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Message from the President

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Obstructive sleep apnea (OSA) is a prevalent disorder characterized by recurrent episodes of complete or partial collapse of the upper airway during sleep leading to intermittent hypoxemia and hypercapnia as well as sleep fragmentation. A recent community-based study reported an increasing prevalence of OSA in parallel with the obesity epidemic. [1] Concurrently, the number of surgical cases performed globally is increasing. In fact, Weiser and colleagues estimated that 234 million major surgeries were performed in 2004 worldwide. [2] Although the reported prevalence of OSA in presurgical cohorts has varied, undoubtedly the vast majority of anesthesiologists are bound to encounter patients with OSA in their daily clinical practice. [3-7] This is of clinical relevance since sedatives, narcotics and anesthetics can exacerbate upper airway collapsibility and blunt the arousal response.

Several single-institution studies have reported an association between OSA and a myriad of adverse postoperative outcomes. [8-11] In the absence of large-scale well-controlled prospective studies, analysis of administrative databases can shed some light on the association between OSA and postoperative outcomes and provide data that is more generalizable than single-center smaller studies. This is of importance because implementation of systematic screening for OSA and initiating treatment in the perioperative period for those patients at risk would impose a significant cost burden, particularly in the setting of large surgical volumes.

In an observational study performed using the Premier Perspective database, Memtsoudis and colleagues extracted data on 530,089 patients who underwent total hip or total knee arthroplasty between 2006 and 2010 in nearly 400 hospitals in the United States. [12] OSA was present in 8.4% of the cohort based on the International Classification of Diseases 9th Revision-Clinical Modification (ICD-9-CM) diagnostic codes. With

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Editor's File

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The Trouble with Teams

The trouble with teams is that every team member has to share the same mental model necessary to achieve a goal. The advent of a few key team concepts in perioperative medicine, notably the perioperative surgical home and enhanced recovery protocols, are set to change the culture of patient care in the coming years. These processes have a direct impact on our ability to efficiently screen and treat conditions such as sleep disorders before elective surgery, employ robust risk reduction strategies and enable effective postoperative care. I would like to talk about one such function that has direct implications to our interest in sleep disorders. As several of us have already experienced, a tremendous amount of effort and investment is required to coordinate implementation of a preoperative fast-track sleep study protocol. Our efforts are typically challenged by two major constraints: one, surgical scheduling preferences and urgency of surgery are still the most important considerations in determining the available time between preoperative clinic visit and surgical date. Two, the need for pre-authorization of key steps in polysomnography and positive airway pressure (PAP) fitting introduces a minimum delay of days between steps, with additional steps needed postoperatively to maintain therapy. At the risk of preaching to the converted, the evidence that PAP treatment of OSA has a large impact on surgical outcomes is accumulating rapidly. Dr. Babak Mokhlesi's recent studies highlight better outcomes in patients with sleep disordered breathing, largely driven by the temporary and early presentation of postoperative respiratory failure. The studies also describe a greater usage of postoperative PAP in patients with SDB. Squadrone previously showed a several-fold reduction of respiratory failure when PAP was used to treat early postoperative hypoxia. This is relevant to the perioperative surgical home because patients who are adherent with preoperative PAP therapy are more likely to use it in the early postoperative period. Thus, key metrics of success of the preoperative surgical home should include PAP rates in patients screened to be high risk for OSA, and PAP adherence rates in patients with known OSA. We look to expert bodies like the SASM to provide more detailed process guides to help develop OSA protocols for local implementation.

Introducing a perioperative OSA protocol in the framework of a busy perioperative surgical home would address many of the challenges we face. But, for these fairly complex processes to take root, it is imperative for us to participate in the planning and implementation of these surgical homes. I'm sure we all will have slightly different experiences of the surgical home team, but our common goal should remain the allocation of appropriate resources to this population of patients who are at greater risk of postoperative complications. Go team! ❖

robust statistical methodology and after adjusting for important confounders, they found that **OSA was independently associated with increased odds ratio for the composite outcome of major postoperative adverse events (OR 1.47; 95% CI 1.39-1.55). The association was stronger with pulmonary complications (OR 1.86; 95% CI 1.65-2.09) than cardiac complications (OR 1.59; 95% CI 1.48-1.71) with the risk of cardiac complications mainly due to atrial fibrillation.** The risk of emergent reintubation was significantly increased in patients with OSA (OR 10.26; 95% CI 9.01-11.69). OSA patients without hypertension and COPD were 14 times more likely to receive mechanical ventilation and 46 times more likely to undergo non-invasive ventilation. **OSA was also independently associated with escalation of care, increased health care resource utilization and length of stay.** [12]

The types of complications associated with OSA reported by Memtsoudis and colleagues are similar to the findings from a recent analysis of the Nationwide Inpatient Sample.[14,15] Mokhlesi et al examined a cohort of 1,058,710 hospitalized adult patients undergoing 4 categories of elective procedures (orthopedic, prostate, abdominal and cardiovascular cases) and a cohort of 91,028 adult patients undergoing bariatric surgeries between 2004 and 2008. Similar to the Premier Perspective database, **OSA was independently associated with significantly increased odds of emergent intubation and mechanical ventilation, noninvasive ventilation, respiratory failure, and atrial fibrillation.** [14,15] **A recent meta-analysis of 13 single-center studies also demonstrated a higher incidence of respiratory failure, cardiac events and ICU transfers in patients with OSA.** [8]

In the study by Memtsoudis et al, despite the increased rates of complications, there was no significant increase in the risk of in-hospital mortality in patients with OSA. [12] In patients undergoing elective surgeries and bariatric surgeries OSA was also found not to be associated with increased in-hospital mortality. [14,15] D'Apuzzo et al examined a cohort of 258,488 patients undergoing revision total hip arthroplasty or total knee arthroplasty surgeries between 2006-2008. Contrary to these studies, OSA was associated with increase in-hospital mortality (odds ratio 1.9; 95% CI 1.3-2.8) with a mortality of 0.2% in patients without OSA and 0.4% in patients with OSA.[16] However, this study only included patients undergoing revision arthroplasty which may suggest a higher comorbidity burden.

So what do these results tell us? First and foremost, it appears that OSA is consistently and independently associated with increased postoperative respiratory failure requiring invasive or noninvasive mechanical ventilation, pulmonary complications, and atrial fibrillation.[4,8,12,14-16] Second, despite an increase in adverse events and resource utilization, OSA does not appear to be associated with increased risk of in-hospital mortality with the exception of revision total hip or revision total knee arthroplasty.[12,14-16] One can only speculate as to why increased postoperative complications do not lead to an increase in in-hospital mortality. A few possibilities include obesity paradox or ischemia preconditioning playing a protective role.[17-20] It is also possible that OSA patients with impending respiratory failure were recognized earlier and definitive treatment (i.e. endotracheal intubation or NIV) was implemented in a more timely fashion. Indeed, Mokhlesi et al reported that in the subgroup of postoperative patients who were emergently reintubated, reintubation occurred significantly earlier in OSA patients.[14,15] Another speculation is that some of the patients without a diagnosis of OSA may have had unrecognized OSA leading to an under-estimation of mortality rates.[5-7] Indeed, studies utilizing cohorts from databases to identify OSA patients are bound to include only those patients with diagnosed OSA, leaving us to wonder, if outcomes in undiagnosed patients may be worse. Irrespective of the reasons for these findings, however, one should not lose sight of the fact that mortality is a rare outcome in total hip and knee arthroplasties and that other more frequently encountered complications, although less severe, may be more relevant drivers of medical decision making and resource utilization.

Most large administrative databases lack longitudinal data therefore limiting inferences about outcomes after hospital discharge. A recent observational cohort study of 14,962 patients undergoing elective surgery at a single institution over a 4-year period also did not find an independent association between

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having high-risk for OSA and 30-day or 1 year mortality.[21] However, there is overwhelming evidence from longitudinal community and clinic-based studies that untreated severe OSA is an independent predictor of mortality.[22,23] **Since the vast majority of patients with clinically significant OSA remain undiagnosed, anesthesiologists can have a pivotal role in recognizing these patients and referring them for clinical evaluation.**[5-7] **Recent studies have indeed shown that continuous positive airway pressure (CPAP) can effectively treat OSA during the perioperative period,**[24] **decrease the risk of postoperative emergent intubation,**[25] **and have a beneficial long-term effect.**[26] However, it is important to note that adherence to CPAP therapy during the perioperative period is suboptimal and there is a need to explore ways to improve compliance to CPAP as well as explore alternative treatment modalities.[24,27,28]

The results of these desperately needed trials will also provide guidance for protocol developments that are supported by evidence and not by opinions.[29-33] **Such significant increases in adverse postoperative outcomes in patients with diagnosed OSA is a wake up call for all stakeholders (i.e. patients, patient advocates, healthcare providers, hospital administrators, policy makers and funding agencies). Without their collective support we will continue to lack the high level of evidence needed to guide us in providing the best possible perioperative care to our surgical patients** ❖

This President's message was written together with Babak Mokhlesi M.D. M.Sc. and is adopted from "Post-operative complications associated with obstructive sleep apnea: Time to wake up! Chung F, Mokhlesi B, Anesth Analg 2014; 118:251-3"

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Holding Your Breath….Too Long

Apnea is a major concern in both anesthesia and sleep medicine: inability to ventilate a patient made unconscious by an anesthesiologist and OSA are clinical examples of involuntary apnea. On the other hand, voluntary apnea is practiced by millions of breath-hold divers around the world, with a few of them able to reach incredible depths and/or apnea durations on a single breath of air. In fact, the present depth record is a breath-hold dive to 700 ft (214 m) by the Austrian Herbert Nitsch and the duration record of breath-holding at the surface is 11 min 35 s by the French Stéphane Mifsud[1].

Contributing to these elite performances are the diving response, vigorous pre-dive hyperventilation and the use of glossopharyngeal breathing techniques. The diving response consists mainly of a vagally-induced bradycardia, reduced cardiac output and an intense peripheral vasoconstriction which conserves the limited oxygen available during a dive for the organs that are more sensitive to hypoxia, such as the heart and brain[2]. Interestingly, a more pronounced diving response can result in a slower hemoglobin desaturation in the arterial blood and a longer breath-holding time. Hyperventilation effectively decreases CO_2 stores at the beginning of a breath-hold, greatly delaying the diver's hypercapnic respiratory drive. End-tidal PCO_2 of around 20 Torr are frequently observed prior to a dive and they appear to be well tolerated by elite divers, typically without any neurological symptoms or signs of severe hypocapnia, such as paresthesias and tetanic contractions. Unfortunately, hyperventilation increases only slightly the oxygen stores; therefore the diver may lose consciousness from hypoxia before feeling the urge to breathe from hypercapnia. With regard to glossopharyngeal breathing, breath-hold divers use muscles of the mouth and pharynx to move air into (glossopharyngeal insufflation, GI) and out of the lungs (glossopharyngeal exsufflation, GE)[3]. With GI before a dive, elite divers are able to increase their lung volume above their total lung capacity by almost 3 liters, resulting in a 4 liter increase in the amount of gas in the lungs due to the dangerously elevated intrapulmonary pressures (exceeding 100 cmH_2O) that they produce[4]. This provides both additional oxygen stores during the apneic period and additional volume of intrapulmonary gas during descent to counteract dangerous compression of their chest. By using GE at great depths, divers can extract up to an additional 0.5 liters from the compressed lungs (below residual volume at that time) into their pharynx, to be used for pressure equalization in their middle ears, when conventional expiratory muscles are no longer effective.

An obvious danger of both deep breath-hold diving and competitive breath-holding at the surface is hypoxia, with different time courses in the two sports: sudden in the former and gradual in the latter [cf 2]. Actually, the worst hypoxia will be experienced by the brain 10-15 s after breathing

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has resumed, reflecting the lungs-to-brain circulation time. During diving, oxygen pressure in the arterial blood drops quickly and dramatically in the very last part of the ascent, due to the rapid fall in water pressure surrounding the diver's chest, a phenomenon called "hypoxia of ascent". For example, according to Boyle's law, lung pressure (and, consequently, arterial O_2 pressure) will be halved during ascent from 20 m (66 ft, 2 ATA) to the surface (1 ATA). Unfortunately, this sometimes leads to hypoxic loss of consciousness in divers who were otherwise not dangerously hypoxic at depth. Measurements taken at the end of breath-hold dives attest to this risk; for example, we recorded an alveolar PO_2 of 30.6 Torr at the end of a 70 m (230 ft) dive lasting about 150 s[5]. During competitive breath-holding at the surface, divers typically float motionless face down in a swimming pool, a practice called "static apnea". In this situation, hypoxia develops more slowly, gradually during the course of several minutes, frequently reaching very low values that lead to hypoxic loss of motor control (ironically referred as "Samba" by elite divers) or even loss of consciousness. End-tidal PO_2 values as low as 19.6 Torr have been measured at the end of maximal breath-holds lasting between 256 and 306 s[6]. Similar to what has been described in aviation medicine during acute high-altitude exposures, the arterial PO_2 values causing unconsciousness probably lie between 20 and 35 Torr, depending on the concomitant arterial PCO_2 values, with hypocapnia having a deleterious effect[7].

At this point, the natural question is whether these repeated episodes of hypoxia can cause injury to the breath-holder's brain. An increase in the concentration of the protein S100B in serum has been measured following maximal breath-holds ranging from 281 to 403 s[8]. This protein is a nonspecific marker of brain damage and its increase could be caused by asphyxia or other physiological responses to apnea, for example the increased arterial blood pressure that accompanies the intense peripheral vasoconstriction of the diving response. Still, we cannot conclude that this observation reflects a serious injury to the breath-holder's brain, but it raises suspicion that repeated episodes of hypoxia may have cumulative, deleterious effects.

I hope that our clinical readers find the above information on voluntary forms of apnea both interesting and, hopefully, relevant to their practice. Thanks to these elite divers, we have learned a great deal on respiratory mechanics. Maybe, the same will be possible with OSA, where involuntary apnea plays a central role. ❖

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Apnea and Prematurity: A Need for Better Understanding to Improve Perioperative Neonatal Care

Apnea and prematurity: a need for better understanding to improve perioperative neonatal care.

Every year, an estimated 15 million babies are born preterm, defined as born alive before 37 weeks of pregnancy and this number continues to rise, leading to an increase in the number of 'preemies' presenting for surgical procedures [1]. Most premature infants born in the United States each year are classified as either moderately or late preterm infants (32 to <37 weeks) accounting for more than 70% of the preterm population[2]. Prematurity increases the severity of conditions such as jaundice, anemia, infections, and patent ductus arteriosus. In addition, apnea of prematurity, respiratory distress syndrome, bronchopulmonary dysplasia, intraventricular hemorrhages, necrotizing enterocolitis, gastroesophageal reflux, and retinopathy of prematurity occur frequently in the preterm infant and may have lasting consequences[3,4,5].

With the advances in intensive care medicines and increased survival of neonates and especially preemies, understanding neonatal apnea becomes a must. Neonatal sleep medicine in general is a domain under development and may have substantially different considerations related to prematurity compared to adults. The maturity of the central nervous system (CNS) sleep center or malfunction in the respiratory network, including the brain centers (frontal and insular cortex, hypothalamus, RAS, amygdala), the mechanoreceptors in the lungs and upper airways, the peripheral chemoreceptors on the carotid body, and the central chemoreceptors on the ventral medullary surface affect the output to the muscles of respiration. Immaturity in these areas of the CNS then can easily result in apnea.

A prospective study currently in press showed that between the first two weeks and reaching term age, sleep patterns in premature, very low birth weight newborns undergo major developmental changes, expressed by more mature electroencephalography indexes and sleep parameters. However, when reaching term age, babies born prematurely still show altered EEG patterns when compared to newborns delivered at term, indicating a delay in the acquisition of normal maturational sleep patterns. Defining this difference in sleep pattern and the timeline between premature newborns and full term or even adults may be helpful in the future in predicting the neonates at higher risk for apnea and more importantly postoperative apnea.

While apnea and short respiratory pauses may be of minimal consequence if oxygenation is maintained, they can be challenging if accompanied by hypoxemia.

How is apnea defined in neonates? Based on the definition by the American Academy of Pediatrics, it is the cessation of breathing for more than 20 sec duration[5,6]. If a shorter pause of breathing associated with bradycardia or oxygen desaturation occurs, it may be labeled as apnea. However, there is no current evidence-based research defining a respiratory event as pathological based on the degree of change in heart rate and oxygen saturation rather than duration[7].

The initial documentation of postoperative apnea in former premature infants after general anesthesia appeared in 1982[8]. The most common causes of apnea after surgery besides prematurity are metabolic derangements (hypothermia, hypoglycemia, hypocalcemia, acidosis, and hypoxemia) and pharmacologic effects. Pharmacologic effects cannot be avoided because most drugs used in anesthesia affect the

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respiratory system. Most inhalational agents, opioids, and sedatives depress the central response to carbon dioxide in adults in a dose-related fashion. And this respiratory depression is probably more pronounced in neonates who have an immature respiratory center. Studies of adults have demonstrated both lack of the response to hypoxia and potentiation of that response by hypercarbia in the presence of halothane in concentrations as low as 0.1%; thus, residual anesthetic action may contribute to the development of apnea in infants[9]. In addition, most pharmacologic agents used in anesthesia decrease muscle tone of the upper airway, contributing to upper airway obstruction and decrease intercostal muscle tone, reducing functional residual capacity[10,11]. Currently, it has been shown that there is no significant difference between general vs. regional anesthetic techniques with respect to the occurrence of postoperative apneas in infants[12]. In a review of four studies that utilized regional (spinal, epidural, caudal) versus general anesthesia in former preterm infants undergoing inguinal herniorrhaphy in early infancy, there was no convincing evidence to support the use of spinal anesthesia, although it was observed that spinal anesthesia reduced the incidence of postoperative apnea in those who were not given additional sedation[13]. This is similar to emerging data in adults with sleep disordered breathing. One explanation may be that deafferentation under conditions of regional anesthesia could exacerbate (centrally mediated) sleep-disordered breathing (SDB) symptoms in adults and inhibit excitatory pathways in the respiratory centers in infants, triggering apneas in both instances. This should be an area of active research for both of these populations and SASM can play a role.

The risk of perioperative apneic events in infants decreases with increasing post conceptual age (PCA). Some have suggested that the likelihood of apnea was nearly absent by 44 weeks PCA[14], whereas others reported that the risk of apnea persisted until as late as 60 weeks PCA[15,16]. Although a debate developed centered entirely around the post conceptual age at which infants remain at risk of apnea, no unified widely accepted guidelines for perioperative monitoring have emerged. Preemies younger than 55 weeks PCA, especially if anemic or with other cardiopulmonary and neurologic disorders, should be admitted and monitored for twelve hours prior to discharge. Caffeine, although used to reduce the risk of apnea, does alter the need for such monitoring. The landmark 1995 meta-analysis by Coté et al used the incidences reported in the included studies to establish a prediction curve, which pointed to a significant reduction in the incidence of apnea at 52 to 54 weeks PCA, with an apnea incidence of less than 1% at 54 weeks PCA[17,18]. The curve created by this model had an upper confidence interval that extended to 60 weeks PCA, which represents the most conservative interpretation for a safety margin based on these data[17]. This conservative estimate is currently used in most centers. However, a more recent retrospective study conducted on former preterm infants admitted for inguinal herniorrhaphy showed that a conservative approach for admission of patients born before 37 weeks of gestation could be set for 50 weeks PCA[19]. Many hospitals have written policies based on the 60 weeks PCA data. Is it time to reevaluate? Open questions remain regarding the maturation of sleep architecture in infancy, and the exact role of PCA, and what, if anything, could be applied to adulthood.

Neonatal perioperative apnea is of major importance, affecting the patient's safety, length of hospital stay and impacting the cost of medical care. Review of the current data, but likely a prospective study using a clear definition of neonatal apnea duration, and tracking of associated bradycardia and hypoxia may lead to an updated guideline or validation of the current practice in anesthesiology. In addition, an in-depth understanding of the neonatal sleep patterns and the relationship to apnea may help us understand perioperative apnea, its etiology and potentially guide therapy accordingly. ❖

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Strategies to Understand and Modify Postoperative Cognitive Dysfunction: A Sleep Perspective

Impairment of cognition after surgery is a disturbing reality. Postoperative delirium (POD), listed in the *Diagnostic and Statistical Manual of Mental Disorder* (DSM-5)[1], is characterized by inattention, disorganized thinking and altered level of consciousness with acute onset and fluctuating course. While some patients develop POD, others develop a later onset form of postoperative cognitive decline known as postoperative cognitive dysfunction (POCD). It is estimated that POCD occurs in more than 10% of non-cardiac surgical patients[2] over 60 years of age[3] and is independently associated with poor short-term and long-term outcomes including an increased risk of mortality[4,5]. Given the number of major surgical interventions (requiring anaesthesia) and the increasing prevalence of surgical interventions in patients with comorbidities, we can expect that many millions of patients will run the risk of developing POCD every year. This possibility raises the stakes considerably: not only on an individual level, but also on a societal scale.

Despite this potential for disaster, the exact pathophysiology that underlies POCD remains undefined. According to rodent models of postoperative cognitive decline, activation of the innate immune response following aseptic surgical trauma results in the elaboration of hippocampal proinflammatory cytokines, which are capable of disrupting long-term potentiation, the neurobiologic correlate of memory[6]. Assuming that postoperative neuroinflammatory changes noted in rodent models also occur in humans, the underlying mystery is that POCD is a relatively infrequent clinical event (± 10%)[7] whereas neuroinflammation always occurs[8,9]. Is this because there are several clinical conditions that can transform the self-limiting post-surgical neuroinflammatory response into one that is persistent?

Studies have sought to identify factors that may contribute to POCD, which include surgery, as well as in-patient care factors, and patient-related factors. If we divide the possible risk factors into categories of modifiable/non-modifiable and patient related/environmental, we can both disentangle the causes of the neuroinflammatory cascade and also focus on possible clinical adjustments and applications to stave it off.

In the majority of patients, postoperative neuroinflammation is part of the normal protective mechanism to peripheral trauma and resolves properly with no residual cognitive consequences. Indeed, it is also possible that surgery for a chronic inflammatory disease may result in cognitive improvement by eliminating disease-inducing cognitive impairment that may be associated with chronic inflammatory disease. That said, some risk factors, such as obstructive sleep apnea (OSA), Metabolic Syndrome (MetaS), patients prone to neurological disease, and poor selection of sedative agents may each promote the intractable persistence of neuroinflammatory response to surgery[10-12]. For an increasing number of patients with advanced age, POCD is alarmingly common, making postoperative central nervous system dysfunction a looming public health crisis given world's rising elderly population.

Clearly, the surgical effect of this neuroinflammatory trigger is just one possible mechanism. Indeed, environmental culprits can also offer a window into the postoperative cognitive decline conundrum. One great suspect in this complex puzzle is that of sleep disruption. Sleep is crucial for the repair of many types of injury and disease, especially with regard to the central nervous

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and immune systems; it also has anabolic, restorative properties that improve both neurocognitive and immune function. During non rapid eye movement (NREM) sleep slow wave activity performs a homeostatic function to reduce the strength of synapses that has been acquired during wakeful activity[13]. 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 while sleep deprivation results in cognitive dysfunction[14].

Sleep disturbance is commonly observed in the hospital setting and include changes to sleep patterns and quality (especially sleep fragmentation), as well as sleep architecture. Polysomnographic studies revealed extreme sleep disruption in Intensive Care Unit (ICU) patients with decreases in total sleep-time, altered sleep architecture (predominance of stage 1 and 2 sleep, decreased or absent stage 3 NREM and REM sleep), and sleep fragmentation[15,16]; also, up to 50% of the total sleep-time occurred during daytime. Studies have shown that fragmented sleep is prevalent due to frequent arousals and awakenings, and that sleep architecture is altered with an increase in light sleep, and a decrease in restorative slow wave sleep[17].

Environmental factors and health care practices further contribute to sleep disruption in critically ill patients; these include disturbances like inappropriately high noise levels, continuous ambient light, and the near constant performance of medical tests procedure and procedures. Lack of sleep hygiene results in cognitive dysfunction, contributes to delirium, adversely affects immunity, and independently increases both morbidity and mortality. Sleep disruption during hospital care has the potential to adversely impact patients' outcome and also provides a direct financial cost with respect to the length of hospital stay and depletion of healthcare resources. A recent prospective study has also shown that patients with sleep disorders have an increased likelihood of exhibiting postoperative delirium[10]. Despite the common occurrence of both ICU delirium and sleep disruption in critically ill patients, a causal relationship has not yet been well described. Still, the question remains if we are doing all in our power to avoid the development of POCD.

While we realize that the etiology of cognitive dysfunction in surgical/ICU patients is multi-factorial, if the restorative and reparative benefits of sleep mitigate the development of inflammation and cognitive dysfunction, this may result in shorter ICU or postoperative lengths of stay for critically ill patients with a concomitant reduction in healthcare costs. Furthermore, it is possible that the restorative properties of sleep for cognition in the central nervous system can extend to the immune system with less infection and/or greater likelihood of survival from sepsis[18,19].

Non-resolution of inflammation is a factor that contributes to the pathogenesis of POCD, which in turn significantly increases morbidity and mortality in surgical patients. We might be witnessing a perfect and unfortunate storm of factors with regard to POCD: to put it another way, given the rise in surgeries and increasing number of patients with chronic conditions worldwide, the stakes could not be higher.

Vulnerable patients need to be identified and risk/benefit should be considered before contemplating the efficacy of surgical intervention. Further studies are needed to understand which patients will suffer from exacerbated inflammation with an aim toward developing a biomarker that is quick to assay for clinicians and easy to comprehend for patients and their families. Concurrently, clinical interventions need to be further developed to promote the resolution of neuroinflammation in the postoperative patient population. Following both tracks, we anticipate that postoperative recovery for vulnerable patients will be greatly enhanced and possible long-term consequences, such as postoperative neurodegeneration, can be significantly reduced. Additional study is essential to elucidate on preventative strategies, and underlying pathophysiology of this disorder. If these studies can succeed in identifying patients prospectively, or early enough in the advent of persistent inflammation, interventions can be judiciously and appropriately launched. ❖

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Sleep Apnea: An Update of Pharmacologic Therapies

Current standard therapy for obstructive sleep apnea (OSA) relies exclusively on mechanical devices whose effectiveness is hampered by poor compliance due to lack of tolerability, sometimes as high 50%[1]. Oral appliances may be better tolerated but are not as effective, and upper airway surgery has limited long term success. While there is a need for systemic therapeutic agents, the investigation into pharmacologic modalities has been hampered by the absence of a suitable animal model for drug screening and many drugs have been the result of serendipitous observations in other studies. This review will describe several of the treatments that have been evaluated and their shortcomings.

Serotonergic Agents

Serotonin is known to alter sleep and influence upper airway hypoglossal motor neurons. The post synaptic receptors associated with dilator neurons centrally are predominantly 5-HT2A and 5-HT2C subtypes, while the 5-HT1B and 5-HT2 receptors are inhibitory. Stimulation of the peripheral 5-HT2A, 5-HT2c, and 5-HT3 receptor subtypes has an inhibitory effect on respiration (2). The functions of these receptors are species specific. The 5-HT3 antagonist, ondansetron reduces the respiratory disturbance index (RDI) in bulldogs but not in humans[3,4].

Based on successful use in narcolepsy, the tricyclic antidepressant, protriptyline was studied in patients with OSA. A reduction of REM sleep and improved nocturnal oxygenation was observed, although the incidence of apneas and their duration was not altered[5]. Another small study in severe OSA showed a decrease in nocturnal hypoxemia and daytime somnolence[6]. The improvement may have been related to the reduction in REM sleep or the antidepressant effects. However, in a randomized controlled trial (RCT) no significant difference was noted after 2 weeks of treatment[7].

Trials of the selective serotonin re-uptake inhibitors, fluoxetine and paroxetine have been shown to reduce the apnea-hypopnea index (AHI) by 40 and 20% respectively[8,9]. Paroxetine has also been shown to increase genioglossus muscle tone in awake healthy volunteers[10]. Mirtapazine is an antidepressant with 5-HT1agonist and 5-HT2 and 5-HT3antagonist properties and in a placebo controlled study has been shown to decrease AHI by 46-52%. Day time alertness, however, was not improved and in fact, sedation and weight gain resulted, both undesirable side effects[11].

Serotonergic agents seem to have positive effects in OSA and may have increased efficacy in combination with other agents.

Acetylcholinesterase Inhibitors

The cholinergic system plays an important role in the neural control of respiration and acetylcholine is one of the main neurotransmitters involved in respiratory modulation during REM sleep[12]. Application of acetylcholine agonists to the hypoglossal nerve in rats has been shown to reduce genioglossus muscle tone[13]. Pontine injection of the anticholinesterase drug carbachol in cats results in increased hypoglossal nerve activity, while the injection of physostigmine into the cholinergic neurons in the rostral ventrolateral medulla resulted in prolonged firing of the hypoglossal and phrenic nerves and improvement in respiration[14].

The cholinergic system affects regulation of breathing during sleep. Cholinergic stimulation of the respiratory center and carotid bodies increases the sensitivity to hypoxia and hypercarbia and plays an important role in the regulation of ventilation in OSA[12,15-17]. Cholinergic pathways are also involved in cerebral cortex activation related to

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arousal and vigilance[18].

Acetylcholinesterase inhibitors increase central and peripheral acetylcholine levels and also effect sleep. A double-blind placebo controlled RCT with intravenous physostigmine in patients with OSA, resulted in an increase in REM sleep and a decrease in AHI by 23%[19]. Similar results have been reported with Donepezil, an oral cholinesterase inhibitor[20]. Another recent double-blind, placebo controlled RCT of Donepezil in OSA patients demonstrated a significant improvement in AHI, % time with oxygen saturations <3% of baseline and desaturation index after one month of therapy[21]. Nicotine is a respiratory stimulant and while nicotine gum has been associated with a reduction of AHI, transdermal nicotine did not have this effect[22-24].

Methylxanthines

In patients with central sleep apnea (CSA), theophylline has been shown to significantly reduce AHI and improve oxygenation without reduction in sleep[25]. In OSA on the other hand, the reduction in AHI was small, but significant, however sleep quality was worsened[26]. Aminophylline also has similar effects[27].

Acetazolamide

Acetazolamide is a carbonic anhydrase inhibitor and stimulates ventilation by inducing a metabolic acidosis. Acetazolamide is more effective in CSA than in OSA. In CSA apneic episodes were reduced by as much as 80%, while in OSA the reduction was only 20%[28,29].

Glutamate Antagonists

The ventilatory responses to hypoxia are dependent on activation of the NMDA glutamate receptors and sabeluzole; a glutamate antagonist reduced hypoxemic episodes in patients with moderate to severe OSA[30].

Hormones

The effects of estrogen and progesterone on sleep-disordered breathing are inconsistent. Estrogen has been noted to reduce AHI by 25% and the combination of estradiol and progestin reduced apneic episodes by 50%[31,32]. OSA is common in hypothyroid patients, however the results of hormone therapy has only been shown to be beneficial in a couple of small studies[33]. This may be related to the resolution of macroglossia. In acromegaly treatment with octreotide reduced the AHI by 50%[34].

Weight Reduction Medication

Patients with OSA are frequently morbidly obese and there is data that suggests that every 1% reduction in weight results in a 3% reduction in AHI[35]. The use of sibutramine in a group of obese men resulted in an 8.5% weight reduction that was accompanied by a 35% reduction in the respiratory desaturation index (RDI)[36].

Antihypertensive Agents

There is a strong association between hypertension and OSA and it has been suggested that antihypertensive agents may improve OSA by altering the afferent baroreceptor activity and input to respiratory center in the brain. However, studies of antihypertensive agents in this population have been inconsistent. A large double-blind RCT comparing metoprolol and cilazapril found that both drugs reduced the AHI by 50%[37]. Another RCT comparing atenolol, amlodipine, enalapril, hydrochlorthiazide and losartan demonstrated no effect by any of the drugs[38]. Clonidine is an alpha-2 adrenergic agonist with REM suppressant activity and has been shown to reduce REM-related apnea in a small study of hypertensive patients with OSA, but is unsafe in non-hypertensive patients[39].

Wakefulness Promoting Agents

OSA is associated with daytime somnolence, which may not resolve with CPAP therapy. Modafinil is widely used in narcolepsy to promote wakefulness. In OSA patients, modafinil and armodafinil reduced sleepiness and increased vigilance, but did not reduce AHI[40,41].

Cytokine Inhibitor

Pro-inflammatory cytokines such as TNF-alpha are elevated in OSA and etanercept, which is an inhibitor of the agent that has been shown to reduce AHI by 15% and also reduce daytime sleepiness[42].

It is clear from this review that while several agents have been studied, there is no reliable and effective pharmacologic therapy for OSA. Development of these agents is limited by a lack of understanding of the etiology and mechanism of OSA and of an adequate animal model. Drug therapy for OSA will be limited until there is a clearer understanding of the disease. ❖

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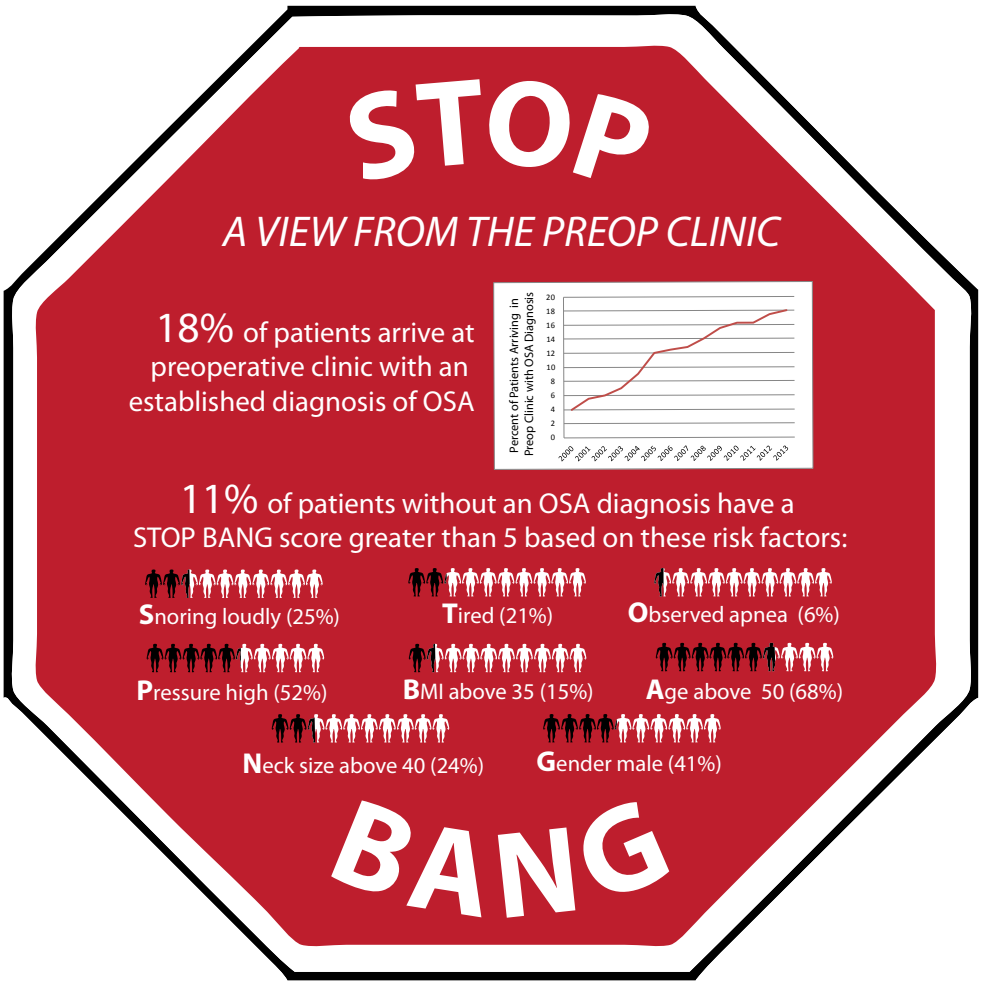

We queried Vanderbilt University's Perioperative Data Warehouse to identify diagnostic trends and risk factors associated with obstructive sleep apnea (OSA) after receiving approval from our institutional review board. Preoperative evaluations were identified for 173,583 patients evaluated between 1/1/2000 and 11/16/2013 in the Vanderbilt Preoperative Evaluation Center (VPEC) where the presence or absence of OSA was documented. These data were divided by year and are displayed as a percentage of patients seen each year with an established diagnosis of OSA at the tie of preoperative evaluation. VPEC implemented an electronic STOP-BANG screening tool[1] in 3/2013. Preoperative evaluations were identified for 8,955 patients evaluated between 3/2013 and 11/16/2016 that took place in VPEC where the STOP-BANG screening tool was fully completed and patients did not have a diagnosis of OSA. The proportion of patients with a STOP-BANG score of 5 or greater was calculated. The prevalence of each risk factor in this population was determined, and is shown with patient icons that each represent 10% of that population.

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Infographic created by Jonathan P. Wanderer, Medical Director, Vanderbilt Preoperative Evaluation Center, Associate Medical Director, Vanderbilt Anesthesiology & Perioperative Informatics Research Division, Instructor, Department of Anesthesiology, Vanderbilt University School of Medicine, jon.wanderer@vanderbilt.edu.

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The Society of Anesthesia and Sleep Medicine (SASM) is a multidisciplinary group of clinicians and researchers who have an interest in topics concerning many aspects of perioperative care that are at the heart of anesthesiology practice and education, including the basic science and clinical aspects of sleep disordered breathing, airway management, pulmonary medicine as well as patient safety.

Sleep medicine has recently been accredited by the American Board of Anesthesiology (ABA) as a board certifiable sub-specialty in anesthesiology, thus opening up tremendous opportunities to our specialty and its trainees in the practice of perioperative medicine.

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4th Annual Meeting • Hotel Monteleone, New Orleans, LA
October 9-10, 2014 • Schedule of Events

Thursday, October 9, 2014		
Time	**Topic**	**Moderator**
1:00 - 1:05 pm	Welcome	*Peter Gay, MD*
1:05 - 3:00 pm	Anesthesia Safety	
	• **Pain and Disrupted Sleep - A Bidirectional Relationship** *David Hillman, MD* • **Can Dexmedetomidine Replace Opioids?** *Mervyn Maze, MB, ChB* • **Carotid Body Chemoreceptor Function and Relationship to Anesthetic Agents** *Malin Fagerlund, MD, PhD* • **Is There An Ideal Anesthetic Regime for OSA?** *Matthias Eikermann, MD, PhD* • **The Mechanisms Underlying Long-term Memory Deficits After Anesthesia** *Beverley Orser, MD, PhD* • **Discussion/Q&A**	*Bhargavi Gali, MD*
3:00 - 3:25 pm	Break	
3:25 - 5:00 pm	Workshop: Postoperative Monitoring & Non-Invasive Ventilation	
	Respiratory Rate, Acoustic Monitor, Minute Ventilation, Expired CO2 • **Respiratory Rate: Plethysmography vs. Acoustic Monitor** *Scott Kelley, MD vs. Michael Ramsay, MD* • **Minute Ventilation vs. Expired CO2 Monitoring** *Evan Pivalizza, MBChB, MD vs. Satya Krishna Ramachandran, MD* • **Discussion/Q&A**	*Stavros Memtsoudis, MD, PhD*
5:00 - 6:00 pm	**How to Do PAP Therapy:** • **AVAPS, Trilogy -** *Lisa Wolfe, MD* • **ASV, VPAP Adapt –** *Peter Gay, MD* • **Discussion/Q&A**	*Michael Pilla, MD*
6:00 - 6:30 pm	Welcome Reception	
6:30 - 8:30 pm	Dinner	
6:30 - 6:35 pm **6:35 - 6:45 pm** **6:45 - 7:30 pm** **7:30 - 8:00 pm** **8:00 - 8:30 pm**	Welcome and Introductions IARS President Address – *Denise Wedel, MD* Dinner Followed by Additional Speakers **Propofol: Murder, Mayhem and Mercy -** *Steven Shafer, MD* **Zero by 2020: Time to Co-Operate -** *Joe Kiani, EEE*	*Frances Chung, MB BS*
Friday, October 10, 2014		
7:00 - 7:55 am	Registration and Continental Breakfast	
7:15 - 7:55 am	Annual General Meeting	
7:55 - 8:00 am	Welcome	*Frances Chung, MB BS*
	Moderator: *Peter Gay, MD*	
8:00 - 8:50 am	***Keynote:* How New Technologies Will Impact Patient Safety**	*Mark Warner, MD*
8:50 - 9:30 am	***Keynote:* Predicting Safety Hazards - MEWS, PEWS, SCHMEWS**	*Tim Morgenthaler, MD*
9:30 - 10:00 am	**Life Threatening Respiratory Events**	*Lorri Lee, MD*
10:00 - 10:15 am	**Q & A**	
10:15 – 10:45 am	Refreshment Break and Poster Viewing	

4th Annual Meeting • Hotel Monteleone, New Orleans, LA
October 9-10, 2014 • Schedule of Events

Friday, October 10, 2014 (continued)		
	Moderator: *Babak Mokhlesi, MD*	
10:45 - 11:10 am	**The Obstructive Sleep Apnea Phenotype**	*Atul Malhotra, MD*
11:10 - 11:35 am	**Preoperative Red Flags and Preparation of Patients with OSA**	*Amy Guralnick, MD*
11:35 am - 12:00 pm	**Rational Pain Management in the Patient with Sleep Disordered Breathing**	*Girish P. Joshi, MBBS*
12:00 - 12:15 pm	**Q & A**	
12:15 - 1:15 pm	Lunch Break and Poster Viewing	
1:15 - 1:45 pm	Awards to Research Grant and Scientific Abstracts Winners Presentations from Research Grant and Best of Abstract Winners	*Frances Chung, MB BS* *Anthony Doufas, MD, PhD*
	Moderator: *Roop Kaw, MD*	
1:45 - 2:10 pm	**Should Upper Airway Surgery be Done as an Outpatient Surgery?**	*Tucker Woodson, MD*
2:10 - 2:35 pm	**Predicting Cardiac Arrest on the Wards: Past, Present and Future**	*Matthew Churpek, MD, PhD*
2:35 - 2:45 pm	**Q & A**	
2:45 - 3:15 pm	Refreshment Break and Poster Viewing	
	Moderator: *Dennis Auckley, MD*	
3:15 - 3:40 pm	**Pregnancy and Obstructive Sleep Apnea**	*Ellen Lockhart, MD*
3:40 - 4:05 pm	**Adenotonsillectomy Outcomes in Treatment of Obstructive Sleep Apnea in Children**	*Rakesh Bhattacharjee, MD*
4:05 - 4:25 pm	**Guidelines for Perioperative Management of Patients with OSA**	*Tracey Stierer, MD*
4:25 - 4:45 pm	**Perioperative CPAP: Is It Efficacious?**	*Frances Chung, MB BS*
4:45 - 5:00 pm	**Q & A**	
5:00 pm	i-Pad Giveaway and Closing Remarks	*Peter Gay, MD*

Invited Faculty

Dennis Auckley, MD
MetroHealth Medical Center

Rakesh Bhattacharjee, MD
University of Chicago

Frances Chung, MB BS
University of Toronto

Matthew Churpek, MD, PhD
University of Chicago Hospitals

Anthony Doufas, MD, PhD
Stanford University School of Medicine

Matthias Eikermann, MD, PhD
Massachusetts General Hospital

Malin Fagerlund, MD, PhD
Karolinska Institutet and Karolinska University

Bhargavi Gali, MD
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Roop Kaw, MD
Cleveland Clinic

Scott Kelley, MD
Covidien

Joe Kiani, EEE
Masimo Corporation

Lorri Lee, MD
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Ellen Lockhart, MD
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Mervyn Maze, MB, ChB
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Stavros Memtsoudis, MD, PhD
Weill Cornell Medical College

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Satya Krishna Ramachandran, MD
University of Michigan Medical Center

Michael Ramsay, MD
Baylor University Medical Center

Steven Shafer, MD
Stanford University

Tracey Stierer, MD
John Hopkins University

Mark Warner, MD
Mayo Clinic

Denise Wedel, MD
Mayo Clinic

Lisa Wolfe, MD
Northwestern University Feinberg School of Medicine

Tucker Woodson, MD
Medical College of Wisconsin

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- Get Advice and Counsel from Other Members Regarding Various Practice Paradigms

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- This donation is inclusive of annual membership and available for all classes of membership.

❑ **Active Member - $100**
- Physicians and Scientists. Active Members have voting rights, can hold office and serve on the Board of Directors.

❑ **Associate Member - $50**
- Non-Physicians and Non-Scientists. Associate Members do NOT have voting rights.

❑ **Educational Member - $50**
- Fellows, Residents, Medical Students or other undergraduates. Educational Members do NOT have voting rights.

Please consider joining as a "Gold Patron" for 2014

The additional donation beyond general membership will be used to promote scholarly activity in the area of anesthesia and sleep medicine and promote patient care programs in areas common to anesthesia and sleep medicine. Gold Patrons will be recognized on our website for their extraordinary support of SASM efforts and will be invited to special events highlighting the programs made possible with their donations, including a keynote speaker dinner at the Annual Meeting.

SASM - NEW OFFICE LOCATION!
6737 W Washington Street, Suite 1300
Milwaukee, Wisconsin 53214

SASM is a 501(C)(3) non-profit organization. Membership dues may be deductible as a business expense. **SASM Tax ID number is 27–4613034**