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Effects of Obstructive Sleep Apnea Risk on Postoperative Respiratory Complications: Protocol for a Retrospective Cohort Study

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ABSTRACT

Introduction: Obstructive sleep apnea (OSA), the most common type of sleep-disordered breathing, is associated with significant immediate and long-term morbidity, including fragmented sleep and impaired daytime functioning, as well as more severe consequences, such as hypertension, impaired cognitive function, and reduced quality of life. Perioperatively, OSA occurs frequently as a consequence of preexisting vulnerability, surgery, and drug effects. The impact of OSA on postoperative respiratory complications (PRC) needs to be better characterized. As OSA is associated with significant comorbidities, such as obesity and pulmonary hypertension, it is unclear whether OSA or its comorbidities are the mechanism of PRCs. This project aims to 1) develop a novel prediction score identifying surgical patients at high risk of OSA, 2) evaluate the association of OSA risk on PRCs, and 3) evaluate if pharmacologic agents used during surgery modify this association.

Methods: A retrospective cohort study using hospital-based electronic patient data and perioperative data on medications administered and vital signs. We will utilize data from clinical databases at Massachusetts General Hospital (MGH), Boston, Massachusetts. First, a prediction model for OSA will be developed using OSA diagnostic codes and polysomnography procedural codes as the reference standard, and will be validated by medical record review. Results of the prediction model will be used to classify patients in the database as high, medium, or low risk of OSA and we will investigate the effect of OSA on risk of PRCs. Finally, we will test whether the effect of OSA on PRCs is modified by the use of intraoperative pharmacologic agents known to increase upper airway instability, including neuromuscular blockade, neostigmine, opioids, anesthetics, and sedatives.

Ethics and dissemination: The Partners Human Research Committee approved this study (Protocol number: 2014P000218). The study results will be made available in the form of manuscripts for publication and presentations at national and international meetings.

Article Summary

Article Focus

- This article describes the protocol for the development of a novel clinical prediction score to determine those adult surgical patients at high risk for obstructive sleep apnea in order to better evaluate in the perioperative setting the patient's risk of developing postoperative respiratory complications.

Key Messages

- Current screening and prediction scores for OSA rely on patient-reported symptoms and do not consider OSA risk in the setting of surgery and general anesthesia, as it relates to subsequent risk of postoperative outcomes

Strengths and Limitations

- This work utilizes a large clinical database consisting of pre-, intra-, and post-operative patient data.
- Our prediction model draws on well-established clinical characteristics associated with OSA as well as new measures aimed at improving dynamic risk assessment in a perioperative setting.
- The results of this study will enable perioperative clinicians to identify adult surgical patients at highest risk for OSA, optimize preoperative interventions, and appropriately triage care postoperatively based on intraoperative events.
- Potential limitations relate to the need for validation studies in datasets from other institutions to determine generalizability of prediction score

INTRODUCTION

Background

Obstructive sleep apnea (OSA) is a common disorder characterized by recurrent collapse of the upper airway. This chronic condition may be diagnosed by the presence of symptoms and, depending on the specific criteria used for making the diagnosis, more than 5 episodes of apnea, hypopnea, or respiratory effort-related arousal per hour of sleep.[1,2] Daytime symptoms refer to excessive daytime sleepiness, morning headaches, decreased concentration, memory loss, decreased libido and irritability. Other OSA-related symptoms include witnessed apnea, snoring, non-refreshing sleep, and gasping or choking at night.[3]

Recent epidemiologic data report that an estimated 70 million people in the United States alone are affected by OSA, making it the most common type of sleep-disordered breathing (SDB).[4] In the general adult population, the prevalence of OSA with daytime symptoms is 2% to 5% in women and 3% to 7% in men.[5] The prevalence of OSA without daytime symptoms is even higher and reaches values of up to 9% in women and 24% in men.[2,6] It is possible that such epidemiological data underestimate the frequency of OSA among today's general population since obesity, a major driver of OSA,[7] has greatly increased in the last decade.[8] Furthermore, studies have shown that OSA is commonly undiagnosed, suggesting an even higher prevalence of adults who suffer from this sleep disorder.[9-11]

Surgical patients with OSA are at a higher risk of developing postoperative respiratory complications, such as reintubation and requirement of non-invasive ventilation.[12-14] Upper airway collapse in the perioperative setting results in hypoventilation and is an important component of the mechanism of postoperative respiratory complications. In studies previously reported by our lab, independent of OSA, reintubation and unplanned ICU admission result in a 70 to 90-fold increase in in-hospital mortality.[15,16] However, despite an increased rate of postoperative respiratory complications, SDB, as identified by diagnostic codes, was paradoxically associated with lower mortality, hospital length of stay and costs among certain surgical specialties.[12] The mechanisms of the opposed effects of OSA on respiratory complication rate and mortality are unclear. We speculate that reintubation in patients with OSA is typically the consequence of upper airway dysfunction rather than pulmonary pathology, and the former can be treated more efficiently.

Mechanism of Perioperative Obstructive Sleep Apnea

Quantification of perioperative vulnerability to upper airway collapse requires consideration of preoperative and perioperative risk factors that affect the balance between collapsing forces and dilating forces of the upper airway. Perioperative anatomical and physiological factors need to be taken into account.

1. Anatomical Abnormalities Increase Collapsing Forces

Anatomical risk factors in patients with OSA include a reduction in the size of the retropalatal and retroglossal airway.[17,18] Perioperatively, anatomical vulnerability is augmented, thereby increasing upper airway instability. Figure 1a summarizes perioperative risk factors that can compromise upper airway anatomy. Mechanical loads to the collapsible segments of the retropalatal and retropharyngeal upper airway lead to physical compression of the airway. Clinically, such an extraluminal mechanical load can occur as a consequence of a postoperative hematoma following cervical, ENT or thyroid surgery.[19,20] In addition, peripharyngeal edema may occur in perioperative medicine as a consequence of fluid overload. Bradley and colleagues studied the effects of antishock trouser inflation on upper airway size and reported narrowed pharynx and enlarged neck circumference measured by acoustic pharyngometry.[21] Congestive heart failure increases the AHI, which presumably is the consequence of nocturnal rostral fluid shift.[22] Airway patency may also be affected by peripharyngeal inflammation and edema in the setting of intubation and extubation.

2. Impaired Caudal Traction on the Trachea Increases Collapsibility

Isono and colleagues have conducted extensive investigations of position-dependent effects on airway obstruction. In anesthetized and paralyzed patients with OSA, the authors found that the lateral and sitting positions improve the collapsibility of the passive pharyngeal airway.[23,24]

Among patients with OSA, the supine position not only promotes a more obstructive orientation of the pharyngeal soft tissues, but also reduces caudal traction, thereby increasing vulnerability to upper airway collapse. During inspiration, caudal traction on the airway due to lung expansion dilates and stabilizes the upper airway, a force that opposes the negative intra-luminal pressure and prevents collapse.[25] The supine position during

surgery, immediate postoperative period, and transition to sleep impairs tracheal traction on the airway and promotes collapse,[23,24] as illustrated in Figure 1a. Tracheal traction is also impaired by any event that reduces lung volume, often secondary to diaphragmatic dysfunction. Impaired function of the respiratory pump muscles (diaphragm and intercostal muscles) results in ineffective expansion of the lung and occurs in the setting of surgery and trauma.[26] Pain-induced splinting and pharmacologic agents, such as opioids, decrease drive to the respiratory pump muscles, thereby preventing full lung inflation and reducing tracheal traction.[27] Studies in the intensive care unit have demonstrated how systemic inflammation and mechanical ventilation dramatically disrupts diaphragmatic function.[28,29]

3. Neuromuscular Mechanisms of Perioperative Airway Collapse

A balance between the upper airway dilator muscles (genioglossus, tensor palatine) and the respiratory pump muscles (diaphragm, intercostal muscles) exist to maintain upper airway patency during wakefulness and sleep, as illustrated in Figure 1b. Respiratory pump muscles generate inspiratory airflow associated with negative intra-luminal pressure, which is detected by mechanoreceptors and transmitted to the upper airway dilator muscles via the hypoglossal nerve. As a result, the genioglossus contracts and stabilizes the upper airway. Respiration is also stimulated by hypoxia and hypercarbia, which are detected by chemoreceptors. In addition to wakefulness, information transmitted by mechanoreceptors and chemoreceptors stimulate respiratory arousal, which has been previously defined as arousal from sleep and other drug-induced or endogenous impairments of consciousness.[30] Cortical effects on respiratory arousal are important, and any decrease in arousal can impair the voluntary effort to breathe spontaneously through a patent upper airway.[31]

A variety of pharmacologic and non-pharmacologic perioperative factors affect respiratory arousal. While the specific effects of perioperative pharmacologic agents depend on agent, dose, and specific muscle group, studies have shown that such agents largely dampen stimulation to the nerves controlling respiratory muscles.

Anesthetics and Sedatives

Studies in humans and animals have demonstrated the effects of anesthetics on the upper airway by a variety of mechanisms. Anesthetics decrease muscle and neural activity important for respiration as well as wakefulness

through varying mechanisms.[32] Propofol, an agent commonly used for induction and maintenance of anesthesia, dose-dependently increases collapsibility of the upper airway through depressed respiratory drive to and direct inhibition of upper airway dilator muscle activity in humans.[33] In humans anesthetized with isoflurane, reflexive activity, or the responsiveness of upper airway dilator muscles to negative pressure, was found to be greatly reduced.[34] The diminishing effects of anesthetics on neuronal activity also differ between hypoglossal and phrenic nerve.[35] With a focus on neural mechanisms for altered upper airway activity, Nishino and colleagues investigated the differential effects of anesthetics and found greater dampening of hypoglossal nerve input relative to the phrenic nerve.[36] This effect may result in greater anesthesia-induced impairment of upper airway dilators compared to respiratory pump muscles, increasing the upper airway's propensity for collapse. While this effect was observed across three classes of drugs (volatile, barbiturate, and benzodiazepine), ketamine reduced neural input to the upper airway dilator muscles and respiratory pump muscles equally. Furthermore, ketamine's effect on the upper airway dilator muscles was less relative to GABAergic anesthetics.[36] Such findings are corroborated by mechanistic studies in rats that demonstrate a dissociation between loss of consciousness and upper airway dilator muscle function under ketamine anesthesia.[37] Taken together, studies suggest that patients with OSA, who have preoperative upper airway instability, may be at a heightened risk of upper airway collapse when under the influence of anesthetics. The unique effects associated with ketamine, however, suggest that this drug may be a safer choice for patients with OSA.

Opioids

Patients with OSA have been found to have heightened sensitivity to pain[38-40] as well as heightened sensitivity to the effects of opioids.[41] Such findings are particularly relevant to the postoperative OSA patient given the effects of opioids on upper airway patency. Animal studies have shown that opioids increase upper airway resistance, resulting in obstruction.[42] Opioids also directly inhibit hypoglossal motoneurons, which leads to suppressed genioglossus activity.[43] Thus, the use of opioids during and immediately after surgery is an important perioperative factor to consider in patients with OSA when assessing the risk of upper airway instability and the postoperative respiratory complications that may arise as a consequence.

Neuromuscular Blocking Agents and Reversal Agents

Neuromuscular blockade agents (NMBAs) act longer than the duration of surgery and postoperative residual curarization affects postoperative respiratory outcome.[44] Upper airway dilators are more vulnerable to minimal effects of NMBAs compared to the respiratory pump muscles.[45,46] This differential activation of pump vs. dilator muscles may set off an unwanted chain of events such that the relatively more active respiratory pump muscles generate excessive negative intrathoracic pressure, resulting in negative pressure pulmonary edema.[47] Even at levels producing minimal blockade, as measured by train-of-four ratio 0.5-1, NMBAs increased upper airway collapsibility and impaired compensatory genioglossus response to negative pharyngeal pressure challenges.[48] Studies in surgical patients have demonstrated the dose-dependent association between intermediate-acting NMBAs and postoperative respiratory complications, an effect shown to be unyielding despite neostigmine-based reversal at end of surgery.[16,49,50] Based on the pathophysiology of the disease, patients with OSA should have an increased vulnerability to the effects of NMBAs and reversal agents.[45,48] However, population-based studies aiming to quantify the effects of residual neuromuscular blockade in patients with and without risk of OSA are currently missing.

The impact of such pharmacologic agents commonly used in anesthesia care on the risk of respiratory outcomes in patients with OSA has yet to be determined. Our study will address the unmet need of evaluating the perioperative effect of NMBAs, reversal agents, opioids, sedatives, and anesthetics in patients at risk of OSA.

Non-Pharmacologic Events

Non-pharmacologic perioperative events, such as REM rebound, encephalopathy, delirium, can disrupt respiratory arousal and result in upper airway collapse.[30] In the immediate postoperative period, patients commonly experience poor quality, disrupted, and reduced sleep, resulting in a deficit of rapid eye movement sleep (REM).[51] Sleep studies in surgical patients have identified a REM rebound effect, in which REM sleep returns acutely and suddenly.[51,52] Increased amounts of REM during sleep is associated with impaired respiratory arousal and more frequent episodes of nocturnal hypoxemia.[53] The impact of REM rebound is particularly relevant to patients with comorbid conditions like OSA. OSA patients also have diminished or lost airway reflex during NREM sleep, implying that patients with OSA are at an even greater propensity for upper airway collapse and hypoxemia with phenomenon of REM rebound. While OSA patients have been shown to compensate for

diminished airway sizes with higher basal genioglossus muscle activity,[54] this neuromuscular compensation has been found to be present only during wakefulness, and thus futile in the setting of REM-predominant sleep. Additionally, events that impair a patient's level of consciousness also disrupt respiratory arousal and result in upper airway instability. Such events include delirium, stroke, septic encephalopathy, systemic inflammation, and metabolic disturbances, like hypoglycemia and hypothyroidism.[30]

Study Rationale

In order to evaluate the perioperative risk of patients presenting with OSA, it is important to take into account the "true" prevalence of the disease in the perioperative cohort. An important limitation of the existing literature relates to the focus on patients who carry the clinical diagnosis of OSA. As a consequence of analyzing only those patients with an International Classification of Diseases-9 (ICD-9) diagnostic code for SDB, a large subpopulation with undiagnosed OSA remain undetected.

The gold standard for the diagnosis of OSA is polysomnography (PSG). According to current clinical guidelines for OSA evaluation, patients are prompted to undergo this sleep study if determined to be high risk by their physician.[3] As a routine evaluation for OSA, PSG is impractical because of its limited availability, discomfort to the patient, and high cost.[55,56] The use of screening tools for OSA helps identify patients at risk of OSA. Widely used scores include the P-SAP score,[57] the STOP-Bang[58] and Berlin Questionnaires,[59] and the Epworth Sleepiness Scale.[60] Such scores rely on a clinical exam to determine neck circumference and/or patient questionnaire of daytime OSA symptoms. Not all patients are able to have their necks measured and many patients are asymptomatic or unaware of their symptoms, limiting the ability of the existing scores to assess true prevalence of OSA. Anesthesiologists have also used scores, such as the Mallampati Score and the American Society of Anesthesiologists (ASA) Checklist, to assess difficulty of intubation, as related to a narrow upper airway,[61] but there is inconsistency in reported sensitivity and specificity of the Mallampati score as a predictor of OSA.[60] Furthermore, the currently available scores require data not routinely available from clinical databases, such as history of snoring and witnessed apnea. This proposal is based on the consideration that other data available in the patient's electronic medical record may be sufficient to predict OSA and its associated increased risk of postoperative respiratory complications. Application of our prediction score on large perioperative datasets will

permit research endeavors, such as the evaluation of the effect of OSA on patient outcomes and the justification of health care resource utilization.

Furthermore, understanding how pharmacologic agents commonly used in perioperative care impact postoperative outcomes among patients with high risk of OSA will improve our ability to provide better care for this vulnerable surgical population. Traditionally, anesthesia providers have determined dosing of various drugs based on standard parameters of age, gender, height and weight. However, such practices may not sufficiently guide providers in optimal drug administration, especially in a subpopulation more vulnerable to the effects of those drugs as already demonstrated in the literature. More specifically, we would like to better understand the interaction between the disease OSA and opioids, neuromuscular blocking agents, neostigmine, sedatives and anesthetics to optimally predict postoperative respiratory outcomes. Using our prediction score for OSA in a large perioperative database, we will evaluate how the use of pharmacologic agents modifies the risk of postoperative respiratory complications in patients with OSA.

Objectives

The primary objectives are to:

1. Develop a novel prediction score of OSA to identify patients at high risk of OSA based on markers of the disease easily available from clinical databases.
   1.1. Validate OSA prediction based on medical record review.
2. Evaluate the effect of being at high risk of OSA, as defined by the prediction score, on the primary outcome of postoperative respiratory complications among patients undergoing surgery at Massachusetts General Hospital.
3. Evaluate if use of neuromuscular blockade, neostigmine-based reversal of neuromuscular blockade, opioids, sedatives, and anesthetics modify the risk of OSA on postoperative respiratory complications.

The secondary objective is to:

1. Investigate whether the association between OSA risk and postoperative respiratory complications is modified by age, gender, BMI and major comorbidities.

Hypotheses for the Primary Outcome

Based on previous data,[12] we hypothesize that patients with a high risk of OSA, as identified by our new prediction instrument, are more vulnerable to acute postoperative upper airway failure that leads to re-intubation. We further hypothesize that such patients will experience more favorable outcomes and thus the additional manifestations of postoperative respiratory complications will not significantly depend on the perioperative condition of OSA.

As a departure from the current literature on the perioperative effects of OSA, we believe that perioperative variables, which increase the vulnerability to airway collapse, will give us clinically meaningful information in order to predict which patient with OSA will develop postoperative respiratory complications.

METHODS AND ANALYSIS

Study Overview

The proposed study is a retrospective cohort analysis using hospital-based electronic patient data and perioperative data on medications administered and patient vital signs. We will utilize data from major clinical databases at Massachusetts General Hospital (MGH), a tertiary care facility and teaching hospital of Harvard Medical School in Boston, Massachusetts.

As previously used for epidemiological studies by our group, data from two clinical databases will be retrieved and combined to provide de-identified pre-, intra-, and postoperative information: the Research Patient Data Registry (RPDR) and the Anesthesia Information Management System (AIMS).[15,16,49,62] The RPDR contains demographic and billing data regarding patient comorbidities and postoperative outcome and survival. The AIMS contains physiological data from patient monitors as well as information on medical history and documentation of important surgery and anesthesia-related events, including adverse events, perioperative procedures, and drug and fluid therapy. Patient data from these databases are linked through unique patient identifiers and the variables described in this protocol will be abstracted to form one database. The present database spans January 2007 to August 2012 and includes 90,990 surgical cases. Based on previous work, we will conservatively anticipate that 25% of the cases will not satisfy inclusion criteria due to patient's age, emergency status and missing data.[15,49] Thus we estimate 68,000 patient cases will meet our inclusion criteria.

Subject Selection

For the three primary objectives, we will include all adult surgical patients who underwent general anesthesia and receive endotracheal intubation or airway management by supraglottic airway device at MGH, for whom inpatient admission was planned, between January 2007 and August 2012. Included patients must also have had removal of all airway management devices within the operating room after the procedure. Surgical procedures followed by reintubation for an additional surgical procedure in the operating room after initial extubation or removal of airway device will be excluded from the study. Patients who underwent surgery in the four weeks prior to the study case will be excluded. Patients will be identified using anesthesia data obtained from RPDR and AIMS.

The study methods are outlined in three sections to address the three primary objectives.

Objective 1: Development of Prediction Model for OSA

Prediction Model Reference Standard

The reference standard for the prediction model will be defined as patients with an ICD-9 OSA diagnosis following the appearance of a PSG procedural (CPT) code in our medical databases (Figure 2). From this specific sequence of events, we infer that these patients had their clinically suspected OSA diagnosis confirmed by the PSG study.

Validation of Reference Standard for the Diagnosis of OSA

Prior to the development of the prediction model, we will conduct a medical chart review of 100 randomly selected patients meeting our OSA criteria of an ICD-9 diagnostic code and PSG procedure code in order to determine whether or not such patients actually have evidence of OSA in the time between their PSG and surgery. These patients will not be considered for inclusion into the predictive model, but instead will be used to assess the positive predictive value of the ICD-9 and CPT code combination for identifying OSA. Confirmatory evidence of OSA would include a reported apnea hypopnea index (AHI) > 5 as documented in a patient's medical chart[2] or treatment with continuous positive airway pressure (CPAP). The predictive model will be performed if the ICD-9 and CPT code combination has an acceptable positive predictive value (≥0.8).

Predictor Variables

A number of variables have been found to be associated with an increased prevalence of OSA and are currently used for different screening tools for OSA in surgical patients.[58,61,63] From the AIMS and RPDR databases, we will obtain and include the following data in our prediction score: age, weight, BMI, gender, and the American Society of Anesthesiologists (ASA) physical status classification (Figure 2). We will incorporate medical comorbidities using ICD9 diagnostic codes, some of which are defined by the Deyo-Charlson Comorbidity Index (Table 1).[64] All covariates included in the prediction model must be present within one year of surgery date. In addition, as a departure from current literature on developing OSA screening scores, we will consider oxygen desaturation immediately after extubation as a predictor. This strategy will most likely increase the predictive value of our score

– patients with OSA are very vulnerable to desaturation after surgery and we have the unique opportunity to use this characteristic of OSA desaturation after anesthesia that has not yet been utilized in existing prediction scores. Post-extubation oxygen desaturation will be defined as an oxyhemoglobin reading less than 90% and less than 80% for at least one minute, as measured by pulse oximetry during the first 10 minutes after extubation in the operating room.

Development of Prediction Model

We will use an unconditional logistic regression model with an automated forward selection procedure to select for predictors of our a priori defined reference standard. As entry criteria we will set a P value of 0.01.

To determine the goodness of fit of the final prediction model, we will use the Hosmer-Lemeshow test, which indicates that there is no significant difference between observed and expected OSA status if P-value ≥ 0.05. A point value will be assigned to each predictor variable proportional to the estimates from the logistic regression. The predictive value of the score for OSA will be assessed using c-statistics, which is equivalent to the area under the ROC curve.[65] We will aim to achieve a minimum c-statistic of 0.8. We will calculate positive and negative likelihood ratios for each stratum of the score. We will use bootstrap techniques to determine the robustness of included variables, which are close to the P-value cut-off of 0.05. We will then use classification tables to determine the best cut-off value for the prediction score to classify patients at high risk for OSA.

Objective 2: Effect of High OSA risk on Postoperative Respiratory Complications

Exposure Variables

Our primary exposure variable of interest is OSA risk, as defined by our prediction model developed in Aim 1. We will identify patients in our population as having a high, moderate, and low risk for OSA using our prediction model and produce three cohorts of patients, which we will follow for the occurrence of outcome events.

Outcome Variables

The primary outcome of this part of the study is a composite outcome defined as the incidence of re-intubation, pulmonary edema, pneumonia and respiratory failure within the first three postoperative days. Secondary

outcomes include the aforementioned individual outcomes as well as hospital length of stay, duration of post-anesthesia care unit treatment, and in-hospital mortality. The primary outcome has been previously used and validated by chart review.[49,62] The outcomes events for the primary analysis will be identified by ICD-9 diagnostic and CPT procedural codes obtained from the RPDR database (Table 1).

Outcome Model

We will perform multivariable logistic regression analyses to evaluate the effect of estimated OSA risk on our respiratory outcomes. Results will be presented as an age- and multivariable-adjusted odds ratio with 95% confidence intervals. We will consider a two-tailed P-value of less than 0.05 as statistically significant.

To control for confounding effects, we will consider a priori the following risk factors: age, gender, body weight, BMI, ASA physical status classification, comorbidities, surgical specialty, duration of the surgical procedure, and emergency status.[16] We will additionally control for dose of anesthesia (median dose of anesthetic agents corrected for age),[66] opioids (calculated as total morphine equivalent dose),[67] vasopressors (calculated as norepinephrine equivalent dose per hour),[68] sedatives, neuromuscular blocking agents, and neostigmine use (Figure 3).

The effect of surgery type will be analyzed in greater detail by grouping similar types of surgery (e.g. cardiovascular, laparoscopic) to determine if surgery type is an effect modifier and not a confounder. If this is found to be the case, surgical specialty will no longer be included as a covariate, and the previously described model will be stratified by surgery type.

Sample Size and Power Calculations

Based on previous work with data from surgical patients in our institution, we expect approximately 68,000 patients undergoing inpatient surgery to meet our inclusion criteria during the observational period. Studies on prevalence of OSA in the general surgical population provide a range of estimates: one study found 17% of surgical patients as having severe OSA (AHI >30).[69] Other studies relying on screening scores found anywhere from 4.8%[70] to 41.6%[71] of surgical patients at high risk of OSA. Thus, we conservatively estimate 5% (n=3,400)

patients in our surgical population to have a high likelihood of OSA. Our exposure groups of high, moderate, and low OSA risk will each have a sample size of 3,400 patients.

Previous work by our lab[49] found an overall incidence of 3.7% for our primary outcome of postoperative respiratory complications. Data on differences in postoperative outcomes between OSA and non-OSA groups provide us with estimates for our predicted intergroup differences. Liao et al found an intergroup (OSA vs Non-OSA) difference of 11% for their composite outcome of total respiratory complications.[13] Mokhlesi et al investigated the incidence of emergent intubation following elective surgery among patients with and without SDB.[12] Emergent intubation occurred at a rate of 3.5-11.4% among patients with SDB vs. 0.3-7% among patients without SDB across four categories of elective surgery.[12] The intergroup difference observed was approximately 3%.[12] Based on this data, we will conservatively estimate an intergroup difference of 10% for our composite outcome, with smaller differences observed for outcomes with lower frequencies. Power is calculated based on comparing proportions of outcome rates between expected patients with OSA and the reference population without OSA. Our fixed sample size of 68,000 will provide us with a power greater than 90% to identify a 10% intergroup difference with an alpha error of 0.05.

Objective 3: Risk modification by Pharmacologic Agents

Exposure Variable and Rationale

We will obtain data on the intraoperative use of intermediate-acting neuromuscular blocking agents, neostigmine-based reversal of neuromuscular blockade, opioids, anesthetics, and sedatives as additional independent variables in the analysis to test whether or not such pharmacologic agents modify the effect of OSA on the risk for postoperative respiratory complications. We have previously studied the use of intermediate-acting neuromuscular blocking agents and found that their use was associated with an increased risk of respiratory complications.[16] In addition, we have observed that the use of the reversal agent neostigmine does not decrease but increase the risk of postoperative respiratory complications.[16,50] However, more recent work demonstrates that such effects could be mitigated by neostigmine only at low doses and with simultaneous careful monitoring of neuromuscular transmission (train-of-four).[49]

Patients with OSA should be at high risk of respiratory complications induced by pharmacologic agents because such agents can affect upper airway patency.[35,42,46,72] We thus expand our investigation to include the risk modification effect of pharmacologic agents (neuromuscular blocking agents, neostigmine, opioids, anesthetics, and sedatives) on postoperative respiratory complications in a subpopulation of surgical patients who may be at an inherent higher vulnerability towards upper airway collapse and subsequent poor respiratory outcomes. Similar to previous work, we will extract information on administration of pharmacologic agents from the AIMS database.[49]

Outcome Variables

The primary outcome is the composite variable of postoperative respiratory complications, consisting of: reintubation, pulmonary edema, pneumonia and respiratory failure. Secondary outcomes include hospital length of stay, duration of post-anesthesia care unit treatment, in-hospital mortality, as well as the aforementioned outcomes. These outcomes are defined by ICD-9 and CPT codes located in the RPDR database and have been previously validated by chart review by our lab (Table 1).[49]

Stratified Analysis to Assess for Effect Modification by Pharmacologic Agents

To evaluate potential effect modification by neuromuscular blockade, neostigmine, opioid, anesthetic, and sedative use, we will run stratified analyses of the association between OSA and the outcome events based on intraoperative use of pharmacologic agents. We will use the likelihood ratio test to contrast a main model to a model also including appropriate interaction terms. To control for confounding effects, we will consider a priori the following risk factors: age, gender, body weight, BMI, ASA physical status classification, comorbidities, surgical specialty, duration of the surgical procedure, and emergency status.[16] The stratified analyses for neuromuscular blockade, opioid, anesthetic, and sedative use will be performed independently using stratified versions of the previously described model. The potential for risk modification of neostigmine will be performed in the subset of patients receiving neuromuscular blockade.

Study Cohorts

Based on previous work with data from surgical patients in our institution, approximately 68,000 patients will meet inclusion criteria. Based on data estimating OSA prevalence in the general surgical population, we conservatively expect to find approximately 3,400 patients with high likelihood of OSA in our surgical population. Using our prediction model from Aim 1, we will determine the risk of OSA and assign patients found to be at high, moderate and low risk of OSA. Each of these three exposure groups will consist of approximately 3,400 patients, as in Aim 2.

Ethics and Dissemination

This study utilizes internal hospital-based data routinely collected for medical documentation purposes. As it is a systematic review of the data, there is little ethical risk. Patient privacy and protection of health information will be maintained. The results of this study will be shared in the form of presentations at national and international meetings. The complete study and conclusions regarding the primary objectives will be presented in manuscript form.

Limitations and Strengths

This article presents the protocol and data analysis plan for the development of a novel prediction score for OSA and application of the score to more accurately characterize the risk imparted by OSA condition on postoperative respiratory complications.

Our approach relies on the investigation of patient data on file. Thus, our findings depend on the quality of the database, which is susceptible to measurement biases. There is potential for variability in the input of billing diagnoses and codes. This database has been used in previous studies[15,16] and demonstrated to have high specificity following verification of diagnostic codes positive for study's composite outcome variable. Furthermore, we will validate the use of diagnostic and procedural codes in the development of our prediction model by medical record review. Nevertheless, it is possible that information is left out of some patients' charts and consequently, our database of our composite outcomes and independent variables. A second limitation involves our inability to capture those patients admitted to an outside hospital with postoperative respiratory complications after discharge from our institution. A third limitation rises from the multifactorial and dynamic nature of OSA: patients diagnosed with OSA, even by PSG, may not necessarily have evidence of OSA on the day of surgery. An example would be a patient who loses significant weight just prior to surgery. Diagnosis of OSA by PSG prior to weight loss may be no longer valid following weight loss.[73] Thus we are limited in our development of a prediction model since we initially rely on PSG procedure codes and ICD-9 diagnoses as our standard. We hope to minimize this limitation by developing a prediction model that relies on variables that are highly likely to predict OSA even in the absence of polysomnographic evidence or clinical diagnosis.

In spite of these limitations, our study derives its strengths from a number of key elements. Our database is large and includes a variety of surgical procedure types and methods of anesthesia, thus increasing the generalizability of the study results and applicability of our prediction score models. In addition, we have a multidisciplinary team, which includes population scientists, data analysts, and clinicians. Such a team provides the experience and skill level needed for efficient, accurate, and precise design and analysis of the current study. Our team has also previously developed prediction scores for postoperative respiratory complications.[15]

Conclusions

The present study examines patients who we presume to have a high risk of perioperative respiratory failure: patients with obstructive sleep apnea. The prediction score we develop for to assess OSA risk will be a useful and practical tool for further OSA research and care. We believe the results of this study will provide new insight on whether or not high risk for OSA increases a patient's risk of developing postoperative respiratory complications, independent of other perioperative risk factors. Moreover, the results of this study might be important to evaluate the effects of interventions, such as reversing neuromuscular blockade, on respiratory outcome of OSA in the perioperative setting.

By developing a prediction score for OSA risk, we hope to identify those patients who would benefit from specific preoperative interventions to minimize postoperative morbidity and mortality.

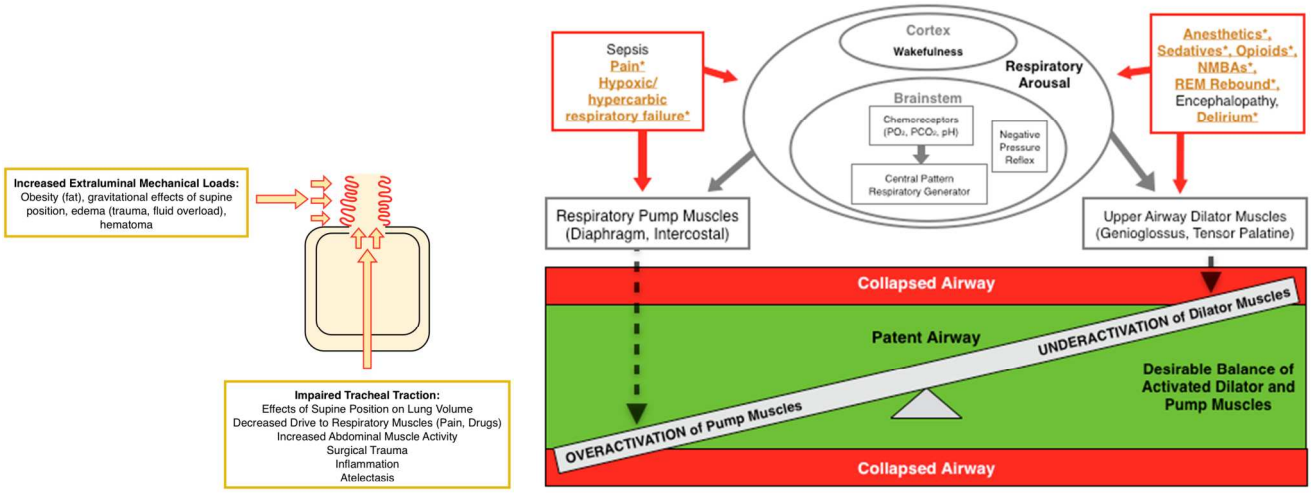

Figure 1. Pathophysiology of Perioperative Obstructive Sleep Apnea

A. Pathological Anatomy. This schematic of the respiratory system demonstrates the anatomical forces (red arrows) increasing collapsibility of the upper airway (red curly lines). Caudal tracheal traction stabilizes the upper airway such that it is less vulnerable to collapse. CPAP treatment can evoke caudal tracheal traction and increase end-expiratory lung volume.

Collapsing physical forces are those that increase the mechanical load on the upper airway (hematoma, edema, fat) and those that reduce caudal tracheal traction (atelectasis, supine, flat position).

B. Pathological Physiology. The vulnerable perioperative upper airway physiology is illustrated as a scale, demonstrating the fragile balance between activation of respiratory pump muscles and upper airway dilator muscles (green zone). When activated, pump muscles generate negative inspiratory pressure and tip the balance to upper airway collapse (red zone). In normal physiology, upper airway dilator muscles activate to counterbalance the negative inspiratory pressure and dilate the upper airway. Underactivation of airway dilator muscles, such as the tongue muscle, will result in collapse (red zone). A variety of perioperative events affect respiratory arousal, which can impair airway patency by overactivating pump or underactivating dilator muscles, respectively.

Patients with OSA are at higher vulnerability towards collapse, and the specific pathophysiological mechanism of the increased perioperative vulnerability to collapse in OSA are emphasized in yellow color and denoted with an asterisk*.

CPAP – continuous positive airway pressure; OSA – obstructive sleep apnea

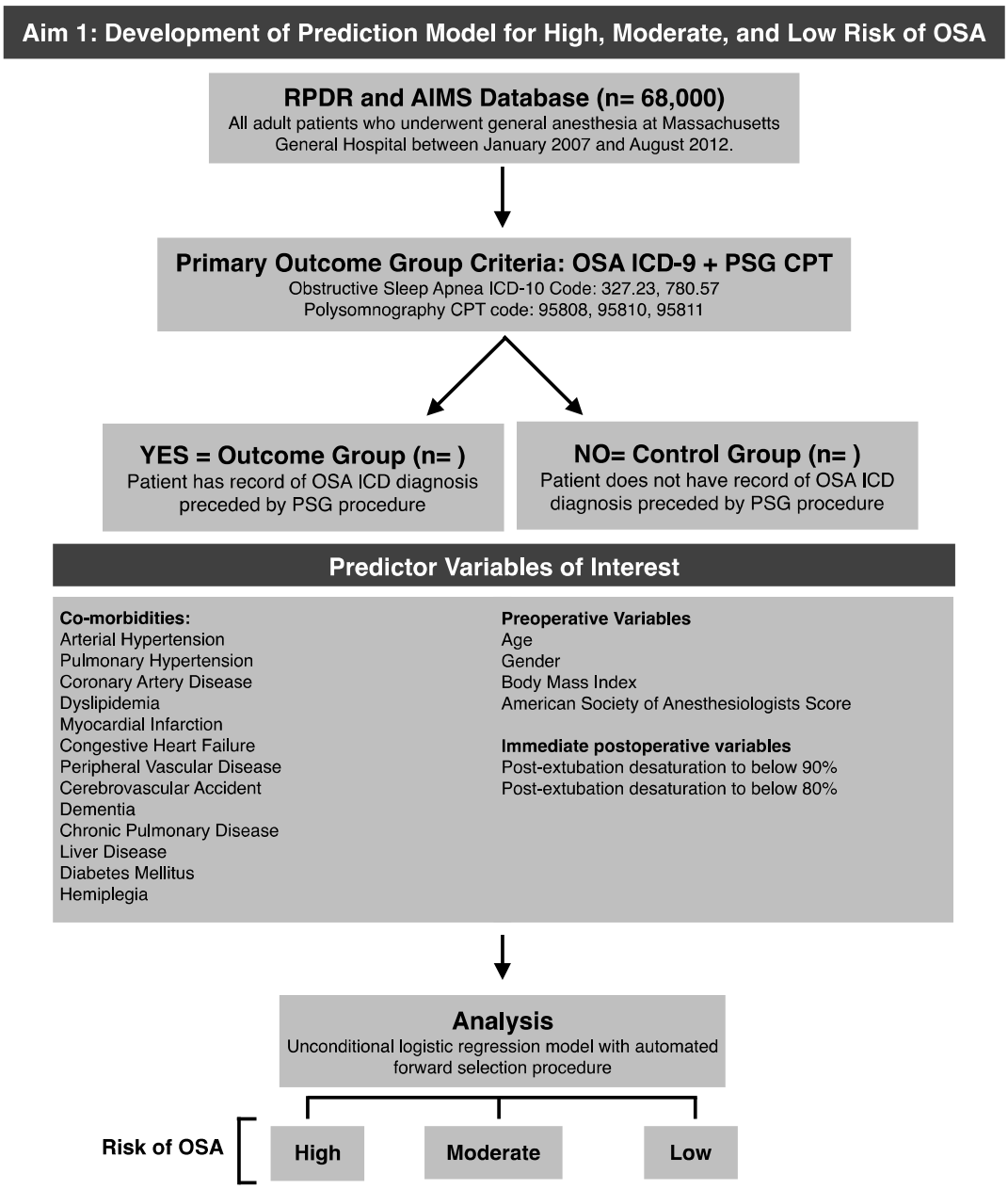

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Table 1: Diagnostic (ICD-9) and Procedural (CPT) codes used to generate predictor and outcome variables.

Variable	Diagnostic or Procedure Name	Code Type	Code
Reference Standard Outcome for Prediction Model of Aim 1			
Obstructive Sleep Apnea	Obstructive sleep apnea (adult or pediatric)	ICD-9	327.23
	Unspecified sleep apnea	ICD-9	780.57
Polysomnography	Any age, sleep staging with 1-3 additional parameters of sleep, attended by a technologist	CPT	95808
	Age 6 years or older, sleep staging with 4 or more additional parameters of sleep, attended by a technologist	CPT	95810
	Age 6 years or older, sleep staging with 4 or more additional parameters of sleep, with continuous positive airway pressure therapy or bi-level ventilation, attended by a technologist	CPT	95811
Medical Comorbidities			
Arterial Hypertension	Malignant Essential Hypertension	ICD-9	401.0
	Benign essential hypertension	ICD-9	401.1
	Unspecified essential hypertension	ICD-9	401.9
	Other malignant secondary hypertension	ICD-9	405.09
	Other benign secondary hypertension	ICD-9	405.19
	Other unspecified secondary hypertension	ICD-9	405.99
Pulmonary Hypertension	Pulmonary Hypertension		416.0
Coronary Artery Disease	Coronary atherosclerosis		414.0
Dyslipidemia	Other and unspecified hyperlipidemia		272.4
The following medical comorbidities are derived from ICD9 Codes, as defined by the Deyo Charlson Comorbidity Index[64]: Myocardial Infarction, Congestive Heart Failure, Peripheral Vascular Disease, Cerebrovascular Accident, Dementia, Chronic Pulmonary Disease, Mild Liver Disease, Moderate to Severe Liver Disease, Diabetes with Chronic Complications, Diabetes without Chronic Complications, Hemiplegia or Paraplegia, Peptic Ulcer Disease, Renal Disease, Any Malignancy including Leukemia and Lymphoma but excluding malignant neoplasm of skin, Metastatic Solid Tumor, AIDS/HIV, Rheumatic Disease			
Primary Outcome for Aim 2 and Aim 3			
Pneumonia	Pneumococcal pneumonia [Streptococcus pneumonia]	ICD-9	481

	Pneumonia due to Klebsiella pneumoniae	ICD-9	482.0
	Pneumonia due to Pseudomonas	ICD-9	482.1
	Pneumonia due to Streptococcus, unspecified	ICD-9	482.30
	Pneumonia due to Staphylococcus, unspecified	ICD-9	482.40
	Pneumonia due to Staphylococcus aureus	ICD-9	482.41
	Methicillin resistant pneumonia due to staphylococcus aureus	ICD-9	482.42
	Pneumonia due to Escherichia coli [E. coli]	ICD-9	482.82
	Pneumonia due to other gram-negative bacteria	ICD-9	482.83
	Pneumonia due to other specified bacteria	ICD-9	482.89
	Bacterial pneumonia, unspecified	ICD-9	482.9
	Pneumonia, organism unspecified	ICD-9	486
	Pneumonia due to other specified organism	ICD-9	483.8
	Pneumonia in aspergillosis	ICD-9	484.6
	Bronchopneumonia, organism unspecified	ICD-9	485
	Pneumonitis due to inhalation of food or vomitus	ICD-9	507.0
Pulmonary Edema	Pulmonary congestion and hypostasis	ICD-9	514
	Acute edema of lung, unspecified	ICD-9	518.4
	Congestive heart failure	ICD-9	428.0
	Fluid overload	ICD-9	276.6
	Other fluid overload	ICD-9	276.69
Reintubation	Intubation, endotracheal, emergency procedure	CPT	31500
	Ventilation assist and management, initiation of pressure or volume preset ventilators for assisted or controlled breathing; hospital inpatient/observation, initial day	CPT	94002
Respiratory Failure	Pulmonary insufficiency following trauma and surgery	ICD-9	518.5
	Acute respiratory failure following trauma and surgery	ICD-9	518.51
	Other pulmonary insufficiency, not elsewhere classified, following trauma and surgery	ICD-9	518.52
	Respiratory failure	ICD-9	518.81
	Other pulmonary insufficiency, not elsewhere classified	ICD-9	518.82
	Acute and chronic respiratory failure	ICD-9	518.84

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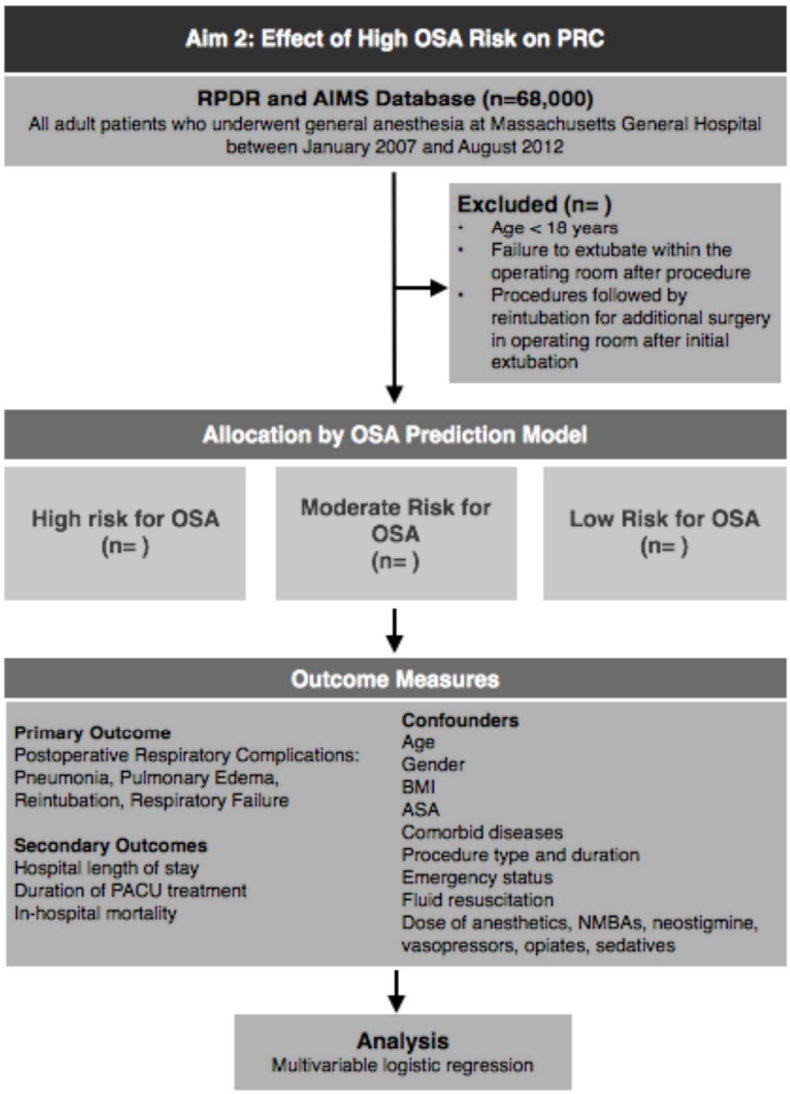

Figure 3: Aim 2: Effect of High OSA Risk on Postoperative Respiratory Complications

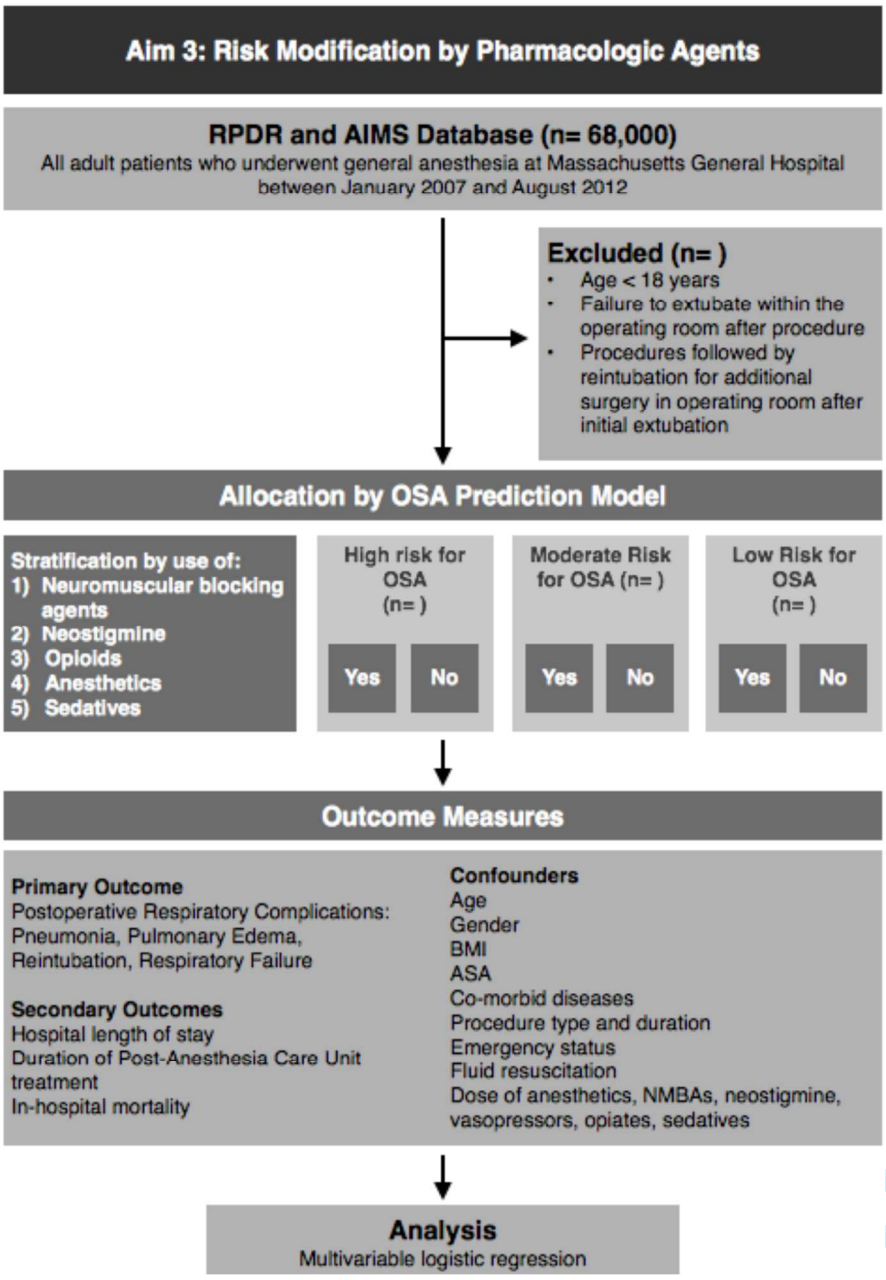

Figure 4: Aim 3: Risk Modification by Pharmacologic Agents

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Author's Contributions: ME and TK contributed equally as senior authors for the study and developed the original study concept and design. CHS wrote the first draft of the manuscript and contributed to the design of the study. SD advised on the study design. CHS, SZ, TK, and ME refined the protocol. MN contributed to the acquisition and analysis of data for the work. All authors revised the protocol critically for important intellectual content and approved the final manuscript.

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Effects of Obstructive Sleep Apnea Risk on Postoperative Respiratory Complications: Protocol for a Retrospective Cohort Study

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Effects of Obstructive Sleep Apnea Risk on Postoperative Respiratory Complications: Protocol for a Retrospective Cohort Study

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ABSTRACT

Introduction: Obstructive sleep apnea (OSA), the most common type of sleep-disordered breathing, is associated with significant immediate and long-term morbidity, including fragmented sleep and impaired daytime functioning, as well as more severe consequences, such as hypertension, impaired cognitive function, and reduced quality of life. Perioperatively, OSA occurs frequently as a consequence of preexisting vulnerability, surgery, and drug effects. The impact of OSA on postoperative respiratory complications (PRC) needs to be better characterized. As OSA is associated with significant comorbidities, such as obesity, pulmonary hypertension, myocardial infarction, and stroke, it is unclear whether OSA or its comorbidities are the mechanism of PRCs. This project aims to 1) develop a novel prediction score identifying surgical patients at high risk of OSA, 2) evaluate the association of OSA risk on PRCs, and 3) evaluate if pharmacologic agents used during surgery modify this association.

Methods: Retrospective cohort study using hospital-based electronic patient data and perioperative data on medications administered and vital signs. We will utilize data from Partners Healthcare clinical databases, Boston, Massachusetts. First, a prediction model for OSA will be developed using OSA diagnostic codes and polysomnography procedural codes as the reference standard, and will be validated by medical record review. Results of the prediction model will be used to classify patients in the database as high, medium, or low risk of OSA and we will investigate the effect of OSA on risk of PRCs. Finally, we will test whether the effect of OSA on PRCs is modified by the use of intraoperative pharmacologic agents known to increase upper airway instability, including neuromuscular blockade, neostigmine, opioids, anesthetics, and sedatives.

Ethics and dissemination: The Partners Human Research Committee approved this study (Protocol number: 2014P000218). Study results will be made available in the form of manuscripts for publication and presentations at national and international meetings.

Article Summary

Article Focus

- This article describes the protocol for the development of a novel clinical prediction score to determine those adult surgical patients at high risk for obstructive sleep apnea in order to better evaluate in the perioperative setting the patient's risk of developing postoperative respiratory complications.

Key Messages

- Current screening and prediction scores for obstructive sleep apnea rely on patient-reported symptoms and do not consider obstructive sleep apnea risk in the setting of surgery and general anesthesia, as it relates to subsequent risk of postoperative outcomes

Strengths and Limitations

- This work utilizes a large clinical database consisting of pre-, intra-, and postoperative patient data.
- Our prediction model draws on well-established clinical characteristics associated with obstructive sleep apnea as well as new measures aimed at improving dynamic risk assessment in a perioperative setting.
- The results of this study may enable perioperative clinicians to identify adult surgical patients at highest risk for obstructive sleep apnea, optimize preoperative interventions, and appropriately triage care postoperatively based on intraoperative events.
- Potential limitations relate to the need for validation studies in datasets from other institutions to determine generalizability of prediction score

INTRODUCTION

Background

Obstructive sleep apnea (OSA) is a common disorder characterized by recurrent collapse of the upper airway. This chronic condition may be diagnosed by the presence of symptoms and, depending on the specific criteria used for making the diagnosis, more than 5 episodes of apnea, hypopnea, or respiratory effort-related arousal per hour of sleep (apnea hypopnea index, AHI ≥ 5/h).[1,2] Daytime symptoms refer to excessive daytime sleepiness, morning headaches, decreased concentration, memory loss, decreased libido and irritability. Other OSA-related symptoms include witnessed apnea, snoring, non-refreshing sleep, and gasping or choking at night.[3]

Recent epidemiologic data report that an estimated 70 million people in the United States alone are affected by OSA, making it the most common type of sleep-disordered breathing (SDB).[4,5] In the general adult population, approximately 13% of men and 6 % of women have moderate-to-severe SDB, defined as AHI≥15/hr.[5] It is also estimated that 14% of men and 5% of women have AHI≥5/hr plus daytime symptoms.[5] The prevalence of SDB without daytime symptoms is even higher and reaches values of up to 9% in women and 24% in men.[2,6] It is possible that such epidemiological data underestimate the frequency of OSA among today's general population since obesity, a major driver of OSA,[7] has greatly increased in the last decade.[5,8] Furthermore, studies have shown that OSA is commonly undiagnosed, suggesting an even higher prevalence of adults who suffer from this sleep disorder.[9-11]

Surgical patients with OSA are at a higher risk of developing postoperative respiratory complications, such as reintubation and requirement of non-invasive ventilation.[12-14] Upper airway collapse in the perioperative setting results in hypoventilation and is an important component of the mechanism of postoperative respiratory complications. In studies previously reported by our lab, independent of OSA, reintubation and unplanned ICU admission result in a 70 to 90-fold increase in in-hospital mortality.[15,16] However, despite an increased rate of postoperative respiratory complications, SDB, as identified by diagnostic codes, was paradoxically associated with lower mortality, hospital length of stay and costs among certain surgical specialties.[12] The mechanisms of the opposed effects of OSA on respiratory complication rate and mortality are unclear. We speculate that reintubation in patients with OSA is typically the consequence of upper airway dysfunction rather than pulmonary pathology, and the former can be treated more efficiently.

Mechanism of Perioperative Obstructive Sleep Apnea

Quantification of perioperative vulnerability to upper airway collapse requires consideration of preoperative and perioperative risk factors that affect the balance between collapsing forces and dilating forces of the upper airway. Perioperative anatomical and physiological factors need to be taken into account.

1. Anatomical Abnormalities Increase Collapsing Forces

Anatomical risk factors in patients with OSA include a reduction in the size of the retropalatal and retroglossal airway.[17,18] Perioperatively, anatomical vulnerability is augmented, thereby increasing upper airway instability.

Figure 1a summarizes perioperative risk factors that can compromise upper airway anatomy. Mechanical loads to the collapsible segments of the retropalatal and retropharyngeal upper airway lead to physical compression of the airway. Clinically, such an extraluminal mechanical load can occur as a consequence of a postoperative hematoma following cervical, otolaryngology, or thyroid surgery.[19,20] In addition, peripharyngeal edema may occur in perioperative medicine as a consequence of fluid overload. Bradley and colleagues studied the effects of antishock trouser inflation on upper airway size and reported narrowed pharynx and enlarged neck circumference measured by acoustic pharyngometry.[21] Congestive heart failure increases the AHI, which presumably is the consequence of nocturnal rostral fluid shift.[22] Airway patency may also be affected by peripharyngeal inflammation and edema in the setting of intubation and extubation.

2. Impaired Caudal Traction on the Trachea Increases Collapsibility

Isono and colleagues have conducted extensive investigations of position-dependent effects on airway obstruction. In anesthetized and paralyzed patients with OSA, the authors found that the lateral and sitting positions improve the collapsibility of the passive pharyngeal airway.[23,24]

Among patients with OSA, the supine position not only promotes a more obstructive orientation of the pharyngeal soft tissues, but also reduces caudal traction, thereby increasing vulnerability to upper airway collapse. During inspiration, caudal traction on the airway due to lung expansion dilates and stabilizes the upper airway, a force that opposes the negative intra-luminal pressure and prevents collapse.[25] The supine position during surgery, immediate postoperative period, and transition to sleep impairs tracheal traction on the airway and promotes collapse,[23,24] as illustrated in Figure 1a. Tracheal traction is also impaired by any event that reduces lung volume, often secondary to diaphragmatic

dysfunction. Impaired function of the respiratory pump muscles (diaphragm and intercostal muscles) results in ineffective expansion of the lung and occurs in the setting of surgery and trauma.[26] Pain-induced splinting and pharmacologic agents, such as opioids, decrease drive to the respiratory pump muscles, thereby preventing full lung inflation and reducing tracheal traction.[27] Studies in the intensive care unit have demonstrated how systemic inflammation and mechanical ventilation dramatically disrupts diaphragmatic function.[28,29]

3. Neuromuscular Mechanisms of Perioperative Airway Collapse

A balance between the upper airway dilator muscles (genioglossus, tensor palatine) and the respiratory pump muscles (diaphragm, intercostal muscles) exist to maintain upper airway patency during wakefulness and sleep, as illustrated in Figure 1b. Respiratory pump muscles generate inspiratory airflow associated with negative intra-luminal pressure, which is detected by mechanoreceptors and transmitted to the upper airway dilator muscles via the hypoglossal nerve. As a result, the genioglossus contracts and stabilizes the upper airway. Respiration is also stimulated by hypoxia and hypercarbia, which are detected by chemoreceptors. In addition to wakefulness, information transmitted by mechanoreceptors and chemoreceptors stimulate respiratory arousal, which has been previously defined as arousal from sleep and other drug-induced or endogenous impairments of consciousness.[30] Cortical effects on respiratory arousal are important, and any decrease in arousal can impair the voluntary effort to breathe spontaneously through a patent upper airway.[31]

A variety of pharmacologic and non-pharmacologic perioperative factors affect respiratory arousal. While the specific effects of perioperative pharmacologic agents depend on agent, dose, and specific muscle group, studies have shown that such agents largely dampen stimulation to the nerves controlling respiratory muscles.

Anesthetics and Sedatives

Studies in humans and animals have demonstrated the effects of anesthetics on the upper airway by a variety of mechanisms. Anesthetics decrease muscle and neural activity important for respiration as well as wakefulness through varying mechanisms.[32] Propofol, an agent commonly used for induction and maintenance of anesthesia, dose-dependently increases collapsibility of the upper airway through depressed respiratory drive to and direct inhibition of upper airway dilator muscle activity in humans.[33] In humans anesthetized with isoflurane, reflexive activity, or the responsiveness of upper airway dilator muscles to negative pressure, was found to be greatly reduced.[34] The diminishing effects of anesthetics on neuronal activity

also differ between hypoglossal and phrenic nerve.[35] With a focus on neural mechanisms for altered upper airway activity, Nishino and colleagues investigated the differential effects of anesthetics and found greater dampening of hypoglossal nerve input relative to the phrenic nerve.[36] This effect may result in greater anesthesia-induced impairment of upper airway dilators compared to respiratory pump muscles, increasing the upper airway's propensity for collapse. While this effect was observed across three classes of drugs (volatile, barbiturate, and benzodiazepine), ketamine reduced neural input to the upper airway dilator muscles and respiratory pump muscles equally. Furthermore, ketamine's effect on the upper airway dilator muscles was less relative to GABAergic anesthetics.[36] Such findings are corroborated by mechanistic studies in rats that demonstrate a dissociation between loss of consciousness and upper airway dilator muscle function under ketamine anesthesia.[37] Taken together, studies suggest that patients with OSA, who have preoperative upper airway instability, may be at a heightened risk of upper airway collapse when under the influence of anesthetics. The unique effects associated with ketamine, however, suggest that this drug may be a safer choice for patients with OSA.

Opioids

The use of opioids for postoperative pain management has been increasingly identified as a contributor to postoperative exacerbation of SDB.[38,39] Studies in human and animal subjects have investigated the mechanism by which patients with preoperative OSA may be vulnerable to the effects of perioperative opioids. Patients with OSA have increased sensitivity to pain[40-42] as well as increased sensitivity to the respiratory depressant effects of opioids.[43] Such findings are particularly relevant to the postoperative OSA patient given the effects of opioids on upper airway patency. Animal studies have shown that opioids increase upper airway resistance, resulting in obstruction.[44] Opioids directly inhibit hypoglossal motoneurons, which leads to suppressed genioglossus activity.[45] Thus, the use of opioids during and immediately after surgery is an important perioperative factor to consider in patients with OSA when assessing the risk of upper airway instability and the postoperative respiratory complications that may arise as a consequence.

Neuromuscular Blocking Agents and Reversal Agents

Neuromuscular blockade agents act longer than the duration of surgery and postoperative residual curarization affects postoperative respiratory outcome.[46] Upper airway dilators are more vulnerable to minimal effects of neuromuscular blocking agents compared to the respiratory pump muscles.[47,48] This differential activation of pump vs. dilator muscles may set off an unwanted chain of events such that the relatively more active respiratory pump muscles generate excessive negative

intrathoracic pressure, resulting in negative pressure pulmonary edema.[49] Even at levels producing minimal blockade, as measured by train-of-four ratio 0.5-1, neuromuscular blocking agents increased upper airway collapsibility and impaired compensatory genioglossus response to negative pharyngeal pressure challenges.[50] Studies in surgical patients have demonstrated the dose-dependent association between intermediate-acting neuromuscular blocking agents and postoperative respiratory complications, an effect shown to be unyielding despite neostigmine-based reversal at end of surgery.[16,51,52] Based on the pathophysiology of the disease, patients with OSA should have an increased vulnerability to the effects of neuromuscular blocking agents and reversal agents. [47,50,53] However, population-based studies aiming to quantify the effects of residual neuromuscular blockade in patients with and without risk of OSA are currently missing.

The impact of such pharmacologic agents commonly used in anesthesia care on the risk of respiratory outcomes in patients with OSA has yet to be determined. Our study will address the unmet need of evaluating the perioperative effect of neuromuscular blocking agents, reversal agents, opioids, sedatives, and anesthetics in patients at risk of OSA.

Non-Pharmacologic Events

Non-pharmacologic perioperative events, such as REM rebound, encephalopathy, delirium, can disrupt respiratory arousal and result in upper airway collapse.[30] In the immediate postoperative period, patients commonly experience poor quality, disrupted, and reduced sleep, resulting in a deficit of rapid eye movement sleep (REM).[54] Sleep studies in surgical patients have identified a REM rebound effect, in which REM sleep returns acutely and suddenly.[54,55] Increased amounts of REM during sleep is associated with impaired respiratory arousal and more frequent episodes of nocturnal hypoxemia.[56] OSA patients also have diminished or lost airway reflex during non-REM sleep, so patients with OSA may be at an even greater propensity for upper airway collapse and hypoxemia with phenomenon of REM rebound. While OSA patients have been shown to compensate for diminished airway sizes with higher basal genioglossus muscle activity,[57] this neuromuscular compensation has been found to be present only during wakefulness and thus futile in the setting of REM-predominant sleep. Recent prospective studies have demonstrated a significant reduction in REM sleep in OSA and non-OSA patients during the early postoperative period.[58] Postoperatively, time spent in REM sleep did not consistently predict postoperative OSA severity,[38] which may be the consequence of REM suppression secondary to postoperative pain, as well as administration of opioids and sedatives. Of note, studies have also identified other important contributors to SDB. Events that impair a patient's level of consciousness also disrupt respiratory arousal and result in upper airway instability. Such events include

delirium, stroke, septic encephalopathy, systemic inflammation, and metabolic disturbances, like hypoglycemia and hypothyroidism.[30]

Study Rationale

In order to evaluate the perioperative risk of patients presenting with OSA, it is important to take into account the "true" prevalence of the disease in the perioperative cohort. An important limitation of the existing literature relates to the focus on patients who carry the clinical diagnosis of OSA. As a consequence of analyzing only those patients with an International Classification of Diseases-9 (ICD-9) diagnostic code for SDB, a large subpopulation with undiagnosed OSA remain undetected.

The gold standard for the diagnosis of OSA is polysomnography. According to current clinical guidelines for OSA evaluation, patients are prompted to undergo this sleep study if determined to be high risk by their physician.[3] As a routine evaluation for OSA, polysomnography is impractical because of its limited availability, discomfort to the patient, and high cost.[59,60] The use of screening tools for OSA helps identify patients at risk of OSA. Widely used scores include the Perioperative Sleep Apnea Prediction Score,[61] the STOP-Bang[62] and Berlin Questionnaires,[63] and the Epworth Sleepiness Scale.[64] Such scores rely on a clinical exam to determine neck circumference and/or patient questionnaire of daytime OSA symptoms. Not all patients are able to have their necks measured and many patients are asymptomatic or unaware of their symptoms, limiting the ability of the existing scores to assess true prevalence of OSA. Anesthesiologists have also used scores, such as the Mallampati Score and the American Society of Anesthesiologists (ASA) Checklist, to assess difficulty of intubation as related to a narrow upper airway,[65] but there is inconsistency in reported sensitivity and specificity of the Mallampati score as a predictor of OSA.[64] Furthermore, the currently available scores require data not routinely available from clinical databases, such as history of snoring and witnessed apnea. This proposal is based on the consideration that other data available in the patient's electronic medical record may be sufficient to predict OSA and its associated increased risk of postoperative respiratory complications. Application of our prediction score on large perioperative datasets will permit research endeavors, such as the evaluation of the effect of OSA on patient outcomes and the justification of health care resource utilization.

Furthermore, understanding how pharmacologic agents commonly used in perioperative care impact postoperative outcomes among patients with high risk of OSA will improve our ability to provide better care for this vulnerable surgical population. Traditionally, anesthesia providers have determined dosing of various drugs based on standard parameters of age, gender, height and weight. However, such practices may not sufficiently guide providers in optimal drug administration, especially in a subpopulation more vulnerable to the effects of those drugs as already demonstrated in the literature. More specifically, we would like to better understand the interaction between the disease OSA and opioids, neuromuscular blocking agents, neostigmine, sedatives, and anesthetics to optimally predict postoperative respiratory outcomes. Using our prediction score for OSA in a large perioperative database, we will evaluate how the use of pharmacologic agents modifies the risk of postoperative respiratory complications in patients with OSA.

Objectives

The primary objectives are to:

1. Develop a novel prediction score of OSA to identify patients at high risk of OSA based on markers of the disease easily available from clinical databases.

   1.1. Validate OSA prediction based on medical record review.

2. Evaluate the effect of being at high risk of OSA, as defined by the prediction score, on the primary outcome of postoperative respiratory complications among patients undergoing surgery at Massachusetts General Hospital.

3. Evaluate if use of neuromuscular blockade, neostigmine-based reversal of neuromuscular blockade, opioids, sedatives, and anesthetics modify the risk of OSA on postoperative respiratory complications.

The secondary objective is to:

1. Investigate whether the association between OSA risk and postoperative respiratory complications is modified by age, gender, BMI and major comorbidities.

Hypotheses for the Primary Outcome

Based on previous data,[12] we hypothesize that patients with a high risk of OSA, as identified by our new prediction instrument, are more vulnerable to acute postoperative upper airway failure that leads to re-intubation. We further hypothesize that such patients will experience less favorable outcomes, depicted as intensive care unit admission rate, hospital length of stay, and hospital costs.

As a departure from the current literature on the perioperative effects of OSA, we believe that perioperative variables, which increase the vulnerability to airway collapse, will give us clinically meaningful information in order to predict which patient with OSA will develop postoperative respiratory complications.

METHODS AND ANALYSIS

Study Overview

The proposed study is a retrospective cohort analysis using hospital-based electronic patient data and perioperative data on medications administered and patient vital signs. We will utilize data from major clinical databases at Massachusetts General Hospital, a tertiary care facility and teaching hospital of Harvard Medical School in Boston, Massachusetts. In addition, polysomnography data will be extracted from clinical databases at several hospitals affiliated with Partners Healthcare.

As previously used for epidemiological studies by our group, data from two clinical databases will be retrieved and combined to provide de-identified pre-, intra-, and postoperative information: the Research Patient Data Registry and the Anesthesia Information Management System.[15,16,51,66] The Research Patient Data Registry contains demographic and billing data regarding patient comorbidities and postoperative outcome and survival. The Anesthesia Information Management System contains physiological data from patient monitors as well as information on medical history and documentation of important surgery and anesthesia-related events, including adverse events, perioperative procedures, and drug and fluid therapy. Patient data from these databases are linked through unique patient identifiers and the variables described in this protocol will be abstracted to form one database. The present database spans January 2007 to August 2014 and includes 140,000 surgical cases. Based on previous work, we will conservatively anticipate that 25% of the cases will not satisfy inclusion criteria due to patient's age, emergency status and missing data.[15,51] Thus we estimate 100,000 patient cases will meet our inclusion criteria.

Subject Selection

For the three primary objectives, we will include all adult surgical patients who underwent general anesthesia and receive endotracheal intubation or airway management by supraglottic airway device at our institution, for whom inpatient admission was planned, between January 2007 and August 2014. Because re-intubation is a component of our composite outcome of PRC, we will only include those patients who have had removal of all airway management devices within the operating room after the procedure. Surgical procedures followed by reintubation for an additional scheduled surgical procedure in the operating room after initial extubation or removal of airway device will be excluded from the study, as we presume that such cases did not require reintubation in the setting of adverse postoperative respiratory status. Patients who underwent surgery in the four weeks prior to the study case will be excluded. Finally, all patients with an intraoperative death will be excluded

from the study since OSA is not a biological mechanism of intraoperative death when a patient's airway is secure by an airway device. Patients will be identified using anesthesia data obtained from Research Patient Data Registry and Anesthesia Information Management System.

The study methods are outlined in three sections to address the three primary objectives.

Objective 1: Development of Prediction Model for OSA

Prediction Model Reference Standard

The reference standard for the prediction model will be defined as patients with an ICD-9 OSA diagnosis following the appearance of a polysomnography procedural (CPT, Current Procedural Terminology) code in our medical databases (Figure 2). From this specific sequence of events, we infer that these patients had their clinically suspected OSA diagnosis confirmed by polysomnography.

Validation of Reference Standard for the Diagnosis of OSA

Prior to the development of the prediction model, we will conduct a medical chart review of 100 randomly selected patients meeting our OSA criteria of an ICD-9 diagnostic code and polysomnography CPT code in order to determine whether or not such patients actually have evidence of OSA in the time between their polysomnography and surgery. These patients will not be considered for inclusion into the predictive model, but instead will be used to assess the positive predictive value of the ICD-9 and CPT code combination for identifying OSA. Confirmatory evidence of OSA would include a reported apnea hypopnea index (AHI) ≥ 5 as documented in a patient's medical chart[2] or treatment with continuous positive airway pressure (CPAP). The predictive model will be performed if the ICD-9 and CPT code combination has an acceptable positive predictive value ($\geq$0.8).

Predictor Variables

A number of variables have been found to be associated with an increased prevalence of OSA and are currently used for different screening tools for OSA in surgical patients.[62,65,67] From the Anesthesia Information Management System and Research Patient Data Registry databases, we will obtain and include the following data in our prediction score: age, BMI, gender, and the American Society of Anesthesiologists (ASA) physical status classification (Figure 2). We will incorporate

medical comorbidities using ICD9 diagnostic codes, some of which are defined by the Deyo-Charlson Comorbidity Index (Table 1).[68] All covariates included in the prediction model must be present within one year of surgery date. In addition, as a departure from current literature on developing OSA screening scores, we will consider oxygen desaturation immediately after extubation as a predictor. This strategy will most likely increase the predictive value of our score – patients with OSA are very vulnerable to desaturation after surgery and we have the unique opportunity to use this characteristic of OSA desaturation after anesthesia that has not yet been utilized in existing prediction scores. Post-extubation oxygen desaturation will be defined as an oxyhemoglobin reading less than 90% and less than 80% for at least one minute, as measured by pulse oximetry during the first 10 minutes after extubation in the operating room.

Development of Prediction Model

We will use an unconditional logistic regression model with an automated forward selection procedure to select for predictors of our a priori defined reference standard. As entry criteria we will set a P value of 0.01.

To determine the goodness of fit of the final prediction model, we will use the Hosmer-Lemeshow test, which indicates that there is no significant difference between observed and expected OSA status if P-value ≥ 0.05. A point value will be assigned to each predictor variable proportional to the estimates from the logistic regression. The predictive value of the score for OSA will be assessed using c-statistics, which is equivalent to the area under the ROC curve.[69] We will aim to achieve a minimum c-statistic of 0.8. We will calculate positive and negative likelihood ratios for each stratum of the score. We will use bootstrap techniques to determine the robustness of included variables, which are close to the P-value cut-off of 0.05. We will then use classification tables to determine the best cut-off value for the prediction score to classify patients at high risk for OSA.

Objective 2: Effect of High OSA risk on Postoperative Respiratory Complications

Exposure Variables

Our primary exposure variable of interest is OSA risk, as defined by our prediction model developed in Aim 1. We will identify patients in our population as having a high, moderate, and low risk for OSA using our prediction model and produce three cohorts of patients, which we will follow for the occurrence of outcome events.

Outcome Variables

The primary outcome of this part of the study is a composite outcome defined as the incidence of re-intubation, pulmonary edema, pneumonia and respiratory failure within the first three postoperative days. Secondary outcomes include the aforementioned individual outcomes as well as hospital length of stay, duration of post-anesthesia care unit treatment, and in-hospital mortality. Hospital length of stay will be defined as the postoperative length of hospital stay following surgery. The primary outcome has been previously used and validated by chart review.[51,66] The outcomes events for the primary analysis will be identified by ICD-9 diagnostic and CPT procedural codes obtained from the Research Patient Data Registry database (Table 1).

Outcome Model

We will perform multivariable logistic regression analyses to evaluate the effect of estimated OSA risk on our respiratory outcomes. Results will be presented as an age- and multivariable-adjusted odds ratio with 95% confidence intervals. We will consider a two-tailed P-value of less than 0.05 as statistically significant.

To control for confounding effects, we will consider a priori the following risk factors: age, gender, BMI, ASA physical status classification, comorbidities, surgical specialty, duration of the surgical procedure, admission type, and emergency status.[16] We will additionally control for dose of anesthesia (median dose of anesthetic agents corrected for age),[70] opioids (calculated as total morphine equivalent dose),[71] vasopressors, sedatives, neuromuscular blocking agents, and neostigmine use (Figure 3).

The effect of surgery type will be analyzed in greater detail by grouping similar types of surgery (e.g. cardiovascular, laparoscopic) to determine if surgery type is an effect modifier and not a confounder. If this is found to be the case, surgical specialty will no longer be included as a covariate, and the previously described model will be stratified by surgery type.

Sample Size and Power Calculations

Based on previous work with data from surgical patients in our institution, we expect approximately 100,000 patients undergoing surgery to meet our inclusion criteria during the observational period. Studies on prevalence of OSA in the general surgical population provide a range of estimates: one study found 17% of surgical patients as having severe OSA (AHI >30).[72] Other studies relying on screening scores found anywhere from 4.8%[73] to 41.6%[74] of surgical patients at high

risk of OSA. Thus, we conservatively estimate 3% (n=3,000) patients in our surgical population to have a high likelihood of OSA. Our exposure groups of high, moderate, and low OSA risk will each have a sample size of 3,000 patients.

Previous work by our lab[51] found an overall incidence of 3.7% for our primary outcome of postoperative respiratory complications. Data on differences in postoperative outcomes between OSA and non-OSA groups provide us with estimates for our predicted intergroup differences. Liao et al found an intergroup (OSA vs Non-OSA) difference of 11% for their composite outcome of total respiratory complications.[13] Mokhlesi et al investigated the incidence of emergent intubation following elective surgery among patients with and without SDB.[12] Emergent intubation occurred at a rate of 3.5-11.4% among patients with SDB vs. 0.3-7% among patients without SDB across four categories of elective surgery.[12] The intergroup difference observed was approximately 3%.[12] Based on this data, we will conservatively estimate an intergroup difference of 10% for our composite outcome, with smaller differences observed for outcomes with lower frequencies. Power is calculated based on comparing proportions of outcome rates between expected patients with OSA and the reference population without OSA. Our fixed sample size of 100,000 will provide us with a power greater than 90% to identify a 10% intergroup difference with an alpha error of 0.05.

Objective 3: Risk modification by Pharmacologic Agents

Exposure Variable and Rationale

We will obtain data on the intraoperative use of intermediate-acting neuromuscular blocking agents, neostigmine-based reversal of neuromuscular blockade, opioids, anesthetics, and sedatives as additional independent variables in the analysis to test whether or not such pharmacologic agents modify the effect of OSA on the risk for postoperative respiratory complications. We have previously studied the use of intermediate-acting neuromuscular blocking agents and found that their use was associated with an increased risk of respiratory complications.[16] In addition, we have observed that the use of the reversal agent neostigmine does not decrease but increase the risk of postoperative respiratory complications.[16,52] However, more recent work demonstrates that such effects could be mitigated by neostigmine only at low doses and with simultaneous careful monitoring of neuromuscular transmission (train-of-four).[51]

Patients with OSA should be at high risk of respiratory complications induced by pharmacologic agents because such agents can affect upper airway patency.[35,44,48,75] We thus expand our investigation to include the risk modification effect of

pharmacologic agents (neuromuscular blocking agents, neostigmine, opioids, anesthetics, and sedatives) on postoperative respiratory complications in a subpopulation of surgical patients who may be at an inherent higher vulnerability towards upper airway collapse and subsequent poor respiratory outcomes. Similar to previous work, we will extract information on administration of pharmacologic agents from the Anesthesia Information Management System database.[51]

Outcome Variables

The primary outcome is the composite variable of postoperative respiratory complications, consisting of: reintubation, pulmonary edema, pneumonia and respiratory failure. Secondary outcomes include hospital length of stay, duration of post-anesthesia care unit treatment, in-hospital mortality, as well as the aforementioned outcomes. These outcomes are defined by ICD-9 and CPT codes located in the Research Patient Data Registry database and have been previously validated by chart review by our lab (Table 1).[51]

Stratified Analysis to Assess for Effect Modification by Pharmacologic Agents

To evaluate potential effect modification by neuromuscular blockade, neostigmine, opioid, anesthetic, and sedative use, we will run stratified analyses of the association between OSA and the outcome events based on intraoperative use of pharmacologic agents. We will use the likelihood ratio test to contrast a main model to a model also including appropriate interaction terms. To control for confounding effects, we will consider a priori the following risk factors: age, gender, BMI, ASA physical status classification, comorbidities, surgical specialty, duration of the surgical procedure, and emergency status.[16] The stratified analyses for neuromuscular blockade, opioid, anesthetic, and sedative use will be performed independently using stratified versions of the previously described model. The potential for risk modification of neostigmine will be performed in the subset of patients receiving neuromuscular blockade.

Study Cohorts

Based on previous work with data from surgical patients in our institution, approximately 100,000 patients will meet inclusion criteria. Based on data estimating OSA prevalence in the general surgical population, we conservatively expect to find approximately 3,000 patients with high likelihood of OSA in our surgical population. Using our prediction model from Aim 1, we will determine the risk of OSA and assign patients found to be at high, moderate and low risk of OSA. Each of these three exposure groups will consist of approximately 3,000 patients, as in Aim 2.

Ethics and Dissemination

This study utilizes internal hospital-based data routinely collected for medical documentation purposes. As it is a systematic review of the data, there is little ethical risk. Patient privacy and protection of health information will be maintained. The results of this study will be shared in the form of presentations at national and international meetings. The complete study and conclusions regarding the primary objectives will be presented in manuscript form.

Limitations and Strengths

This article presents the protocol and data analysis plan for the development of a novel prediction score for OSA and application of the score to more accurately characterize the risk imparted by OSA condition on postoperative respiratory complications.

Our approach relies on the investigation of patient data on file. Thus, our findings depend on the quality of the database, which is susceptible to measurement biases. There is potential for variability in the input of billing diagnoses and codes. This database has been used in previous studies[15,16] and demonstrated to have high specificity following verification of diagnostic codes positive for study's composite outcome variable. Furthermore, we will validate the use of diagnostic and procedural codes in the development of our prediction model by medical record review. Nevertheless, it is possible that information is left out of some patients' charts and consequently, our database of our composite outcomes and independent variables. A second limitation involves our inability to capture those patients admitted to an outside hospital with postoperative respiratory complications after discharge from our institution. A third limitation rises from the multifactorial and dynamic nature of OSA: patients diagnosed with OSA, even by polysomnography, may not necessarily have evidence of OSA on the day of surgery. An example would be a patient who loses significant weight just prior to surgery. Diagnosis of OSA by polysomnography prior to weight loss may be no longer valid following weight loss.[76] Thus we are limited in our development of a prediction model since we initially rely on polysomnography procedure codes and ICD-9 diagnoses as our standard. We hope to minimize this limitation by developing a prediction model that relies on variables that are highly likely to predict OSA even in the absence of polysomnographic evidence or clinical diagnosis.

In spite of these limitations, our study derives its strengths from a number of key elements. Our database is large and includes a variety of surgical procedure types and methods of anesthesia, thus increasing the generalizability of the study results and applicability of our prediction score models. In addition, we have a multidisciplinary team, which includes population scientists, data analysts, and clinicians. Such a team provides the experience and skill level needed for efficient, accurate, and precise design and analysis of the current study. Our team has also previously developed prediction scores for postoperative respiratory complications.[15]

Conclusions

The present study examines patients who we presume to have a high risk of perioperative respiratory failure: patients with obstructive sleep apnea. The prediction score we develop for to assess OSA risk will be a useful and practical tool for further OSA research and care. We believe the results of this study will provide new insight on whether or not high risk for OSA increases a patient's risk of developing postoperative respiratory complications, independent of other perioperative risk factors. Moreover, the results of this study might be important to evaluate the effects of interventions, such as reversing neuromuscular blockade, on respiratory outcome of OSA in the perioperative setting.

By developing a prediction score for OSA risk, we hope to identify those patients who would benefit from specific preoperative interventions to minimize postoperative morbidity and mortality.

FIGURE LEGENDS:

Figure 1. Pathophysiology of Perioperative Obstructive Sleep Apnea

A. Pathological Anatomy. This schematic of the respiratory system demonstrates the anatomical forces (red arrows) increasing collapsibility of the upper airway (red curly lines). Caudal tracheal traction stabilizes the upper airway such that it is less vulnerable to collapse. CPAP treatment can evoke caudal tracheal traction and increase end-expiratory lung volume. Collapsing physical forces are those that increase the mechanical load on the upper airway (hematoma, edema, fat) and those that reduce caudal tracheal traction (atelectasis, supine, flat position).

B. Pathological Physiology. The vulnerable perioperative upper airway physiology is illustrated as a scale, demonstrating the fragile balance between activation of respiratory pump muscles and upper airway dilator muscles (green zone). When activated, pump muscles generate negative inspiratory pressure and tip the balance to upper airway collapse (red zone). In normal physiology, upper airway dilator muscles activate to counterbalance the negative inspiratory pressure and dilate the upper airway. Underactivation of airway dilator muscles, such as the tongue muscle, will result in collapse (red zone). A variety of perioperative events affect respiratory arousal, which can impair airway patency by overactivating pump or underactivating dilator muscles, respectively.

Patients with OSA are at higher vulnerability towards collapse, and the specific pathophysiological mechanism of the increased perioperative vulnerability to collapse in OSA are emphasized in yellow color and denoted with an asterisk*.

CPAP – continuous positive airway pressure; OSA – obstructive sleep apnea

Figure 2: Aim 1: Development of Prediction Model for High, Moderate, and Low Risk of OSA

Figure 3: Aim 2: Effect of High OSA Risk on Postoperative Respiratory Complications

Figure 4: Aim 3: Risk Modification by Pharmacologic Agents

Table 1: Diagnostic (ICD-9) and Procedural (CPT) codes used to generate predictor and outcome variables.			
Variable	**Diagnostic or Procedure Name**	**Code Type**	**Code**
Reference Standard Outcome for Prediction Model of Aim 1			
Obstructive Sleep Apnea	Obstructive sleep apnea (adult or pediatric)	ICD-9	327.23
	Unspecified sleep apnea	ICD-9	780.57
Polysomnography	Sleep study, simultaneous recording of ventilation, respiratory effort, ECG or heart rate, oxygen saturation, attended by a technologist	CPT	95807
	Any age, sleep staging with 1-3 additional parameters of sleep, attended by a technologist	CPT	95808
	Age 6 years or older, sleep staging with 4 or more additional parameters of sleep, attended by a technologist	CPT	95810
	Age 6 years or older, sleep staging with 4 or more additional parameters of sleep, with continuous positive airway pressure therapy or bi-level ventilation, attended by a technologist	CPT	95811
Medical Comorbidities			
Arterial Hypertension	Malignant Essential Hypertension	ICD-9	401.0
	Benign essential hypertension	ICD-9	401.1
	Unspecified essential hypertension	ICD-9	401.9
	Other malignant secondary hypertension	ICD-9	405.09
	Other benign secondary hypertension	ICD-9	405.19
	Other unspecified secondary hypertension	ICD-9	405.99
Pulmonary Hypertension	Pulmonary Hypertension	ICD-9	416.0
Coronary Artery Disease	Coronary atherosclerosis	ICD-9	414.0
Dyslipidemia	Other and unspecified hyperlipidemia	ICD-9	272.4
The following medical comorbidities are derived from ICD9 Codes, as defined by the Deyo Charlson Comorbidity Index[68]: Myocardial Infarction, Congestive Heart Failure, Peripheral Vascular Disease, Cerebrovascular Accident, Dementia, Chronic Pulmonary Disease, Mild Liver Disease, Moderate to Severe Liver Disease, Diabetes with Chronic Complications, Diabetes without Chronic Complications, Hemiplegia or Paraplegia, Peptic Ulcer Disease, Renal Disease, Any Malignancy including Leukemia and Lymphoma but excluding malignant neoplasm of skin, Metastatic Solid Tumor, AIDS/HIV, Rheumatic Disease			
Primary Outcome for Aim 2 and Aim 3			
Pneumonia	Pneumococcal pneumonia [Streptococcus pneumonia]	ICD-9	481

	Pneumonia due to Klebsiella pneumoniae	ICD-9	482.0
	Pneumonia due to Pseudomonas	ICD-9	482.1
	Pneumonia due to Streptococcus, unspecified	ICD-9	482.30
	Pneumonia due to Staphylococcus, unspecified	ICD-9	482.40
	Pneumonia due to Staphylococcus aureus	ICD-9	482.41
	Methicillin resistant pneumonia due to staphylococcus aureus	ICD-9	482.42
	Pneumonia due to Escherichia coli [E. coli]	ICD-9	482.82
	Pneumonia due to other gram-negative bacteria	ICD-9	482.83
	Pneumonia due to other specified bacteria	ICD-9	482.89
	Bacterial pneumonia, unspecified	ICD-9	482.9
	Pneumonia, organism unspecified	ICD-9	486
	Pneumonia due to other specified organism	ICD-9	483.8
	Pneumonia in aspergillosis	ICD-9	484.6
	Bronchopneumonia, organism unspecified	ICD-9	485
	Pneumonitis due to inhalation of food or vomitus	ICD-9	507.0
Pulmonary Edema	Pulmonary congestion and hypostasis	ICD-9	514
	Acute edema of lung, unspecified	ICD-9	518.4
	Congestive heart failure	ICD-9	428.0
	Fluid overload	ICD-9	276.6
	Other fluid overload	ICD-9	276.69
Reintubation	Intubation, endotracheal, emergency procedure	CPT	31500
	Ventilation assist and management, initiation of pressure or volume preset ventilators for assisted or controlled breathing; hospital inpatient/observation, initial day	CPT	94002
Respiratory Failure	Pulmonary insufficiency following trauma and surgery	ICD-9	518.5
	Acute respiratory failure following trauma and surgery	ICD-9	518.51
	Other pulmonary insufficiency, not elsewhere classified, following trauma and surgery	ICD-9	518.52
	Respiratory failure	ICD-9	518.81
	Other pulmonary insufficiency, not elsewhere classified	ICD-9	518.82
	Acute and chronic respiratory failure	ICD-9	518.84

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Author's Contributions: ME and TK contributed equally as senior authors and mentors of CHS. They developed the study concept and design. CHS wrote the first draft of the manuscript and contributed to the design of the study. SD advised on the study design. CHS, SZ, TK, and ME refined the protocol. MN contributed to the acquisition and analysis of data for the work. All authors revised the protocol critically for important intellectual content and approved the final manuscript.

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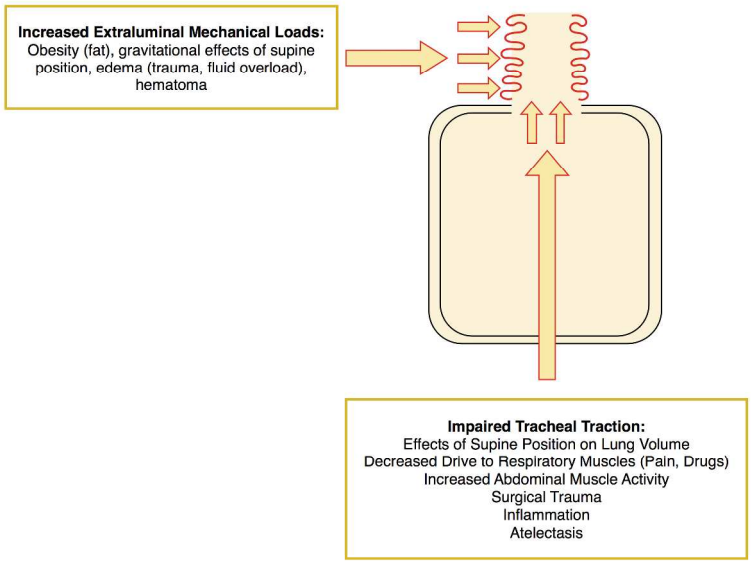

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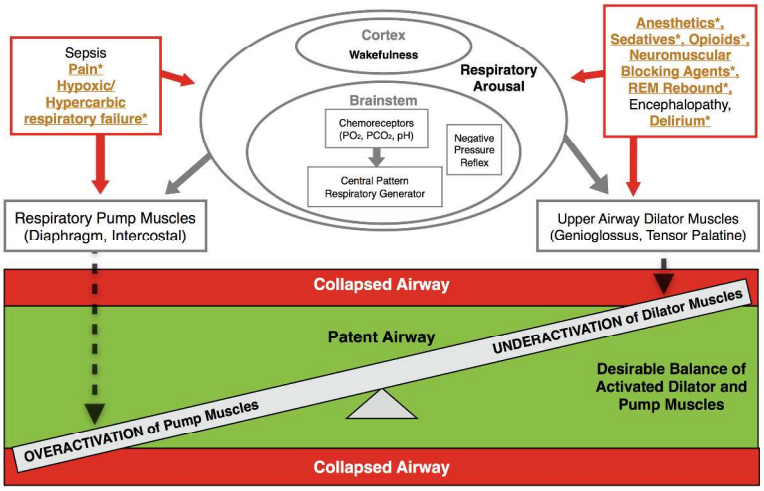

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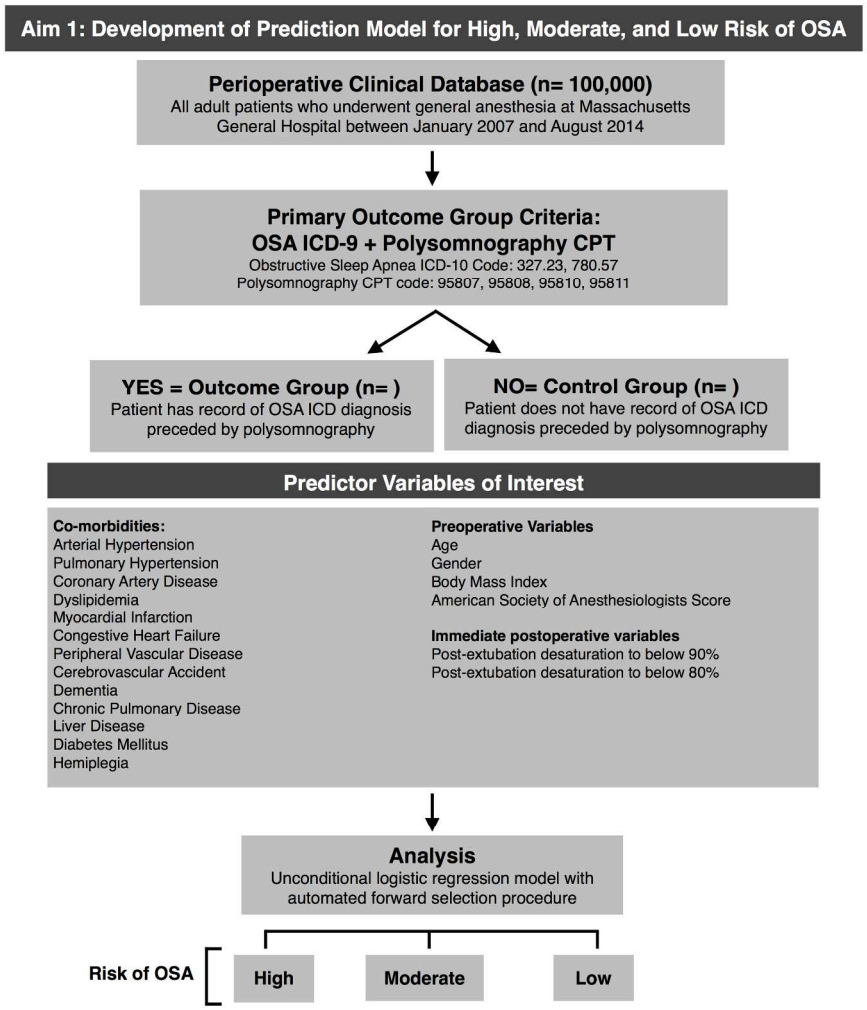

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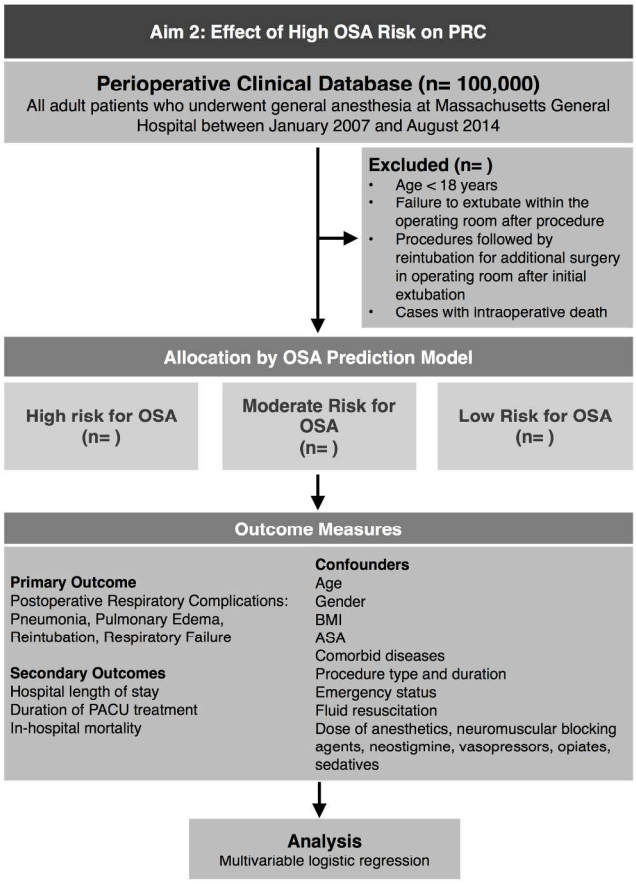

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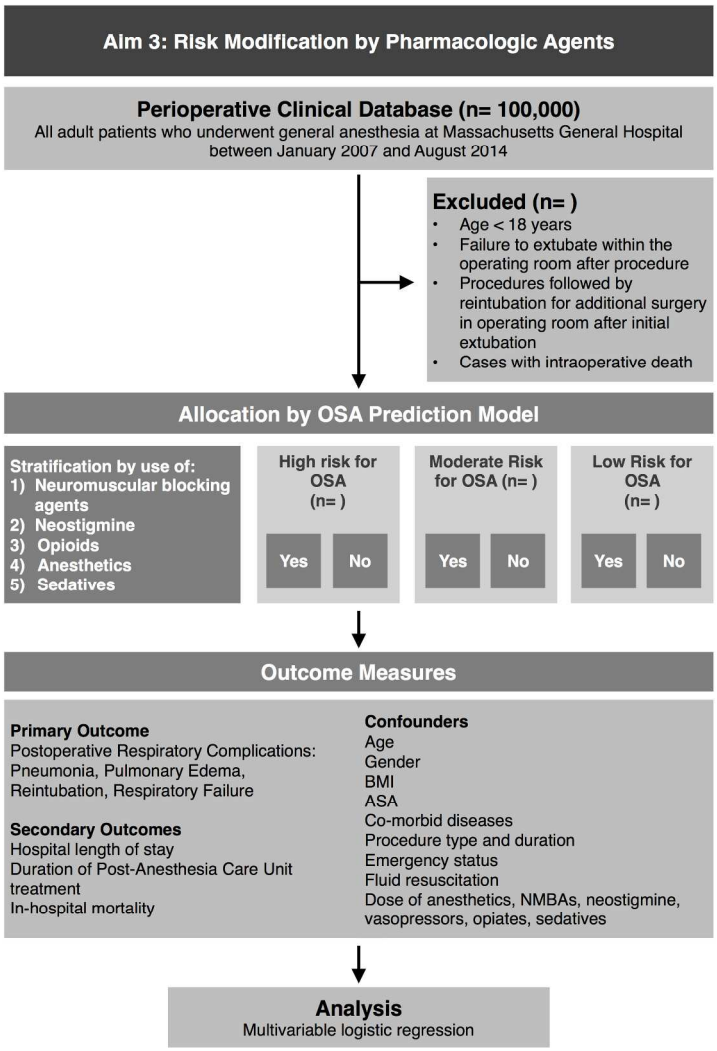

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Effects of Obstructive Sleep Apnea Risk on Postoperative Respiratory Complications: Protocol for a Retrospective Cohort Study

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Effects of Obstructive Sleep Apnea Risk on Postoperative Respiratory Complications: Protocol for a Retrospective Cohort Study

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ABSTRACT

Introduction: Obstructive sleep apnea (OSA), the most common type of sleep-disordered breathing, is associated with significant immediate and long-term morbidity, including fragmented sleep and impaired daytime functioning, as well as more severe consequences, such as hypertension, impaired cognitive function, and reduced quality of life. Perioperatively, OSA occurs frequently as a consequence of preexisting vulnerability, surgery, and drug effects. The impact of OSA on postoperative respiratory complications (PRC) needs to be better characterized. As OSA is associated with significant comorbidities, such as obesity, pulmonary hypertension, myocardial infarction, and stroke, it is unclear whether OSA or its comorbidities are the mechanism of PRCs. This project aims to 1) develop a novel prediction score identifying surgical patients at high risk of OSA, 2) evaluate the association of OSA risk on PRCs, and 3) evaluate if pharmacologic agents used during surgery modify this association.

Methods: Retrospective cohort study using hospital-based electronic patient data and perioperative data on medications administered and vital signs. We will utilize data from Partners Healthcare clinical databases, Boston, Massachusetts. First, a prediction model for OSA will be developed using OSA diagnostic codes and polysomnography procedural codes as the reference standard, and will be validated by medical record review. Results of the prediction model will be used to classify patients in the database as high, medium, or low risk of OSA and we will investigate the effect of OSA on risk of PRCs. Finally, we will test whether the effect of OSA on PRCs is modified by the use of intraoperative pharmacologic agents known to increase upper airway instability, including neuromuscular blockade, neostigmine, opioids, anesthetics, and sedatives.

Ethics and dissemination: The Partners Human Research Committee approved this study (Protocol number: 2014P000218). Study results will be made available in the form of manuscripts for publication and presentations at national and international meetings.

Article Summary

Article Focus

- This article describes the protocol for the development of a novel clinical prediction score to determine those adult surgical patients at high risk for obstructive sleep apnea in order to better evaluate in the perioperative setting the patient's risk of developing postoperative respiratory complications.

Key Messages

- Current screening and prediction scores for obstructive sleep apnea rely on patient-reported symptoms and do not consider obstructive sleep apnea risk in the setting of surgery and general anesthesia, as it relates to subsequent risk of postoperative outcomes

Strengths and Limitations

- This work utilizes a large clinical database consisting of pre-, intra-, and postoperative patient data.
- Our prediction model draws on well-established clinical characteristics associated with obstructive sleep apnea as well as new measures aimed at improving dynamic risk assessment in a perioperative setting.
- The results of this study may enable perioperative clinicians to identify adult surgical patients at highest risk for obstructive sleep apnea, optimize preoperative interventions, and appropriately triage care postoperatively based on intraoperative events.
- Potential limitations relate to the need for validation studies in datasets from other institutions to determine generalizability of prediction score

INTRODUCTION

Background

Obstructive sleep apnea (OSA) is a common disorder characterized by recurrent collapse of the upper airway. This chronic condition may be diagnosed by the presence of symptoms and, depending on the specific criteria used for making the diagnosis, more than 5 episodes of apnea, hypopnea, or respiratory effort-related arousal per hour of sleep (apnea hypopnea index, AHI ≥ 5/h).[1,2] Daytime symptoms refer to excessive daytime sleepiness, morning headaches, decreased concentration, memory loss, decreased libido and irritability. Other OSA-related symptoms include witnessed apnea, snoring, non-refreshing sleep, and gasping or choking at night.[3]

Recent epidemiologic data report that an estimated 70 million people in the United States alone are affected by OSA, making it the most common type of sleep-disordered breathing (SDB).[4,5] In the general adult population, approximately 13% of men and 6 % of women have moderate-to-severe SDB, defined as AHI≥15/hr.[5] It is also estimated that 14% of men and 5% of women have AHI≥5/hr plus daytime symptoms.[5] The prevalence of SDB without daytime symptoms is even higher and reaches values of up to 9% in women and 24% in men.[2,6] It is possible that such epidemiological data underestimate the frequency of OSA among today's general population since obesity, a major driver of OSA,[7] has greatly increased in the last decade.[5,8] Furthermore, studies have shown that OSA is commonly undiagnosed, suggesting an even higher prevalence of adults who suffer from this sleep disorder.[9-11]

Surgical patients with OSA are at a higher risk of developing postoperative respiratory complications, such as reintubation and requirement of non-invasive ventilation.[12-14] Upper airway collapse in the perioperative setting results in hypoventilation and is an important component of the mechanism of postoperative respiratory complications. In studies previously reported by our lab, independent of OSA, reintubation and unplanned ICU admission result in a 70 to 90-fold increase in in-hospital mortality.[15,16] However, despite an increased rate of postoperative respiratory complications, SDB, as identified by diagnostic codes, was paradoxically associated with lower mortality, hospital length of stay and costs among certain surgical specialties.[12] The mechanisms of the opposed effects of OSA on respiratory complication rate and mortality are unclear. We speculate that reintubation in patients with OSA is typically the consequence of upper airway dysfunction rather than pulmonary pathology, and the former can be treated more efficiently.

Mechanism of Perioperative Obstructive Sleep Apnea

Quantification of perioperative vulnerability to upper airway collapse requires consideration of preoperative and perioperative risk factors that affect the balance between collapsing forces and dilating forces of the upper airway. Perioperative anatomical and physiological factors need to be taken into account.

1. Anatomical Abnormalities Increase Collapsing Forces

Anatomical risk factors in patients with OSA include a reduction in the size of the retropalatal and retroglossal airway.[17,18] Perioperatively, anatomical vulnerability is augmented, thereby increasing upper airway instability.

Figure 1a summarizes perioperative risk factors that can compromise upper airway anatomy. Mechanical loads to the collapsible segments of the retropalatal and retropharyngeal upper airway lead to physical compression of the airway. Clinically, such an extraluminal mechanical load can occur as a consequence of a postoperative hematoma following cervical, otolaryngology, or thyroid surgery.[19,20] In addition, peripharyngeal edema may occur in perioperative medicine as a consequence of fluid overload. Bradley and colleagues studied the effects of antishock trouser inflation on upper airway size and reported narrowed pharynx and enlarged neck circumference measured by acoustic pharyngometry.[21] Congestive heart failure increases the AHI, which presumably is the consequence of nocturnal rostral fluid shift.[22] Airway patency may also be affected by peripharyngeal inflammation and edema in the setting of intubation and extubation.

2. Impaired Caudal Traction on the Trachea Increases Collapsibility

Isono and colleagues have conducted extensive investigations of position-dependent effects on airway obstruction. In anesthetized and paralyzed patients with OSA, the authors found that the lateral and sitting positions improve the collapsibility of the passive pharyngeal airway.[23,24]

Among patients with OSA, the supine position not only promotes a more obstructive orientation of the pharyngeal soft tissues, but also reduces caudal traction, thereby increasing vulnerability to upper airway collapse. During inspiration, caudal traction on the airway due to lung expansion dilates and stabilizes the upper airway, a force that opposes the negative intra-luminal pressure and prevents collapse.[25] The supine position during surgery, immediate postoperative period, and transition to sleep impairs tracheal traction on the airway and promotes collapse,[23,24] as illustrated in Figure 1a. Tracheal traction is also impaired by any event that reduces lung volume, often secondary to diaphragmatic

dysfunction. Impaired function of the respiratory pump muscles (diaphragm and intercostal muscles) results in ineffective expansion of the lung and occurs in the setting of surgery and trauma.[26] Pain-induced splinting and pharmacologic agents, such as opioids, decrease drive to the respiratory pump muscles, thereby preventing full lung inflation and reducing tracheal traction.[27] Studies in the intensive care unit have demonstrated how systemic inflammation and mechanical ventilation dramatically disrupts diaphragmatic function.[28,29]

3. Neuromuscular Mechanisms of Perioperative Airway Collapse

A balance between the upper airway dilator muscles (genioglossus, tensor palatine) and the respiratory pump muscles (diaphragm, intercostal muscles) exist to maintain upper airway patency during wakefulness and sleep, as illustrated in Figure 1b. Respiratory pump muscles generate inspiratory airflow associated with negative intra-luminal pressure, which is detected by mechanoreceptors and transmitted to the upper airway dilator muscles via the hypoglossal nerve. As a result, the genioglossus contracts and stabilizes the upper airway. Respiration is also stimulated by hypoxia and hypercarbia, which are detected by chemoreceptors. In addition to wakefulness, information transmitted by mechanoreceptors and chemoreceptors stimulate respiratory arousal, which has been previously defined as arousal from sleep and other drug-induced or endogenous impairments of consciousness.[30] Cortical effects on respiratory arousal are important, and any decrease in arousal can impair the voluntary effort to breathe spontaneously through a patent upper airway.[31]

A variety of pharmacologic and non-pharmacologic perioperative factors affect respiratory arousal. While the specific effects of perioperative pharmacologic agents depend on agent, dose, and specific muscle group, studies have shown that such agents largely dampen stimulation to the nerves controlling respiratory muscles.

Anesthetics and Sedatives

Studies in humans and animals have demonstrated the effects of anesthetics on the upper airway by a variety of mechanisms. Anesthetics decrease muscle and neural activity important for respiration as well as wakefulness through varying mechanisms.[32] Propofol, an agent commonly used for induction and maintenance of anesthesia, dose-dependently increases collapsibility of the upper airway through depressed respiratory drive to and direct inhibition of upper airway dilator muscle activity in humans.[33] In humans anesthetized with isoflurane, reflexive activity, or the responsiveness of upper airway dilator muscles to negative pressure, was found to be greatly reduced.[34] The diminishing effects of anesthetics on neuronal activity

also differ between hypoglossal and phrenic nerve.[35] With a focus on neural mechanisms for altered upper airway activity, Nishino and colleagues investigated the differential effects of anesthetics and found greater dampening of hypoglossal nerve input relative to the phrenic nerve.[36] This effect may result in greater anesthesia-induced impairment of upper airway dilators compared to respiratory pump muscles, increasing the upper airway's propensity for collapse. While this effect was observed across three classes of drugs (volatile, barbiturate, and benzodiazepine), ketamine reduced neural input to the upper airway dilator muscles and respiratory pump muscles equally. Furthermore, ketamine's effect on the upper airway dilator muscles was less relative to GABAergic anesthetics.[36] Such findings are corroborated by mechanistic studies in rats that demonstrate a dissociation between loss of consciousness and upper airway dilator muscle function under ketamine anesthesia.[37] Taken together, studies suggest that patients with OSA, who have preoperative upper airway instability, may be at a heightened risk of upper airway collapse when under the influence of anesthetics. The unique effects associated with ketamine, however, suggest that this drug may be a safer choice for patients with OSA.

Opioids

The use of opioids for postoperative pain management has been increasingly identified as a contributor to postoperative exacerbation of SDB.[38,39] Studies in human and animal subjects have investigated the mechanism by which patients with preoperative OSA may be vulnerable to the effects of perioperative opioids. Patients with OSA have increased sensitivity to pain[40-42] as well as increased sensitivity to the respiratory depressant effects of opioids.[43] Such findings are particularly relevant to the postoperative OSA patient given the effects of opioids on upper airway patency. Animal studies have shown that opioids increase upper airway resistance, resulting in obstruction.[44] Opioids directly inhibit hypoglossal motoneurons, which leads to suppressed genioglossus activity.[45] Thus, the use of opioids during and immediately after surgery is an important perioperative factor to consider in patients with OSA when assessing the risk of upper airway instability and the postoperative respiratory complications that may arise as a consequence.

Neuromuscular Blocking Agents and Reversal Agents

Neuromuscular blockade agents act longer than the duration of surgery and postoperative residual curarization affects postoperative respiratory outcome.[46] Upper airway dilators are more vulnerable to minimal effects of neuromuscular blocking agents compared to the respiratory pump muscles.[47,48] This differential activation of pump vs. dilator muscles may set off an unwanted chain of events such that the relatively more active respiratory pump muscles generate excessive negative

intrathoracic pressure, resulting in negative pressure pulmonary edema.[49] Even at levels producing minimal blockade, as measured by train-of-four ratio 0.5-1, neuromuscular blocking agents increased upper airway collapsibility and impaired compensatory genioglossus response to negative pharyngeal pressure challenges.[50] Studies in surgical patients have demonstrated the dose-dependent association between intermediate-acting neuromuscular blocking agents and postoperative respiratory complications, an effect shown to be unyielding despite neostigmine-based reversal at end of surgery.[16,51,52] Based on the pathophysiology of the disease, patients with OSA should have an increased vulnerability to the effects of neuromuscular blocking agents and reversal agents. [47,50,53] However, population-based studies aiming to quantify the effects of residual neuromuscular blockade in patients with and without risk of OSA are currently missing.

The impact of such pharmacologic agents commonly used in anesthesia care on the risk of respiratory outcomes in patients with OSA has yet to be determined. Our study will address the unmet need of evaluating the perioperative effect of neuromuscular blocking agents, reversal agents, opioids, sedatives, and anesthetics in patients at risk of OSA.

Non-Pharmacologic Events

Non-pharmacologic perioperative events, such as REM rebound, encephalopathy, delirium, can disrupt respiratory arousal and result in upper airway collapse.[30] In the immediate postoperative period, patients commonly experience poor quality, disrupted, and reduced sleep, resulting in a deficit of rapid eye movement sleep (REM).[54] Sleep studies in surgical patients have identified a REM rebound effect, in which REM sleep returns acutely and suddenly.[54,55] Increased amounts of REM during sleep is associated with impaired respiratory arousal and more frequent episodes of nocturnal hypoxemia.[56] OSA patients also have diminished or lost airway reflex during non-REM sleep, so patients with OSA may be at an even greater propensity for upper airway collapse and hypoxemia with phenomenon of REM rebound. While OSA patients have been shown to compensate for diminished airway sizes with higher basal genioglossus muscle activity,[57] this neuromuscular compensation has been found to be present only during wakefulness and thus futile in the setting of REM-predominant sleep. Recent prospective studies have demonstrated a significant reduction in REM sleep in OSA and non-OSA patients during the early postoperative period.[58] Postoperatively, time spent in REM sleep did not consistently predict postoperative OSA severity,[38] which may be the consequence of REM suppression secondary to postoperative pain, as well as administration of opioids and sedatives. Of note, studies have also identified other important contributors to SDB. Events that impair a patient's level of consciousness also disrupt respiratory arousal and result in upper airway instability. Such events include

delirium, stroke, septic encephalopathy, systemic inflammation, and metabolic disturbances, like hypoglycemia and hypothyroidism.[30]

Study Rationale

In order to evaluate the perioperative risk of patients presenting with OSA, it is important to take into account the "true" prevalence of the disease in the perioperative cohort. An important limitation of the existing literature relates to the focus on patients who carry the clinical diagnosis of OSA. As a consequence of analyzing only those patients with an International Classification of Diseases-9 (ICD-9) diagnostic code for SDB, a large subpopulation with undiagnosed OSA remain undetected.

The gold standard for the diagnosis of OSA is polysomnography. According to current clinical guidelines for OSA evaluation, patients are prompted to undergo this sleep study if determined to be high risk by their physician.[3] As a routine evaluation for OSA, polysomnography is impractical because of its limited availability, discomfort to the patient, and high cost.[59,60] The use of screening tools for OSA helps identify patients at risk of OSA. Widely used scores include the Perioperative Sleep Apnea Prediction Score,[61] the STOP-Bang[62] and Berlin Questionnaires,[63] and the Epworth Sleepiness Scale.[64] Such scores rely on a clinical exam to determine neck circumference and/or patient questionnaire of daytime OSA symptoms. Not all patients are able to have their necks measured and many patients are asymptomatic or unaware of their symptoms, limiting the ability of the existing scores to assess true prevalence of OSA. Anesthesiologists have also used scores, such as the Mallampati Score and the American Society of Anesthesiologists (ASA) Checklist, to assess difficulty of intubation as related to a narrow upper airway,[65] but there is inconsistency in reported sensitivity and specificity of the Mallampati score as a predictor of OSA.[64] Furthermore, the currently available scores require data not routinely available from clinical databases, such as history of snoring and witnessed apnea. This proposal is based on the consideration that other data available in the patient's electronic medical record may be sufficient to predict OSA and its associated increased risk of postoperative respiratory complications. Application of our prediction score on large perioperative datasets will permit research endeavors, such as the evaluation of the effect of OSA on patient outcomes and the justification of health care resource utilization.

Furthermore, understanding how pharmacologic agents commonly used in perioperative care impact postoperative outcomes among patients with high risk of OSA will improve our ability to provide better care for this vulnerable surgical population. Traditionally, anesthesia providers have determined dosing of various drugs based on standard parameters of age, gender, height and weight. However, such practices may not sufficiently guide providers in optimal drug administration, especially in a subpopulation more vulnerable to the effects of those drugs as already demonstrated in the literature. More specifically, we would like to better understand the interaction between the disease OSA and opioids, neuromuscular blocking agents, neostigmine, sedatives, and anesthetics to optimally predict postoperative respiratory outcomes. Using our prediction score for OSA in a large perioperative database, we will evaluate how the use of pharmacologic agents modifies the risk of postoperative respiratory complications in patients with OSA.

Objectives

The primary objectives are to:

1. Develop a novel prediction score of OSA to identify patients at high risk of OSA based on markers of the disease easily available from clinical databases.

   1.1. Validate OSA prediction based on medical record review.

2. Evaluate the effect of being at high risk of OSA, as defined by the prediction score, on the primary outcome of postoperative respiratory complications among patients undergoing surgery at Massachusetts General Hospital.

3. Evaluate if use of neuromuscular blockade, neostigmine-based reversal of neuromuscular blockade, opioids, sedatives, and anesthetics modify the risk of OSA on postoperative respiratory complications.

The secondary objective is to:

1. Investigate whether the association between OSA risk and postoperative respiratory complications is modified by age, gender, BMI and major comorbidities.

Hypotheses for the Primary Outcome

Based on previous data,[12] we hypothesize that patients with a high risk of OSA, as identified by our new prediction instrument, are more vulnerable to acute postoperative upper airway failure that leads to re-intubation. We further hypothesize that such patients will experience less favorable outcomes, depicted as intensive care unit admission rate, hospital length of stay, and hospital costs.

As a departure from the current literature on the perioperative effects of OSA, we believe that perioperative variables, which increase the vulnerability to airway collapse, will give us clinically meaningful information in order to predict which patient with OSA will develop postoperative respiratory complications.

METHODS AND ANALYSIS

Study Overview

The proposed study is a retrospective cohort analysis using hospital-based electronic patient data and perioperative data on medications administered and patient vital signs. We will utilize data from major clinical databases at Massachusetts General Hospital, a tertiary care facility and teaching hospital of Harvard Medical School in Boston, Massachusetts. In addition, polysomnography data will be extracted from clinical databases at several hospitals affiliated with Partners Healthcare.

As previously used for epidemiological studies by our group, data from two clinical databases will be retrieved and combined to provide de-identified pre-, intra-, and postoperative information: the Research Patient Data Registry and the Anesthesia Information Management System.[15,16,51,66] The Research Patient Data Registry contains demographic and billing data regarding patient comorbidities and postoperative outcome and survival. The Anesthesia Information Management System contains physiological data from patient monitors as well as information on medical history and documentation of important surgery and anesthesia-related events, including adverse events, perioperative procedures, and drug and fluid therapy. Patient data from these databases are linked through unique patient identifiers and the variables described in this protocol will be abstracted to form one database. The present database spans January 2007 to August 2014 and includes 140,000 surgical cases. Based on previous work, we will conservatively anticipate that 25% of the cases will not satisfy inclusion criteria due to patient's age, emergency status and missing data.[15,51] Thus we estimate 100,000 patient cases will meet our inclusion criteria.

Subject Selection

For the three primary objectives, we will include all adult surgical patients who underwent general anesthesia and receive endotracheal intubation or airway management by supraglottic airway device at our institution, for whom inpatient admission was planned, between January 2007 and August 2014. Because re-intubation is a component of our composite outcome of PRC, we will only include those patients who have had removal of all airway management devices within the operating room after the procedure. Surgical procedures followed by reintubation for an additional scheduled surgical procedure in the operating room after initial extubation or removal of airway device will be excluded from the study, as we presume that such cases did not require reintubation in the setting of adverse postoperative respiratory status. Patients who underwent surgery in the four weeks prior to the study case will be excluded. Finally, all patients with an intraoperative death will be excluded

from the study since OSA is not a biological mechanism of intraoperative death when a patient's airway is secure by an airway device. Patients will be identified using anesthesia data obtained from Research Patient Data Registry and Anesthesia Information Management System.

The study methods are outlined in three sections to address the three primary objectives.

Objective 1: Development of Prediction Model for OSA

Prediction Model Reference Standard

The reference standard for the prediction model will be defined as patients with an ICD-9 OSA diagnosis following the appearance of a polysomnography procedural (CPT, Current Procedural Terminology) code in our medical databases (Figure 2). From this specific sequence of events, we infer that these patients had their clinically suspected OSA diagnosis confirmed by polysomnography.

Validation of Reference Standard for the Diagnosis of OSA

Prior to the development of the prediction model, we will conduct a medical chart review of 100 randomly selected patients meeting our OSA criteria of an ICD-9 diagnostic code and polysomnography CPT code in order to determine whether or not such patients actually have evidence of OSA in the time between their polysomnography and surgery. These patients will not be considered for inclusion into the predictive model, but instead will be used to assess the positive predictive value of the ICD-9 and CPT code combination for identifying OSA. Confirmatory evidence of OSA would include a reported apnea hypopnea index (AHI) ≥ 5 as documented in a patient's medical chart[2] or treatment with continuous positive airway pressure (CPAP). The predictive model will be performed if the ICD-9 and CPT code combination has an acceptable positive predictive value ($\geq$0.8).

Predictor Variables

A number of variables have been found to be associated with an increased prevalence of OSA and are currently used for different screening tools for OSA in surgical patients.[62,65,67] From the Anesthesia Information Management System and Research Patient Data Registry databases, we will obtain and include the following data in our prediction score: age, BMI, gender, and the American Society of Anesthesiologists (ASA) physical status classification (Figure 2). We will incorporate

medical comorbidities using ICD9 diagnostic codes, some of which are defined by the Deyo-Charlson Comorbidity Index (Table 1).[68] All covariates included in the prediction model must be present within one year of surgery date. In addition, as a departure from current literature on developing OSA screening scores, we will consider oxygen desaturation immediately after extubation as a predictor. This strategy will most likely increase the predictive value of our score – patients with OSA are very vulnerable to desaturation after surgery and we have the unique opportunity to use this characteristic of OSA desaturation after anesthesia that has not yet been utilized in existing prediction scores. Post-extubation oxygen desaturation will be defined as an oxyhemoglobin reading less than 90% and less than 80% for at least one minute, as measured by pulse oximetry during the first 10 minutes after extubation in the operating room.

Development of Prediction Model

We will use an unconditional logistic regression model with an automated forward selection procedure to select for predictors of our a priori defined reference standard. To determine the goodness of fit of the final prediction model, we will use the Hosmer-Lemeshow test, which indicates that there is no significant difference between observed and expected OSA status if P-value ≥ 0.05. A point value will be assigned to each predictor variable proportional to the estimates from the logistic regression. The predictive value of the score for OSA will be assessed using c-statistics, which is equivalent to the area under the ROC curve.[69] We will aim to achieve a minimum c-statistic of 0.8. In addition, we will evaluate if the addition of a variable that can be obtained by anesthesiologists at the end of the surgical case, e.g. post-extubation desaturation, improves the predictive ability of the score. For this purpose, we will use risk reclassification analysis to compare the clinical impact of these two models.[70,71] The net reclassification improvement (NRI) will be generated by balancing the proportion of subjects whose risk was more accurately classified using the expanded prediction model with post-extubation desaturation compared with the prediction model without post-extubation desaturation against the proportion of subjects whose risk was less accurately classified.[70]

We will calculate positive and negative likelihood ratios for each stratum of the score. We will use bootstrap techniques to determine the robustness of included variables, which are close to the P-value cut-off of 0.05. We will then use classification tables to determine the best cut-off value for the prediction score to classify patients at high risk for OSA. We will also use cross-validation to evaluate any potential over-fitting of our prediction model.

Objective 2: Effect of High OSA risk on Postoperative Respiratory Complications

Exposure Variables

Our primary exposure variable of interest is OSA risk, as defined by our prediction model developed in Aim 1. We will identify patients in our population as having a high, moderate, and low risk for OSA using our prediction model and produce three cohorts of patients, which we will follow for the occurrence of outcome events.

Outcome Variables

The primary outcome of this part of the study is a composite outcome defined as the incidence of re-intubation, pulmonary edema, pneumonia and respiratory failure within the first three postoperative days. Secondary outcomes include the aforementioned individual outcomes as well as hospital length of stay, duration of post-anesthesia care unit treatment, and in-hospital mortality. Hospital length of stay will be defined as the postoperative length of hospital stay following surgery. The primary outcome has been previously used and validated by chart review.[51,66] The outcomes events for the primary analysis will be identified by ICD-9 diagnostic and CPT procedural codes obtained from the Research Patient Data Registry database (Table 1).

Outcome Model

We will perform multivariable logistic regression analyses to evaluate the effect of estimated OSA risk on our respiratory outcomes. Results will be presented as an age- and multivariable-adjusted odds ratio with 95% confidence intervals. We will consider a two-tailed P-value of less than 0.05 as statistically significant.

To control for confounding effects, we will consider a priori the following risk factors: age, gender, BMI, ASA physical status classification, comorbidities, surgical specialty, duration of the surgical procedure, admission type, and emergency status.[16] We will additionally control for dose of anesthesia (median dose of anesthetic agents corrected for age),[72] opioids (calculated as total morphine equivalent dose),[73] vasopressors, sedatives, neuromuscular blocking agents, and neostigmine use (Figure 3).

The effect of surgery type will be analyzed in greater detail by grouping similar types of surgery (e.g. cardiovascular, laparoscopic) to determine if surgery type is an effect modifier and not a confounder. If this is found to be the case, surgical specialty will no longer be included as a covariate, and the previously described model will be stratified by surgery type.

Sample Size and Power Calculations

Based on previous work with data from surgical patients in our institution, we expect approximately 100,000 patients undergoing surgery to meet our inclusion criteria during the observational period. Studies on prevalence of OSA in the general surgical population provide a range of estimates: one study found 17% of surgical patients as having severe OSA (AHI >30).[74] Other studies relying on screening scores found anywhere from 4.8%[75] to 41.6%[76] of surgical patients at high risk of OSA. Thus, we conservatively estimate 3% (n=3,000) patients in our surgical population to have a high likelihood of OSA. Based on our prediction score, we will classify patients as high, moderate, and low OSA risk.

Previous work by our lab[51] found an overall incidence of 3.7% for our primary outcome of postoperative respiratory complications. Data on differences in postoperative outcomes between OSA and non-OSA groups provide us with estimates for our predicted intergroup differences. Liao et al found an intergroup (OSA vs Non-OSA) difference of 11% for their composite outcome of total respiratory complications.[13] Mokhlesi et al investigated the incidence of emergent intubation following elective surgery among patients with and without SDB.[12] Emergent intubation occurred at a rate of 3.5-11.4% among patients with SDB vs. 0.3-7% among patients without SDB across four categories of elective surgery.[12] The intergroup difference observed was approximately 3%.[12] Based on this data, we will conservatively estimate an intergroup difference of 10% for our composite outcome, with smaller differences observed for outcomes with lower frequencies. Power is calculated based on comparing proportions of outcome rates between expected patients with OSA and the reference population without OSA. Our fixed sample size of 100,000 will provide us with a power greater than 90% to identify a 10% intergroup difference with an alpha error of 0.05.

Objective 3: Risk modification by Pharmacologic Agents

Exposure Variable and Rationale

We will obtain data on the intraoperative use of intermediate-acting neuromuscular blocking agents, neostigmine-based reversal of neuromuscular blockade, opioids, anesthetics, and sedatives as additional independent variables in the analysis to test whether or not such pharmacologic agents modify the effect of OSA on the risk for postoperative respiratory complications. We have previously studied the use of intermediate-acting neuromuscular blocking agents and found that their use was associated with an increased risk of respiratory complications.[16] In addition, we have observed that the use of the

reversal agent neostigmine does not decrease but increase the risk of postoperative respiratory complications.[16,52] However, more recent work demonstrates that such effects could be mitigated by neostigmine only at low doses and with simultaneous careful monitoring of neuromuscular transmission (train-of-four).[51]

Patients with OSA should be at high risk of respiratory complications induced by pharmacologic agents because such agents can affect upper airway patency.[35,44,48,77] We thus expand our investigation to include the risk modification effect of pharmacologic agents (neuromuscular blocking agents, neostigmine, opioids, anesthetics, and sedatives) on postoperative respiratory complications in a subpopulation of surgical patients who may be at an inherent higher vulnerability towards upper airway collapse and subsequent poor respiratory outcomes. Similar to previous work, we will extract information on administration of pharmacologic agents from the Anesthesia Information Management System database.[51]

Outcome Variables

The primary outcome is the composite variable of postoperative respiratory complications, consisting of: reintubation, pulmonary edema, pneumonia and respiratory failure. Secondary outcomes include hospital length of stay, duration of post-anesthesia care unit treatment, in-hospital mortality, as well as the aforementioned outcomes. These outcomes are defined by ICD-9 and CPT codes located in the Research Patient Data Registry database and have been previously validated by chart review by our lab (Table 1).[51]

Stratified Analysis to Assess for Effect Modification by Pharmacologic Agents

To evaluate potential effect modification by neuromuscular blockade, neostigmine, opioid, anesthetic, and sedative use, we will run stratified analyses of the association between OSA and the outcome events based on intraoperative use of pharmacologic agents. We will use the likelihood ratio test to contrast our main model to a model including interaction terms between OSA and the following variables: neuromuscular blocking agent dose, opioid dose, and median effective dose of anesthetics. To control for confounding effects, we will consider *a priori* the following risk factors: age, gender, BMI, ASA physical status classification, comorbidities, surgical specialty, duration of the surgical procedure, and emergency status.[16] The stratified analyses for neuromuscular blockade, opioid, anesthetic, and sedative use will be performed independently using stratified versions of the previously described model. The potential for risk modification of neostigmine will be performed in the subset of patients receiving neuromuscular blockade.

Study Cohorts

Based on previous work with data from surgical patients in our institution, approximately 100,000 patients will meet inclusion criteria. Based on data estimating OSA prevalence in the general surgical population, we conservatively expect to find approximately 3,000 patients with high likelihood of OSA in our surgical population. Using our prediction model from Aim 1, we will determine the risk of OSA and assign patients found to be at high, moderate and low risk of OSA.

Ethics and Dissemination

This study utilizes internal hospital-based data routinely collected for medical documentation purposes. As it is a systematic review of the data, there is little ethical risk. Patient privacy and protection of health information will be maintained. The results of this study will be shared in the form of presentations at national and international meetings. The complete study and conclusions regarding the primary objectives will be presented in manuscript form.

Limitations and Strengths

This article presents the protocol and data analysis plan for the development of a novel prediction score for OSA and application of the score to more accurately characterize the risk imparted by OSA condition on postoperative respiratory complications.

Our approach relies on the investigation of patient data on file. Thus, our findings depend on the quality of the database, which is susceptible to measurement biases. There is potential for variability in the input of billing diagnoses and codes. This database has been used in previous studies[15,16] and demonstrated to have high specificity following verification of diagnostic codes positive for study's composite outcome variable. Furthermore, we will validate the use of diagnostic and procedural codes in the development of our prediction model by medical record review. Nevertheless, it is possible that information is left out of some patients' charts and consequently, our database of our composite outcomes and independent variables. A second limitation involves our inability to capture those patients admitted to an outside hospital with postoperative respiratory complications after discharge from our institution. A third limitation rises from the multifactorial and dynamic nature of OSA: patients diagnosed with OSA, even by polysomnography, may not necessarily have evidence of OSA on the day of surgery. An example would be a patient who loses significant weight just prior to surgery. Diagnosis of OSA by

polysomnography prior to weight loss may be no longer valid following weight loss.[78] Thus we are limited in our development of a prediction model since we initially rely on polysomnography procedure codes and ICD-9 diagnoses as our standard. We hope to minimize this limitation by developing a prediction model that relies on variables that are highly likely to predict OSA even in the absence of polysomnographic evidence or clinical diagnosis.

In spite of these limitations, our study derives its strengths from a number of key elements. Our database is large and includes a variety of surgical procedure types and methods of anesthesia, thus increasing the generalizability of the study results and applicability of our prediction score models. In addition, we have a multidisciplinary team, which includes population scientists, data analysts, and clinicians. Such a team provides the experience and skill level needed for efficient, accurate, and precise design and analysis of the current study. Our team has also previously developed prediction scores for postoperative respiratory complications.[15]

Conclusions

The present study examines patients who we presume to have a high risk of perioperative respiratory failure: patients with obstructive sleep apnea. The prediction score we develop for to assess OSA risk will be a useful and practical tool for further OSA research and care. We believe the results of this study will provide new insight on whether or not high risk for OSA increases a patient's risk of developing postoperative respiratory complications, independent of other perioperative risk factors. Moreover, the results of this study might be important to evaluate the effects of interventions, such as reversing neuromuscular blockade, on respiratory outcome of OSA in the perioperative setting.

By developing a prediction score for OSA risk, we hope to identify those patients who would benefit from specific preoperative interventions to minimize postoperative morbidity and mortality.

FIGURE LEGENDS:

Figure 1. Pathophysiology of Perioperative Obstructive Sleep Apnea

A. Pathological Anatomy. This schematic of the respiratory system demonstrates the anatomical forces (red arrows) increasing collapsibility of the upper airway (red curly lines). Caudal tracheal traction stabilizes the upper airway such that it is less vulnerable to collapse. CPAP treatment can evoke caudal tracheal traction and increase end-expiratory lung volume. Collapsing physical forces are those that increase the mechanical load on the upper airway (hematoma, edema, fat) and those that reduce caudal tracheal traction (atelectasis, supine, flat position).

B. Pathological Physiology. The vulnerable perioperative upper airway physiology is illustrated as a scale, demonstrating the fragile balance between activation of respiratory pump muscles and upper airway dilator muscles (green zone). When activated, pump muscles generate negative inspiratory pressure and tip the balance to upper airway collapse (red zone). In normal physiology, upper airway dilator muscles activate to counterbalance the negative inspiratory pressure and dilate the upper airway. Underactivation of airway dilator muscles, such as the tongue muscle, will result in collapse (red zone). A variety of perioperative events affect respiratory arousal, which can impair airway patency by overactivating pump or underactivating dilator muscles, respectively.

Patients with OSA are at higher vulnerability towards collapse, and the specific pathophysiological mechanism of the increased perioperative vulnerability to collapse in OSA are emphasized in yellow color and denoted with an asterisk*.

CPAP – continuous positive airway pressure; OSA – obstructive sleep apnea

Figure 2: Aim 1: Development of Prediction Model for High, Moderate, and Low Risk of OSA

Figure 3: Aim 2: Effect of High OSA Risk on Postoperative Respiratory Complications

Figure 4: Aim 3: Risk Modification by Pharmacologic Agents

Table 1: Diagnostic (ICD-9) and Procedural (CPT) codes used to generate predictor and outcome variables.			
Variable	**Diagnostic or Procedure Name**	**Code Type**	**Code**
Reference Standard Outcome for Prediction Model of Aim 1			
Obstructive Sleep Apnea	Obstructive sleep apnea (adult or pediatric)	ICD-9	327.23
	Unspecified sleep apnea	ICD-9	780.57
Polysomnography	Sleep study, simultaneous recording of ventilation, respiratory effort, ECG or heart rate, oxygen saturation, attended by a technologist	CPT	95807
	Any age, sleep staging with 1-3 additional parameters of sleep, attended by a technologist	CPT	95808
	Age 6 years or older, sleep staging with 4 or more additional parameters of sleep, attended by a technologist	CPT	95810
	Age 6 years or older, sleep staging with 4 or more additional parameters of sleep, with continuous positive airway pressure therapy or bi-level ventilation, attended by a technologist	CPT	95811
Medical Comorbidities			
Arterial Hypertension	Malignant Essential Hypertension	ICD-9	401.0
	Benign essential hypertension	ICD-9	401.1
	Unspecified essential hypertension	ICD-9	401.9
	Other malignant secondary hypertension	ICD-9	405.09
	Other benign secondary hypertension	ICD-9	405.19
	Other unspecified secondary hypertension	ICD-9	405.99
Pulmonary Hypertension	Pulmonary hypertension	ICD-9	416.0
Coronary Artery Disease	Coronary atherosclerosis of unspecified type of vessel native or graft	ICD-9	414.00
	Coronary atherosclerosis of native coronary artery	ICD-9	414.01
	Coronary atherosclerosis of autologous vein bypass graft	ICD-9	414.02
	Coronary atherosclerosis of nonautologous biological bypass graft	ICD-9	414.03
	Coronary atherosclerosis of artery bypass graft	ICD-9	414.04
	Coronary atherosclerosis of unspecified bypass graft	ICD-9	414.05
	Coronary atherosclerosis of native coronary artery of transplanted heart	ICD-9	414.06
	Coronary atherosclerosis of bypass graft (artery) (vein) of transplanted heart	ICD-9	414.07
	Aneurysm of heart (wall)	ICD-9	414.10
	Aneurysm of coronary vessels	ICD-9	414.11
	Dissection of coronary artery	ICD-9	414.12
	Other aneurysm of heart	ICD-9	414.19
	Chronic total occlusion of coronary artery	ICD-9	414.20
	Coronary atherosclerosis due to lipid rich plaque	ICD-9	414.30
	Coronary atherosclerosis due to calcified coronary lesion	ICD-9	414.40
	Other specified forms of chronic ischemic heart disease	ICD-9	414.80
	Chronic ischemic heart disease unspecified	ICD-9	414.90
Dyslipidemia	Pure hypercholesterolemia	ICD-9	272.0
	Pure hyperglyceridemia	ICD-9	272.1
	Mixed hyperlipidemia	ICD-9	272.2
	Hyperchylomicronemia	ICD-9	272.3
	Other and unspecified hyperlipidemia	ICD-9	272.4
	Other disorders of lipoid metabolism	ICD-9	272.8
The following medical comorbidities are derived from ICD9 Codes, as defined by the Deyo Charlson Comorbidity Index[68]: Myocardial Infarction, Congestive Heart Failure, Peripheral Vascular Disease, Cerebrovascular Accident, Dementia, Chronic Pulmonary Disease, Mild Liver Disease, Moderate to Severe Liver Disease, Diabetes with Chronic			

Complications, Diabetes without Chronic Complications, Hemiplegia or Paraplegia, Peptic Ulcer Disease, Renal Disease, Any Malignancy including Leukemia and Lymphoma but excluding malignant neoplasm of skin, Metastatic Solid Tumor, AIDS/HIV, Rheumatic Disease			
Primary Outcome for Aim 2 and Aim 3			
Pneumonia	Pneumococcal pneumonia [Streptococcus pneumonia]	ICD-9	481
	Pneumonia due to Klebsiella pneumoniae	ICD-9	482.0
	Pneumonia due to Pseudomonas	ICD-9	482.1
	Pneumonia due to Streptococcus, unspecified	ICD-9	482.30
	Pneumonia due to Staphylococcus, unspecified	ICD-9	482.40
	Pneumonia due to Staphylococcus aureus	ICD-9	482.41
	Methicillin resistant pneumonia due to staphylococcus aureus	ICD-9	482.42
	Pneumonia due to Escherichia coli [E. coli]	ICD-9	482.82
	Pneumonia due to other gram-negative bacteria	ICD-9	482.83
	Pneumonia due to other specified bacteria	ICD-9	482.89
	Bacterial pneumonia, unspecified	ICD-9	482.9
	Pneumonia, organism unspecified	ICD-9	486
	Pneumonia due to other specified organism	ICD-9	483.8
	Pneumonia in aspergillosis	ICD-9	484.6
	Bronchopneumonia, organism unspecified	ICD-9	485
	Pneumonitis due to inhalation of food or vomitus	ICD-9	507.0
Pulmonary Edema	Pulmonary congestion and hypostasis	ICD-9	514
	Acute edema of lung, unspecified	ICD-9	518.4
	Congestive heart failure	ICD-9	428.0
	Fluid overload	ICD-9	276.6
	Other fluid overload	ICD-9	276.69
Reintubation	Intubation, endotracheal, emergency procedure	CPT	31500
	Ventilation assist and management, initiation of pressure or volume preset ventilators for assisted or controlled breathing; hospital inpatient/observation, initial day	CPT	94002
Respiratory Failure	Pulmonary insufficiency following trauma and surgery	ICD-9	518.5
	Acute respiratory failure following trauma and surgery	ICD-9	518.51
	Other pulmonary insufficiency, not elsewhere classified, following trauma and surgery	ICD-9	518.52
	Respiratory failure	ICD-9	518.81
	Other pulmonary insufficiency, not elsewhere classified	ICD-9	518.82
	Acute and chronic respiratory failure	ICD-9	518.84

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Author's Contributions: ME and TK contributed equally as senior authors and mentors of CHS. They developed the study concept and design. CHS wrote the first draft of the manuscript and contributed to the design of the study. SD advised on the study design. CHS, SZ, TK, and ME refined the protocol. MN contributed to the acquisition and analysis of data for the work. All authors revised the protocol critically for important intellectual content and approved the final manuscript.

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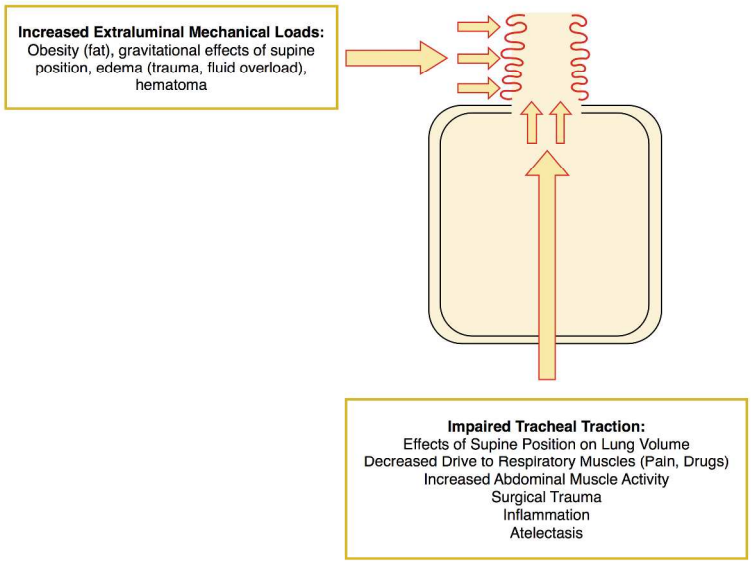
Competing Interests: Scott Devine is a Merck employee and Merck is the sponsor of this study.

Ethics Approval: Partners Human Research Committee, Protocol number: 2014P000218.



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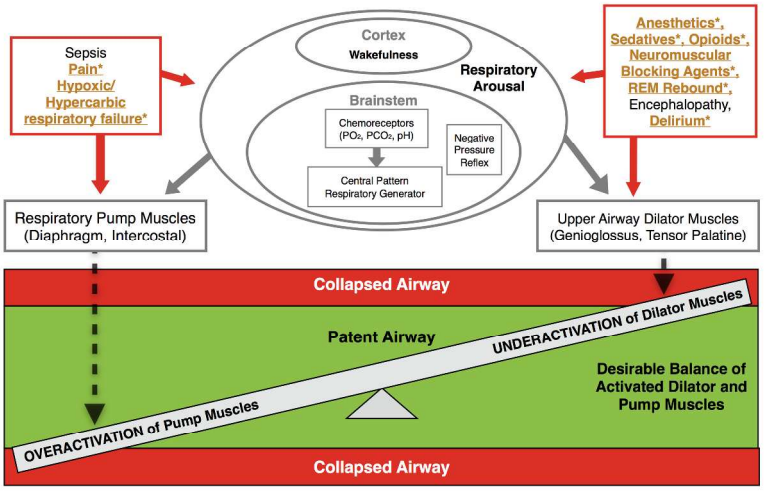

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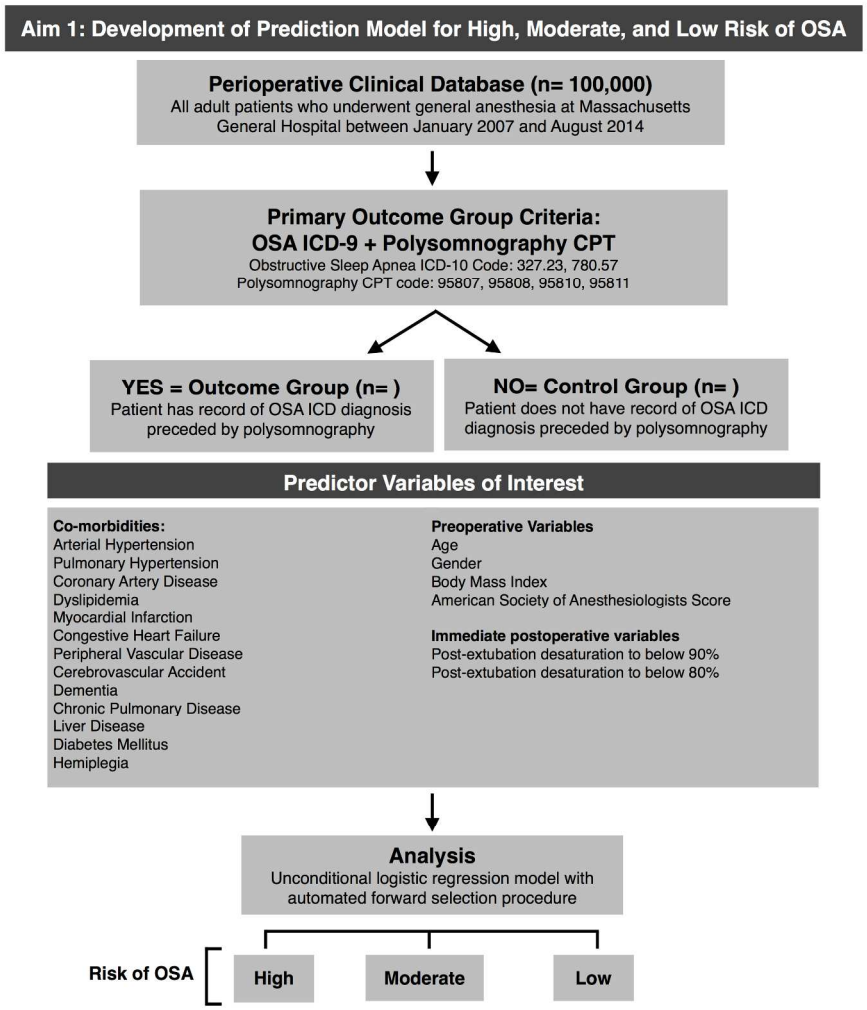

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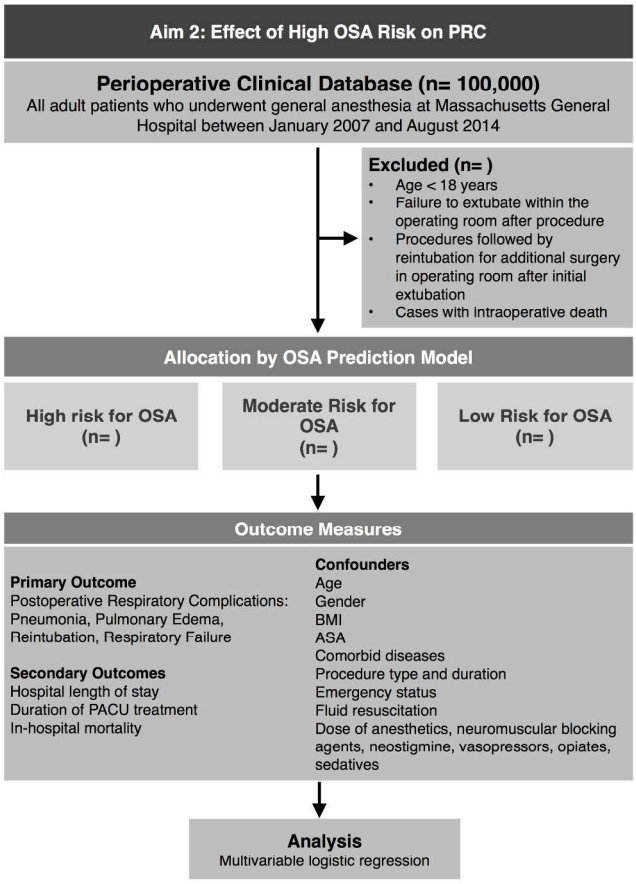

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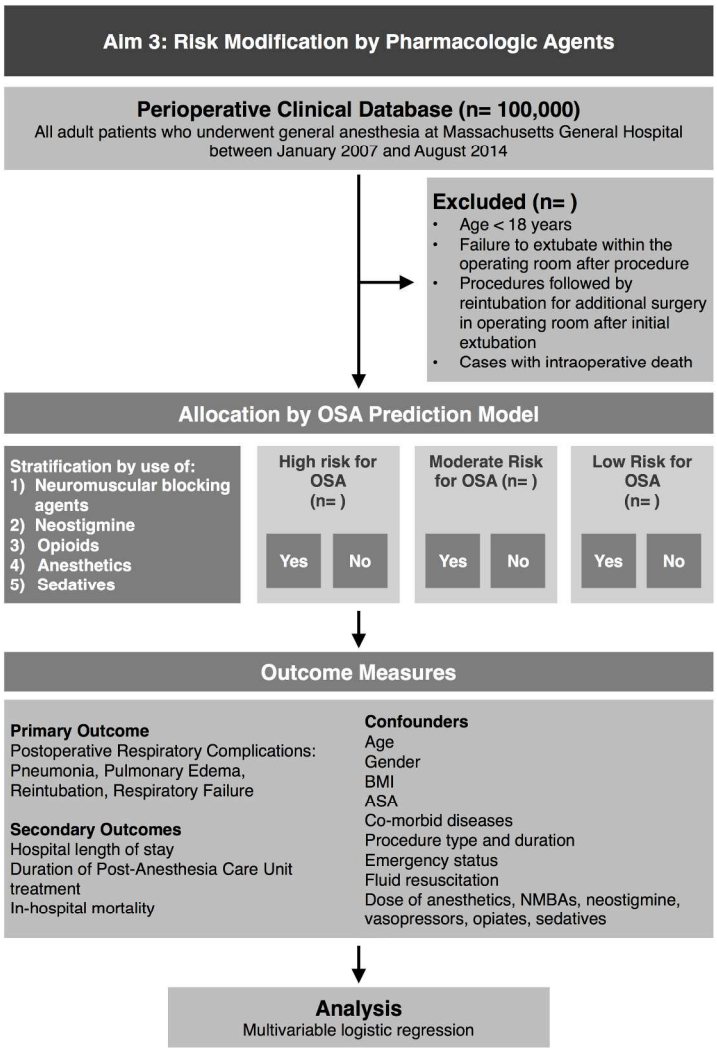

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