SPEAKER ABSTRACTS

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SPEAKER ABSTRACTS

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What Every Health Professional Should Know About Sleep Apneas and the Impact Of Sedatives/Narcotics on Sleep-Disordered Breathing

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A Prevalent Situation

It is estimated that approximately 2.5% of North American adults use prescription hypnotics,[1] and a projected 201.9 million opioid prescriptions were dispensed in the US in 2009.[2] The rate of prescription use of these medications is growing rapidly. It is also estimated that approximately one out of four American adults in the general population are at risk for obstructive sleep apnea.[3] This prevalence may be higher in referral populations, such as primary care practices and inpatient practices, where the risk for obstructive sleep apnea in middle-aged patients approximates 23-32%.[4,5] Considering the likely intersection of patients at risk for OSA and those prescribed opioids or hypnosedating agents, understanding the impact of such commonly prescribed medications on manifestations of OSA is of great importance. Understanding the effects of these medications, and in particular the possible deleterious effects on patients with OSA, would be necessary to make an informed decision that takes into account both goals and risks when prescribing these substances. Considering that 93% of women and 82% men with moderate to severe OSA remain undiagnosed, careful screening of patients at high risk for obstructive sleep apnea.[6] Several reviews of screening techniques for OSA risk stratification will be reviewed at this conference. The goal of this quick review is to characterize the effects of these medications in patients with sleep disordered breathing, sifting through the details derived from animal studies and clinical studies to evaluate the effects of hypnotics, narcotics, benzodiazepines, and non-benzodiazepine GABA agonists on the clinical manifestations of sleep disordered breathing.

GABAA Receptor Agonists: Hypnotics and Sedative/Anxiolytics

Although the literature is replete with admonitions to avoid BZD in patients with OSA, much of this advice is based upon scant data, often involving older long acting and/or non-selective BZD and much is extrapolated from animal studies. The actions of BZDs on the respiratory system depend on pharmacokinetic variables such as dose, route, persistence of active drug and/or metabolite in the body (elimination half-life), and major metabolic breakdown pathways (conjugation versus oxidation). Particularly in animal studies, BDZs have been associated with reduction of upper airway muscle tone, with increased upper airway resistance as well as blunting of the ventilatory response to hypoxia.[7] Although some studies show benzodiazepines increasing the arousal threshold[8] and worsening oxygen saturation, others do not.[9] Contrary to BDZs, GABAergic non-benzodiazepine (non-BDZ) agents, especially those containing α_1 subunit selectivity, have fewer muscle relaxant effects.[10]

Relatively few of the non-selective BDZs have been specifically evaluated in patients with OSA (flurazepam, midazolam, nitrazepam, temazepam, triazolam), while recent attention has been focused on the interaction of non-BDZs (zolpidem, zaleplon, zopiclone, eszopiclone) and OSA. Clinically important conclusions from these studies include:

1. Midazolam is most reliably implicated for reducing upper airway tone, increasing upper airway resistance, and depressing ventilatory drive. There are case reports of ventilatory failure in patients with existing or risk for OSA. However, use of standard attended sedation techniques appear to be associated with safe outcomes.
2. There appears to be greater safety margin with use of non-BDZ hypnotics in patients at risk for having OSA, but both BDZ and non-BDZ appear to have limited effects on insomnia symptoms. Non-pharmacologic methods of addressing insomnia should be considered first.
3. In certain phenotypes of patients with OSA, careful use of non-BDZ hypnotics may help stabilize ventilation by raising the arousal threshold, thereby decreasing sleep stage related ventilatory overshoot. This is a developing and promising area of therapeutic investigation. In patients with primary central sleep apnea, BDZ may have a limited role in reducing central apnea and arousal frequency.

Opioid agonists

The effects of opioids upon respiration have been well studied. Most studies are either mechanistic ones performed on isolated chemosensitive neural areas such as the brainstem or carotid bodies of animals, or more systemic administration to awake, sleeping, or anesthetized animals or humans. Animal research, supported by limited work in humans, describes opioids acting on medullary respiratory neurons with suppression of respiration rate and respiratory drive (pre-Botzinger complex), central chemoreceptors' response to hypercapnia, peripheral response to hypoxemia (glomus cell of carotid body), and depression of the arousal system. In animal models, μ-opioid receptors and δ-receptors in the motor neuron of the hypoglossal nerve induce suppression of hypoglossal muscle activity with a resultant tendency towards collapse of upper airways.[11] These changes certainly suggest increased risk for patients who have a predilection towards OSA.

Clinical studies again consist of case descriptions of ventilatory emergencies. Others will review studies of larger groups of patients receiving opioid analgesia at this conference. Notably, during chronic opioid administration, the decreases in slow-wave and REM sleep tend to normalize with improvement in sleep efficiency.[12,13] Additionally, most patients develop a tendency towards central or complex sleep apnea patterns, and in some series mild hypoxemia. These effects reverse when opiates doses are lowered or eliminated.[14]

Clinically important conclusions from these studies include:

1. Acute opiate agonist administration may contribute to upper airway collapse and inhibit airway protective mechanisms and ventilatory drive. In susceptible individuals, this may lead to ventilatory emergencies. At present, it is recommended that the risk for underlying tendency towards OSA and ventilatory suppression be assessed prior to administration of opiate agonists. If these agents are needed, enhanced monitoring is advisable.
2. Chronic opiate usage is associated with central and complex sleep apnea syndromes. The clinical implications of these syndromes are not entirely certain, but treatment often involves use of adaptive servoventilation. These sleep disordered breathing problems abate when opiate dosages are reduced or eliminated. Underlying OSA may yet be present in the absence of opiates as in other populations.

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Perioperative Complications of Obstructive Sleep Apnea

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Obstructive sleep apnea (OSA) is a common condition with major neurocognitive and cardiovascular sequelae[1]. Despite the well recognized consequences of this condition, the majority of cases remain undiagnosed and therefore untreated[2]. The reasons for this lack of diagnoses are unclear but likely involve a number of factors. First, there is a general lack of awareness of OSA since patients as well as doctors may be unaware of the established literature in this area. Second, many patients and practioners view the therapy for OSA as cumbersome, thus some may avoid the diagnosis of OSA recognizing that the eventual therapy in most cases is CPAP (continuous positive airway pressure)[3]. Third, in-laboratory polysomnography is expensive and time consuming, leading some to suggest that screening for OSA is impractical particularly in a perioperative setting[4]. Thus, efforts to improve simple and inexpensive screening methods are desirable. Fourth, some have questioned the quality of the data regarding the perioperative complications of OSA, particularly when considering the benefits of intervention[5-7]. For example, although a robust association between OSA and perioperative complications has been observed, the data showing that therapeutic intervention with CPAP prevents complications are more sparse. Thus, some would argue for more compelling data before the major expense and efforts required to address OSA systematically in the perioperative setting can be justified.

Obstructive sleep apnea is characterized by repetitive pharyngeal collapse during sleep[4]. The disease is multifactorial involving a combination of anatomical compromise and failure of protective pharyngeal reflexes to maintain adequate upper airway dilator muscle function. These protective reflexes are selectively lost during sleep (or with certain anesthetics) leading to a predisposition for pharyngeal collapse among those who are anatomically predisposed[8-10]. Other factors also influence upper airway patency including end-expiratory lung volume and ventilatory control instability[11-14]. Recent data suggest highly variable mechanisms underlying OSA in different patients. Thus, strategies to target the mechanism(s) underlying apnea in a given individual have been recommended[15]. Such an individualized approach to OSA therapy has not been studied systematically but the concept of 'personalized medicine' in OSA is now being investigated[16, 17].

OSA complications are also multifactorial, likely a result of intermittent hypoxemia, hypercapnia, catecholamine surges and swings in intrathoracic pressure[1]. With repetitive pharyngeal collapse, gas exchange is compromised leading to hypoxemia and hypercapnia. Most respiratory events terminate with arousal from sleep. Recurrent arousals plus intermittent hypoxemia are thought to contribute to neurocognitive sequelae of OSA. With each respiratory event, catecholamine surges occur leading to tachycardia and blood pressure surges. Evidence suggests that sympathoexcitation is sustained during the daytime as a result of nocturnal surges in catecholamines[18-20]. Negative intrathoracic pressure occurs with respiratory effort against an occluded airway. Negative pleural pressure can contribute to increased cardiac preload and cardiac afterload[21]. Nasal CPAP therapy has been shown to improve OSA by eliminating respiratory events. CPAP leads to improvements in daytime sleepiness (presumably by suppressing arousals and hypoxemia) as well as blood pressure[22-25]. Whether nasal CPAP prevents cardiovascular sequelae is less clear, but some data suggest improvements in arrhythmias and other surrogate outcomes[26].

Nasal CPAP has been associated with improved incidence of fatal and non-fatal cardiovascular events in observational studies[27], although randomized trials will be required to draw any definitive conclusions. Such randomized clinical trials are challenging to perform due to logistical and ethical challenges[4]. In highly symptomatic patients, nasal CPAP is generally recommended to prevent motor vehicle accidents and debilitating symptoms[28, 29]. On the other hand, asymptomatic patients are often poorly adherent with CPAP making any conclusions hard to reach. Thus, advances in outcome data will be challenging, but may require the identification of appropriate surrogate outcome measures, the elucidation of new therapies, and/or comparative effectiveness research to show CPAP is potentially superior to other therapies (e.g. uvulopalatopharyngoplasty or oral appliance)[30, 31].

In the perioperative setting, nasal CPAP therapy likely improves pharyngeal patency and gas exchange abnormalities. Because anesthetic agents can compromise upper airway mechanics[32-34], the peri-operative or post-extubation period represents a time of particular vulnerability for collapse. OSA patients may be particularly susceptible to anesthetic complications due to the pharyngeal compromise induced by pharmacological agents. Thus, nasal CPAP therapy may be highly effective in preventing pharyngeal collapse in the perioperative period. However, definitive data in the perioperative setting for CPAP therapy are lacking. Nasal CPAP may be difficult to tolerate in patients after surgery, particularly in those who have not previously experienced this treatment. As a result,

pre-operative CPAP may help to preserve airway patency and allow experienced patients to tolerate a nasal mask following surgery.

Several factors contribute to the challenge of showing benefits to perioperative CPAP. First, hard perioperative complications are relatively rare in most hospitals such that the ability of CPAP to lower event rates will be difficult to assess without a very large sample size. Minor complications such as brief post-operative desaturation may not be predictive particularly when OSA is defined by intermittent hypoxemia[35]. Second, randomized trials are difficult to blind since anesthesiologists can easily judge which patients may have difficult airways. Risk factors such as neck circumference and Mallampati score are used to assess intubation challenges but are also likely surrogates for OSA. Thus, anesthesiologists may already account for OSA risk based on well established risk factors. Third, the Hawthorne effect describes a phenomenon whereby an outcome measure may be changed simply by measuring it. For example, the knowledge that OSA complications are being monitored may change behaviors (e.g. attending vs. nurse or resident involvement) such that event rates are lowered. Thus, a well designed study to assess whether CPAP prevents hard cardiovascular complications in the peri-operative setting would be challenging.

Given the high prevalence of OSA and the frequency of general anesthesia, major questions remain regarding the optimal management of these patients. The screening for asymptomatic OSA pre-operatively would be cumbersome and potentially expensive and has no proven outcome benefit. Further research will thus be required to optimize management of these patients and to determine the roll of peri-operative CPAP therapy in patient management. Investigation into the mechanisms underlying anesthetic effects on the upper airway would also be desirable to identify new therapeutic targets.

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Sleep Apnea and Inflammation: Perioperative Implications

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Disclosure

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Learning Objectives

Upon completion of this session, participants should be able to

1. Learn the overwhelming evidence supporting the role of obstructive sleep apnea in chronic inflammation
2. Identify the important interactions between obesity, inflammation and sleep apnea
3. Learn how obstructive sleep apnea affects cardiovascular risk

Obstructive sleep apnea (OSA) is characterized by repetitive cessation (apnea) or reduction (hypopnea) of airflow during sleep despite the presence of respiratory efforts due to complete (apnea) or partial (hypopnea) upper airway occlusion during sleep. Although its pathogenetic origins relate to upper airway narrowing during sleep, OSA is associated with adverse effects on various organ systems, including the cardiovascular system.

Endothelial dysfunction due to chronic systemic inflammation and intermittent hypoxia (IH) /oxidative stress plays a key role in accelerated atherosclerosis and increases the risk of cardiovascular disease. Intermittent hypoxia (IH), or repetitive short cycles of desaturation followed by rapid reoxygenation, as seen in OSA may lead to reperfusion injury and atherosclerosis. Hypoxia activates both hypoxia inducible factor-1 (HIF-1), resulting in increased expression of products to increase tissue adaptation to hypoxia such as erythropoietin, vascular endothelial growth factor (VGEF) and inducible nitric oxide synthase (iNOS); and nuclear factor kappa beta (NFκβ), with subsequent increased production of pro-inflammatory cytokines including tumor necrosis factor α (TNF-α), interleukin 6 (IL-6) and IL-8. In persons with OSA, there appears to be relatively greater activation of the NF-κβ-dependent pathway and less activation of the HIF-1–dependent pathway. Obstructive sleep apnea is also associated with changes in endothelial vasoactive mediators, adhesion molecules and coagulation factors.

Both local (upper airway) and systemic inflammation are present in OSA. Proposed mechanisms for upper airway inflammation include (a) mechanical injury from intermittent obstruction leading to airflow turbulence and subsequent pharyngeal mucosal inflammation, as well as (b) systemic hypoxia. There is evidence of local inflammation from nasal lavage fluid (showing increased PMNs, bradykinin and vasoactive intestinal peptide), induced sputum (increased percentage of neutrophils), exhaled markers of airway inflammation (increased IL-6, NO and 8-isopentane), and soft tissues (soft palate muscles and mucosa).

More importantly, OSA is associated with systemic inflammation, and increased levels of circulating inflammatory markers have been described in these patients, including high-sensitivity C-reactive protein (hsCRP), TNF-α, IL-6, IL-8, intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), monocyte chemoattractant protein-1/C–C chemokine ligand 2 (MCP-1/CCL2), and serum amyloid A. Activation of endothelial cells, neutrophils, monocytes and T cells are present in OSA.

There are two general classes of cytokines, pro-inflammatory (TNF-α, IL-6 and IL-8) and anti-inflammatory (IL-10).Cytokines are important mediators of fatigue and sleepiness in OSA. In addition, they serve as markers of inflammation and are predictive of future risk of cardiovascular disease (CVD).

Nuclear factor-κβ (NF-κβ) levels are increased in in neutrophils and monocytes in persons with OSA, correlate with disease severity, and are reduced with positive airway pressure (PAP) therapy.

C-reactive protein (CRP) is an acute phase reactant and nonspecific biomarker of inflammation. It has been shown that hsCRP levels are independent predictors of future CVD events. Data on CRP in persons with OSA are inconsistent. Some studies report that CRP levels are increased in OSA, and that PAP therapy reduces CRP levels. Other studies have found no independent association between CRP and OSA after adjustment for body mass index (BMI).

Tumor necrosis factor α is a pro-inflammatory cytokine, levels of which correlate with signs of early atherosclerosis. Increased levels of TNF-α predict greater risk for future ischemic CVD. Circulating TNF-α levels are elevated in OSA independent of obesity. Hypoxia is the strongest predictor of TNF-α levels in OSA. Levels of TNF-α decrease or normalize with PAP therapy. Finally, TNF-α, itself, may contribute to the pathogenesis of OSA by worsening somnolence and fatigue, and promoting UA inspiratory muscle dysfunction.

Interleukin 6 (IL-6) is another pro-inflammatory cytokine. Increased IL-6 levels are correlated with insulin resistance, atherosclerosis and greater risk for future ischemic CVD events. Early studies suggested increased IL-6 levels in OSA, but more recent studies demonstrate no increase in IL-6 levels after adjustment for BMI. Data on effects on PAP therapy on IL-6 are inconsistent, with some studies showing improvements and others noting no benefit.

Interleukin-8 enhances oxidative stress and elevated levels of this cytokine are associated with increased risk of CVD. Levels of IL-8 are increased in OSA compared to controls, and are reduced by PAP therapy.

Vascular endothelial growth factor (VEGF) is involved with vessel growth and enhances endothelial cell proliferation. The main stimulus for expression of VEGF is chronic hypoxia. Levels of VGEF are increased in OSA, correlate with apnea-hypopnea indices, and are decreased by PAP therapy.

Endothelial vasoactive mediators are involved with vascular homeostasis, and consist of either vasocontrictive factors (endothelin-1, renin-angiotensin-aldosterone system and thromboxane) or vasorelaxant factors (nitric oxide [NO] and prostacyclin). Circulating levels of NO are decreased in OSA, and return to normal with PAP therapy.

Adhesion molecules facilitate interactions between endothelial cells and leukocytes and are upregulated in response to IH. Obstructive sleep apnea is associated with increased levels of ICAM-1, VCAM-1 E-selectin, P-selectin levels. Therapy with PAP has been shown to reduce ICAM-1 levels.

Lastly, a hypercoagulable state is seen in many persons with OSA. Increased levels of activated coagulation factors XIIa and VIIa, fibrinogen, plasminogen activator inhibitor 1 (PAI-1) and thrombin/antithrombin III complexes have been reported in OSA. Positive airway pressure therapy decreases fibrinogen levels and PAI-1 activity.

In summary, OSA can be considered an inflammatory disorder, an oxidative stress disorder, and an atherosclerogenic disorder.

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Pre-Operative Evaluation of OSA: When Can Home Sleep Testing Replace In-Lab Sleep Testing?

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October 11th, 2012

Obstructive sleep apnea (OSA) is a highly prevalent condition affecting 2-4% of the general population. The disorder is characterized by recurrent reductions and cessation in breathing in the face of continued respiratory effort with physiologic sequelae of intermittent oxyhemoglobin desaturations and arousals from sleep. The disorder is associated with excessive sleepiness, neurocognitive impairment, cardiovascular and metabolic outcomes, and early mortality. Concurrent with the increasing recognition of the impact of OSA on general health, there are widespread concerns about undiagnosed and untreated OSA in the peri- and post-operative setting and the potential for complications. Identification of OSA in at risk patients prior to surgery is ideal, but can be limited by the timely availability of in-laboratory testing and patient's reticence for spending a night in the laboratory.

Home sleep testing (HST) represents a specific, focused diagnostic tool that can facilitate the timely diagnosis of OSA in the pre-operative patient when appropriately used. With improvement's in technology polysomnography devices, i.e. HST devices, have become compact and portable and can be performed in the home. The number of physiologic signals increases the complexity of an HST. The majority of HST's that are performed in the United States utilize what are called either type 3 (a minimum of 4 channels – respiratory movement/airflow, ECG/heart rate, and oxygen saturation) or type 4 devices (a minimum of 3 channels, which includes oxygen saturation). More recently, a revised classification system for HST devices has been created by the American Academy of Sleep Medicine (AASM) called SCOPER (Sleep, Cardiovascular, Oximetry, Position, Effort, Respiratory), which may eventually replace the current classification scheme. SCOPER is an attempt to summarize the range of physiologic signals recorded by an HST device. Due to the limited number of channels recorded in type 3 and type 4 HST devices, the standard HST is suited only for the diagnosis of OSA. If respiratory effort is recorded, then the HST can be used to discern between OSA and central sleep apnea (CSA).

Clinicians should, therefore, only order HST, in the setting of a comprehensive sleep medicine evaluation, where OSA is the sole focus of diagnosis. Thirty one percent of patients were estimated to have a concomitant sleep disorder such as chronic insufficient sleep, primary hypersomnia, periodic limb movement disorder, insomnia, or a circadian rhythm disorder. In such situations it may be more appropriate to have full polysomnorgraphy performed rather than HST. An HST is best utilized in patient groups with a high pre-test probability of moderate-severe OSA. The pre-test probability can often be determined by the use of short questionnaires that assess pertinent risk factors for OSA including but not limited to age, obesity, neck circumference, the presence of snoring, and witnessed apneas. HSTs can also be used to monitor response to non positive airway pressure (PAP) therapies or in certain situations where in-laboratory testing is not possible due to patient safety or mobility issues. Based on current AASM guidelines, HST should not be performed in patient's with significant comorbid conditions such as moderate to severe pulmonary disease, neuromuscular disease, or congestive heart failure since these devices generally cannot evaluate for hypoventilation and may not be able to detect central or "complex" sleep apnea. The use of HST is currently discouraged in asymptomatic population since the ramifications of OSA in asymptomatic patients is less understood.

There are certain advantages and disadvantages to HST. In places where access to a sleep laboratory is limited, an HST represents an alternative approach in identifying OSA. Theoretically, since there are less sensors, patients may have improved sleep on the night of testing. In addition, the sleep in the home environment may be more representative of a patient's sleep. Furthermore, HST may allow for performing multiple night monitoring and can assist in monitoring response to therapy more frequently. There are, however, disadvantages to HST. Most HST devices do not assess sleep. The severity of OSA is therefore the sum of apneas and hypopneas divided by recording time. Disordered breathing events due to arousal but with minimal desaturations, cannot be determined. The inability to assess arousal or total sleep time often results in an underestimation of the AHI, with an increased probability of false negative results. Therefore, a negative HST result in a symptomatic patient should be followed by an in-lab polysomnography test. Since most HST does not assess sleep, the test cannot differentiate between REM and NREM sleep. If the device does not have body position sensors or effort sensors, the presence of positional OSA and OSA vs. CSA, respectively, cannot be determined. In addition, since an HST is typically unattended, there is increased propensity for technical failures due to a sensor inadvertently coming off, which may require repeat HST or bringing the patient to the lab. Furthermore, different manufacturers use different sensors to determine the AHI, making comparison between diagnostic devices difficult.

Multiple studies have been performed to validate the use of HST devices. A recent AHRQ sponsored technology assessment recently reviewed the current state of the evidence. With respect to the AHI, the assessment performed a literature review and examined how HST compared with in-lab polysomnography (PSG) performed at different AHI cutpoints. The report concluded that there was moderate evidence that type 3 and type 4 HST devices accurately predict the AHI with reasonable positive and negative likelihood ratios. Type 3 devices alone had a sensitivity of 64-100% and specificity of 48-100% in the identification of moderate-severe OSA (AHI ≥ 15 events/h). It was recognized however, that there was wide range of mean bias when compared to in-lab PSG from -10 to +24 events/h, and that with increasing severity of OSA there is greater disagreement in the AHI between the HST and in-lab PSG as seen by the presence of heteroskesdaticity in a Bland-Altman plot.

Given that HST can identify patients with sleep apnea, the question remains whether a home based approach to diagnosis and therapy results in similar improvements in patient outcomes seen with the standard in-laboratory assessment. Several studies have been published over the last 4 years to address this question. In these studies, patients are randomized to a carepath that involves either standard in-laboratory testing (in-laboratory PSG and CPAP titration study) vs. home-testing (an HST and autoCPAP). Most of the studies included patients referred to a sleep center for evaluation and in some instances were further screened for OSA risk with the use of a questionnaire. The studies were designed as non-inferiority studies with the primary outcomes assessing the change in quality of life, improvements in sleepiness, or the use of CPAP. In the studies, a home-based approach was found to be non-inferior to an in-lab approach to testing. Interestingly in 2 of the studies, the home testing pathway favored increased CPAP utilization, at approximately 30-60 minutes. There are, however, some important caveats with these studies. First, the studies were all done performed in academic settings, in sleep centers with experience sleep physicians, Second, the patients studied were at high risk of OSA based on their referral to a sleep center and/or the additional use of survey instruments to enrich the pre-test probability of OSA. Third, most of the studies allowed for repeat in-home testing and potential cross-over to in-lab testing if needed. Thus, further research is needed to assess this carepath strategy when performed in primary care clinics or pre-operative clinics.

How could HST be implemented in the pre-operative setting? In this situation, the clinician is concerned about the potential for and the prevention of post-operative complications. The limited availability of monitored or intensive care bed resources in a hospital post surgical procedures would suggest that timely identification of OSA in the at-risk patient is desirable. With any test there is typically a trade-off between a highly sensitive (few false negatives) or highly specific test (few false positives). In the pre-operative setting, one would most likely to seek to minimize false negative results for moderate sleep apnea at the expense of increased false positive results. The clinician would therefore favor a screening process with higher sensitivity at the expense of specificity. A staged approach using a two tier testing strategy can facilitate this process where an initial survey instrument to assess sleep apnea risk, followed by HST can identify patients with moderate-severe OSA.

In summary, HST is a test that can be reasonably utilized to assess for OSA in the hands of providers that understand the limitations and pitfalls of HST. The reporting of non-inferior outcomes with a home based strategy compared to an in-laboratory strategy is promising, although further validation in primary care and pre-operative settings is desirable.

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Cannot Intubate, Cannot Ventilate, Can We Eliminate?

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Mask ventilation as an initial ventilation support in emergencies is widely used. There are about 250,000 cases of cardiac arrest annually occurring outside of hospitals, and 370,000 to 750,000 cases occur in hospitals. The total number is close to one million emergent mask ventilations required per year. In addition, about 21 million surgical cases are performed under general anesthesia (GA) and the majority requires mask ventilation during induction of GA. Such emergent ventilation is nearly always provided using a full face mask. Unfortunately, full face mask ventilation is difficult to master, and the skill is hard to retain without frequent re-enforcement. The rescuer has to ensure adequate mask seal, head placement and low jaw advance with one hand and perform bag ventilation with the other hand. Considering the need for emergent ventilation can occur at anytime and anywhere, in-hospital, public places and at home, the ability of medical personnel and the lay public to perform adequate emergent ventilation is far from satisfactory.

The mechanism of UAO in unconscious victims is not fully understood. However, it shares many similarities with that of obstructive sleep apnea (OSA). Continuous positive airway pressure (CPAP) is the standard treatment for maintaining upper airway patency in OSA patients. If the patient is able to tolerate CPAP and use it correctly, its effective rate is nearly 100%. The majority of patients with OSA fail the treatment not because of its low efficacy but because of intolerance. In addition, CPAP via nasal mask (nCPAP) is more effective maintaining airway patency than a full face mask (FmCPAP) in OSA patients. Recently, we demonstrated that applying ventilation through both the mouth and nose was less effective than through the nose alone, and that ventilation occurs primarily through the nasal route even when both routes are used. We also reported that direct mouth to nose breathing is more effective than mouth to mouth breathing in unconsciousness apneic adult subjects. Because the high success rate in OSA patients results from not only the nasal mask, but also from employing CPAP, nCPAP should be more effective in reducing UAO for unconscious victims than FmCPAP.

Currently, it was believed that there are three major components contributing to airway obstruction of the patient with OSA, including muscle relaxation of the pharyngeal dilators, gravity pulling tongue and soft palate down in supine position and the lung volume (FRC) reduction. Likely these three factors play important role in development of upper airway obstruction in patient under general anesthesia. Because nCPAP overcomes the effects of the three attributors in patients with OSA, it should be effective in minimizing the airway obstruction and maintain airway patent during induction of anesthesia. Induction with nCPAP may reduce the incidence of difficult mask ventilation rate, if it can not complete eliminate it.

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Developing Clinical Pathways to Screen, Diagnose and Manage Sleep-Disordered Breathing in the Perioperative Period

- Review challenges in implementing a perioperative OSA program
- Provide an outline for postoperative monitoring
- How to do PAP therapy

The Mayo Clinic Experience

Bhargavi Gali, MD and Peter Gay, MD

Perioperative Management of Patients with Known OSA

Preoperative PAP

Positive airway pressure (PAP) therapy can be administered as a fixed pressure level (CPAP), a variable auto-titrating pressure (APAP), or a bilevel setting (BPAP). Patients with previously known OSA who are non-compliant with their PAP therapy are a challenge in the perioperative period and during an informal poll over 3 weeks time in our preoperative evaluation clinic, an average of 6 OSA patients a week of all severities are not using their CPAP when evaluated. We commonly urge re-initiation of PAP prior to surgery but this is often not considered by the patient, and there is little data on this. We encourage patients with OSA who have been utilizing PAP to continue this preoperatively and to bring their equipment with them to the hospital on the day of surgery as stated by the Anesthesiologists Task Force on perioperative management of patients with obstructive sleep apnea.[2] Many OSA patients still forget to bring their equipment and subsequently cannot recall the pressure for their PAP treatment, so in the cooperative patient we will use an APAP device usually set with a floating pressure window between 5-15cmH_2O while they are in the hospital. In the month of January 2012 alone, our respiratory therapists had 373 first time visits to patients for either a BPAP or CPAP setup while in hospital indicating the large volume of patients using PAP therapy monthly.

A recent study was presented in abstract form at last year's SASM meeting by a Toronto team of investigators.[6] Patients at high risk for OSA based on the STOPBANG questionnaire underwent a home sleep study (Embletta, ResMed Poway, CA) and those patients with an AHI>15 events/hr were subsequently randomized into APAP (64 patients with mean AHI=28.6/hr) or a Control Group (67 patients with mean AHI=25/hr). Patients in the APAP group received APAP for 3 nights preoperatively and then 5 nights postoperatively. Although APAP reduced the mean AHI to 3.2 events/hr, less than half of the patients (N=27) were still using APAP on the third postoperative night, indicating the difficulty with compliance in these recently diagnosed OSA patients who were early APAP users.

Another retrospective observational study from Chicago sought to objectively quantify CPAP adherence in a cohort of presurgical patients diagnosed with OSA during their preoperative workup again using the STOP-BANG screening questionnaire.[7] The patients were seen in their Anesthesia Perioperative Medicine Clinic and underwent a lab-based split night diagnostic and therapeutic titration polysomnogram (PSG) before surgery. Patients newly diagnosed with moderate to severe OSA (AHI of ≥ 15) were offered APAP to take home before surgery and asked to bring the device with them for the perioperative period. There were 211 of 431 referred patients that 'showed up' and completed a PSG and 65% of patients required PAP therapy and started APAP an average of 4 days before surgery. In 75% of patients, the objective CPAP adherence was available from the first 30 days at 6-8 weeks with a sleep specialist guided follow-up and the median adherence was disappointingly very low at 2.5 hours per night with only 25% of patients using their CPAP devices for >4.5 hours/night. Independent predictors of reduced CPAP adherence included African American race, male gender and depressive mood, but it should be noted that patients were not initially seen by a sleep physician prior to the PSG and home APAP titration. Regardless, the protocol as designed did not provide strong encouragement to continue this method of preoperative PAP therapy introduction in first time users.

Postoperative PAP Protocols

Attempts have been made to provide 'just in time' hospital introduction of APAP use in undiagnosed patients who prove to be at high risk for OSA based on a previously verified Sleep Apnea Clinical Score (SACS) questionnaire.[8,9] These authors applied APAP

to patients at high-risk for OSA in the postoperative period following elective total knee or hip arthroplasty and hypothesized that this would reduce postoperative complications and shorten hospital stays. The high-risk patients were randomized to receive standard care plus postoperative APAP or standard care, while low-risk patients also received standard care alone. There were 115 patients of the total 138 (52 low-risk with median AHI= 12.7/hr and 86 high-risk group with median AHI near 25 in both the APAP and control groups) enrolled who also underwent a pre-dismissal (median 3d post-op day), cardio-respiratory sleep study. In the 38 of the 43 APAP patients with adherence data, the median time on PAP while in hospital was 184 minutes/day although first night use was higher at 373 minutes. There were no significant differences in complication rates or length of stay (P = 0.65) for the high risk randomized groups, but patients with an AHI of ≥ 15 randomized to APAP actually had a one day median longer postoperative stay (p = 0.02) possibly due to more sleep deprivation or reduced mobility. Although probably underpowered for the endpoints, this study still could not show any benefit to empiric postoperative use of APAP in first-time users at high risk for OSA.

Presently we use a systematic approach in both surgical and medical hospitalized patients called Obstructive Apnea Systematic Intervention Strategy (OASIS) guided by our sleep specialists who now spend half a day in the hospital seeing patients with observed or suspected sleep disordered breathing.[10] Patients with more hypercapnia and hypersomnolence or overt respiratory failure are transferred to the ICU for initiation of BPAP therapy. If patients are suspected to have OSA as is common on the cardiology and surgical services, they are asked to undergo overnight oximetry. Depending on the severity of the findings they may continue with supplemental oxygen and be offered an outpatient sleep lab followup, trial empiric APAP therapy, or undergo portable cardiorespiratory studies without PSG to obtain an AHI to allow prescription of home going PAP therapy. Although this method is only approved for 'uncomplicated OSA,' we are not paid for any study in the Medicare population anyway and in-hospital PSG studies are notoriously of poor quality. Sadly, those who are offered outpatient evaluations in the sleep lab 'show-up' only about half the time. We are continuing to pursue modifications of the OASIS protocol to optimize treatment plans for all our hospitalized patients with known or suspected OSA, but the Mayo experience is far from finalized.

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The Northwestern Experience

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Developing Clinical Pathways to Screen, Diagnose and Manage Sleep Disordered Breathing in the Perioperative Period

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Challenges in implementing a perioperative OSA program and outline for postoperative monitoring: Northwestern Experience

Increase in perioperative adverse outcomes with obstructive sleep apnea (OSA), American Society of Anesthesiologists published guidelines in the perioperative management of these patients in 2006. OSA has been a growing concern especially in the Midwest with the growing size of our patient population. At Northwestern University in 2006-7 1798 patients (1449 inpatients) had ICD-9 codes indicating OSA. 142 of these patients (7.9%) experienced a Rapid Response Call, a Code Call, or were transferred from the floor to an intensive care unit. This amounted to 1 OSA patient every 4.5 days having an adverse event. This prompted the formation of a multidisciplinary OSA Task force in 2007. The task at hand was to create a perioperative pathway. The team consisted of anesthesiologists, sleep medicine pulmonologist and neurologists, hospitalists, postoperative care unit nurses, floor nurses, respiratory therapists, hospital administration, information technology.

One of the first tasks was screening.

Where to screen? Given the significant limitations of screening in the surgeon's office, or in preoperative holding on the day of surgery, we chose to develop a preoperative clinic. Key to the success of this program is the integration of anesthesia and hospitalist.

How to screen? Although many questionnaires are options we chose to use the Berlin questionnaire to avoid the need to measure neck size.

Developing a testing program for patients screened positive for OSA was the next task. Many options remain available including: A) No testing: we use for emergency surgeries, patient not able to present for testing or surgery date too close to the diagnosis). B) Home testing with overnight pulse oximetry (one channel): we use only to screen those already on therapy to confirm the efficacy of the current CPAP settings. C) Home polysomnogram (4 channels): We use when the patient is within of 5 days of surgery. D) Standard polysomnogram with CPAP titration (8 channels): We use as a gold standard

Developing a testing program for patients with known OSA remained a concern. First home devices were downloaded. No further testing necessary if: AHI<5, SpO2< 90% for <10 % of the time, and compliant with the use of CPAP >4 hours/night. Further testing is necessary if: AHI>5, SpO2< 90% for <10 % of the time and if CPAP compliance < 4 hours/night.

At Northwestern the challenge was to have the surgeons buy-in. We have found that surgeons did not want the extra burden of giving patients a questionnaire and directing them to the sleep medicine clinic. Therefore we have chosen to have the surgeons refer their patients to the perioperative clinic run by anesthesiologists and hospitalists in return for fewer cancellations of their cases and by providing postoperative management of these patients. Thereby, the anesthesiologists/hospitalists taking the burden off the

surgeons' hands. This practice also proved to be favored by the internists/primary care doctors of these patients, whom have moved to more outpatient based practices, opting to transfer care of their patients to the hospitalists postoperatively.

An open policy was set for the preoperative clinic to overcome scheduling issues, to increase surgeon and patient compliance. For this preoperative program to work, it was necessary to educate the patient to the adverse effects of OSA and to the importance of being tested and treated with perioperative PAP therapy. A liaison to the sleep clinic was assigned to arrange for walk-in sleep clinic consult and testing, with results of PSG and PAP treatment recommendations guaranteed before day of surgery. Patient education in the use of the device by the sleep lab and the durable medical equipment (DME) providing the machine became essential to patient compliance. A united electronic medical record (EMR) for ordering and recording patient information was developed to assist with perioperative care.

On the day of surgery more challenges were met during the immediate perioperative period including

Patient challenges: Compliance with use of their PAP therapy especially in the nights leading up to their surgery and forgetting to bring in their system to the hospital. This was attempted to be remedied by calling and instructing patients to use their PAP therapy the night before and to bring in only the mask and tubing of their machines. This also cut down on the need for the respiratory therapists to be familiar with multiple different kinds of machines, which can result in mistakes.

Anesthesiologist challenges: Education and compliance of the anesthesiology team with assessment of OSA patients and calculation of an ASA OSA risk score. The risk score is used to aid in disposition of the patient (outpatient vs. in-patient; if an in-patient: floor vs. continuous pulse oximetry vs. ICU), type of anesthetic, choice of medications, PACU length of stay and appropriation of PAP devices and continuous pulse oximetry units. Initially, a paper calculation of the ASA OSA risk score was used. This was followed only by approximetly half of anesthesia providers. Later, with the help of IT, the ASA OSA risk score was transferred to the EMR of patients' preoperative assessment. This tool automatically calculates the patients risk with modifiers such as preoperative PAP use, high PaCO2 >50 or HCo3>30 or significant cardiac problems and the risk score is populated into the anesthesia assessment and postanesthesia care unit nurses notes automatically. Again with IT's help postoperative OSA order sets were built-in to the existing Phase I postop order sets which decreased the anesthesiologists' workload.

Postanesthesia Care Unit (PACU) Nursing challenges: Education and compliance with the postoperative care of these patients was remedied by repeated in-services on perioperative management of these patients' and their risks. Once the nurses were on board they were instrumental in increasing compliance of the anesthesia team to designate an ASA OSA risk score and follow the patient in PACU. There were written instructions for the PACU nurses to follow depending on the patients' OSA score. Another challenge was to get patients off of oxygen in the PACU as soon as possible and to start their PAP therapy. The written instructions have helped in this regard. The other was that the patients would be monitored in the PACU for 2 hours on room air with/without PAP therapy. Since they did not want to keep the patient in PACU longer than necessary, they were motivated to wean the patients' oxygen to room air.

Floor Nursing Challenges: Education of the nurses on management of OSA patient was the most important on the floor, since they are the first responders. The use of the continuous pulse oximetry system was new to our hospital as well as the floor nurses. Therefore education via lectures and in-services were carried out, with several nursing managers available when questions arose. Details of the management protocol are outlined in the flowchart as well as in the postoperative PAP therapy section.

Respiratory Therapists challenges: Education and increasing work load were the major challenges, which were met by teaching and designation of few more super user respiratory therapists.

Hospital Administration challenges: This was the biggest challenge in term s of this programs success. If there were no allocated funds designated to the purchase of continuous pulse oximeters with the wiring on certain floors to accommodate the remote monitoring of these monitors and automatic paging system this effort would have been futile.

Peri- Operative planning:

1. Timing- When to start PAP: PAP therapy is more successful in reducing peri-operative complications when introduced at home, with sufficient time and support to assure comfort and compliance.

2. Home device vs Hospital device: Many hospitals make the choice to use patient owned equipment in the peri-operative setting. This is done to both reduce cost and in an attempt to improve comfort and compliance by keeping things as familiar as possible for the patient. There are significant limitations when using these strategies: 1) Lose of RT training and mastery of the PAP device is a patient safety issue. 2) Patients should not be relied upon to bring their own devices as their failure to remember the device will lead to a failure to receive therapy. 3) Need for biomedical clearance of every home device may slow down the process.

3. CPAP vs APAP: There have been suggestions that APAP may be a better option in the Perioperative period as compared to CPAP. No head to head trials have been published. The concern is that APAP may not respond well to narcotic related central apnea events. This concern should be balanced against the need to have a therapy that will be available when the patient has not had previous titration to establish appropriate PAP settings. We chose to obtain Bi-Level auto devices, as these allowed us to use many modes which would be available in that device (CPAP, Bilevel (S), auto Bilevel). We developed an "NMH standard" for auto settings (EPAP min= 5, IPAP max=15, PSmax=4). This was developed so that MD's that are unfamiliar with the technology to have a starting place. We kept IPAP max low to reduce the risk of 1) central apnea 2) runaway pressure due to mask leak 3) aerophagia and 4) pressure intolerance. The caveats are that 1) starting pressure this low may result in ineffective therapy 2) hypoventilation without upper airway obstruction and/ or central apnea will not be addressed by this technology and 3) this not critical care level equipment and has no display of wave forms.

4. Should good CPAP users be put on APAP in the peri-operative setting? It has been suggested by some that everyone should go on APAP in the peri-operative period. If the patient is well controlled and compliant on a standard CPAP device, we do not change the settings or empirically use an APAP. There may be a need for setting changes in response to anesthetic, so monitoring is needed. The patients should use hospital equipment so that adjustments could be made if needed.

5. When it is preferable to use patient owned equipment? There are patients whose needs cannot be meet by APAP or CPAP, such as those with neuromuscular disease, primary central apnea or complex apnea. We have pragmatically agreed that for these patients use of home equipment is necessary and encouraged. These patients are instructed to bring their home devices, and an assessment is made by anesthesia about the need to extubate in the PACU vs ICU. Remember that the devices have no batteries and would not be available for transport if needed.

6. Improving Comfort and Tolerability: We chose a device with an internal heated humidifier to improve comfort. Avoid using heated wire systems as this would make O2 bleed-in a challenge. Use independent stands so that the device can get close to the bed and have more stability (also less likely to "walk off"). Nasal bridge gel pads should be available if needed.

7. Mask issues: Patients should be encouraged to bring their home masks as these will fit best although a variety of mask should be available including nasal pillows and nasal masks in addition to full face masks. Ordering specialty masks ahead of time will help. "Around the ear masks" may be needed for those with a Halo or Neck brace (IE: Bella or Nasalaire). "Oral only masks" may be needed for those with nasal or sinus surgery (IE: Oracle or Liberty sans pillows). Chin straps should be available to treat mouth leak.

8. Contraindications to PAP: Those with poor mental status, dementia, bulbar impairment, severe nausea/vomiting or severe claustrophobia may not be able to PAP successfully and need other plans. Elevating the head of bed to 35-45 degrees may help. Use of lung volume recruitment maneuvers may reduce atelectasis and hypoventilation.

9. The role of the DME company in peri-operative PAP use: Engaging a group of DME companies to facilitate the program PAP devices will be helpful. They will have to be able to provide equipment with fast response times, work well with the sleep lab as well as hospital discharge planners.

10. Hospital monitoring of PAP therapy: Telemetry pulse oximetry as well as PAP downloads should be available in real time through the hospital computer network. This will facilitate sleep consultation when needed. This will allow for evaluation of respiratory status before discharge or before discontinuing aggressive in patient monitoring. Should there be a need to triage the use of monitors the ability to review PAP and saturation data will be very helpful.

Uncovering the Genetic Architecture of Ventilatory Traits

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The generation of the respiratory rhythm involves interactions among genes, development and organ systems, reflexes, etc. and reacts to changes in the internal disorders (e.g. disease) and external environments (e.g. altitude). An inherited basis for respiratory instability is shown from familial studies in humans of these disorders and from studies in genetically engineered knock-out mice (Han and Strohl 2000). The problem is that a physical location of naturally occurring genetic variations has not been identified (Yamauchi, Kimura et al. 2010).

The C57BL/6J (B6) strain is a preclinical model that may give some insight in to which part of genome infers genetic risk. The B6 strain of mice exhibits during resting breathing spontaneous pauses and post-sigh apneas (Stettner, Zanella et al. 2008; Yamauchi, Ocak et al. 2008), as well as the trait of post-hypoxic recurrent apneas, in contrast to the A/J strain which do not (Han, Subramanian et al. 2002). This basic observation indicates an inherent respiratory stability somewhere in the A/J genome. Furthermore, while breathing rate is lower in both strains, apnea length is prolonged in the B6 with administration of an inhibitor of neural nitric oxide synthase, but apnea is not produced in the A/J strain (Price, Han et al. 2003). Use of buspirone either acutely or chronically, as a 5-HT agonist (Yamauchi, Dostal et al. 2008; Moore, Chai et al. 2012), inhibitors of hydrogen sulfide produce (Donovan, Moore et al. 2011), and acetazolamide (Yamauchi, Dostal et al. 2007) mitigate apnea and pauses in the B6.

We previously reported, using mouse chromosomal substitution strains (Nadeau, Singer et al. 2000), that post-sigh apneas in the B6 could be reversed by introducing chromosome 1 from the A/J on the B6 background (the C57BL/6J-Chr $1^{A/J}$/NaJ or B6a1 mouse) (Yamauchi, Ocak et al. 2008). A follow-up study of this strain was designed to uncover candidate genes and regulatory pathways that are involved in ventilatory stability (Gillombardo, Yamauchi et al. 2012). A genetic and phenotypic analysis of an intercross study between these strains uncovered three quantitative trait loci (QTLs) on mouse chromosome 1, with phenotypic effects. Fine-mapping reduced the genomic intervals and gene content, and the introgression of one QTL region back onto the C57BL/6J-Chr $1^{A/J}$/NaJ restored the trait. This work directly demonstrates the impact of elements on mouse chromosome 1 in respiratory rhythmogenesis (Figure 1).

In order to further elucidate potential subcellular differences between the B6, B6a1 and A/J which may underlie differential control of breathing in these animals, we subjected medulla and pons to microarray analysis. Figure 2 describes the strategy for data collection prior to the mRNA array analyses. Tissue was collected from the medulla as it is the location of the nucleus tractus solitarius (NTS) which receives afferent projections from the carotid body via the glossopharyngeal nerve. The medulla also harbors the pre-Botzinger complex — widely regarded as the main pacemaker of respiratory frequency (Spyer and Gourine 2009). Tissue was also collected from the pons, a chief modulator of medullary output, and abolition of the PHFD phenomenon has been found following lesions in the A5 region of the ventrolateral pons in rats (Coles and Dick 1996).

The medulla is the so-called "inspiratory center", which is innervated by branches of the vagus and known to both communicate the information from pulmonary stretch receptors and contribute to the Herring-Breuer reflex. Some have theorized that inspiratory inhibition generated by this region of the medulla, in response to stretching of the pulmonary parenchyma, is a mechanism by which post-sigh apneas are produced (Rybak, Shevtsova et al. 2004). When examining medullary transcriptome A/J, B6a1 and B6 mice, we observed that 2 upregulated and 3 downregulated genes in the B6a1, A/J pair versus the B6 which were encoded on chromosome 1 and possessed non-synonymous SNPs in the A/J vs the B6. The two downregulated genes were apoa2, and vcpip1. Apoa2 is an apolipoprotein which is found most abundantly in HDL, and when overexpressed in mouse tissue is found to result in amyloidosis in liver, heart, and tongue but was not detectable brain using current techniques (Ge, Yao et al. 2007). In humans, polymorphisms in Apoa2 have been associated with increased BMI (Corella, Peloso et al. 2009). The two genes upregulated in the B6a1- A/J medulla in comparison to that of the B6 were Sdhc and Mpz. Sdhc is the c subunit of succinate dehydrogenase, a component of complex

II of the electron transport chain, and has been associated with multiple endocrine neoplasia syndromes, pheochromocytomas, and paragangliomas in humans (Pasini and Stratakis 2009). Sdhc also known to increase intracellular oxidative stress resulting in apoptosis and tumorigenesis (Ishii, Yasuda et al. 2005). Furthermore, mutations in succinate dehydrogenase have been found to upregulate HIF-1-alpha expression in response to "pseudohypoxia" (Cervera, Apostolova et al. 2008). Mpz, or myelin protein zero, is a glycoprotein which is known to be integral in the compaction of myelin in the peripheral nervous system, and mutations in mpz are thought to be the cause of peripheral neuropathy in Charcot Marie Tooth disease (Shy 2006).

The pons has long been known to play a crucial role in the control of respiration. The rostral pons contains the pneumotaxic respiratory center. This region is capable of limiting inspiration by inhibition of the dorsal medullary ventilator group. This is evidenced by the apneusis which occurs when this area is ablated (St-John 1998). Caudal portions of the pons are thought to provide tonic excitatory drive to the medulla. In the pontine samples of the B6 versus the A/J and B6a1 animals, four genes were found that differed significantly between these two groups, were found on chromosome 1, and had non-synonymous SNPs. Two of these genes were downregulated in the B6a1-A/J versus the B6, and these included apoa2, and cd84. Cd84 is a receptor of the SLAM (signaling lymphocytic activating molecule) family found primarily on lymphocytes (Limaye, Belobrajdic et al. 2008). This gene was also previously found in a region of interest on chromosome 1 which was associated with neural tube defects in the loop-tail mouse (Doudney, Murdoch et al. 2001). Similar to the medulla, the two genes which are upregulated in the B6a1-A/J versus the B6 are mpz, and sdhc.

As for genes which were either upregulated or down regulated in the B6 (unstable breathing) vs. the B6a1-A/J (stable breathing) differences in both the medulla and pons might indicated stability in genetic architecture across the respiratory neuroaxis in the brainstem. SDHC was observed to be upregulated in both the medulla and pons. Downregulated in both regions were the genes TnnI1, Wdfy1, Arl4c, CDH20, DARC, and Apoa2. TnnI1 encodes Troponin I type 1 and has been previously been found using expression QTL (eQTL) techniques to be a candidate gene for differential forebrain mass in B6 versus DBA2J mice (Lu, Wei et al. 2008). Wdfy1 is a zinc binding domain containing protein which has been found to be related to alcohol consumption in mice (Mulligan, Ponomarev et al. 2008). Arl4C is also known as ADP ribosylation Like 7 and has been found to interact with tubulin and modulate intracellular transport of vesicles (Wei, Xie et al. 2009). CDH20 is a cadherin which is present in the neural tube during embryogenesis, and is thought to play a role in the developmental organization of neural circuitry (Moore, Champeval et al. 2004). Darc is a chemokine receptor which has been found to be expressed in the CNS in the purkinje cells of the cerebellum (Horuk, Martin et al. 1996). Another chemokine receptor not found to be significant in this particular analysis, CXCR4, has been found recently to play a role in glutamate synaptic activity in the dorsal raphe nucleus, (Heinisch and Kirby).

Although we are, at present, unable to mechanistically link these candidate molecules to ventilatory phenotype, the gene products and pathways associated with loci reported herein should inform future research on central respiratory control.

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Figure 1. Plethysmographic Tracings of Breathing Behavior

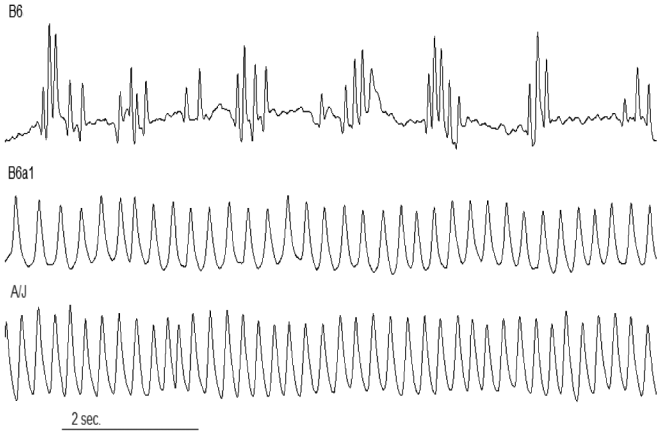
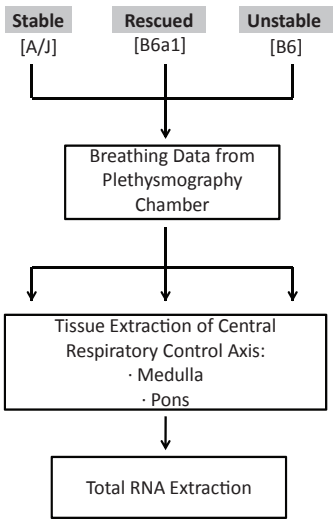


Fig1. Representative tracings of B6, B6a1, and A/J breathing behavior in the first 30 seconds of reoxygenation with 100% O_2 following 5 minutes of poikilocapnic hypoxia (8% O_2, bal-N_2).

Figure 2. Flow Chart of Data Collection Stable [A/J]Rescued [B6a1] Unstable [B6] Breathing Data from Plethysmography ChamberTissue Extraction of Central Respiratory Control Axis:· Medulla· PonsTotal RNA Extraction



Sleep and Anesthesia: Common Mechanism of Action?

Mervyn Maze, MBBS

Introduction

Many sedatives, while producing a state akin to "pharmacologically-induced sleep", in fact produce a state with important differences to natural sleep. An important exception are the alpha2 agonists that produce a state of sedation that is closer to natural sleep than drugs that target the $GABA_A$ receptor (that includes the benzodiazepines and propofol). Here we review the neurobiology of natural sleep, comparing and contrasting to different types of sedation and discuss the potential consequences thereof.

Function of sleep

Sleep has anabolic, restorative properties that improves both neurocognitive and immune function. During NREM sleep slow wave activity performs a homeostatic function to reduce the strength of synapses that has been acquired during wakeful activity[1]. This synaptic homeostasis improves subsequent cognitive function by allowing new changes in synaptic strength. For example both NREM and REM sleep are necessary for the consolidation of learning and memory and sleep deprivation results in cognitive dysfunction perhaps predisposing to delirium[2].

Overlapping Neural Mechanisms of Sleep & Sedation/Anesthesia

The circadian rhythm determines the appropriate timing of sleep while the aforementioned homeostatic process regulates sleep debt and depth depending on wakeful activity[1]. It follows that a subject can regulate the type of sleep (e.g. duration of slow wave activity) that is required based on need and that sleep is not a homogenous state. The stages of sleep are well categorized and have distinct behavioral and EEG signatures influenced by the balance between the ascending arousal and sleep promoting systems. These circuits are probably arranged in a manner analogous to a flip-flop or bistable switch of mutual inhibition to provide stability — so that once in a particular state (awake or asleep), each side of the switch inhibits the activity of the other side (i.e. the wake cells inhibit the sleep cells and vice-versa). This arrangement ensures that the person does not frequently transition between states of sleep and wakefulness; abnormal function of this switch is thought to explain narcolepsy.

A pivotal role for inhibitory hypothalamic nuclei, the venterolateral preoptic (VLPO) and median preoptic nucleus have been demonstrated in numerous studies of sleep[3]. During sleep these inhibitory nuclei are active (ie. they are inactive in the awake state), releasing inhibitory neurotransmitters to suppress excitatory nuclei (that release arousal promoting amine-based neurotransmitters). The majority of the sleep-active neurons of the median preoptic nucleus release GABA into the arousal promoting nuclei of the lateral hypothalamus including the orexinergic perifornical nucleus (Pef). The VLPO contains both inhibitory γ-amino-butyric acid type (GABAergic) and galanin type neurons. When activated, during sleep, the VLPO inhibits the histaminergic tuberomamillary nucleus (TMN), the orexinergic perifornical nucleus (Pef) and the norepinephrinergic locus ceruleus (LC) reducing the excitatory drive produced by histamine, orexin and norepinephrine neurotransmission[3]. Conversely during wakefulness the VLPO is itself inhibited by excitatory activity in the TMN and LC. Excitatory orexinergic neurons act to stabilize this sleep-wake switch, as they do not innervate the VLPO and thus reinforce activity in arousal systems when activated. Sedatives and anesthetics target the sleep pathway to produce some of their sedative-hypnotic effects[4,5]. The majority of sedatives such as the benzodiazepines and propofol, act by activating $GABA_A$ receptors[12]. GABAergic anesthetics increase activity in the VLPO (though to a lesser degree than in NREM sleep[6]) and inhibit activity in critical arousal-promoting nuclei such as the histaminergic TMN[4,7] and the orexinergic Pef [8] similar to sleep. Unlike natural sleep, however, they exert little effect on norepinephrinergic activity in the LC [4,9]. Sedatives also act in a less discrete fashion (than sleep), targeting the cortex at lower doses and at higher doses targeting the spinal cord to inhibit motor reflexes.

In contrast alpha2 agonists reduce noradrenergic activity in the LC and thus activate the VLPO thus their mechanism of action overlaps more closely with sleep). However alpha2 agonists do not blunt orexinergic signaling this may explain the relative rousability of patients from dexmedetomidine sedation[2]. In turn this may allow better neurological examination of the patient and weaning from mechanical ventilation.

Overlapping Neuroimaging & Electroencephalographic Signatures of Sleep & Sedativehypnosis?

Many of the restorative properties of sleep occur during the slow wave activity phase of NREM sleep; here delta waves predominate. In lighter stages of sleep waxing and waning alpha frequency oscillations (so-called "sleep spindles" characteristic of stage II NREM sleep) occur as the thalamus becomes hyperpolarized and enters a bursting mode. In contrast, the EEG during REM sleep shows asynchronous high frequency activity and hippocampal theta rhythm.

The EEG patterns under sedative-hypnosis are typically poorly defined versions of the patterns seen during NREM sleep (e.g. spindles are typically slower). While GABAergic drugs may induce sleep-like patterns of activity (likely via modulating hypothalamic activity), they also distort the EEG by direct effects on corticothalamic networks. Notably alpha2 agonists produce a state that shares remarkable similarities with NREM sleep: showing both spindles and delta waves. Spindles are a late phenomenon during GABAergic sedation as the thalamus is only deactivated at higher drug doses. We attribute this to unperturbed noradrenergic signaling from the LC during GABAergic sedation. In contrast, alpha2 agonists suppress noradrenergic signaling and thus reduce thalamic activity. We have recently proposed that curtailing noradrenergic signaling during sedation is important to reduce connectedness to the environment (akin to lack of awareness of our surroundings in sleep where noradrenergic signaling is also blunted). GABAergic drugs suppress consciousness, but not connectedness, and thus patients are able to interact with their environment at reduced levels of consciousness. This produces an acute confusional state similar to sleep inertia, delirium. Sleep inertia is rare on arousal from REM sleep as the patients are conscious (dreaming) before they become connected to the external world. However in contrast to abundant evidence for NREM patterns of neural activity during sedation, evidence for REM-like activity during sedation is rare. It is therefore unlikely that the physiological roles of REM sleep are fulfilled by sedation.

An aim of sedation should be to reduce connectedness to the environment, limiting the unpleasant experience of critical illness and the ability to interact with the environment. The latter is important at reduced levels of consciousness where interaction with the environment may lead to the inadvertent removal of lines or endotracheal tube.

Can sedation fulfill the physiological role of sleep? In humans EEG data support the concept that alpha2 agonists produce a state more akin to NREM sleep than GABAergic agents. This is supported by the drugs' mechanisms of action and further indirect evidence such as the release of growth hormone. Growth hormone is released during slow wave sleep and is higher in patients sedated with dexmedetomidine than propofol. Patients sedated with dexmedetomidine are also less susceptible to infections than counterparts on GABAergic medication[10], while this is plausibly related to direct effects on the immune system, it could be that dexmedetomidine produces a more restorative state of sedation[2]. Nonetheless we stress that definitive outcome studies showing patients sedated with dexmedetomidine have "better" sleep than patients on GABAergic drugs are still lacking.

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Pathogenesis of Upper Airway Obstruction During Sleep: Implications for Sedative Management

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Obstructive sleep apnea is a disorder caused by recurrent episodes of upper airway obstruction during sleep. These episodes lead to repeated oxyhemoglobin desaturations and arousals from sleep, accounting for significant neurocognitive, metabolic and cardiovascular morbidity and mortality. Obesity, male sex and postmenopausal status constitute major risk factors for this disorder. The impact of these risk factors on upper airway function, however, is not well understood.

Investigators have demonstrated that upper airway function can be modeled as a simple collapsible conduit or Starling resistor[1]. In this model, a collapsible segment is subject to a surrounding or critical pressure (P_{crit}) that governs its collapsibility. The critical pressure determines the degree of upper airway obstruction as follows. First, the upper airway collapses and flow limits on inspiration as the downstream (tracheal) pressure falls below P_{crit}. In fact, as downstream pressure falls, inspiratory airflow rises to a maximal level and plateaus thereafter, becoming independent of further decreases in downstream pressure. This pattern is often associated with snoring during inspiration, which is due to vibratory collapse and reopening of the upper airway as flow oscillates around a maximal level. Nonetheless, the flow-limited upper airway does not occlude, indicating that downstream 'suction' pressures cannot account for the development of complete obstruction in sleep apneic patients.

To occlude the upper airway, the pressure upstream to the collapsible (flow-limiting) site must be lower than a critical tissue pressure surrounding that site. When upstream pressure is lowered experimentally in normal individuals below a critical pressure, the upper airway occludes and recurrent obstructive apneas ensue[2]. Alternatively, when the critical pressure rises above atmospheric pressure, obstructive apneic episodes are observed repeatedly in patients with obstructive sleep apnea. Investigators have demonstrated that quantitative differences in critical pressures, reflecting differences in pharyngeal collapsibility, distinguish among groups with varying degrees of upper airway obstruction clinically between health (normal breathing) and disease (obstructive sleep apnea).

In general, increases in pharyngeal collapsibility are related to structural alterations in pharyngeal anatomy and/or disturbances in its neuromuscular control. Investigators have developed precise methods for characterizing pharyngeal structural and neuromuscular properties in sleeping individuals[3], and have applied these methods to determine whether structural and/or neuromuscular defects play a role in the pathogenesis of obstructive sleep apnea[4;5]. Recent studies have documented a structural/anatomic predisposition to upper airway obstruction in apneic patients compared to normal individuals, as characterized by elevations in passive P_{crit}. Obesity and male sex increase passive P_{crit}, as do positional maneuvers such as mouth opening, mandibular retrusion, neck flexion and lying supine rather than on the side.

While anatomic loads can increase in an individual's susceptibility to sleep apnea, this defect can be mitigated by upper airway neuromuscular activity, which can restore pharyngeal patency during sleep. This activity can be modulated by chemical and mechanical stimuli to ventilation including airway pressures, pulmonary stretch receptor feedback, and alterations in gas exchange. These afferent signals are triggers by upper airway obstruction, and can restore upper airway patency. Investigators have provided strong evidence for disturbances in upper airway neuromuscular responses to airway obstruction in sleep apnea compared to normal individuals. These disturbances are related to a loss of tonic (expiratory) pharyngeal neuromuscular activity, leading to a primary defect in upper airway neuromuscular control in patients. As tonic neuromuscular activity wanes at sleep onset, obstruction ensues when reflex responses fail to relieve the obstruction during sleep.

These findings suggest a "two hit" hypothesis for sleep apnea pathogenesis consisting of both defects in structural and neuromuscular control.

Obesity is a major risk factor for obstructive sleep apnea. In further studies, investigators have demonstrated that obesity leads to elevations in passive P_{crit}, reflecting increased anatomic loading of pharyngeal structures. This defect may be caused by adipose deposition around upper airway structures and by concomitant decreases in resting lung volumes which elevates the passive P_{crit} when

caudal traction on upper airway structures falls at lower lung volumes. In fact, a male distribution of adiposity (central) is associated with further elevations in passive P_{crit} compared to similarly obese women with a peripheral pattern of fat distribution. Women are further protected from developing upper airway obstruction during sleep because their active neuromuscular responses are generally better preserved than their male counterparts. Thus, differences in fat distribution as well as active neuromuscular responses protect premenopausal women from developing sleep apnea compared to men and postmenopausal women.

In summary, obstructive sleep apnea is caused by elevations in upper airway collapsibility during sleep, which is produced by alterations in upper airway anatomy and disturbances in neuromuscular control. Sedation and anesthesia mimic the sleep state, and predispose to upper airway obstruction with potentially devastating consequences. Clinically, it is important to identify patients at risk for developing airway obstruction in the peri-operative setting, monitor these patients and detect obstruction before ventilation and oxygenation deteriorate and untoward cardiovascular compromise occurs. Complementary approaches to the study of upper airway function will serve to establish specific pathogenic mechanisms and to probe the specific humoral and genetic factors that modulate the development and expression of this disorder.

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Nasal or Oral Ventilation in Anesthetized Subjects?

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Human subjects have two breathing routes; nasal airway route and oral airway route. Depending on the tasks, ventilatory demand, and preference, we can voluntarily or involuntarily breathe through either the nose or mouth, or both during wakefulness. Obviously, anesthetized and paralyzed subjects do not have the neural control of selecting the optimal breathing route and the route of ventilation is determined by the anesthesiologist's techniques used for artificial mechanical ventilation in addition to the structural properties of the airway routes.

Optimal Ventilation Routes in Anesthetized Subjects

Upon introduction of positive pressure ventilation for resuscitating apneic victims, Safar et al. first systematically examined effective ventilation route to obtain successful larger tidal volume in anesthetized subjects while the airway maneuvers were performed (Safar P, et al. *JAMA* 1958). They found that the mouth-to-mouth ventilation produced more tidal volume than the mouth-to-nose ventilation. Since then, the mouth-to-mouth ventilation with triple airway maneuver (mouth opening, mandible advancement, neck extension) became our standard for cardiopulmonary resuscitation. Nobody questioned this principle until Jiang and his colleagues just recently re-examined it and found that ventilation through the nose produced greater tidal volume than ventilation through the mouth in anesthetized non-paralyzed subjects without airway maintenance maneuvers (Jiang Y, et al. *Anesthesiology* 2011). Noticeably, no significant difference of ventilation efficacy was observed when the head was extended.

We recently tested a hypothesis that optimal ventilation route varies depending on the maneuvers used for airway maintenance. The hypothesis was tested by measuring tidal volumes during oro-nasal, nasal and oral ventilation with using a custom-made oro-nasal portioning full facemask in anesthetized and paralyzed patients receiving pressure controlled ventilation (unpublished). Despite using different ventilation routes, we found no difference of the tidal volume when the head and mandible was maintained in the neutral position and when the head was extended. In contrast, when the mandible was advanced, the tidal volume was smaller during nasal ventilation than oro-nasal and oral ventilations. Our results agree with our previous finding that mandible advancement failed to improve nasal airway patency in obese subjects (Isono S, et al. *Anesthesiology* 1997) and the finding by Safar et al. that the mouth-to-nose ventilation failed particularly in obese subjects (Safar P, et al. *J Appl Physiol* 1959).

Effects of Muscle Paralysis on Contribution of Nasal and Oral Airway Route to Ventilation

We systematically examined influences of muscle relaxants on ventilation efficacy and contribution of nasal and oral airway route to the ventilation in anesthetized subjects while receiving positive pressure ventilation in the neutral head and mandible position (Ikeda A, et al. *Anesthesiology* 2012). We found that rocuronium administration did not change the ventilation efficacy and ventilation partitioning between the airway routes. In contrast, succinylcholine administration improved the ventilation efficacy by 30% primarily because of increase of oral ventilation partition. We endoscopically observed oral airway dilation at the isthmus of the fauces during succinylcholine-induced fasciculation. The results do not support advantage of the nasal ventilation but rather support either oral or oronasal ventilation during anesthesia induction particularly with using succinylcholine. In fact, Amathieu et al. recently reported that difficulty of facemask ventilation improved after succinylcholine injection in morbidly obese patients with oral airways (Amathieu, et al. *Anesthesiology* 2011).

Obstruction at the Soft Palate During Nasal Ventilation

In our series of human studies under general anesthesia and paralysis, collapsibility of the retropalatal airway region was significantly higher than that of the retroglossal region in both apneic and non-apneic subjects even during airway improving maneuvers, suggesting an advantage of the oral ventilation by avoiding the most collapsible airway route. However, this is still speculative since the airway at the isthmus of the fauces, possibly the narrowest and most collapsible region along the oral airway route, was not assessed and compared with the retropalatal airway in these studies. Furthermore, the airway collapsibility was assessed under static, no airflow situation in these studies and dynamic pharyngeal airway behavior during mechanical ventilation may differ from the behavior under static condition.

Safar et al. previously noticed impairment of the mouth-to-nose ventilation due to expiratory obstruction in subjects with mouth tightly closed (Safar P, et al. *Anesthesiology* 1959). He speculated that the phenomenon was possibly caused by a valve-like behavior of the soft palate resulting in progressive increase of the lung volume without exhalation. We endoscopically confirmed his speculation and found that the expiratory obstruction at the soft palate occurred in patients with higher closing pressure at the soft palate and patients with sleep disordered breathing (Iiyori, et al. ATS abstract). Increase of EPAP level above the closing pressure reversed the expiratory obstruction. Buffington et al. recently reported that anesthesiologists experienced expiratory obstruction in 34% of 90 adult surgical patients during anesthesia induction despite airway maneuvers while inspiratory obstruction was effectively reversed by the maneuvers (Buffington CW, et al. *Open Journal of Anesthesiology* 2012). They found the expiratory obstruction more frequently occurred in patients with impaired retropalatal space and identified advanced age, large tongue, and large uvula as clinical predictors of the expiratory obstruction.

In conclusion, in anesthetized subjects, there is only limited evidence supporting advantage of ventilation through the nose and the combined oral and nasal ventilation with a full facemask while applying triple airway maneuvers is recommended.

Perioperative Pulmonary Complications In Patients with Obstructive Sleep Apnea

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Adverse events affecting the pulmonary system remain one of the most common and significant complications in the perioperative period.[1] Patients with obstructive sleep apnea represent an especially challenging patient population to the perioperative physician and may be at particularly high risk for pulmonary complications.[2] However, the mechanisms that lead to increased vulnerability among this patient group remain poorly understood. The goal of this presentation is to discuss the epidemiology of pulmonary complications and present potential reasons for the increased risk of this phenomenon among SA patients. Special attention will be given to orthopedic patients, as this population is increasing dramatically and has an especially high incidence of SA.

Recent publications have shown that SA represents an independent risk factor for complications involving the lung. Gupta et al[3] and Kaw et al.[4] showed that SA was associated with significantly increased odds for repiratory failure, reintubation and intensive care admissions. Further, a population based study patients with SA developed pulmonary complications more frequently than their matched controls after both orthopedic and general surgical procedures, respectively (i.e., aspiration pneumonia: 1.18% vs 0.84% and 2.79% vs 2.05%; ARDS: 1.06% vs 0.45% and 3.79% vs 2.44%; intubation/mechanical ventilation: 3.99% vs 0.79% and 10.8% vs 5.94%, all P values <0.0001). Comparatively, PE was more frequent in SA patients after orthopedic procedures (0.51% vs 0.42%, P = 0.0038) but not after general surgical procedures (0.45% vs 0.49%, P = 0.22). SA was associated with a significantly higher adjusted OR of developing pulmonary complications after both orthopedic and general surgical procedures, respectively, with the exception of PE (OR for aspiration pneumonia: 1.41 [1.35, 1.47] and 1.37 [1.33, 1.41]; for ARDS: 2.39 [2.28, 2.51] and 1.58 [1.54, 1.62]; for PE: OR 1.22 [1.15, 1.29] and 0.90 [0.84, 0.97]; for intubation/mechanical ventilation: 5.20 [5.05, 5.37] and 1.95 [1.91, 1.98]).[2]

While some pulmonary events such as aspiration pneumonias may be linked to relative dysfunction of the pharyngeal muscle in SA patients, we hypothesize that the reasons for other complications like ARDS may at least in part be linked to the relatively high rates of pulmonary hypertension found among patients with SA.[5] Pulmonary hypertension is known to be associated right heart dysfunction as well as pulmonary inflammation.[6] Perioperative events such as hypoventilation and dose dependent exposure exposure of the lung to intraoperative embolization of fat, marrow and cement debris resulting from intravasation during the implantation process of orthopedic prostheses may worsen these conditions.[7,8] Indeed, population based data show that patients with preexisting pulmonary hypertension suffer from significantly higher rates of mortality and lung injury, suggesting a lower capacity of the pulmonary system to deal with any perioperative insults.[9]

In conclusion, while patients with SA may suffer form pulmonary complications such as aspiration pneumonias and hypoxemic events due the inherent pharyngeal anatomical and functional abnormalities associated with the disease, the high incidence and role of pulmonary hypertension in the development of perioperative pulmonary complications is a less well appreciated entity. Further research is necessary to study the association of pulmonary hypertension and SA in order to allow interventions to potentially decrease pulmonary complications. The perioperative evaluation of SA may need to be expanded from the usual focus on respiratory abnormalities to include effects on the cardiovascular system in order to allow for better risk stratification of SA patients.

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Perioperative Complications in Patients with OSA and Challenges in Implementation of a Perioperative OSA Protocol

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Three recent studies regarding postoperative complications among patients with OSA undergoing elective non-cardiac surgery highlight the importance of OSA as a probable perioperative risk factor. Recently a large study of approximately 50,000 patients with OSA undergoing surgery reported a fivefold increase in intubation and mechanical ventilation after orthopedic surgery and twofold increase after general surgery compared to matched controls.[1] Although the information about OSA was collected from billing (ICD-9) data and information about severity of OSA was therefore not possible, this study has the advantages of multi-institutional and large national sample as compared to previously reported single institution studies. Subsequently, in a recent case-control study of 471 patients, presence of OSA was associated with higher incidence of postoperative hypoxemia (OR= 7.9; p=0.009), overall complications (OR= 6.9; p=0.003); ICU transfer (OR 4.43; p=0.069); and higher length of hospital stay, (OR= 1.65; p=0.049).[2] All patients including controls underwent polysomnography within 3 years before or after surgery and propensity matching was used to control for major medical morbidities including obesity. Neither apnea-hypopnea index (AHI), nor use of home CPAP before surgery was associated with postoperative complications (p=0.3; 0.75 respectively) or length of stay (p = 0.97; 0.21 respectively). Although the study was sample-sized for achieving significance in the outcome of postoperative respiratory failure (4.9% vs 2.1%; OR 4.3) the limited number of events in the control arm restricted a meaningful comparison. More recently a meta-analysis of 3942 patients with OSA reported postoperative respiratory failure 1.96 vs 0.70 OR 2.43, 95% CI 1.34- 4.39, p=0.003 and a postoperative cardiac event rate 3.76 vs 1.69 OR 2.07, 95% CI 1.23- 3.50, p=0.007.[3] Case control studies with missing information regarding controls, studies reporting upper airway surgery and studies reporting OSA by ICD-9 codes only were excluded from the meta-analysis. These results were not affected by inclusion of 4 studies which originated as clinical practice improvement studies and studies that reported prior use of CPAP. Early reports also show that the incidence of postoperative respiratory failure may be particularly high amongst patients with obesity hypoventilation syndrome, a condition which is more likely to be unrecognized before elective non-cardiac surgery.[4]

Any talk about a standardized or universal perioperative OSA protocol at a given institution should be accompanied by a discussion about patient safety systems already in place or required to prevent or mitigate morbid outcomes among screened patients. Although we still may not have a perfect screening tool, the real question may be do we really need to test a certain group of patients for severity of sleep apnea with more formal studies before they undergo elective surgery. Whether efforts in screening for OSA and preoperative assessment of risk are as important as universal improved monitoring of all postoperative patients proposed in recent times in predicting postoperative cardiopulmonary arrest or near-arrest is pretty open to debate. Excessive focus on screening particularly preoperatively in the absence of clear knowledge of who to monitor and how, may not in any way improve patient safety but increase medicolegal burden. Majority case control studies assessing postoperative complications in patients with OSA are unable to show that severity of OSA as measured by the AHI index, predicts the development or severity of morbid postoperative outcomes.[2,5,6] Additionally issues like 'Opioid responsiveness' and or 'chronic arousal failure' in the perioperative period cannot be predicted by preoperative screening.

Despite these limitations one may find themselves forced to believe that certain patients with OSA may pose higher risk for postoperative complications than others. One might argue that a liberal policy of screening for OSA and selecting appropriate management preoperatively and ensuring it is continued perioperatively may have possibly made today's bariatric surgery much safer as opposed to similar outcomes in other non-cardiac surgeries where such measures may not be always possible or practical.[6] Our surgical colleagues may at times be not too happy with any additional delay that such measures can impose when the evidence for such a practice may not be thought of as substantial. Contrary to this belief the associated morbid burden with conditions like Obesity hypoventilation syndrome suspected during a preoperative examination may make such preoperative investigations imperative. Similar case can be made among subpopulations of patients who have been on chronic opioid therapy or have previously been documented to have episodes of 'repetitive hypoxia' or CPAP titration failure.

Moving beyond the subject of preoperative screening, any perioperative protocol needs to have some sort of multi-specialty participation or 'buy-in' for successful implementation. By way of example, surgeons should be aware of such perioperative outcomes/accidents byway of their own clinical experience or reports in recent literature and hence be able to seek assistance by seeking referrals to obtain preoperative consultations when necessary. Similarly if testing like polysomnography or overnight desaturation is obtained

preoperatively, the findings and recommendations should be clearly communicated to the surgical team and implementation of postoperative recommendations properly ascertained.

The other critical components of an OSA protocol pertain to postoperative monitoring. More research is required to help identify which patients with OSA need close postoperative monitoring and or where as well as how long these patients need to be monitored. Improvements in monitoring for respiratory events (e.g, high resolution pulse oximetry or capnography) and or consensus regarding routine/universal improved monitoring of all postoperative patients may in future obviate the need for such an exclusive patient safety protocol.

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STOP-Bang Screening: How to Make it Work?

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Preoperative screening, evaluation and optimization of the patient's medical condition before surgery are important components of safe practice. Obstructive sleep apnea (OSA) is a common disorder (2%–26% of the population) that is caused by repetitive partial or complete obstruction of upper airway, characterized by episodes of breathing cessation during sleep. Patients with OSA may pose significant problems in the perioperative period. Some studies showed that OSA is associated with increase in postoperative complication and is an independent risk factor for increased morbidity and mortality. Therefore, it is imperative to have an early diagnosis of OSA.

It has been estimated that 82% of men and 92% of women with moderate-to-severe sleep apnea have not been diagnosed. The diagnosis of OSA is established by an overnight sleep study, polysomnography. Although polysomnography (PSG) is the gold standard for identification of patient with OSA, it is expensive, requiring highly trained personnel and sophisticated equipment. The limited availability of PSG has created demand to use clinical features to screen patients for OSA. Simpler strategies are needed in the diagnostic clinical pathway for OSA. A screening tool is necessary to stratify patients based on their clinical symptoms, their physical examinations, and their risk factors, in order to ascertain patients at high risk and in urgent need of PSG and/or further treatment and patients at low risk who may not need PSG. The use of preoperative screening tools will help to identify the patients with undiagnosed OSA.

Numerous efforts have been done to devise alternate clinical methods of predicting OSA, which is broadly classified as questionnaires and clinical prediction models. A clinical model combines elements of history and physical examination, with or without additional measurements and investigations such as radiological findings or oximetry. A questionnaire is defined as a set of questions with no physical measurement. Clinical models designed for OSA screening often require specific technology, such as cephalometry and/or the assistance of a computer. In spite of high test accuracy, these models may not be suitable for clinical bedside practice because they are cumbersome in routine evaluation. Most of predictive models, based on the different combinations of witnessed apneas, snoring, gasping, BMI, age, sex, and hypertension, were developed and validated in patients from sleep center. They may not apply to the patients in general because there are basic differences between the study population in sleep laboratories and the general population.

A recent meta-analysis reported that clinical models using additional cephalometry and morphometry from upper airway measurements are the most accurate for identifying OSA. However, the complexity of these tests could hinder their addition into standard preoperative evaluation. A number of questionnaire-based screening tools for OSA are currently available, such as the STOP-Bang questionnaires (Chung, *Anesthesiology* 2008), Snoring questionnaire (Bliwise DL, *Chest* 1991), Sleep questionnaire (Haraldsson PO, *Sleep* 1992), the Berlin Questionnaire (Netzer NC, *Ann Intern Med* 1999), the Sleep Apnea Clinical Score (Flemons, *NEJM* 2002), SA-SDQ (Weatherwax KJ, Sleep Med 2003) the ASA checklist (Gross, *Anesthesiology* 2006), the P-SAP score (Ramachandran, *Anesth Analg* 2010) and the Epworth Sleepiness Scale etc (Johns MW., *Sleep* 1991).

The Berlin questionnaire is a widely used screening tool for OSA with 10 questions and was developed for a primary care population. It consists of 5 items on snoring, 3 items on excessive daytime sleepiness, 1 item on sleepiness while driving, and 1 item inquiring about a history of hypertension. The ASA checklist was developed by the American Society of Anesthesiologists (ASA) taskforce on OSA and comprises 14 items categorized into physical characteristics, history of apparent airway obstruction during sleep, and complaints of somnolence.

The STOP-Bang questionnaire comprises of 8 items on snoring, tiredness/sleepiness, observed apnea, hypertension, BMI, age, neck circumference and gender (Table).

Development of STOP-Bang Questionnaire

The STOP-Bang questionnaire was developed and validated in surgical patients. The Berlin Questionnaire was condensed and modified into a shorter four-item OSA screening questionnaire (STOP). The STOP questionnaire contains four questions: **S**, 'Do

you snore loudly, loud enough to be heard through closed door?'; **T**, 'Do you feel tired or fatigued during the daytime almost every day?'; **O**, 'Has anyone observed that you stop breathing during sleep?'; and **P**, 'Do you have a history of high blood pressure with or without treatment?' The sensitivity of the STOP questionnaire with AHI > 15 and >30 as cutoffs was 74% and 80%, respectively, and the specificity 53% and 49%, respectively

The STOP-Bang Questionnaire

When incorporating four additional variables with the acronym Bang (**B**, body mass index [BMI, calculated as weight in kilograms divided by the square of height in meters] >35 kg/m^2; **A**, more than 50 years old; **N**, neck circumference greater than 40 cm; **G**, male gender), the STOP-Bang questionnaire improved the sensitivity to 93% and 100% at AHI cutoffs of 15 or more and 30 or more, respectively. The specificity of the STOP-Bang was 43% and 37%. By incorporating BMI, age, neck circumference, and male gender (Bang) into the STOP questionnaire, the STOP-Bang model reached a very high level of sensitivity and NPV, especially for patients with moderate and severe OSA. If the patient is ranked as a low risk of OSA by the STOP-Bang scoring model, we could be highly confident about excluding the possibility that the patient would have moderate-to-severe sleep apnea.

We have shown that there was no significant difference in the predictive parameters of the Berlin questionnaire, the ASA checklist, and the STOP questionnaire. (Chung F, et al *Anesthesiology* 2008) All the questionnaires showed a moderately high level of sensitivity for OSA screening. The sensitivities of the Berlin questionnaire, the ASA checklist, and STOP questionnaire were similar: 69% to 87%, 72% to 87%, and 66% to 80% at different AHI cutoffs.

In a study of 1426 patient who were referred to the Sleep Disorder Center, Farney and colleagues evaluated the possibility of using the STOP-Bang model to identify OSA (Farney RJ, *J Clin Sleep Med*. 2011). They concluded that the STOP-Bang questionnaire could be used to estimate the probabilities of no OSA, mild, moderate, or severe OSA. There is a greater probability of more severe OSA with a greater cumulative score of the known risk factors as reflected by the STOP-Bang score. With any score >4, the probability of having severe OSA increases continuously. With a score of 8, the probability of severe OSA was 81.9%.

Chung and colleagues also evaluated the association between the STOP-Bang score and the probability of OSA in 746 surgical patients. With an increase in the STOP-Bang score, there was a corresponding increase in the predicted probability, odds ratio, and specificity for having OSA, moderate/severe, and severe OSA (Chung F et al, *Br J Anaesth* 2012). For a STOP-Bang score of 5, the OR for moderate/severe and severe OSA was 4.8 and 10.4, respectively. For STOP-Bang 7 and 8, the OR for moderate/severe and severe OSA was 6.9 and 14.9, respectively. As the STOP-Bang score increased from 0–2 to 7 and 8, the probability of having OSA, moderate/severe OSA, and severe OSA increased from 46% to 86%, 18% to 60%, and 4% to 38%, respectively.

The association between the STOP-Bang score and the probability of OSA would provide the perioperative care team a useful tool to stratify patients for unrecognized OSA and triage patients for diagnosis and treatment. Since a STOP-Bang score ≥3 demonstrated a very high sensitivity and NPV for moderate/severe OSA, this cut-off may be good for a surgical population with high OSA prevalence such as bariatric surgical patients. We would be confident in excluding the possibility of moderate/severe or severe OSA in patients with a STOP-Bang score of 0–2. On the other hand, the patients with a STOP-Bang score of 5–8 have a high specificity to detect moderate and severe OSA. These scores may be useful in the general patient population which has a low OSA prevalence to reduce false-positive rate. It enables identification of those patients most in need of urgent evaluation and to exclude patients from possible harm due to unrecognized sleep apnea.

Essentially, A STOP-Bang score of 0–2 will allow the healthcare team to rule out patients who do not have OSA. A STOP-Bang score of 5–8 will allow the team to identify patients with increased probability of moderate/severe OSA. In the patients with a score of 3 and 4, they are at intermediate risk of OSA. The STOP-Bang score can help the healthcare team to stratify patients for unrecognized OSA, practice perioperative precautions, or triage patients for diagnosis and treatment.

Serum Bicarbonate Can Improve Specificity of STOP-Bang Questionnaire

A low specificity is a disadvantage of a screening tool. STOP-Bang score ≥3 only yields a specificity of 43% and 37% for moderate and severe OSA, respectively, suggesting a high false positive rate.

Chronic daytime hypercapnia ($PaCO_2$ ≥ 45 mmHg) is found in 10–38% of patients with OSA (Mokhlesi B, *Respir Care* 2010). As OSA severity increases (as measured by the apnea-hypopnea index (AHI) or the degree of nocturnal hypoxemia), the risk of chronic

daytime hypercapnia may increase (Kaw R, *Chest* 2009). However, it is plausible that serum HCO_3^- may increase in moderate/severe OSA without reaching overt chronic daytime hypercapnia.

A recent study by Chung and colleagues (E. Chau, ASA abstract 2011) evaluates the predictive parameters of the STOP-Bang questionnaire at various levels of serum HCO_3^- for screening patient with high risk of OSA. The addition of serum HCO_3^- to the STOP-Bang questionnaire improve its specificity for detecting OSA. Using the combination of HCO_3^- ≥28 mol/L and STOP-Bang score ≥3, the specificity for all OSA, moderate/severe and severe OSA were 85.2%, 81.7% and 79.4%, respectively. Serum HCO_3^- is easily measured from a venous blood sample and can be ordered in the preoperative clinic. Thus, it is a valuable tool in the preoperative stratification of patients with unrecognized OSA.

Conclusion

A STOP-Bang score of 0–2 indicates a low risk of OSA. A STOP-Bang score of 3–4 indicates an intermediate risk of OSA. A STOP-Bang score of 5–8 indicates a high risk of OSA. A STOP-Bang score ≥3 plus HCO_3^- ≥28 mmol/L, the specificity for moderate/severe and severe OSA were 82%.

Further information is available on www.stopbang.ca

Figure 1. STOP-Bang score and risk of OSA

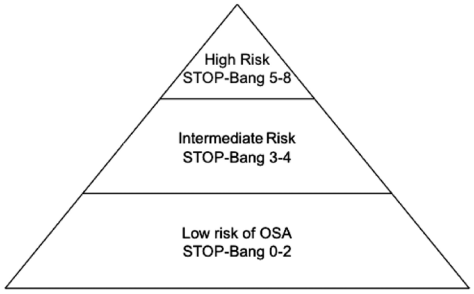

Table 1. STOP-Bang Questionnaire

	Question	Answer	Answer
S	**S**noring: Do you snore loudly (louder than talking or loud enough to be heard through closed doors)?	Yes	No
T	**T**ired: Do you often feel tired, fatigued, or sleepy during daytime?	Yes	No
O	**O**bserved: Has anyone observed you stop breathing during your sleep?	Yes	No
P	Blood **P**ressure: Do you have or are you being treated for high blood pressure?	Yes	No
B	**B**MI: BMI more than 35 kg/m^2?	Yes	No
A	**A**ge: Age over 50 years old?	Yes	No
N	**N**eck circumference: Neck circumference greater than 40 cm?	Yes	No
G	**G**ender: Male?	Yes	No

STOP-Bang score 0-2, low risk of OSA.
STOP-Bang score 3-4, intermediate risk of OSA
STOP-Bang score 5-8, high risk of OSA

Modified from F Chung, et al. *Anesthesiology*. 2008; 108: 812-821, and F Chung, et al. *Br J Anaesth* 2012; 108: 768-75.

OSA Patient For Ambulatory Surgery: SAMBA Patient Selection Guidelines

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The suitability of ambulatory surgery in patients with obstructive sleep apnea (OSA) remains controversial because of the concerns of increased perioperative complications[1-4]. In 2006, the American Society of Anesthesiologists (ASA) published practice guidelines for management of surgical patients with OSA, including patient selection for ambulatory surgery[4]. These guidelines proposed a scoring system based upon the severity of OSA, the invasiveness of the surgery, the type of anesthetic technique, and the need for postoperative opioids. This scoring system has not yet been validated. Furthermore, the guidelines recommended that upper abdominal procedures and airway procedures are not suitable for ambulatory setting.

Since the publication of the ASA practice guidelines, several studies have been published assessing perioperative complications after ambulatory surgery in OSA patients including those undergoing laparoscopic bariatric surgery and upper airway surgery. A systematic review of published literature evaluating the perioperative complications in OSA patients undergoing ambulatory surgery was performed. The preoperative factors that may influence the perioperative outcome (e.g., severity of OSA, co-existing medical conditions, and invasiveness of the surgical procedure) were assessed. This systematic review identified 7 studies (2 prospective cohorts and 5 retrospective chart reviews) assessing perioperative complications in a wide variety of ambulatory surgical procedures such as general surgery, orthopedic surgery, laparoscopic bariatric surgery, and upper airway surgery[5-11]. A total of 1491 OSA patients, 2036 low-risk OSA patients, and 2095 non-OSA patients were included the selected studies. Compared with non-OSA patients, OSA patients had a higher body mass index (BMI) and more co-morbidities including diabetes, hypertension, stroke, myocardial infarction and congestive heart failure.

Although the studies evaluating perioperative outcome in OSA patients undergoing ambulatory surgery are sparse and of limited quality, they do provide useful information that can guide clinical practice. In patients with an established diagnosis of OSA (either by a sleep study or presumptive diagnosis), an adverse perioperative outcome is associated with a complex interplay of factors, particularly coexisting medical conditions and the use of opioids. Patients with non-optimized comorbid medical conditions may not be good candidates for ambulatory surgery.

The Society for Ambulatory Anesthesia (SAMBA) consensus statement recommends the use of the STOP-Bang criteria for preoperative OSA screening[12-14]. If OSA is suspected during the preoperative evaluation, one could proceed with an assumption that the patient has OSA (i.e., presumptive diagnosis of OSA) because there is no clear evidence to suggest that a sleep study and preoperative continuous positive airway pressure (CPAP) or bi-level positive airway pressure (BiPAP) use would improve the perioperative outcome. Also, the optimal duration of CPAP or BiPAP therapy before proceeding with elective surgical procedures is unknown.

Patients with a known diagnosis of OSA and optimized comorbid medical conditions can be considered for ambulatory surgery, if they are able to use a CPAP device in the postoperative period, because in the included studies a majority of the OSA patients used CPAP or BiPAP postoperatively, which may have contributed to a safe perioperative course. Patients who are unable or unwilling to use CPAP after discharge may not be appropriate for ambulatory surgery.

Patients with a presumed diagnosis of OSA, based on screening tools such as the STOP-Bang questionnaire, and optimized comorbid conditions can be considered for most types of ambulatory surgery, if postoperative pain relief can be provided predominantly with non-opioid analgesic techniques, because opioids have a significant propensity to exacerbate OSA and prevent arousal. No guidance can be provided for OSA patients undergoing upper airway surgery due to limited evidence.

It is necessary to educate surgeons, patients and their family (or caregivers) regarding the need for increased vigilance after discharge home. Patients on preoperative CPAP should be advised to use their CPAP device for several days postoperatively, as the potential risks can last for several days after surgery. In addition to the usual nocturnal CPAP use, patients should be advised to use CPAP whenever sleeping even during the daytime. Also, patients should be advised against sleeping in the supine position. Patients who are assumed to have OSA based on the screening questionnaire should be advised to follow-up with their primary physician for

possible sleep study. Finally, the deleterious effects of opioids must be emphasized, and patients should be asked to limit opioid use.

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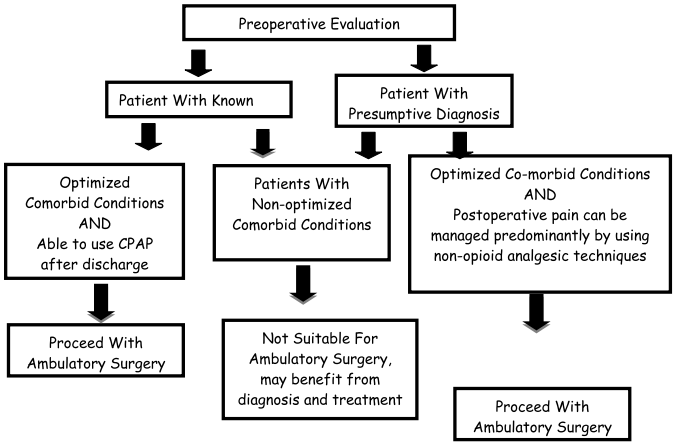
Figure 1. Decision making in preoperative selection of a patient with obstructive sleep apnea scheduled for ambulatory surgery.



- **Preoperative Considerations**:
  - Comorbid medical conditions include hypertension, arrhythmias, heart failure, cerebrovascular disease, and metabolic syndrome.
  - If OSA is suspected during the preoperative evaluation, one could proceed with a presumptive diagnosis of OSA albeit with caution.
  - Educate surgeon, patient and family (see the text for details)
- **Intraoperative Considerations:**
  - Use non-opioid analgesic techniques, when possible.
- **Postoperative Considerations:**
  - Exercise caution in OSA patients who develop prolonged and frequent severe

Using OSA Near Misses (and Catastrophes) as Teaching Tools: Sharing the Metro Experience

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There is considerable evidence that patients with Obstructive Sleep Apnea (OSA) are at risk for adverse events in the perioperative period.[1-4] For this reason, various medical organizations have recommended that hospitals develop protocols to manage OSA patients to improve the margin of safety during perioperative management.[5-6] It is clear however, that most hospitals in Canada and the United States have yet to do so.

Following a catastrophic event (Case 1), in 1999, MetroHealth Medical Center in Cleveland Ohio implemented an OSA protocol to improve the safety margin when managing patients with OSA following surgery. There were considerable obstacles to implementing a protocol including: resistance from surgeons questioning the utility of such a protocol and pointing out that most other centers did not have similar protocols in place; resistance from nursing due to the increased demands placed upon them for additional monitoring; increased cost to the institution brought on by the need to secure additional monitors; and potential lost revenue to the institution resulting from the practice of "bundling" fees for surgical procedures by insurance companies where additional care is provided without added revenue to the physicians and/or medical facilities.

By documenting our experience, and presenting information from the medical literature to the Hospital Quality Committee, the Operating Room Committee, and the Medical Executive Committee, we were able to garner support throughout our institution for a perioperative OSA protocol. Since most patients with OSA are undiagnosed, it was important to implement a screening process for OSA in our Pre-Surgical Evaluation (PSE) clinic.[11]

As part of a quality initiative, after implementing our protocol, we reviewed data for an 18 month period.[10] We found that despite patients having very significant episodes of hypoxemia and apnea (Figure 1), when the monitors alarmed, the nurses were able to intervene and arouse patients during periods of prolonged apnea and hypoxemia and encourage them to take deep breaths. This led to an extremely low rate of urgent/emergent transfer of these patients to intensive care settings compared to rates of transfer noted in other series for OSA patients following surgery.[1-2]

We also looked for adverse events and readmissions for patients for 72 hours following discharge. We identified a patient who sustained apnea and cardiac arrest after taking oral pain medications at home one day following surgery (Case 2). This patient had mild OSA. While our protocol does allow (some) OSA patients to have surgery performed on an ambulatory (outpatient) basis, as highlighted by this case, we believe concern is still warranted when ambulatory patients are discharged with oral narcotics (Case 2 and Case 3).

Many medical providers incorrectly believe that patients who have undergone surgery to correct OSA (such as uvulopalatopharyngoplasty [UPPP]) are necessarily "cured", and those who have lost considerable weight following bariatric surgery are similarly "cured". These misperceptions can endanger patients (Case 4). Successful UPPP surgery is often defined as a 50% improvement in the apnea hypopnea index, and only 50% of patients will have a successful surgery. Hence, it is clear that most patients who undergo UPPP surgery will not be "cured" of OSA.

Complications following UPPP surgery include respiratory events (post extubation obstruction, need for reintubation or tracheostomy, hypoxemia) cardiac events, bleeding, and velopharyngeal insufficiency.[19-22] (Case 5). There is considerable debate regarding what is the most appropriate monitoring for OSA patients following UP3 surgery, and whether it is appropriate to perform these procedures on an ambulatory basis.[23-26]

We have found that ongoing institutional educational efforts are extremely important to ensure that all providers are aware of and understand the OSA protocol in place and that all areas providing sedation follow the OSA protocol (Case 6). This opportunity can be utilized to educate medical providers about OSA, who can in turn educate patients with OSA. Additionally, since all surgery is not performed on an elective basis, and since patients with undiagnosed OSA will certainly undergo surgery on an urgent/emergent

basis, we felt it was imperative that the OSA protocol make accommodations to manage patients with OSA who are suspected of having OSA, but who have not had a formal polysomnogram (sleep study) to diagnose OSA. (Case 7)

It is impossible to determine with 100% accuracy which OSA patient will have an adverse perioperative event; thus, the goal of an OSA protocol is to improve the margin of safety when managing these patients (Case 8).

While considerable attention has been directed at the risk of OSA patients during the perioperative period, OSA patients on medical floors receiving opioids and sedatives (without recent surgery) are also at risk for adverse events (Case 9). Thus, continuous monitoring of OSA patients on medical floors receiving parenteral narcotics and sedatives also deserves consideration.

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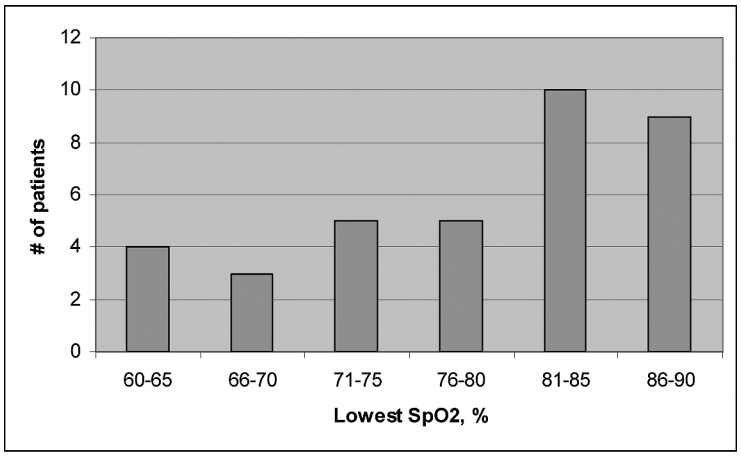
Table 1.

Case	Description
1	50 y/o male recently diagnosed with OSA involved in MVA. BMI=40. Seen in ED with Tibial fracture. Received MS for pain. Became cyanotic requiring mask ventilation. Underwent ORIF tibial fracture under general anesthesia (GA). Extubated at completion. Periods of apnea in PACU. D/C to floor with request for continuous pulse ox and CPAP. Pulse ox not measured and CPAP not instituted. Surgeon orders: Morphine 2-10 mg IV with Hydroxyzine q 2-4 hours. Two hours after MS administratpatient found unresponsive. Resuscitated. No brain activity. Life support withdrawn.
2	Patient with mild OSA underwent laminectomy under GA. Monitored overnight in OSA bed. Discharged home on Percocet and Flexeril. Took meds at home and fell asleep in family room. Wife witnessed patient turn blue. Wife started CPR. Called 911. Patient transported back to hospital. VT in ED. Rhythm stabilized. Cardiac w/u initiated: Cardiac catheterization, echo, EP study all normal. No other cause for cardiac arrest identified other than hypoxia from OSA with subsequent arrhythmia. ICD placed by cardiology.
3	27 y/o male with mild mental retardation, BMI=40, HTN, and myotonic dystrophy underwent dental extractions under GA. STOP Bang +. Received 100mcg Fentanyl and 50 mg Rocuronium for 5 hour case. Weak at completion of case. Reversed. Extubated in PACU 30 minutes after arrival. No pain in PACU. Discharged home with Motrin and Tylenol #3 only if needed. Patient ate breakfast and lunch the following day. Appeared totally normal. Took Tylenol #3 in early evening. Became very sleepy. Went to sleep at 6pm. Never woke up. Autopsy: Codeine levels =wnl. Lungs bilateral exudates. Cause of death: Bilateral pneumonia. But patient not febrile. No previous pulmonary symptoms! Not ill! Could this have been negative pressure pulmonary edema secondary to airway obstruction?
4	55 y/o male with severe OSA on CPAP (18) underwent TURP under GA. S/P Gastric bypass 18mos ago with 100 # wt loss (BMI decreased from 51 to 32). 100 mcg Fentanyl for 2 hour procedure. Extubated in OR. 30 minutes after arrival in PACU, noted to have obstructive episodes with sats in 60s. Reintubated. F/u PSG revealed AHI 38 (severe OSA) despite > 100# weight loss.
5	34 y/o male (BMI = 40) with h/o HTN, Asthma, OSA (BiPAP 18) underwent UP3/T&A . 2 man mask ventilation following induction. Fiberoptic intubation. At completion of procedure, patient opening eyes, following commands, sustained head lift, placed in sitting position and extubated. Obstructive sounds noted. Nasal airway inserted. Attempted mask ventilation. Intubation performed (cords not visualized). Loss of pulse. Chest compressions. ACLS. Patient resuscitated. Anoxic Brain Injury. Tracheostomy performed and patient transferred to NH for long-term care.
6	Patient suspected of OSA by family medicine. Recommended PSG. Patient did not obtain. Patient underwent uterine artery embolization in radiology with IV sedation. Sent to floor on Dilaudid PCA (per radiology protocol). No OSA monitoring requested. Cardiac arrest. Difficult Intubation. Aspiration during intubation. Prolonged ICU stay. Sleep study following discharge revealed Mod/Severe OSA with desats to 70. Desats eliminated with CPAP.
7	49 y/o female (BMI 50) underwent bilateral total knee replacements under GA. STOP screen +. No arrangements were made for OSA monitoring following surgery despite a protocol in place that recommended this. Patient sent to surgical floor on Dilaudid PCA. Patient found lethargic with sats in 60s at 11AM. Narcan administered. Transferred to monitored bed. F/u PSG two weeks followingdischarge revealed AHI 95 with sats 55-89 during non-rem sleep. Patient did not tolerate CPAP.
8	35 y/o male with Chrohn's disease s/p colectomy underwent exploratory laparotomy for SBO. H/o HTN, DM, BMI 45, Severe OSA, Obesity Hypoventilation Syndrome. Extubated in OR at completion of case. Pain 9-10 in PACU despite dilaudid PCA. Transferred From PACU to OSA bed. Multiple episodes of desats to 70 despite BiPAP. Patient aroused with nursing stimulation with adequate oxygenation. Nurses responded to alarm in 70s. No response to sternal rub. Rapid Response team called. Mask ventilated. Narcan X 2 given. Anesthesia stat called. Patient breathing properly when anesthesia arrived. Patient transferred to SICU. Discharged without complication.
9	Patient seen in ED with perineal abscess and observed overnight in "clinical decision unit". Known OSA. Non compliant with CPAP. Low sats while sleeping. Supplemental oxygen applied. Patient given Morphine prior to exam by surgery. No additional monitoring requested. Patient found in full arrest. Resuscitated. Expired in MICU.

Figure 1. Degree of postoperative hemoglobinoxygen desaturation (SpO_2 < 90%) in 36 patients with known or suspected OSA.



Opioids and OSA; Monitoring Miracles and Mishaps on the Med/Surg Floor

Frank J. Overdyk, MSEE, MD

Abstract

Undetected respiratory depression in patients receiving opioids on medical surgical floors with intermittent monitoring continuous to be a major source of preventablemorbidity and mortality in hospitals. These risks are accentuated in the population of patients with occult or diagnosed sleep apneas syndromes.

This presentation describes the circumstances of a series of cases in which patients in this cohort suffered unanticipated, catastrophic outcomes. The potential for prevention of this reduction in these tragic outcomes will be discussed in the context of increased awareness and education on the dangers of opioids and sedatives in this population, and the role of improved continuous electronic monitoring technologies in attaining this goal. Recent monitoring strategies to address this patient safety as proposed by organizations including the Joint Commission and the Anesthesia Patient Safety Foundation will compared and contrasted.

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Table 1.

DO's	DON'T's	DO's	DON'T's
Inadequate monitoring of patients on opioids (29% of ADE's): REC: Serial assessments; continuous SpO_2 And capno when used. The APSF and ISMP and others recommend continuous monitoring of oxygenation and/or ventilation		Continuous monitoring of oxygenation and ventilation	Spot check monitoring of oxygenation and 'manual' assessment of ventilation
Risk Stratification; RF: • Higher opioid doses • Sleep apnea/snoring (?) • Morbid obese • Extremes of age • ASA 3/4 • Synergistic RD drugs • Tolerance/abuse • Opioid naïve • Surgery type/duration • Smoking (?) REC: Screen pt for RF:	"Avoid rapid dose escalation of opioid analgesia above routine dose levels in opioid-tolerant patients"	Continuous monitoring should be available for ALL patients. ZERO RISK TOLERANCE	Risk stratification places patients at undue risk and is likely to miss OIRD in patients w/o RF
	Staff should be educated not to rely on SpO_2 alone…when supp O_2 is used	Capnograpphy and other ventilation and airflow monitors are to be used with suppl O_2	
58% of ADE's (wrong/ excessive dose) Educate and assess the understanding of staff that care for patients receiving opioids about the potential effect of opioid therapy on sedation and respiratory depression, the continuum of consciousness, the difference between ventilation and oxygenation, and technological and clinical monitoring		Education of providers (all levels) in: • Pathophysiology • Pharmacology • Clinical assessment for OIRD incl LOC. • Supplemental O_2	
Use PCA to reduce the risk of oversedation. Smart infusion pump technology with dosage error reduction software can add another layer of safety.		Integration and trend analysis of > 1 physiologic parameter (ie SpO_2 and RR) by smart alarm driven clinical decision support	Reliance on single threshold alarms using point in time (or delayed) signal values

1. http://www.jointcommission.org/assets/1/18/SEA_49_opioid s_8_2_12_final.pdf
2. http://www.apsf.org/newsletters/html/2011/fall/index.htm

Anesthesia for Children with Obstructive Sleep Apnea

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In this presentation, I will review several major topic areas concerning pediatric OSA. First, I will briefly discuss the pathophysiology, clinical characteristics, and treatment of children with OSA. Second, I will review recent studies that suggest changes in the way we conduct general anesthesia in children with OSA. I will then review recent developments in this area, such as the ASA's Practice Guidelines, the Clinical Practice Guidelines by the American Academy of Pediatrics, and the statement by the FDA concerning the use of codeine in children with OSA following tonsillectomy. Finally, I will review unresolved controversies in the management of children with OSA undergoing tonsillectomy.

Pathophysiology

In children without craniofacial abnormalities, obstructive sleep apnea (OSA) in children is the result of adenotonsillar hypertrophy, usually combined with an abnormally small retropharyngeal space, and altered neuromuscular control of upper airway patency during sleep.

Clinical Characteristics

Pediatric OSA mainly occurs in children between the ages of 2 and 6 years, (although infants and older children may also have it), and is especially prevalent in children with obesity and trisomy 21. The clinical manifestations include partial or complete upper airway obstruction during sleep, restless sleep, morning headaches, behavioral disturbances, and daytime somnolence. Severe cases of untreated longstanding OSA can result in chronic hypoxemia, polycythemia, cor pulmonale, growth delays, and learning difficulties.

Diagnosis

Diagnosis of OSA in children is mainly by clinical characteristics, but an overnight sleep study using polysomnography (PSG) may be performed to confirm the diagnosis, and is recommended in children with comorbidities, such as obesity, trisomy 21, craniofacial abnormalities, neuromuscular disorders, sickle cell disease, or mucopolysaccharidosis. OSA is measured by the apnea-hypopnea index (AHI), which is defined as the average number of apnea or hypopnea events per hour.

OSA can be categorized as:

Mild: AHI 1-5; SpO_2 < 90% for 2–5% of total sleep time;

Moderate: AHI 5–10/h; SpO_2 < 90% for 5–10% of total sleep time; and

Severe: AHI >10/h; SpO_2 < 90% for >10% of total sleep time.

Treatment

The most common and effective therapy for pediatric OSA is adenotonsillectomy, which alleviates symptoms in most children, but some may continue to demonstrate obstructive sleep patterns into adulthood.

Differences in Anesthetic Management

Preoperative assessment should include knowledge of the severity of the child's OSA based on nighttime oximetry readings. It is not unusual to have some children that desaturate into the 50's or 60's. This is useful as a baseline marker and gives the anesthesiologist an idea of the severity of the underlying disease. Some anesthesiologists will reduce the dose of the preoperative sedative in children with OSA, for fear of causing life-threatening upper airway obstruction in an unmonitored environment. During induction of general anesthesia, virtually all children with untreated OSA will exhibit partial or complete upper airway obstruction. Insertion of an artificial oral airway device after loss of consciousness will bypass the obstruction and allow easy bag-mask ventilation. In the

immediate postoperative period following adenotonsillectomy, the incidence of airway obstruction is higher in children with OSA when compared with those who undergo adenotonsillectomy for recurrent infections. Therefore, children with significant OSA, especially if less than 4 years of age, should be hospitalized overnight following the procedure. Children with severe OSA may have decreased analgesic requirements compared to controls. Chronic hypoxemia in childhood may result in up-regulation of central opioid receptors. Even some time after adenotonsillectomy, a predisposition toward upper airway obstruction during sleep or sedation may persist throughout childhood because of the aforementioned neurological abnormalities.

Recent Developments

1. AAP Clinical Practice Guidelines
2. FDA Statement on Codeine Use after Tonsillectomy in Children with OSA

Unresolved Controversies

1. What are patient risk factors that predict postoperative complications after tonsillectomy?
2. Which patients with OSA are eligible for ambulatory surgery?
3. Which patients with OSA need ICU observation?