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Pediatric considerations in sedation for patients with the obstructive sleep apnea syndrome

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During sedation and recovery the airway of children with obstructive sleep apnea is vulnerable to collapse. This vulnerability arises from both an inherent collapsibility of the pharyngeal airway in these children and a heightened sensitivity to sedative and anesthetic agents. Pharmacologic and non-pharmacologic support may be required to defend pharyngeal airway patency in children with obstructive sleep apnea both during sedation and recovery.

In many ways, the obstructive sleep apnea (OSA) syndrome is the Achilles heel of pediatric sedation and analgesic programs, particularly if medications are administered by non-anesthesiologists. The prevalence of OSA is high, estimated in the pediatric population to be 1-3%.[1-4] The peak incidence of OSA in children occurs between 2 and 6 years of age, an age range that commonly requires pharmacologic intervention to submit to painful diagnostic and therapeutic procedures.

Awake, the apparently healthy child with undiagnosed severe OSA is difficult to identify on clinical grounds alone. Once subjected to sedative and anesthetic drugs, the airway in this child becomes very difficult to manage. Upper airway obstruction during anesthesia may be the first sign of severe OSA.[5]

The OSA syndrome is characterized by sleep fragmentation, episodic apnea, and recurrent hypoxemia and hypercarbia during sleep. Exposure to intermittent hypercarbic hypoxia (IHH) during development is an experimental model for two clinical entities important to child health, namely the sudden infant death syndrome and the obstructive sleep apnea syndrome. Long-term follow up of infants suffering acute life-threatening events report a higher incidence of OSA in childhood and adolescence.[6-8] Exposure to intermittent hypoxia (IH) during development has a profound effect on central neuromodulator systems including the opioid system, altering the sensitivity to exogenously administered opioids. In addition, the neurotransmitters important to activation of the respiratory-related activity in the pharyngeal dilator muscles are the same neurotransmitters targeted by most sedative and anesthetic agents. Therefore, an appreciation of the vulnerability of the airway in OSA to pharyngeal collapse and upper airway obstruction during sedation/anesthesia is essential to effectively manage these children.

The severity of OSA is assessed by the frequency and severity of the obstructive respiratory events during sleep. The frequency of obstructive events is quantitated by the Apnea/Hypopnea index (AHI), also referred to as the Respiratory Disturbance index (RDI). Pediatric diagnostic criteria for OSA are an AHI in excess of 1 event per hour and a saturation nadir below 92%.[9,10] The level of OSA severity may also be stratified by the frequency and level of desaturation which occurs during the obstructive respiratory

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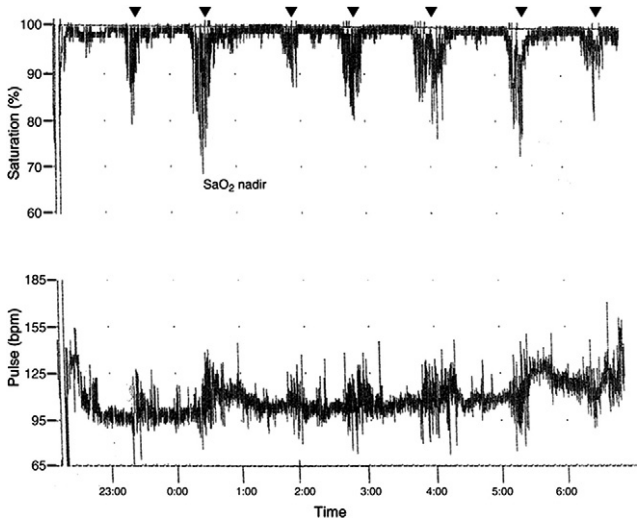

Figure 1 Representative abnormal nocturnal oximetry study, recorded between 22:00 and 7:00 h, shows seven clusters (arrows) of desaturations associated with an increase in heart rate variability. Four clusters show desaturations less than 80%. Bpm, beats per minute.

event.[11] Criteria for an abnormal *oximetry trend record* include at least three clusters of desaturation (Figure 1). A number of desaturation indices are used to assess sleep disordered breathing: the desaturation index is the number of desaturation events per hour, the time spent below a threshold saturation, the averaged value of the nadir saturation of each cluster, and the saturation nadir of the entire record. In the context of a clinical history suggestive of sleep disordered breathing and an abnormal *oximetry trend record*, the saturation nadir, a single data point in the entire record, has proven to be a robust predictor of postoperative risk.[11]

The frequency and severity of obstructive respiratory events and desaturation vary with sleep stage and occur most frequently during active, rapid eye movement (REM) sleep.[2,11] The frequency and severity of obstructive events worsen after midnight, and this is thought to reflect the higher proportion of REM sleep in the latter part of the night. Upper airway muscle fatigue[12] is also proposed as a mechanism and is supported by the finding that exposure to episodic hypercapnic hypoxia in the rat model alters upper airway muscle structure and function.[13]

Establishing the diagnosis of the OSA syndrome in children

A high index of suspicion is required to identify the child with OSA on clinical criteria. There is an ethnic vulnerability to the development of OSA and a higher incidence is found in Asian and African American populations.[14,15] African American children desaturate more profoundly during sleep-related obstructive airway events than Caucasian or Latino children.[16] Medical complexity should alert the clinician to the potential for OSA and may be of two forms: 1) an associated medical condition which predisposes to the development of OSA[17] or 2) the medical sequelae of OSA.

Medical conditions which predispose to OSA

Anatomical features including increased nasal resistance may underlie the pathogenesis of OSA.[18,19] Craniofacial syndromes which are associated mid-face hypoplasia, micro/retrognathia, macroglossia, and narrow facies including the craniosynostoses (Crouzons, Apert's, and Pfeiffer syndrome), Trisomy 21, Treacher Collins syndrome, the Pierre Robin Sequence, Goldenhar syndrome, and achondroplasia also predispose to OSA. Disorders of the cranial base which impair the function of cranial nerves, including the Arnold Chiari abnormality, are associated with OSA. Neuromuscular disorders associated with abnormalities of muscle tone, including both hypotonia and spasticity, predispose to OSA. The formerly premature infant is at increased risk of OSA. Children with infiltrative disorders such as the mucopolysaccaridoses (Hunter's and Hurler's syndrome) and acromegaly are at risk for OSA. Children with obesity and the Prader-Willi syndrome have a higher incidence of OSA. Seizure disorders may predispose to the development of OSA both because of an underlying neurologic disorder and because many of the anti-seizure medications inhibit the function of the upper airway muscles.[20-28]

Medical conditions which are sequelae of OSA

The obstructive events which characterize OSA result in recurrent episodes of hypoxia, hypercarbia, and sleep disruption. This trilogy has been linked to the development of medical sequelae which accompany severe OSA such that the child with moderate/severe OSA presents a spectrum of diseases affecting multiple organ systems. Failure to thrive is common[22,29,30] and may arise from both a disruption in the circadian secretion of growth hormone and the increased work of breathing.[28] There is evidence of cardiovascular abnormalities,[29] including ventricular dysfunction, a depressed ventricular ejection fraction, and ventricular hypertrophy[31,32] and pulmonary hypertension.[1,4] Repeated respiratory infections affecting both the lower and upper respiratory tracts are common. Lower respiratory infections have been linked to chronic aspiration during sleep.[33]

Children with severe OSA have a blunted response to hypercarbic challenge during anesthesia.[34] They demonstrate subtle dynamic changes in ventilatory responses. Consecutive hypercapnic challenge, upon arousal from sleep, does not produce the progressive increase in ventilation with time which is seen in normal children.[35] Most of the medical sequelae of OSA resolve with treatment.[35,36]

Table 1 Clinical diagnostic criteria for pediatric obstructive sleep apnea syndrome*

1) Predisposing physical characteristics
   a) Body Mass Index greater than 95%ile for age and gender.
   b) Craniofacial abnormalities affecting the airway.
   c) Anatomical nasal obstruction.
   d) Tonsils nearly touching or touching in the midline.
2) History of apparent airway obstruction during sleep (two or more of the following):
   a) Loud snoring (loud enough to be heard through a closed door.)
   b) Frequent snoring
   c) Observed pauses in breathing during sleep.
   d) Frequent arousals from sleep.
   e) Intermittent vocalization during sleep.
   f) Parental report of restless sleep, difficulty breathing, or struggling respiratory efforts during sleep.
3) Somnolence (One or more of the following)
   a) Parent or teacher comments that the child appears sleepy during the day, is easily distracted, is overly aggressive, or has difficulty concentrating.
   b) Child often is difficult to arouse at the usual awakening time.

*If signs and symptoms in at least two categories are present, there is a significant probability of moderate OSA. If severe abnormalities are present, children should be treated as severe OSA. Adapted from Table 1 in Recent Practice Guidelines for the Perioperative Management of Patients with OSA.[10]

An associated medical condition predisposing to OSA is easily identifiable during the pre-sedation assessment of the child. However, the otherwise healthy, apparent American Society of Anesthesiology physical status 1 child with medical sequelae of severe OSA is not so easily identified by clinical criteria alone.[22,37] Recently published practice guidelines for perioperative management of patients with OSA[10] propose clinical criteria to establish a diagnosis of OSA in children (Table 1). However, clinical acumen for both the diagnosis of OSA and the stratification of disease severity is poor, and only 55% of children with a clinical criteria suggestive of OSA subsequently meet sleep laboratory diagnostic criteria.[38]

A history of snoring has been recognized as a predictor of anesthetic adverse respiratory events.[39] However, whereas 14% of children have primary benign snoring, only 1-3% of children meet the diagnostic criteria for the OSA syndrome.[2] Establishing a diagnosis of OSA and stratification of the level of OSA severity is important for accurate prediction of anesthetic risk during anesthesia and sedation. In children with OSA who were premedicated with midazolam, an RDI of 20 events per hour was associated with a higher incidence of laryngospasm during induction of anesthesia, and an RDI of 30 events per hour was associated with laryngospasm and desaturation on emergence from anesthesia.[40] Ten obstructive events per hour and a saturation nadir $<80\%$ are the threshold values for increased risk of severe respiratory complications following adenotonsillectomy for OSA.[29,41,42]

The upper airway in OSA syndrome: pharyngeal patency during wakefulness, sleep, and anesthesia

Sedation protocols for painful diagnostic and therapeutic procedures produce an altered state of consciousness. Because this altered state of consciousness is in fact a continuum from conscious sedation to anesthesia, discussion of the specific effects of pharmacologic agents on the upper airway in patients with OSA must also include wakefulness and anesthesia. Patients with OSA demonstrate a heightened sensitivity to sedative and analgesic agents. Consensus opinion is that general anesthesia with a secure airway is preferable to deep sedation for the patient with moderate/severe OSA syndrome.[10]

Pharyngeal patency during wakefulness

Compared with normal subjects, the dimension of pharyngeal airway in OSA is anatomically smaller.[38,43,44] In addition, the pharynx is inherently more collapsible even during wakefulness.[45-47] The negative pressure generated by inspiration will narrow and collapse the pharyngeal airway unless countered by inspiratory activity in the pharyngeal dilator muscles.[1] During wakefulness, both tonic and peak activity in the genioglossus muscle is higher in patients with OSA compared with control, suggesting that during wakefulness, airway patency is relatively more dependant on the function of the pharyngeal dilators in patients with OSA.[48-51] This greater dependence on the pharyngeal dilators is underscored by the influence of local anesthesia applied during wakefulness on airway dimension. Topical anesthesia applied to the pharynx of children with OSA results in a much greater reduction in pharyngeal caliber compared with controls.[52]

Pharyngeal patency during sleep

Sleep is associated with a decrease in pharyngeal caliber, an increase in the compliance of the pharynx, and an inhibition of the pharyngeal dilator muscles, all promoting collapse of the upper airway.[49] Compared with adults, children with OSA seem better able to maintain inspiratory activity of the pharyngeal dilators during sleep.[46] Unlike adults with OSA in whom cortical arousal is required to terminate obstructive apnea, in children with OSA, recruitment of the upper airway dilators is the usual mechanism whereby the obstructive apnea is terminated.[18]

Sleep onset is associated with a loss of tonic neck activity promoting flexion of the neck and a decreased dimension

of the pharynx.[49,53-55] Activation of the upper airway activity precedes activation of the primary respiratory muscles.[56] Sleep disrupts this coordination. The pharyngeal dilator reflex, first reported in man in 1991, describes a reflex activation of the pharyngeal dilator muscles when negative suction forces are applied to the pharyngeal airway.[48,50] Sleep inhibits the responsiveness of both the tensor palatine and genioglossus muscles to the pharyngeal dilator reflex.[51,57] Active REM sleep is associated with a heightened respiratory drive to the diaphragm and a lesser drive to the musculature of the upper airway, resulting in collapse of the pharyngeal airway during REM sleep.[49]

Anesthesia/sedation

Pharyngeal patency during anesthesia

The physiologic and pharmacologic effects of sedation and anesthesia simulate the effects of sleep and promote collapse of the upper airway. The pharyngeal airway of patients with OSA is especially vulnerable to collapse during anesthesia/sedation.[5,45-47]

Physiologic effects

Hypercarbia and a loss of lung volume (functional lung capacity) commonly accompany anesthesia and sedation. Both promote collapse of the pharyngeal airway. The threshold carbon dioxide stimulation for recruitment of the diaphragm is lower than the genioglossus,[49] a differential sensitivity which increases pharyngeal collapsibility. Loss of lung volume acts to displace the trachea in a rostral direction, thereby decreasing the longitudinal tension of the upper airway and increasing the collapsibility of the pharyngeal airway both in wakefulness[58] and during anesthesia.[47]

Pharmacologic effects

Muscle relaxants

The muscles of respiration display a differential sensitivity to sub-maximal neuromuscular blockade such that the geniohyoid muscle is more sensitive than the diaphragm.[59] Residual neuromuscular blockade will selectively depress the function of the upper airway dilators relative to the diaphragm, promoting collapse of the pharyngeal airway. Residual neuromuscular blockade was present in the majority of patients even 2 hours after administration of intermediate duration muscle relaxants.[60] Although studies specific to the patients with OSA are lacking, it seems likely that these patients would be very sensitive to residual neuromuscular blockade. Full reversal of neuromuscular blockade is strongly recommended prior to extubation of the patient with OSA.[10]

Anesthetic/sedative agents

A differential sensitivity of the muscles of respiration was reported for halothane.[61] This differential sensitivity has subsequently been reported for most anesthetic and sedative agents.[62,63] Glycine and gamma amino butyric acid (GABA) are inhibitory neurotransmitters to the genioglossus muscle, a major upper airway dilator.[64] Sedative and anesthetic agents, acting as agonists at these receptors, preferentially inhibit the activity of the pharyngeal dilator muscles,[63] favoring collapse of the pharyngeal airway during sedation/anesthesia.

Adults

Although the focus of this discussion is pediatric OSA, studies in adults which assess the effect of sedative and anesthetic agents on the airway are instructive (see article in this issue by Dr. Hillman). In healthy adult volunteers, mild to moderate levels of sedation with midazolam were associated with a greater tendency for upper airway obstruction than equivalent levels of sedation with propofol. Recovery was more rapid following termination of the propofol infusion.[65] Although propofol inhibits activity of the upper airway dilators, at low doses there is some preservation of activity.[66] This is in contrast to the abolition of phasic activity at even low concentrations of isoflurane.[47] It is not known whether there is a clinical advantage of propofol, or any other sedative/anesthetic agent for that matter, in children with OSA. Indeed, consensus opinion does not advocate any particular general anesthetic agent in patients with OSA.[10]

Children

Studies of children with normal airways show a graded reduction in airway caliber with increasing concentrations of sevoflurane.[55] Propofol administration is associated with a dose-dependent decrease in pharyngeal cross sectional area, due primarily to a decrease in the anterior–posterior dimension.[67] Magnetic imaging studies of children with OSA, during sedation, indicate that the level of airway obstruction occurs in the upper two-thirds of the pharyngeal airway and the smallest pharyngeal dimension is in the area of overlap between the adenoids and tonsils.[44]

The selective sensitivity of the upper airway muscles to the physiologic and pharmacologic effects of anesthesia/sedation result in a reduction of pharyngeal dimension and an increase in pharyngeal collapsibility. In patients with OSA, this collapse will occur at supra-atmospheric pressure.[5] Support of the pharyngeal airway during anesthesia/sedation may require bypass of the pharyngeal airway by insertion of endotracheal tubes, oro/nasopharyngeal airways, or laryngeal masks. Since most sedation protocols aim for light levels of sedation, the sedated child may not be sufficiently deep to tolerate insertion of these airways. In addition, the patient with OSA has a higher incidence of intubation difficulties because of anatomical features which reduce the skeletal confines of the tongue present in both the

patient with OSA and the difficult airway[68] (see article in this issue by Drs. Stearns and Stierer).

Alternately, the airway may be stabilized by the application of continuous positive airway pressure (CPAP). Small increments in CPAP between 5 and 10 cm H_2O result in a marked increase in the dimension of the pharyngeal airway.[28,69] The important role of CPAP in maintaining pharyngeal caliber is illustrated by the fact that the propofol-associated loss in airway caliber was reversed with the application of CPAP.[70]

Consensus (anesthetic) opinion is that general anesthesia with a secured airway is preferable to deep sedation, and is equivocal regarding whether general anesthesia with a secured airway is preferable to moderate sedation for superficial procedures. General anesthesia with a secured airway is preferable for procedures involving the upper airway including endoscopy. The guidelines for the perioperative management of patients with OSA assign equivalent risk scores to superficial surgery with general anesthesia and airway surgery with moderate sedation.[10] Implied in these consensus guidelines is a recommendation that patients with moderate/severe OSA be excluded from sedation programs delivered by non-anesthesiologists.

Extubation practice

Extubation strategy has been highlighted as important to outcome in patients with OSA. A diagnosis of OSA was a risk factor associated with death/brain damage following extubation.[19,71] Although awake extubation is recommended,[10] wakefulness in patients with OSA may not ensure full return of the pharyngeal dilator muscle function if suppression of the upper airway dilator musculature continues into the post-operative period. Therefore, delayed awake extubation may be advantageous, especially if the tracheal intubation has been difficult. The use of a tube exchanger during the extubation is invaluable, and it may be prudent to perform extubation in an OR setting with the otolaryngologist ready for rigid bronchoscopy or tracheostomy, should airway obstruction occur.

Postoperative period

Pharmacologic support

Two drugs, atropine and naloxone, have the potential to augment the function of the upper airway and may prove useful in the management of children with severe OSA. Endogenous acetylcholine modulates activity of the genioglossus muscle, the major muscle responsible for anterior displacement of the tongue. Muscarinic blockade of the hypoglossal nucleus, in the rat model, enhances activity of the genioglossus muscle.[72] Atropine may enhance the function of the upper airway dilator muscles in children with severe OSA.

Opioid receptors are widely distributed throughout the brainstem, including the neural networks which control the pharyngeal dilator muscles. Opioids modulate respiratory-related activity of the pharyngeal dilator muscles. Mu opioid stimulation depresses the activity of the pharyngeal dilator muscles including the genioglossus muscle, thereby promoting upper airway collapse.[36,73] A heightened sensitivity to both the analgesic and respiratory effects of exogenously administered opioids has been reported in children with severe OSA (see below). It is probable that this heightened sensitivity to exogenous opioids also extends to the respiratory-related activity of the pharyngeal musculature. In children with OSA, there is a role for naloxone to support pharyngeal patency during recovery from anesthesia/sedation if exogenous opioids have been administered. Relatively low doses of naloxone alleviate upper airway obstruction in this clinical scenario.

Non-pharmacologic support

Support of the OSA airway during recovery from anesthesia/sedation is primarily non-pharmacologic. Studies specific to the patients with OSA are emerging, and small manipulations in the determinants of pharyngeal collapsibility make a large difference to the pharyngeal dimension.[53] These determinants include the position of the head and neck and airway pressure support.

Positioning

During recovery from anesthesia and surgery, while pharmacologic and physiologic inhibition of the upper airway dilators may be present, meticulous attention to the position of the head and neck is important to optimize pharyngeal dimension.[74] The triple airway maneuver (neck extension, the sniffing position, and mouth opening with anterior advancement of the mandible) maximizes the caliber of the pharynx[44,75] (see article in this issue by Dr. Isono). In addition, lengthening of the pharyngeal airway, ie, by extension of the cervical spine or caudal displacement of the trachea, alters the longitudinal tension of the pharynx and decreases the collapsibility of the upper airway.[76]

The lateral position with OSA markedly increases the dimension of the pharynx.[28] In normal children sedated with propofol, the loss in airway caliber in the supine position was reversed in the lateral position.[77] During induction of anesthesia for pediatric adenotonsillectomy, the lateral position relieved the signs of upper airway obstruction.[74] There is an interaction between passive caudal tracheal displacement and anterior displacement of the tongue such that the increase in pharyngeal caliber was greatest with the combined maneuver.[78]

CPAP support

Long-term application of CPAP during sleep has become the mainstay of OSA therapy in the adult population. Application of CPAP to the upper airway acts as a pneumatic splint to increase its caliber.[79] Of equal importance, CPAP increases lung volume and thereby the longitudinal tension on the pharyngeal airway, thus decreasing the collapsibility of the upper airway.[58,80]

The use of CPAP has a role in the perioperative management of patients with OSA. Application of CPAP following extubation promotes upper airway stability in the immediate post-extubation period. In children, use of the Mapleson circuits may confer an advantage because of the ease with which CPAP may be applied and titrated to effect. Unlike the home application, the use of CPAP in the postoperative period may be indicated both during sleep and wakefulness. Indeed, the continuous use of nasal CPAP in adult patients with OSA, in the initial postoperative days, allowed the unrestricted use of sedative, opioid, and anesthetic drugs.[81]

Analgesia: opioids

Severe OSA is characterized by recurrent episodes of hypoxia and hypercarbia during sleep. Exposure to intermittent hypoxia (IH) during development, in animals, affects two neurotransmitter systems important to anesthesia and sedation, namely the opioid system and the glutaminergic system. Exposure to IH during development is associated with an increase in the density of mu-opioid receptors in the brainstem. The cellular mechanism whereby this increased density is achieved is unknown, but it may represent an adaptive response to the effects of recurrent hypoxia which allows the influence of mu-opioid respiratory effects to predominate.[36,82-84]

Children with severe OSA exhibit recurrent hypoxemia, and the severity of the hypoxemia correlates with the sensitivity to exogenously administered opioids.[85,86] Indeed, the morphine dosage required to achieve a uniform analgesic endpoint in children with OSA, whose preoperative saturation nadir was less that 85%, was half that required in children whose saturation nadir was greater than 85%.[86] Forty-six percent of children with severe OSA characterized by a low saturation nadir experienced apnea following a uniform dose of fentanyl, compared with 4% of controls.[87] A heightened sensitivity to the respiratory effects of fentanyl is supported by the fact that exposure to IH in developing rat pups was associated with an exaggerated respiratory depression to subsequent administration of a uniform dose of fentanyl.[88]

In addition to the opioid system, hypoxia activates other neurotransmitters important to respiratory control and arousal, including neuromodulators which stimulate (glutamate) and inhibit (GABA and adenosine) respiration. Stimulation of the glutaminergic system by exposure to IHH during development activates the N-methyl-D-aspartate (NMDA) pathways,[89,90] which are widely distributed in areas of the brainstem involved with cardiorespiratory homeostasis. The anesthetic implications of this activation are unstudied.

Guidelines for the perioperative management of OSA[10] assign a higher risk score if opioids are used for postoperative analgesic regimens in patients with OSA. The notion that opioid administration increases risk in children is supported by reports of a decreased opioid dosage to achieve a uniform analgesic endpoint,[85,86] coupled with a heightened respiratory sensitivity to a uniform dose of fentanyl in children with OSA.[87] An unforeseen advantage of untreated severe OSA may be that analgesia is easily obtained with minimal opioid dosage. However, there is also great risk for respiratory depression with standard opioid dosing, highlighted by anecdotal reports of neurologic injury and death associated with the use of opioids in patients with OSA.[91] Although the mechanism of the heightened sensitivity of opioids is unknown, treatment of OSA may reset opioid sensitivity since patients with severe OSA (untreated OSA saturation nadir 65%) for whom nasal CPAP was instituted pre-operatively (treated OSA saturation nadir 88%) tolerated the unrestricted use of sedative, opioid, and anesthetic drugs without respiratory morbidity.[81]

Although the guidelines for the perioperative management of OSA[10] suggest that the use of low-potency oral opioid analgesia carries a reduced risk, the use of codeine, a low-dose oral opioid commonly used in the ambulatory setting, may be problematic in children with OSA. Codeine is metabolized by the cytochrome P450 desbrisoquine 4 hydroxylase (CYP2D6) to its active analgesic metabolites morphine-6-glucuronide and morphine-3-glucuronide. The CYP2D6 gene displays polymorphism including gene duplication. Gene duplication results in ultrarapid metabolism, which for prodrugs like codeine results in a higher fraction of the active opioid agonist metabolites. Respiratory arrest with codeine in a patient who demonstrated ultrarapid metabolism of codeine has been reported.[92]

Exposure to IH and IHH during development in experimental models is associated with an increase in the arousal latency to hypoxia[89,93] and may be mediated by central inhibitory neurotransmittors.[93] A prior history of IH and IHH may impair arousal to both hypoxia and hypercarbia during sleep.[94] Morphine obtunds arousal.[95] If the heightened sensitivity to both the analgesic and respiratory effects of exogenously administered opioids reported in children extends to arousal mechanisms, the use of opioids in patients with severe OSA may impair arousal mechanisms. In an experimental rat model, activation of the glutaminergic system by exposure to IHH is linked to excitotoxic cellular injury and apoptosis. Subsequent hypoxic episodes such as might occur during anesthesia/sedation may be associated with greater neurologic injury in children with severe OSA.[90]

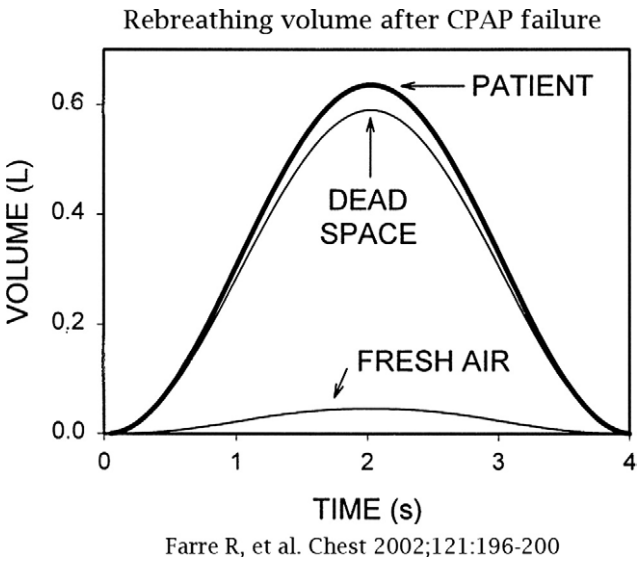

Figure 2 Proportioning of the tidal volume while breathing from a sleep apnea device. Most of the tidal volume inspired by the patient comes from the breathing tube connecting the face mask to the CPAP device (Dead Space). Only a minor portion is derived from atmospheric (fresh air) through the exhalation port. Washout of exhaled gases is achieved by the flowrate generated by the sleep apnea device.

Discharge criteria

The guidelines for the perioperative management of OSA[10] suggest that the patient whose OSA is treated with a domiciliary sleep apnea therapy device may be managed in ambulatory programs. Fundamental to this recommendation is the assumption that the physiologic control and arousal mechanisms of patients are intact in the post-operative period. Sleep apnea therapy devices are not classified as life-sustaining, and therefore are not equipped with the alarm and safety features of ventilators. Rather, they rely on physiologic control and arousal mechanisms to awaken the patient.[96] Sleep apnea therapy devices deliver the therapeutic positive pressure to the patient by imposing airflow through a resistive exhalation port located in the mask. The inspired and exhaled gases share a common pathway, namely the breathing tube connecting the mask to the flow generator in the sleep apnea device. Elimination of exhaled carbon dioxide from the breathing tube depends primarily on gas flow from the sleep apnea device (Figure 2). In the absence of airflow, as might occur during electrical power failure, rebreathing may occur and the patient must rouse from sleep to remove the mask.[97,98]

Discharge criteria based on street fitness during wakefulness are poorly suited for children with OSA. Sleep onset may be associated with sleep disordered breathing which may worsen under effects of residual sedative/anesthetic/analgesic medication. Furthermore, the reference breathing pattern for the parents of children with untreated OSA is one of heavy snoring, confusional arousals, witnessed apnea, and struggling respiratory efforts.[4,10] They are ill-prepared to detect and monitor changes in the respiratory status of their children during recovery from sedation/anesthesia.

Summary and conclusion

The OSA syndrome is indeed the Achilles heel of sedation protocols and acute pain services. The disease prevalence is high. Clinicians must have a very high index of suspicion for OSA since the apparently healthy child with undiagnosed severe OSA is difficult to identify by clinical criteria. He/she may have pulmonary hypertension, lower respiratory disease, and cardiac dysfunction, all of which increase the risk of respiratory complications. There is evidence that exposure to IH/IHH during development, as is seen in children with severe OSA, profoundly alters central neuromodulator systems, including the opioid system. Preoperative assessment for children must include an assessment for sleep disordered breathing in order to judge opioid dosage. The airway of the child with OSA becomes difficult to manage once sedative and opioid medications have been administered. An excessive tendency for airway collapse during anesthesia/sedation may be the first sign of severe OSA. These children have a higher incidence of airway complications and intubation difficulties during anesthesia and sedation. Appropriate post-procedure monitoring and care for these children must be secured. Recently published consensus guidelines may help clinicians in the decision-making process.[10]

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References

1. Dyson M, Beckerman RC, Brouillette RT: Obstructive sleep apnea syndrome, in Beckerman RC, Brouillette RT, Hunt CE (eds). Respiratory Control Disorders in Infants and Children. Baltimore, MD, Williams & Wilkins, 1992, pp 212-230
2. Davidson SL, Marcus CL: Obstructive sleep apnea in infants and young children. J Clin Neurophysiol 13:198-207, 1996
3. Marcus CL: Clinical and pathophysiological aspects of obstructive sleep apnea in children. Pediatr Pulmonol 16:123-124, 1997
4. Guilleminault C, Pelayo R, Leger D, et al: Recognition of sleep-disordered breathing in children. Pediatrics 98:871-882, 1996
5. Eastwood PR, Szollosi I, Platt PR, et al: Comparison of upper airway collapse during general anaesthesia and sleep. Lancet 359:1207-1209, 2002
6. McNamara F, Sullivan CE: Obstructive sleep apnea in infants: relation to family history of sudden infant death syndrome, apparent life-threatening events, and obstructive sleep apnea. J Pediatr 136:318-323, 2000

7. Guilleminault C, Stoohs R: From apnea of infancy to obstructive sleep apnea syndrome in the young child. Chest 102:1065-1071, 1992
8. Guilleminault C, Robinson A: Developmental aspects of sleep and breathing. Curr Opin Pulm Med 2:492-499, 1996
9. Marcus CL, Omlin KJ, Basinski DJ, et al: Normal polysomnographic values for children and adolescents. Am Rev Respir Dis 146:1235-1239, 1992
10. Practice Guidelines for the Perioperative Management of Patients with Obstructive Sleep Apnea: A Report by the American Society of Anesthesiologists Task Force on Perioperative Management of Patients with Obstructive Sleep Apnea. Anesthesiology 104:1081-1093, 2006
11. Nixon GM, Kermack AS, Davis GM, et al: Planning adenotonsillectomy in children with obstructive sleep apnea: the role of overnight oximetry. Pediatrics 113:e19-e25, 2004
12. Goh DYT, Galster P, Marcus CL: Sleep architecture and respiratory disturbances in children with obstructive sleep apnea. Am J Respir Crit Care Med 162:682-686, 2000
13. McGuire M, MacDermott M, Bradford A: The effects of chronic episodic hypercapnic hypoxia on rat upper airway muscle contractile properties and fiber-type distribution. Chest 122:1400-1406, 2002
14. Redline S, Tishler PV, Hans MG: Racial differences in sleep-disordered breathing in African-Americans and Caucasians. Am J Respir Crit Care Med 155:186-192, 1997
15. Palmer LJ, Buxbaum SG, Larkin EK, et al: Whole genome scan for obstructive sleep apnea and obesity in african-american families. Am J Respir Crit Care Med 169:1314-1321, 2004
16. Stepanski E, Zayyad A, Nigro C, et al: Sleep-disordered breathing in a predominantly African-American pediatric population. J Sleep Res 8:65-70, 1999
17. Crysdale WS, Djupesland P: Nasal obstruction in children with craniofacial malformations. Int J Pediatr Otorhinolaryngol 49:S63-S67, 1999
18. McNamara F, Sullivan CE: The genesis of adult sleep apnoea in childhood. Thorax 55:964-969, 2000
19. Isono S: Contribution of obesity and craniofacial abnormalities to pharyngeal collapsibility in patients with obstructive sleep apnea. Sleep Biol Rhythms 2:17-21, 2004
20. Marcus CL, Keens TG, Bautista DB, et al: Obstructive sleep apnea in children with down syndrome. Pediatrics 88:132-139, 1991
21. Hoeve HLJ, Joosten KFM, van den Berg S: Management of obstructive sleep apnea syndrome in children with craniofacial malformation. Int J Pediatr Otorhinolaryngol 49:S59-S61, 1999
22. McGowan FX, Kenna MA, Fleming JA, et al: Adenotonsillectomy for upper airway obstruction carries increased risk in children with a history of prematurity. Pediatr Pulmonol 13:222-226, 1992
23. Isono S, Saeki N, Tanaka A, et al: Collapsibility of passive pharynx in patients with acromegaly. Am J Respir Crit Care Med 160:64-68, 1999
24. Nixon GM, Brouillette RT: Sleep and breathing in prader-willi syndrome. Pediatr Pulmonol 34:209-217, 2002
25. Hiroe Y, Inoue Y, Higami S, et al: Relationship between hypersomnia and respiratory disorder during sleep in Prader-Willi syndrome. Psychiatry Clin Neurosci 54:323-325, 2000
26. Marcus CL, Curtis S, Koerner CB, et al: Evaluation of pulmonary function and polysomnography in obese children and adolescents. Pediatr Pulmonol 21:176-183, 1996
27. Ng DKK, Lam YY, Kwok KL, et al: Obstructive sleep apnoea syndrome and obesity in children. Hong Kong Med J 10:44-48, 2004
28. Isono S, Tanaka A, Nishino T: Lateral position decreases collapsibility of the passive pharynx in patients with obstructive sleep apnea. Anesthesiology 97:780-785, 2002
29. McColley SA, April MM, Carroll JL, et al: Respiratory compromise after adenotonsillectomy in children with obstructive sleep apnea. Arch Otolaryngol Head Neck Surg 118:940-943, 1992
30. Lamarche Y, Martin R, Reiher J, et al: The sleep apnoea syndrome and epidural morphine. Can Anaesth Soc J 33:231-233, 1986
31. Tal A, Leiberman A, Margulis G, et al: Ventricular dysfunction in children with obstructive sleep apnea: radionuclide assessment. Pediatr Pulmonol 4:139-143, 1988
32. Amin RS, Kimball TR, Bean JA, et al: Left ventricular hypertrophy and abnormal ventricular geometry in children and adolescents with obstructive sleep apnea. Am J Respir Crit Care Med 165:1395-1399, 2002
33. Konno A, Hoshino T, Togawa K: Influence of upper airway obstruction by enlarged tonsils and adenoids upon recurrent infection of the lower airway in childhood. Laryngoscope 90:1709-1716, 1980
34. Strauss SG, Lynn AM, Bratton SL, et al: Ventilatory response to CO2 in children with obstructive sleep apnea from adenotonsillar hypertrophy. Anesth Analg 89:328-332, 1999
35. Gozal D, Arens R, Omlin KJ, et al: Ventilatory response to consecutive short hypercapnic challenges in children with obstructive sleep apnea. J Appl Physiol 79:1608-1614, 1995
36. Lalley PM: μ-Opioid receptor agonist effects on medullary respiratory neurons in the cat: evidence for involvement in certain types of ventilatory disturbances. Am J Physiol Regul Integr Comp Physiol 285:1287-1304, 2003
37. Suen JS, Arnold JE, Brooks LJ: Adenotonsillectomy for treatment of obstructive sleep apnea in children. Arch Otolaryngol Head Neck Surg 121:525-530, 1995
38. Arens R, McDonough JM, Costarino AT, et al: Magnetic resonance imaging of the upper airway structure of children with obstructive sleep apnea syndrome. Am J Respir Crit Care Med 164:698-703, 2001
39. Parnis SJ, Barker DS, Van Der Walt JH: Clinical predictors of anaesthetic complications in children with respiratory tract infections. Paed Anesth 11:29-40, 2001
40. Sanders JC, King MA, Mitchell RB, et al: Perioperative complications of adenotonsillectomy in children with obstructive sleep apnea syndrome. Anesth Analg 103:1115-1121, 2006
41. Rosen GM, Muckle RP, Mahowald MW, et al: Postoperative respiratory compromise in children with obstructive sleep apnea syndrome: can it be anticipated? Pediatrics 93:784-788, 1994
42. Wilson K, Lakheeram I, Morielli A, et al: Can assessment for obstructive sleep apnea help predict postadenotonsillectomy respiratory complications? Anesthesiology 96:313-322, 2002
43. Schwab RJ, Gupta KB, Gefter WB, et al: Upper airway and soft tissue anatomy in normal subjects and patients with sleep-disordered breathing. Am J Respir Crit Care Med 152:1673-1689, 1995
44. Arens R, McDonough JM, Corbin AM, et al: Upper airway size analysis by magnetic resonance imaging of children with obstructive sleep apnea syndrome. Am J Respir Crit Care Med 167:65-70, 2003
45. Isono S, Remmers JE, Tanaka A, et al: Anatomy of pharynx in patients with obstructive sleep apnea and in normal subjects. J Appl Physiol 82:1319-1326, 1997
46. Isono S, Shimada A, Utsugi M, et al: Comparison of static mechanical properties of the passive pharynx between normal children and children with sleep-disordered breathing. Am J Respir Crit Care Med 157:1204-1212, 1998
47. Eastwood PR, Szollosi I, Platt PR, et al: Collapsibility of the upper airway during anesthesia with isoflurane. Anesthesiology 97:786-793, 2002
48. Mezzanotte WS, Tangel DJ, White DP: Waking genioglossal electromyogram in sleep apnea patients versus normal controls (a neuromuscular compensatory mechanism). J Clin Invest 89:1571-1579, 1992
49. Horner RL, Liu X, Gill H, et al: Functional genomics of sleep and circadian rhythm selected contribution: Effects of sleep-wake state on the genioglossus vs. diaphragm muscle responses to CO_2 in rats. J Appl Physiol 92:878-887, 2002
50. Horner RL, Innes JA, Murphy K, et al: Evidence for reflex upper airway dilator muscle activation by sudden negative airway pressure in man. J Physiol 436:15-29, 1991
51. Wheatley JR, Tangel DJ, Mezzanotte WS, et al: Influence of sleep on response to negative airway pressure of tensor palatini muscle and retropalatal airway. J Appl Physiol 75:2117-2124, 1993
52. Gozal D, Burnside MM: Increased upper airway collapsibility in children with obstructive sleep apnea during wakefulness. Am J Respir Crit Care Med 169:164-167, 2004

53. Gleadhill IC, Schwartz AR, Schubert N, et al: Upper airway collapsibility in snorers and in patients with obstructive hypopnea and apnea. Am Rev Respir Dis 143:1300-1303, 1991
54. Marcus CL, McColley SA, Carroll JL, et al: Upper airway collapsibility in children with obstructive sleep apnea syndrome. J Appl Physiol 77:918-924, 1994
55. Crawford MW, Arrica M, Macgowan CK, et al: Extent and localization of changes in upper airway caliber with varying concentrations of sevoflurane in children. Anesthesiology 105:1147-1152, 2006
56. Strohl KP: Con: Sleep apnea is not an anatomic disorder. Am J Respir Crit Care Med 168:271-272, 2003
57. Rowley JA, Sanders CS, Zahn BR, et al: Effect of REM sleep on retroglossal cross-sectional area and compliance in normal subjects. J Appl Physiol 91:239-248, 2001
58. Hoffstein V, Zamel N, Phillipson EA: Lung volume dependence of pharyngeal cross-sectional area in patients with obstructive sleep apnea. Am Rev Respir Dis 130:175-178, 1984
59. Isono S, Kochi T, Ide T, et al: Differential effects of vecuronium on diaphragm and geniohyoid muscle in anaesthetized dogs. Br J Anaesth 68:239-243, 1992
60. Debaene B, Plaud B, Dilly M-P, et al: Residual paralysis in the PACU after a single intubating dose of nondepolarizing muscle relaxant with an intermediate duration of action. Anesthesiology 98:1042-1048, 2003
61. Ochiai R, Guthrie RD, Motoyama EK: Effects of varying concentrations of halothane on the activity of the genioglossus, intercostals, and diaphragm in cats: an electromyographic study. Anesthesiology 70: 812-816, 1989
62. Drummond GB: Signs of sage sedation researched, reviewed. J Clin Monit 12:101-102, 1996
63. Drummond GB: Comparison of sedation with midazolam and ketamine: effects on airway muscle activity. Br J Anaesth 76:663-667, 1996
64. Morrison JL, Sood S, Liu H, et al: Role of inhibitory amino acids in control of hypoglossal motor outflow to genioglossus muscle in naturally sleeping rats. J Physiol 552.3:975-991, 2003
65. Norton JR, Ward DS, Karan S, et al: Differences between midazolam and propofol sedation on upper airway collapsibility using dynamic negative airway pressure. Anesthesiology 104:1155-1164, 2006
66. Eastwood PR, Platt PR, Shepherd K, et al: Collapsibility of the upper airway at different concentrations of propofol anesthesia. Anesthesiology 103:470-477, 2005
67. Evans RG, Crawford MW, Noseworthy MD, et al: Effect of increasing depth of propofol anesthesia on upper airway configuration in children. Anesthesiology 99:596-602, 2003
68. Hiremath AS, Hillman DR, James AL, et al: Relationship between difficult tracheal intubation and obstructive sleep apnoea. Br J Anaesth 80:606-611, 1998
69. Isono S, Remmers JE, Tanaka A, et al: Static properties of the passive pharynx in sleep apnea. Sleep 19:S175-S177, 1996
70. Crawford MW, Rohan D, Macgowan CK, et al: Effect of propofol anesthesia and continuous positive airway pressure on upper airway size and configuration in infants. Anesthesiology 105:45-50, 2006
71. Peterson GN, Domino KB, Caplan RA, et al: Management of the difficult airway. A closed claims analysis. Anesthesiology 103:33-39, 2005
72. Liu X, Sood S, Liu H, et al: Opposing muscarinic and nicotinic modulation of hypoglossal motor output to genioglossus muscle in rats in vivo. J Physiol 565:965-980, 2005
73. Bouryi VA, Lewis DI: Enkephalinergic inhibition of raphe pallidus inputs to rat hypoglossal motoneurones in vitro. Neuroscience 129:55-64, 2004
74. Arai Y-CP, Fukunaga K, Hirota S, et al: The effects of chin lift and jaw thrust while in the lateral position on stridor score in anesthetized children with adenotonsillar hypertrophy. Anesth Analg 99:1638-1641, 2004
75. Gentil B, de Larminat JM, Boucherez C, et al: Difficult intubation and obstructive sleep apnoea syndrome. Br J Anaesth 72:368, 1994
76. Thut DC, Schwartz AR, Roach D, et al: Tracheal and neck position influence upper airway airflow dynamics by altering airway length. J Appl Physiol 75:2084-2090, 1993
77. Litman RS, Wake N, Chan L-ML, et al: Effect of lateral positioning on upper airway size and morphology in sedated children. Anesthesiology 103:484-488, 2005
78. Rowley JA, Permutt S, Willey S, et al: Effect of tracheal and tongue displacement on upper airway airflow dynamics. J Appl Physiol 80: 2171-2178, 1996
79. Issa FG, Sullivan CE: Upper airway closing pressures in obstructive sleep apnea. J Appl Physiol Respirat Environ Exercise Physiol 57:520-527, 1984
80. Schwab RJ, Pack AI, Gupta KB, et al: Upper airway and soft tissue structural changes induced by CPAP in normal subjects. Am J Respir Crit Care Med 154:1106-1116, 1996
81. Rennotte M-T, Baele P, Aubert G, et al: Nasal continuous positive airway pressure in the perioperative management of patients with obstructive sleep apnea submitted to surgery. Chest 107:367-374, 1995
82. Laferrière A, Liu J-K, Moss IR: Neurokinin-1 versus mu-opioid receptor binding in rat nucleus tractus solitarius after single and recurrent intermittent hypoxia. Brain Res Bull 59:307-313, 2003
83. Moss IR, Laferrière A: Central neuropeptide systems and respiratory control during development. Respir Physiol Neurobiol 131:15-27, 2002
84. Moss IR: Maturation of respiratory control in the behaving mammal. Respir Physiol Neurobiol 132:131-144, 2002
85. Brown KA, Laferrière A, Moss IR: Recurrent hypoxemia in young children with obstructive sleep apnea is associated with reduced opioid requirements for analgesia. Anesthesiology 100:806-810, 2004
86. Brown KA, Laferrière A, Lakheeram I, et al: Recurrent hypoxemia in children is associated with increased analgesic sensitivity to opiates. Anesthesiology 105:665-669, 2006
87. Waters KA, McBrien F, Stewart P, et al: Effects of OSA, inhalational anesthesia, and fentanyl on the airway and ventilation of children. J Appl Physiol 92:1987-1994, 2002
88. Moss IR, Brown KA, Laferrière A: Recurrent hypoxia in rats during development increases subsequent respiratory sensitivity to fentanyl. Anesthesiology 105:715-718, 2006
89. Waters KA, Tinworth KD: Habituation of arousal responses after intermittent hypercapnic hypoxia in piglets. Am J Respir Crit Care Med 171:1305-1311, 2005
90. Machaalani R, Waters KA: Distribution and quantification on NMDA R1 mRNA and protein in the piglet brainstem and effects of intermittent hypercapnic hypoxia (IHH). Brain Res 951:293-300, 2002
91. Cullen DJ: Obstructive sleep apnea and postoperative analgesia: a potentially dangerous combination. J Clin Anesth 13:83-85, 2001
92. Gasche Y, Daali Y, Fathi M, et al: Codeine intoxication associated with ultrarapid CYP2D6 metabolism. N Engl J Med 351:2827-2831, 2004
93. Durand E, Lofaso F, Dauger S, et al: Intermittent hypoxia induces transient arousal delay in newborn mice. J Appl Physiol 96:1216-1222, 2003
94. Waters KA, Tinworth KD: Depression of ventilatory responses after daily, cyclic hypercapnic hypoxia in piglets. J Appl Physiol 90:1065-1073, 2001
95. Osman NI, Baghdoyan HA, Lydic R: Morphine inhibits acetylcholine release in rat prefrontal cortex when delivered systemically or by microdialysis to basal forebrain. Anesthesiology 103:779-787, 2005
96. International Standard ISO/DIS 17510-1. Sleep apnoea breathing therapy. Part 1. Sleep apnoea breathing therapy equipment. 2005. Geveva, Switzerland, International Organization for Standardization.
97. Farré R, Montserrat JM, Ballester E, et al: Potential rebreathing after continuous positive airway pressure failure during sleep. Chest 121: 196-200, 2002
98. International Standard ISO/DIS 17510-2. Sleep apnoea breathing therapy - Part 2. Masks and application accessories. 2005. Geneva, Switzerland, International Organization for Standardization