may not be published. For example, modifications in anesthetic practice with a reduction in doses of opioids with multimodal analgesia and regional anesthesia technique may reduce postoperative risk in patients with OSA independently of targeted algorithms. Many challenges that are faced by researchers evaluating algorithms were raised. In many centers, a minority of patients attend a preoperative clinic, which limits opportunity for patient identification before surgery. There needs to be substantial support from surgical services. Many questions potentially inform us about the value of algorithms of care: How much OSA confers risk? What is the best screening test? What is the most cost-effective postoperative monitoring strategy? What is the best intervention or therapy, and how should it be implemented? Three protocols from the University of Pittsburgh Medical Centre and Northwestern University were discussed in this presentation, and key features of these algorithms, and the barriers encountered, are outlined subsequently here.

Strategies to increase the detection rate of patients at risk of OSA or OHS are ongoing. One strategy under evaluation is to screen patients diagnosed without OSA with a STOP-Bang score administered on the day of surgery; if the patient scored 5 or greater, the anesthesiologist was made aware and an OSA wrist band applied. Preoperative sleep testing was a challenge, as many patients would not attend a PSG appointment, and

ambulatory testing has not been extensively studied as a preoperative strategy to mitigate perioperative risk.

Enhanced monitoring strategies are being considered. This has been captured in algorithms that prespecify increased monitoring time in the PACU for those identified as high risk. Wireless continuous pulse oximetry/pulse rate monitoring system with direct notifications through a pager system is another possible monitoring strategy being tested. The threshold oxygen saturation was set low (<82%) because of significant false positives above this threshold. It is not clear how cost effective this was, and various process barriers were encountered that are elaborated upon in the section PATIENT SAFETY AND HEALTHCARE MANAGEMENT CONSIDERATIONS. The role of capnography for postoperative monitoring has been considered. Barriers encountered with implementing algorithms with capnography were frequent. Interpretation of the signals was challenging, given the lack of a secured airway and the discrepancy between nasal/mouth capture end-tidal carbon dioxide and arterial partial pressure of carbon dioxide, particularly when the patient is on oxygen therapy or has an elevated respiratory rate. The increased skill and training requirement to appropriately apply end-tidal carbon dioxide monitoring is also a substantial challenge.

Intervention strategies are a final suggested component of the algorithms in use. Educational interventions may be a useful component of management algorithms. Educational interventions may be targeted toward increasing positive airway pressure use before surgery. As an example of a method that has been tried, patients with a pre-existing diagnosis of OSA were contacted preoperatively, and were advised to use CPAP for 2 weeks before surgery and to bring CPAP to the hospital. For patients identified as having a high risk of OSA, family and patient education regarding OSA and risks with surgery is another possibility that is being explored. Incentive spirometry, use of local or regional anesthesia if possible, minimizing opioid use, and prespecified PACU protocols are possible interventions that require more study. CPAP or automatic positive airway pressure (APAP) initiation in the pre- or postoperative period is further discussed in the subsequent section. Use of perioperative oxygen improves oxygenation and AHI on postoperative Nights 1–3 (33); however, a subset of patients retain carbon dioxide with

this therapy for unclear reasons (33). The role of supplemental oxygen postoperatively requires further study.

## Perioperative Use of Positive Airway Pressure

Optimization of OSA treatment preoperatively is thought to be high-quality care. Because CPAP may have significant long-term benefits in terms of improvements in quality of life, preoperative clinics provide an opportunity for identification of patients with undiagnosed OSA who may symptomatically benefit from treatment (34–36). Two recent matched observational studies using large administrative databases suggest benefits of CPAP use perioperatively in patients with diagnosed and undiagnosed OSA (21, 37); however, limitations exist in these studies (discussed in a subsequent section). In one study, patients diagnosed with OSA with a CPAP prescription had reduced risk of cardiovascular adverse events compared with patients with undiagnosed OSA (OR = 0.34; 95% CI = 0.15–0.77;  $P = 0.009$ ) (21). In another study, patients with documented OSA without therapy or suspected OSA had more frequent cardiopulmonary complications compared with patients with OSA with positive airway pressure therapy (risk-adjusted rates of 6.7% vs. 4%;  $P = 0.001$ ) (37). In addition, there are data to support the use of CPAP to modulate the respiratory depressant effects of opioids given for pain (38).

In randomized trials, the institution of positive airway pressure perioperatively has not been highly effective. Meta-analysis of clinical trials, including data from 904 patients, suggests that postoperative CPAP results in a reduction in AHI, a trend to a reduction in LOS, but no significant impact on postoperative adverse events (39). The lack of clear improvement in outcomes might be due to low adherence to positive airway pressure therapy (2.4–4.6 h/night) (40–42). In addition, full resolution of sleep-disordered breathing may not occur with positive airway pressure (39). There are three prospective trials evaluating the institution of empiric positive airway pressure postoperatively, in patients with undiagnosed or untreated OSA; all three studies used automatic positive airway pressure (36, 39). In those continuing previously prescribed positive airway

pressure therapy in the postoperative period, one study suggests that 18% of patients spent at least 30 minutes with oxygen saturations less than 90% the night after surgery, despite use of their prescribed positive airway pressure therapy (43).

Further work needs to be done to determine how and when to effectively implement positive airway pressure. A number of potential questions were discussed. What are the barriers to CPAP adherence in the perioperative setting? Can patient adherence and positive airway pressure effectiveness be increased with educational resources (e.g., digital tablets)? Should other respiratory support interventions be examined either in isolation or bundled with positive airway pressure? For example, could flags for OSA (similar to an allergy alert) be used to alert pharmacy/nurses/medical staff, initiate automatic orders (e.g., block certain drugs, such as bolus opioids/certain hypnotics), improve gas exchange (stimulation, frequent vitals and sedation scale assessments, raise head of the bed, oxygen), and identify hypercapnia early? Is there a role for targeted positive airway pressure therapy to very high-risk groups, such as patients with severe OSA, patients with OHS, or patients with uncontrolled systemic diseases, such as pulmonary hypertension? What is the medicolegal liability and patient safety factors to consider when starting positive airway pressure in the hospital?

## Obesity Hypoventilation Syndrome in the Perioperative Period

To be diagnosed with OHS, the patient should have a body mass index of 30 kg/m<sup>2</sup> or greater an arterial partial pressure of carbon dioxide of 45 mm Hg or greater during wakefulness, and exclusion of other causes of hypercapnia (44). Approximately 90% of patients with OHS have concomitant OSA (45). OHS is estimated to occur in 1/160 adults (46). OHS should be suspected in very obese patients (46), obese patients with an increased serum bicarbonate ( $\geq 27$  mEq/L) (47), room air hypoxemia while resting, persistent hypoxemia during PSG, or when a restrictive ventilatory defect is present. An elevated serum bicarbonate or base excess may be a better marker of prolonged hypoventilation as opposed to daytime arterial blood gases (patients may

hyperventilate during the sampling) (48). The use of serum bicarbonate in addition to the STOP-Bang questionnaire may identify potential patients with OHS (49).

Compared with patients with OSA alone, in the perioperative setting, patients with OHS have an increased risk of respiratory failure (OR = 10.9; 95% CI = 3.7–32.3), heart failure (OR = 5.4; 95% CI = 1.9–15.7), prolonged intubation (OR = 3.1; 95% CI = 0.6–15.3), tracheostomy (OR = 3.8; 95% CI = 1.7–8.6), and ICU transfer (OR = 10.9; 95% CI = 3.7–32.3) (11). Patients with OHS also have longer ICU LOS and hospital LOS (11). Thus, the perioperative management of OHS requires expertise and attention (50).

Research questions proposed included the following. How should we screen for unrecognized OHS? How should we approach patients with OHS who are nonadherent to positive airway pressure? How safe is postoperative supplemental oxygen in patients with OHS? What are the best monitoring strategies for patients with hypercapnia? How can we avoid management pitfalls, such as over-diuresis or excessive oxygen supplementation that may worsen hypoventilation? What is the ideal positive airway pressure strategy in patients with OHS? Could respiratory stimulants be useful?

## Opioids and the Surgical Patient with Obstructive Sleep Apnea

Although postoperative hypoxemia due to opioid analgesia is common and persistent (51, 52), life-threatening, opioid-induced respiratory depression (OIRD) is an uncommon event (53). Nevertheless, a closed-claims analysis by the American Society of Anesthesiologists (54) has identified OSA and OSA-related phenotypes as common conditions among patients who suffered brain damage or died in a setting of postoperative OIRD, thus potentially implicating OSA as a risk marker for unwanted respiratory effects in the context of opioid administration.

The interaction between several anatomical (e.g., pharyngeal airway dimensions) (55) and functional (i.e., gain of respiratory control, arousal threshold, responsiveness of the airway dilator muscles) endotypes (27) at multiple levels of breathing regulation is of central importance in the development of apnea-hypopnea in patients

with OSA (*see also* OSA ENDOTYPES AND POTENTIAL RELEVANCE IN THE PERIOPERATIVE PERIOD) (16, 56–59). As a result, increasing arousal threshold with hypnotics (30), and/or suppressing chemoreflex sensitivity by oxygen inhalation (60), improved apnea severity in certain groups of patients. Because opioids can exert similar actions via their sedative and chemoreception-suppressing effects, it is reasonable to hypothesize that the respiratory behavior of patients with OSA under opioids, as well as their vulnerability to OIRD, may depend on the effect of opioids on individual OSA endotypes, and that knowing the latter may help in predicting the former.

In support of this hypothesis is also the substantial variability in the observed respiratory effects of opioids in patients with OSA (61–64), where both harmful (62) and beneficial (63) effects on apnea severity during sleep have been demonstrated. Characteristically, in a randomized, placebo-controlled trial, Bernards and colleagues (64) have shown a dramatic increase of central apnea (from 0.8 to 43 events/h) in only 4 out of 10 patients with moderate OSA who received an opioid infusion during PSG, emphasizing the existing variability in the respiratory response to opioids in this population. Although differences in the study methods might have been responsible for these heterogeneous findings, the endotypic variability of OSA condition is also a possible explanation (65).

Presently, our strategies to mitigate OIRD in patients with OSA, should not differ from general measures that apply to non-OSA populations, like the use of short-acting anesthetic agents to reduce somnolence postoperatively and the adoption of nonopioid-based analgesia, including nonsteroidal antiinflammatory agents and/or regional anesthesia, to reduce opioid requirement. Furthermore, although the application of positive airway pressure, an airway-stabilizing treatment, has been shown to reduce apnea severity (41) and mitigate the impairing effects of opioids on ventilation (38) in postoperative patients with OSA, this treatment modality requires further investigation as a preventive measure against OIRD, especially when considering issues like opioid-induced central apnea (64), or the emergence of central apnea in CPAP-naive patients (66).

In the discussion, the following questions were also raised. Could pharmacotherapy or other therapies to stimulate the respiratory system be useful (e.g., ampakines [67],

phrenic nerve stimulation [68, 69], and elevated body position [70]), especially given that CPAP use is challenging in the perioperative setting? Do other comorbidities, such as congestive heart failure (71, 72) or diabetes (73), affect opioid sensitivity and the development of sleep-disordered breathing postoperatively? Can we more faithfully define OSA endotypes to better understand the variability in the respiratory and analgesic response to opioids in this patient population?

### The Use of Administrative Databases and Patient Registries

Patient registries and administrative datasets have numerous advantages and disadvantages. Advantages include the large sample size, reduced costs, and data reflecting patients in the real world as opposed to selected cohorts. The large sample size is especially advantageous in the study of infrequent postoperative outcomes, the adjustment for multiple confounders, and to examine subgroups of patients.

The disadvantages include the observational design, difficulty in controlling for confounders or comorbidities, and analyses that are limited to database entries. This may compromise the ability to control for relevant confounders (e.g., body mass index, OSA severity, CPAP adherence) if they were not included in the dataset. Identification of outcomes may be challenging, as it can be difficult to differentiate preexisting diagnoses from new diagnoses. For the assessment of treatment effectiveness, confounding by indication and adherence are significant potential issues. OSA severity is rarely included in these research studies, nor is it often known if these patients are treated for OSA or OHS. There are no validated algorithms with good performance characteristics to identify OSA within administrative data; therefore, the performance characteristics of the algorithms used are not known, although these studies are still thought to have value (74, 75).

Databases enriched for factors leading to or reflecting perioperative OSA complications would be useful. More work is required to better understand which exposures (e.g., OSA severity measures), outcomes, and confounders are important to record. One major confounder that needs to be considered is surgical complexity;

events in the intraoperative period are difficult to control for (e.g., blood loss, intraoperative fluid requirements), but can affect outcomes substantially. There may be opportunities to leverage existing datasets; for example, linking sleep study data to perioperative datasets to examine the impact of disease severity or other PSG data (e.g., sleep stages). Incorporating other data streams, such as nursing records and the electronic medical record (EMR), has potential to increase postoperative respiratory and cardiac event capture.

### Patient Safety and Healthcare Management Considerations

All healthcare institutions seek to avoid patient harm; however, they are also interested in resource utilization, as all centers are resource limited. When harm occurs, costs can be substantial. Pulmonary complications are of particular interest due to their inclusion in “pay for performance” programs, and respiratory outcomes are a component of many publicly reported safety metrics.

The fundamental process to reduce OSA- or OHS-attributable complications extends from patients to procedure to primary prevention of OSA complications to detection of deterioration to recovery after deterioration. Resources consumed per patient generally increase along this process, with prevention being less costly per patient than rescue after a complication has occurred. However, current preoperative OSA screening tools have a high false-positive rate, leading to a waste of resources, as systems deploy funds and personnel to enhanced monitoring and treatment of patients who are not truly at increased risk for OSA- or OHS-related complications.

From the standpoint of monitoring/detection of events postoperatively, there are three different types of alarms: 1) event alarms (e.g., arrhythmia); 2) parameter violation (vital signs); and 3) technical alarm (poor signal, intravenous tubing). Alarms are meant to err on the safe side; however, poor specificity can lead to alarm fatigue, and some consider this the number one hazard of health technology. There are unintended consequences of monitoring interventions: significant waste of resources for false-positive alarms, alarm fatigue, clerical burden, nurse turnover, diversion of resources, and patient delirium/sleep loss. Alarm thresholds for oximetry are commonly set to 90%, but there are few

data supporting this (76). A threshold close to 80% for desaturation was suggested to minimize false positives.

There is insufficient evidence to know if monitoring affects clinical outcomes. Comparative effectiveness studies of interventions with collection of health services outcomes (e.g., workload, total costs of acute care episode, and LOS) would be useful.

## Conclusions

Numerous knowledge gaps have been identified and highlighted. Given that complications are rare events, identification of a sufficient number of patients with OSA to answer the important research questions will require collaborative research networks. A specific high-risk cohort of interest may be individuals with OHS. Agreement on a minimal set of data elements to be collected in prospective cohort studies would facilitate multisite collaboration and meta-analysis of independent studies.

As life-threatening postoperative complications are rare events, analysis of causal factors lends itself to case-control studies. Detailed physiologic endotyping that is not possible in large cohort studies could identify pathophysiologic mechanisms that increase risk of perioperative complications of OSA. Although these studies would necessarily exclude those with the most severe complication (death), deep physiologic endotyping of survivors of postoperative respiratory failure and an appropriately selected control group may be an efficient approach to identifying characteristics that increase risk of postoperative respiratory complications, such as opioid sensitivity, airway anatomy, arousal threshold, and other components of ventilatory control. Such case-control studies might also be nested within larger cohort studies, facilitating choice of an appropriate control group. These studies may improve risk stratification and lead to novel targeted therapies.

The evaluation of interventions that can optimize safety in this population is also important. Testing a bundled approach to care (e.g., an algorithm of care including monitoring, positive airway pressure, education, and other respiratory supports) rather than each component individually might be more useful in initial clinical trials, as this may be more likely to be effective in improving outcomes. Initial intervention trials should likely focus on patients at highest risk

of adverse outcomes, such as those with OHS, high-risk surgery (e.g., spinal, upper abdominal), or particular OSA endotypes.

Key knowledge gaps are summarized in the OVERVIEW section. Much work has been accomplished already in this exciting field. However, many knowledge gaps have been identified and highlighted. It is clearly now time to systematically address these gaps given the importance of this area. Collaboration and strategic use of research resources will lend itself to more rapid improvement in patient care and improvement in patient outcomes. ■

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*Members of the subcommittee are as follows:*

NAJIB T. AYAS, M.D., M.P.H. (*Co-Chair*)  
FRANCES F. CHUNG, M.B.B.S. (*Co-Chair*)  
JOHN M. COLEMAN, M.D.  
ANTHONY G. DOUFAS, M.D., Ph.D.  
MATTHIAS EIKERMANN, M.D., Ph.D.  
PETER C. GAY, M.D.  
DANIEL J. GOTTLIEB, M.D., M.P.H.  
INDIRA GURUBHAGAVATULA, M.D., M.P.H.  
DAVID R. HILLMAN, M.B.  
ROOP KAW, M.D.  
CHERYL R. LARATTA, M.D.  
ATUL MALHOTRA, M.D.  
BABAK MOKHLESI, M.D., M.Sc.  
TIMOTHY I. MORGENTHALER, M.D.  
SAIRAM PARTHASARATHY, M.D.  
SATYA KRISHNA RAMACHANDRAN, M.D.  
KINGMAN P. STROHL, M.D.  
PATRICK J. STROLLO, M.D.  
MICHAEL J. TWERY, Ph.D.  
PHYLLIS C. ZEE, M.D., Ph.D.

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*Workshop speakers are as follows:*

F. F. Chung, M.B.B.S.  
J. M. Coleman, M.D.  
A. G. Doufas, M.D.  
P. C. Gay, M.D.  
R. Kaw, M.D.  
A. Malhotra, M.D.  
B. Mokhlesi, M.D., M.Sc.  
T. I. Morgenthaler, M.D.  
S. K. Ramachandran, M.D.  
P. J. Strollo, M.D.

*Other participants are as follows:*

M. Eikermann, M.D.  
D. J. Gottlieb, M.D., M.P.H.  
I. Gurubhagavatula, M.D., M.P.H.  
D. R. Hillman, M.B.  
C. R. Laratta, M.D.  
S. Parthasarathy, M.D.  
K. P. Strohl, M.D.  
M. J. Twery, Ph.D.  
P. C. Zee, M.D., Ph.D.

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