Title: **Effect of high altitude on sleep apnea and incidence of sleep apnea-related perioperative hypoxemia**

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Introduction

Sleep apnea is associated with nocturnal hypoxemic episodes[1-3], increased inflammation, global oxidative stress[4-6], and increased cardiovascular risk[7,8]. Both the sleep apnea (SA) and obesity-associated hypoventilation (obesity-hypoventilation syndrome, or OHS) can contribute to the development of postoperative hypoxemia; differentiating the diagnosis of SA from OHS is often challenging[9]. However, both SA and OHS increase the incidence of perioperative pulmonary complications, including aspiration pneumonia, need for mechanical ventilation and acute respiratory distress syndrome (ARDS)[10-13].

Obesity is a worldwide epidemic, and a major risk factor for obstructive sleep apnea, (OSA)[2,3,14]. Although the majority of OSA is believed to be related to excess nasopharyngeal soft tissue, lean patients can also have sleep apnea. In this population the diagnosis and treatment of sleep apnea is more challenging[15]. At high altitude there is some evidence that central breathing regulation is impaired leading to an increased incidence in central sleep apnea when compared to a population that lives at sea level[16,17]. Faulty neurological feedback regulation contributes to the unstable ventilatory drive during sleep in sleep apnea patients, and higher altitude can worsen polysomnography results [18-20]. This central contribution to sleep apnea may be associated with different distribution of Body Mass Index (BMI) in patients living at altitude compared to sea level, with a greater proportion of lean sleep apnea patients at altitude. So strong is the association with obesity that the lean sleep apnea patients are often undiagnosed[21] making appropriate perioperative management challenging and increasing an individual patient's risk. Substantiating this proposed effect of altitude on BMI distribution in sleep apnea patients could improve perioperative patient care with better identification at risk patients based of characteristics other than elevated BMI.

Using a multicenter prospectively collected electronic anesthesia database we studied the BMI distribution in surgical patients with a formal diagnosis of sleep apnea, patients with a prescribed treatment for sleep apnea, physician-suspected diagnosis of sleep apnea, or presence of ≥3 risk factors for sleep apnea (secondary analysis). We hypothesized that the prevalence of lean sleep apnea patients (BMI<35) at >4,000 feet elevation would be greater that at <1,500 feet. Adjustment for confounders (i.e. gender, age, other respiratory diseases) would be performed.

Materials and Methods

Institutional review board exemption (University of Michigan, Ann Arbor, MI HUM00033894) was obtained for this observational study of de-identified data.

Patient population

All adult patients (age≥18 years) undergoing anesthesia care at any MPOG institution (University of Michigan, University of Colorado Denver, Oregon Health and Science University, and University of Tennessee, …) with an electronic preoperative history and physical from 2004 to 2012 were eligible for inclusion. Cases without an electronic perioperative record or without required recorded information are excluded. Patients with multiple procedures during the study period will have each surgical event included as a distinct data point.

Commented [LJ1]: Need to estimate frequency of this event.

Data collection

Data were acquired from the Multicenter Perioperative Outcomes Group (MPOG) database, a consortium of medical centers using observational data to assess and improve perioperative outcomes. Each patient has a detailed anesthesia preoperative history and physical that is documented by an anesthesia provider using a perioperative clinical information system (Centricity® from General Electric Healthcare, Waukesha, WI). This history and physical contains discrete data elements regarding patient anthropomorphic details, comorbidities, physical examination and other general patient clinical information (Table 1). For each discrete data element, a user must select from pre-defined pick list, or a user may choose to enter free-text information. To meet the criteria of SA without a statement of formal diagnosis, 3 elements (Table 1) must be present. Free-text information was interrogated for the terms “OSA” and “sleep apnea”.

Each of the study cases were documented for details related to altitude (>4,000 *vs.* <1,500 feet), anthropomorphic data (weight, height, BMI), sleep apnea diagnosis and/or signs (i.e. STOP-Bang signs such as male gender, obesity, thick neck or neck circumference≥16in/40cm, witnessed/admitted snoring, breath holding or daytime sleepiness)[22], type of sleep apnea treatment, other comorbidities and perioperative descriptors (type of anesthetic, surgical procedure service).

Outcomes

The primary outcome was the comparison of the incidence of sleep apnea at the pre-defined low and high altitude centers and the BMI distribution of each group with the formal diagnosis of sleep apnea (formal diagnosis or current treatment prescribed by a physician), or presumptive diagnosis based on 3 or more OSA characteristics from Table 1. Secondary endpoints will include the distribution of other sleep apnea characteristics, demographic information and data from Table 1. We hypothesized that the prevalence of lean sleep apnea, BMI less than 35 kg/m^2 would be higher at altitude than at sea level.

As a secondary analysis we repeated the primary analysis including not only the formal diagnosis or current treatment for sleep apnea patients but also those with suspected sleep apnea, defined by 3 or more positive sleep apnea signs in the preoperative evaluation (male gender, obesity, thick neck or neck circumference≥16in/40cm, admitted/witnessed snoring, breath holding and/or daytime sleepiness).

Statistical Analysis

Statistical analysis was performed using SPSS® Version 195 (SPSS Inc, Chicago, Illinois). Patients were classified into the outcome of either having or not a positive sleep apnea and a BMI<35 depicted. First, descriptive analyses were performed on all independent covariates (table 1) variables and the outcome. Categorical data were assessed using either the chi-square or Fischer's Exact Test as appropriate. Odds ratios and 95% confidence intervals will be reported. Continuous data elements will be first be analyzed for outliers and each outlier will be addressed by either confirmation that the value was correct or by making the value a missing data element. After each outlier has been properly addressed, the data will be assessed for normality. Parametric data will be analyzed using the student's t-test. Non-parametric data will be analyzed using the Mann-Whitney U test. A p-value of <0.05 will be considered statistically significant.

If none of the preoperative sleep apnea associated variables in table 1 are significantly different between high and low altitude centers, then a simple chi-square comparing the incidence of sleep apnea and BMI<35 between the high and low altitude centers will be performed. However, if there are significant differences, the independent effect of center altitude on the prevalence of sleep apnea will be assessed using a multivariate model. A Pearson Correlation matrix will be constructed to determine which

covariates are highly correlated. A pair-wise correlation of >0.70 will be considered highly correlated and the covariates will either be collapsed into one concept or one of the variables will be used in the logistic regression model. The model's fit will be assessed using the Omnibus Test for Model Coefficients and the Hosmer and Lemeshow Test. All variables deemed to be significant in the full model fit ($p < 0.05$) will be established as independent predictors. The effect of high versus low altitude will be assessed using this multivariate model.

Limitations

There were several limitations in our study. Any retrospective analysis of an existing database reflects a historical analysis where information gaps are difficult to accurately confront. Most importantly, the primary outcome in our study is critically affected by a positive diagnosis of sleep apnea. We have determined for this study that a positive sleep apnea is a formal diagnosis or current treatment for sleep apnea (primary analysis) or (secondary analysis) suspected sleep apnea, defined by the presence of ≥3 signs of sleep apnea. These criteria depend on the anesthesia providers charting the pertinent information in the preoperative history and physical; there is subjectivity on the of the provider and the patient in the classification of sleep apnea signs (i.e. snoring, thick neck) or the reporting of a diagnosis. Sleep apnea is an under-diagnosed condition, so the use of "signs of sleep apnea" is clinically relevant, yet may be controversial. Many primary care physicians may diagnosis and prescribe therapy without a sleep study due to the cost and limited access to an evaluation. We are also assuming that patients being anesthetized at an altitude of >4,000 feet live at a similar altitude and have "higher" altitude physiology compared to patients anesthetized at <1,500 feet centers. These factors may affect our results and their interpretation should be used with caution.

Future directions

In the future and when MPOG resources are available we might expand our study into the implications of lean sleep apnea, *vs.* obese (obstructive?) sleep apnea, into clinical outcomes: incidence of perioperative hypoxemia (any recorded Sat<90%), duration of postoperative oxygen therapy, postoperative complications, length of Post-Anesthesia Care Unit (PACU), length of hospital stay.

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Table 1: Perioperative data elements requested

Risk Factor	source	definition
Age (in years)°	Caseinfo.age_in_years	
Body Mass Index (kg/m^2)°	Anthropometrics.MPOG_BMI	
Height	Anthropometrics.MPOG_Height_cm	
Weight	Anthropometrics.MPOG_Weight_kg	
Male sex	demographics.sex	
Sleep apnea	Preop ID 70122	Prescribed CPAP (using or not), stops breathing at night, daytime sleepiness
Snoring	Preop ID 70012	Yes
Presence of beard	Preop ID 70008	Does not include moustache
Edentulous	Preop ID 70003	Includes upper and lower dentures
Thick neck	Preop ID 70062	Subjective assessment, not measured
Neck circumference	Preop ID 70011 and 70010	Measured, or >16 inches
Mallampati III or IV	Preop ID 70006 or 70007	Standard or extended
Social History General	Preop ID 70125	
Social History Alcohol	Preop ID 70126	
Social History Tobacco	Preop ID 70128	
Home medications	Preop ID 70077 of 70079	Opiate / sedatives categorized by RxNorm codes