Intermittent Hypoxia and the Practice of Anesthesia
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Intermittent hypoxia, a powerful and unique stimulus, leads to physiologic changes that are distinct from those associated with either single or continuous hypoxic exposure. There is an accumulating body of evidence that the neurocognitive, inflammatory and cardiovascular symptoms that characterize the syndrome of obstructive sleep apnea are linked to the stimulus of intermittent hypoxia. In addition, altered sensitivities to opiates in children with obstructive sleep apnea have been linked to recurrent hypoxia during sleep. Therefore anesthesiologists should have an understanding of this important stimulus.

OBSTRUCTIVE sleep apnea syndrome (OSAS) is a symptom complex arising from episodic pharyngeal airway obstruction of airflow during sleep and the associated nocturnal hypoxemia, hypercarbia, sleep fragmentation, and arousals from sleep. The disease prevalence is high, estimated at 5–15% of adult populations1 and 2% of children.2 John Benumof predicted that, during this decade, the incidence of adult patients presenting with a diagnosis of OSAS would increase 5–10 fold and that a diagnosis of OSAS would have a major effect on perioperative risk.3 Similarly, children with severe OSAS are also at increased risk for postoperative respiratory morbidity.4–6

In 1998, Isono et al. reported that profound preoperative nocturnal desaturation in adult patients predicted the occurrence of postoperative nocturnal desaturation after surgery.7 The saturation nadir is defined as the lowest saturation recorded during an overnight oximetry study. In children, a nocturnal saturation nadir below 80% is predictive of postadenotonsillectomy respiratory morbidity.4,5 The increased risk for respiratory morbidity associated with OSAS has been attributed to its cardiorespiratory pathophysiology, including ventricular hypertrophy, pulmonary and systemic hypertension,8,9 and lower airway disease.10 These pathophysiologies are all recognized risk factors for postoperative complications. Recently, we11,12 and others13 have reported a heightened sensitivity to opiates in children with severe OSAS who demonstrate recurrent hypoxemia during sleep. This altered sensitivity to opiates may also contribute to postoperative respiratory morbidity. The remainder of this paper discusses OSAS in the context of recent developments in the basic science of intermittent hypoxia, a powerful and unique stimulus that results in distinct physiologic changes from those associated with either single or continuous hypoxic exposure. The respiratory responses to recurrent hypoxia, for example, differ from those after a single hypoxic exposure (reviewed by Moss14). An overview of the subject is presented because, as noted by Moss,14 this field of research is young.

In patients with OSAS, episodic pharyngeal airway obstruction during sleep may result in recurrent clusters of desaturation-reoxygenation sequences as shown in figure 1. Laboratory studies have focused on the stimulus of recurrent or intermittent hypoxia (IH), achieved experimentally by repeated exposure to ambient hypoxia alternating with room air,15 as an experimental model for OSAS.1

The stimulus of IH, “broadly defined as repeated episodes of hypoxia interspersed with episodes of normoxia,” has been of interest to basic scientists for more than 50 yr.16 The stimuli employed in experimental studies vary widely, ranging from seconds to hours of hypoxic exposure. The periods of episodic exposure also vary, ranging from minutes over a single day of study to daily exposure for months. The interval between the hypoxic exposures may be normoxic or hyperoxic.

The Response to Intermittent Hypoxia

Beneficial effects of brief exposure to IH, a form of hypoxic preconditioning, include improved exercise performance in elite athletes and cross-protection for certain diseases.16 Exposure to hypoxic conditioning in adult male mice prolonged survival to subsequent lethal hypoxic exposure. Whereas hypoxic preconditioned mice had lower body temperatures, those pretreated with naloxone did not. In addition, the preferred ambient temperature of the hypoxic conditioned mice pretreated with naloxone was higher than controls, leading the authors to conclude that IH decreased the thermoregulatory setpoint. The finding that the hypoxic conditioning-induced decrease in this setpoint was blocked by naloxone implicates the endogenous δ-opioid system.17

Although brief exposure to IH may be beneficial, exposure for extended periods of time is deleterious.1,16 For example, exposure to IH during development results in neuronal apoptosis in the hippocampus in rat pups as well as cognitive and neurobehavioral deficits in brain regions associated with neurocognitive function.15 Milder degrees of IH produce partially reversible memory and learning impairments. These laboratory findings of neurocognitive impairment linked to IH may be of...
clinical relevance because poor school performance in children with OSAS has also been linked to recurrent hypoxia during sleep.\(^\text{18}\)

The \(\delta\)-opioid system has been implicated in the thermoregulatory response to hypoxic conditioning.\(^\text{17}\) Other central neuropeptides, particularly the endogenous \(\mu\)-opioid neuropeptides, are also sensitive to hypoxic exposure. Mature rats exposed to a single session of IH, consisting of six 5-min hypoxic exposures alternating with normoxia, demonstrate a reduction in \(^{125}\text{I}-\text{substance P}\) binding (using quantitative film autoradiography) 5 min after the session of hypoxic exposure.\(^\text{19}\) Prior exposure to IH, with identical sessions of IH daily for 5 days, prolonged the duration of this reduction for at least 2 h. In contrast, the binding of the \(\mu\)-opioid receptor agonist \(^{125}\text{I}\text{DAMGO (Tyr-d-Ala-Gly-N-Me-Phe-Gly-ol)}\) was unaffected by single or recurrent hypoxia (fig. 2).

**Functionality of Central Neuromodulation Systems after Intermittent Hypoxia**

Both substance P and the opioid neuropeptides are G-protein–coupled receptors.\(^\text{20}\) Many G-protein–coupled receptors are deactivated by internalization, a process that sequesters the receptor within endosomes.\(^\text{21,22}\) (fig. 3) An interpretation of the findings presented in figure 2 is that endocytosis of the neurokinin-1 receptor (NK-1R) removed it from the cell membrane, making it unavailable for interaction with a ligand and resulting in a decrease in binding sites for \(^{125}\text{I-substance P}\). Whereas NK-1R easily undergoes internalization upon activation by a ligand, the \(\mu\)-opioid receptor does not. Binding of \(^{125}\text{I-DAMGO (fig. 2)}\) was therefore unaffected after hypoxic exposure. Resistance to receptor internalization might alter the functionality of the substance P/neurokinin 1 and \(\mu\)-opioid neuropeptide system (reviewed by Moss et al.\(^\text{21}\)). In the respiratory-related regions of the immature brain, substance P stimulates breathing, whereas \(\mu\)-opioid receptor agonists suppress it.\(^\text{19,23}\) Under the influence of a hypoxic stimulus, internalization of the NK-1R might allow the \(\mu\)-opioid receptor influence to dominate, resulting in a change in the functionality of the \(\mu\)-opioid system.\(^\text{14,19,21}\)

**Opioid Sensitivity and Recurrent Hypoxemia**

We hypothesized that children with OSAS who exhibit the pattern of recurrent hypoxemia shown in figure 1 might also have an altered central opioid functionality, which might affect their responsiveness to exogenously administered opiates. Support for this hypothesis was sought in a retrospective analysis of children with OSAS undergoing adenotonsillectomy. The dose of morphine required to achieve comfort correlated with the saturation nadir obtained from the preoperative oximetry study during sleep (fig. 4). Children exhibiting profound recurrent hypoxemia required a smaller dose of morphine to achieve comfort.\(^\text{11}\) A heightened analgesic sensitivity in these children was supported by a prospective study that reported a twofold reduction in morphine requirement in children with OSAS who demonstrated a preoperative saturation nadir less than 85%.\(^\text{12}\)

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Fig. 1. A representative abnormal nocturnal oximetry study recorded between 22:00 and 7:00 h, shows seven clusters (black triangles) of desaturations associated with an increase in heart rate and heart rate variability. Four clusters show desaturations less than 80%. The arterial oxygen saturation (Sa\(\text{O}_2\)) nadir is less than 80%. bpm = beat per minute. Reprinted with permission from Brown K, Morin I, Hickey C, Manoukian JJ, Nixon GM, Brouillette RT: Urgent adenotonsillectomy: An analysis of risk factors associated with postoperative respiratory morbidity. Anaesthesiology 2003; 99:586–95. Copyright © 2003 the American Society of Anesthesiologists, Inc. Lippincott Williams & Wilkins, Inc.\(^\text{44}\)
Waters et al. reported a 10-fold higher incidence in apnea subsequent to uniform dose of fentanyl in children with severe OSAS (mean $\text{SaO}_2$ saturation nadir, 72.7% ± 15.5%) compared to controls. This heightened respiratory sensitivity for opiates was linked to previous exposure to recurrent hypoxia in an experimental model. Rat pups with previous exposure to IH demonstrated greater respiratory depression to a uniform dose of fentanyl than controls rats. In 2007, a direct effect of $\mu$-opioid agonists on the hypoglossal motor nucleus was reported. This novel finding may be of clinical relevance. The patency of the pharyngeal airway is more dependent on the activity of the upper airway dilating muscles, including the genioglossus, in patients with OSAS. For example, unlike healthy controls, the pharyngeal dilating muscles are active during wakefulness in patients with OSAS. The activity of the upper airway dilating musculature is also important to pharyngeal patency during sleep. Autonomic activation of the upper airway dilating muscles during sleep-related episodes of pharyngeal obstruction can, in fact, lead to full reopening of the upper airway without electroencephalographic evidence of cortical arousal from sleep. This autonomic recruitment of the upper airway dilating muscles, without cortical arousal, is especially important in children with OSAS. Impairment of this autonomic control of the pharyngeal airway caliber by opiates would be important. Although speculative, if opiate sensitivity of the pharyngeal dilating muscles is also enhanced by the stimulus of recurrent hypoxia, this could impair the autonomic reopening of the pharyngeal airway during airway obstruction in patients with OSAS who have received opioid medication.

**Fig. 2.** Specific binding of $^{125}$I-substance P and $^{125}$I DAMGO in the nucleus tractus solitarius measured 5 min, 2 h, or 24 h after the last gaseous exposure of mature rats to normoxia (control; open bars), a single intermittent hypoxia (single hypoxia; batched bars), or recurrent intermittent hypoxia (recurrent hypoxia; solid bars). *Significant difference between a hypoxia group and its corresponding normoxic control group. † Significant difference between a recurrent hypoxia groups and its corresponding single hypoxia group. Reproduced with permission from 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 2003; 59:307–13. Copyright © 2003 Elsevier, Inc.

**Fig. 3.** Activation of cell-surface G-protein–coupled receptors leads to phosphorylation of the receptor (denoted by P). Phosphorylated receptors can then undergo internalization and sequestration into endosomes. Reviewed by Carroll et al. Reprinted with permission from Carroll RC, Beattie EC, von Zastraw M, Malenka RC: Role of AMPA receptor endocytosis in synaptic plasticity. Nat Rev Neurosci 2001; 2:315–24. Copyright © 2002 Nature Publishing Group.

**Fig. 4.** Age and preoperative arterial oxygen saturation nadir are significantly correlated with the cumulative postoperative morphine dose required for analgesia after adenotonsillectomy. The magnitude of the cumulative postoperative morphine dose is depicted by the height of the stem supporting each circle. SaO$_2$ = saturation. Reprinted with permission from Brown KA, Laferrière A, Moss IR: Recurrent hypoxemia in young children with obstructive sleep apnea is associated with reduced opioid requirements for analgesia. Anesthesiology 2004; 100:806–10. Copyright © 2004 American Society of Anesthesiologists, Inc. Lippincott Williams & Wilkins, Inc.
Adaptive Cellular Responses to Intermittent Hypoxia

The stimulus of intermittent hypoxia elicits long-term facilitation, a form of neuroplasticity, which distinguishes it from both single and continuous hypoxia. A hallmark of IH is long-term facilitation, which describes a persistent increase in the respiratory motor output after exposure to episodic but not continuous hypoxia. Studies of chronic intermittent hypoxia during development in rats suggest developmental plasticity, which permanently changes normoxic ventilation and the response to acute hypoxia. Long-term facilitation has been implicated in the increased sensitivity of the carotid body to hypoxia and to both the increase in basal ventilation and the increase in the tone of the upper airway after exposure to IH.

The extent, direction, and pattern of this adaptive response is influenced by age, species, gender, genetics, and the nature of the hypoxic stimulus. In addition, the adaptive response to IH is thought to initiate the cardiorespiratory and inflammatory cascades, which lead to the clinical syndrome of OSAS. The link between OSAS, IH, long-term facilitation, and alterations in genomic, proteomic, and phenotypic expression are, at present, poorly understood.

A schematic representation of the adaptive cellular response to IH, modified with permission from N.R. Prabhakar, is shown in figure 5. Although hypoxia is sensed by all cells, the glomus cells of the carotid body have a unique sensitivity to oxygen tension. Hypoxia produces an almost instantaneous release of central neurotransmitters in the brainstem, resulting in the cardiorespiratory response to hypoxia. Evidence of a sympathetic response to recurrent hypoxia is depicted in figure 1 by the increase in heart rate that accompanies each cluster of desaturation. After hypoxic exposure, a relative change in suppressive compared with excitatory neuromodulation may alter the functionality of the system, as has been suggested for the substance P/μ-opioid system. In addition, during the normoxic intervals of the IH stimulus, cells respond by increasing reactive oxygen species, which may further augment the response to hypoxia.

Accumulation of both reactive oxygen species and cytosolic calcium may activate (1) redox-sensitive protein transcription and (2) oxygen-sensitive gene expression. Redox-sensitive protein transcription, for example, has been shown to increase the levels of hypoxia inducible factor, a protein essential for oxygen sensing by the glomus cells of the carotid body. At least 200 genes demonstrate selective regulation by hypoxia and are sensitive to IH but not sustained hypoxia. Oxygen-sensitive gene expression may be upregulated or downregulated. Genes that are upregulated include tyrosine hydroxylase. Genes that are downregulated include the dopamine receptor and cytochrome c oxidase. Redox-sensitive protein transcription and oxygen-sensitive gene expression are the cellular processes implicated in long-term facilitation.

It is not known if the heightened analgesic and respiratory opioid sensitivities subsequent to recurrent hypoxia also involve the cellular processes depicted in figure 5. However, figure 2 indicates that binding of DAMGO increased 24 h after exposure to IH. This increase in μ-opioid receptor density consequent to IH may reflect an increased receptor synthesis. Such an increased receptor synthesis after IH may indeed implicate pathways outlined in figure 5, including both redox-sensitive protein transcription and oxygen-sensitive gene expression. Both opioid analgesia and respiratory depression are linked through the same molecular processes involving the μ-opioid receptor gene. Figure 6 shows that knockout mice without the μ-opioid receptor gene are devoid of opioid analgesia and opioid-induced respiratory depression. Although speculative, an increase in the number of μ-opioid receptors consequent to IH might enhance responsiveness to exogenously administered opioid medication.

The conundrum is the teleological advantage conferred by an upregulation of the opioid systems in response to recurrent hypoxia. A conjecture is that upregulation of opioid neuromodulation mitigates the apoptotic potential of intermittent hypoxia.

Implications of IH to the Practice of Anesthesiology

Polysomnography is the gold standard for diagnosis of OSAS. These sleep studies focus on the indices of upper airway resistance and the events of sleep apnea. The most disturbing feature of sleep apnea is the decrease in oxygen saturation that occurs during sleep. The impact of periodic oxygen desaturation on cardiovascular function is not well understood. The data from animal models of IH and the clinical observations in patients with IH suggest that IH may have important implications for the practice of anesthesia.

Fig. 5. Schematic representation of the cellular response to the stimulus of intermittent hypoxia. Hypoxia is sensed by the carotid body and results in central neurotransmitter release. Normoxic episodes result in accumulation of reactive oxygen species and lead to alterations in both redox-sensitive protein transcription and oxygen-regulated gene expression. m = minutes; O₂ = oxygen; s = seconds. Adapted with permission from Prabhakar NR: Physiologic and genomic consequences of intermittent hypoxia: Invited review: Oxygen sensing during intermittent hypoxia: cellular and molecular mechanisms. J Appl Physiol 2001; 90:1986–94. Copyright © 2001 American Physiological Society.
airway obstruction. Even the recently published practice guidelines for the management of patients with OSAS advocate the use of the apnea hypopnea index to stratify OSAS severity.\(^\text{40}\) There may, however, be poor agreement between the apnea hypopnea index and indices of desaturation. For instance, two children reported by Waters et al.\(^\text{13}\) had similar apnea hypopnea indices, more than 14 events per hour. However their saturation nadirs of 63% and 87% were very different. In addition, African American children with OSAS desaturate to lower values during pharyngeal obstructive events than their peers of European descent.\(^\text{41}\)

An accumulating body of evidence supports the notion that the cellular event of importance is the repeated exposure to episodic hypoxia. The stimulus that alters central neurotransmitter functionality, including opioid sensitivity, has been linked to recurrent hypoxia in children with OSAS. We have focused attention on overnight pulse oximetry in the evaluation of children in whom a diagnosis of OSAS is suspected. It provides an attractive alternate to polysomnography because of its low cost, portability, simplicity and its suitability for both home and hospital applications. In the context of our sleep laboratory, with an inherent high pretest probability, an abnormal nocturnal oximetry study has a positive predictive value for OSAS of 97%.\(^\text{42}\) Overnight oximetry cannot detect those children with OSAS who rouse from airway obstruction before a desaturation event occurs. However it does identify the child with OSAS who demonstrates desaturation during sleep-disordered breathing. These are the children who need to be identified before anesthesia. The saturation nadir has proven in our hands to be helpful in predicting those children with OSAS who are at increased risk for respiratory morbidity after adenotonsillectomy.\(^\text{42,43}\) Furthermore, patients, with OSAS, who exhibit profound nocturnal desaturation during sleep demonstrate both a heightened analgesic and a heightened respiratory sensitivity to opiates. Opioid management in these children needs to be individualized to the severity of the nocturnal recurrent hypoxemia. Future studies that address issues in the anesthetic management of patients with OSAS should include indices of both pharyngeal obstruction and desaturation in the research design.

References

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