Exposure to Sustained Hypoxia Impairs Subsequent Arousal Responses to Compromised Ventilation

Comment on Hlavac MC; Catcheside PG; McDonald R et al. Hypoxia impairs the arousal response to external resistive loading and airway occlusion during sleep. SLEEP 2006;29(5):624-631.

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STUDIES ADDRESSING THE IMPACT OF NOCTURNAL HYPOXEMIA ON ASPECTS OF CENTRAL NERVOUS SYSTEM FUNCTION ARE OF IMPORTANT CLINICAL SIGNIFICANCE given the prevalence of sleep-disordered breathing in the general population. While the prevalence and public-health impact of disorders such as obstructive sleep apnea that are characterized by recurring bouts of intermittent hypoxemia are well appreciated, episodes of chronic nocturnal hypoxemia commonly occur with other respiratory disorders such as chronic obstructive pulmonary disease (COPD), neuromuscular weakness, and restrictive lung diseases such as kyphoscoliosis and obesity hypoventilation syndrome. Given that the prevalence of COPD is increasing worldwide, in association with increased tobacco use, and levels of obesity even among the young are unacceptably high, particularly in North America, there is likely a significant burden of undetected chronic nighttime hypoxia occurring during sleep in such individuals.

With respect to the potential consequences of sleep-related hypoxia, however, most experimental studies, particularly in animal models, have focused attention on the effects of repetitive cycles of intermittent hypoxia on sleep and aspects of neurocognitive performance and brain function. Such attention to intermittent hypoxia is understandable, and clearly warranted, because of the immediate relevance to the common and serious condition of obstructive sleep apnea. In comparison, however, the physiologic consequences of sleep-related chronic hypoxia on arousal mechanisms are less well studied. In this context, the study by Hlavac et al in this issue of Sleep is an important step to address this imbalance. This study reports the effects of periods of sustained hypoxia on the subsequent ventilatory and arousal responses to external resistive loads and airway occlusion during Stage 2 non-rapid eye movement sleep in humans. The hypoxic stimuli were applied for approximately 20 minutes and were sufficient to reduce arterial oxygen saturation to approximately 85%. The focus on arousal as an outcome variable is clearly relevant because arousal from sleep is thought to be an important defense mechanism in sleep-disordered breathing to facilitate protective ventilatory reflexes and behavioral responses. Measurements of the ventilatory effort on the last breath before arousal as an outcome is also pertinent because of the concept that, within an individual, arousal normally occurs at the same level of respiratory effort independent of the nature of the stimulus driving that effort (ie, hypoxia, hypercapnia, or respiratory loading). Based on previous observations by Doug McEvoy and colleagues that sustained hypoxia suppresses perception of respiratory loads in awake subjects, the authors hypothesized that prior experience of sustained hypoxia would increase the level of respiratory effort required to initiate arousal from sleep, so delaying the arousal response to resistive loading or airway occlusions. The studies were performed in young and healthy male subjects.

In accordance with the hypothesis that more respiratory drive would be required to initiate arousal from sleep following sustained hypoxia, the authors report that the time to arousal with application of the resistive loads was effectively doubled after hypoxia (12.6±1.9 to 24.6±4.4 seconds). The minimal esophageal pressure on the last breath prior to arousal from sleep, an index of the level of respiratory effort, was also reported to be significantly more negative by an average of 3.3 cm H2O (13.5±1.3 vs 16.8±1.2 cm H2O). Since the rate of change in esophageal pressure during loading was unaffected by the prior hypoxia, the authors concluded that the hypoxia delays arousal from sleep and increases the level of respiratory effort at arousal. The effects of prior hypoxia on responses to airway occlusion, however, were not as clear cut and only partially fulfilled the a-priori hypothesis. The time to arousal from sleep with airway occlusions was not significantly altered by prior hypoxia (5.3±1.1 to 7.5±1.4 seconds), although the minimal esophageal pressure at arousal was reported to be significantly more negative by an average of 4.5 cm H2O (15.1±1.5 vs 19.6±2.2 cm H2O), again providing evidence for an increased level of respiratory effort at arousal from sleep. The apparent lack of effect of hypoxia on the time to arousal in the second series of experiments may simply reflect the quicker generation of the ventilatory and arousal responses with airway occlusion compared with loading (Figure 3 of Hlavac et al), making it more difficult to detect a consistent difference in the time to arousal.

The observation that prior exposure to hypoxia can delay subsequent arousal from sleep in response to respiratory challenge, and increase the level of respiratory effort at arousal, has clear clinical implications for disorders that result in ventilatory deficiency and chronic hypoxia at night such as COPD and obesity hypoventilation syndrome. Moreover, these data suggest that the previous concept that respiratory-arousal threshold is relatively fixed and that arousal occurs at the same level of respiratory stimulation may need some modification. Before it can be fully accepted, however, that the experience of prior hypoxia increases

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the level of respiratory effort at arousal from sleep, several aspects of the study need some consideration. An important component of the experimental design, for which the authors deserve credit, was the necessity to match, as closely as possible, the ventilation and other sleep variables prior to application of the respiratory loads or airway occlusions. For this reason, the respiratory challenges were all applied in normoxia, which, for the interventions following the low inspired oxygen, was achieved by quickly reversing the hypoxia with 3 breaths of 100% oxygen; a 90-second period of normal room-air breathing then followed before application of the loads. Overall, this strategy led to levels of arterial oxygen saturation and lung ventilation that were similar between the experimental conditions (i.e., prior hypoxia vs normoxia). Nevertheless, it is apparent in Table 3 and Figure 3 of Hlavac et al15 that esophageal pressure at baseline before the interventions was lower after hypoxia compared with normoxia by 1.7 and 2.5 cm H2O for the resistive load and airway occlusion interventions, respectively. This difference in esophageal pressure persisted during the first and final loaded breaths during both resistive loads and occlusions, i.e., the whole response after hypoxia appeared shifted downward compared with normoxia, and this may have contributed to the apparent lower esophageal pressures at arousal from sleep (Figure 3 of Hlavac et al15). Indeed, the esophageal pressures at arousal from sleep were lower after hypoxia compared with normoxia by 3.3 and 4.5 cm H2O for the resistive load and airway occlusion interventions, respectively, i.e., the prior hypoxia added an additional 1.6 and 2.0 cm H2O to the respiratory effort on the last breath before arousal. Importantly, the authors report that the apparent lowering of esophageal pressure at baseline after hypoxia was not statistically significant from normoxia but that the additional lowering of esophageal pressure at arousal from sleep was significant, i.e., indicating a selective effect on respiratory-arousal threshold. It would have been reassuring if the authors had also reported the interaction term from the analysis of variance to show that the responses were not just shifted downward after hypoxia but that there was indeed selective lowering of esophageal pressure at arousal from sleep (i.e., to indicate that the responses represented by the solid and dashed lines in Figure 3 were not parallel15). This caveat notwithstanding, the significant delay in time to arousal after hypoxia, albeit only for the resistive loading interventions, is a robust observation and supports the concept that prior experience of sustained hypoxia delays arousal from sleep in response to compromised ventilation.

The authors performed this initial study in young, non-obese, male subjects who had no history of snoring or abnormal sleep; women were not studied because of concerns of the potential confounding influences of variations in ventilation with the menstrual cycle. Although the subject demographics are clearly different from the subject types that would normally be expected to experience sustained episodes of nighttime hypoxia, such as patients with COPD and obesity-hypoventilation syndrome,6,16 it is nonetheless important to establish baseline physiologic parameters in a normal population, as this study has done. Accordingly, this study provides an important framework to now determine the effects of relevant factors such as age, sex, and body weight on the responses, as well as the potential confounding effects of coexisting sleep-disordered breathing, such as obstructive sleep apnea, and sleep restriction.

The central nervous system mechanisms mediating suppression of arousal responses to prior experience of hypoxia are ultimately difficult to determine in human subjects. Nevertheless, in a recent study by the same group,21 respiratory-related evoked potentials were used to investigate the sensory processes mediating hypoxia-induced suppression of respiratory-load sensation in normal healthy subjects during wakefulness. As expected, hypoxia reduced the perceived magnitude of externally applied resistive loads, but the authors also showed that, following brief inspiratory loads, the amplitude of the first positive peak of the respiratory-related evoked potentials was significantly reduced by approximately 36% during hypoxia compared with normoxia. Since the first positive peak is thought to reflect the arrival of ascending respiratory signals at the somatosensory cortex,21 the data suggested that hypoxia may, at least in part, suppress respiratory afferent information before its arrival at the sensory cortex. It is not known if the mechanisms mediating the effects on the first positive peak may also be contributing to the delayed arousal from sleep after hypoxia in the study by Hlavac et al.15 Nevertheless, an important observation of this study is that episodes of sustained hypoxia lead to impaired arousal responses to respiratory stimuli even when studied several minutes after a return to normoxia. Although it is not known how long such residual impairment of arousal responses would ultimately have lasted, it does implicate some lingering neural mechanism that persists after removal of the hypoxia. One possibility discussed by the authors is the accumulation of inhibitory neuromodulators. For example accumulation of γ-aminobutyric acid can promote sleep and delay arousal by its inhibitory effects on thalamocortical and brainstem arousal neurons, i.e., promoting and reinforcing the sleep side of the hypothalamic “sleep switch.”22,23 Alterations in adenosine levels may also promote sleep23 and increase the vulnerability of neurons to subsequent hypoxic insults,24 with the latter potentially becoming more relevant with more-prolonged or severe hypoxic episodes.

Overall, the study by Hlavac et al15 highlights the relevance and potential adverse respiratory consequences of sustained hypoxia in humans. This and recent studies by the same group18-22 highlight that sustained hypoxia can delay arousal responses to respiratory stimulation and disrupt symptom perception, with persistence of effects after removal of the hypoxia. Given the potential for a significant burden of undetected chronic nighttime hypoxia occurring during sleep in the general population, not least because of the increasing prevalence of COPD and obesity,5,6 studies of the central mechanisms underlying the respiratory consequences of sustained hypoxia are warranted, along similar lines to the studies investigating intermittent hypoxia.

REFERENCES