Editorial

Potential protective mechanism of arousal in obstructive sleep apnea

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Obstructive sleep apnea (OSA) pathophysiology is thought to be due to the interaction of traits including airway anatomy and neuromuscular control which vary between individuals. These traits include a low arousal threshold (wake easily from sleep), upper airway gain (how effectively activation of upper airway dilator muscles improves ventilation), loop gain (stability of the negative feedback chemoreflex control system) and upper airway collapsibility (anatomical predisposition to passive airway collapse) (1). While deficits in these traits and how they interact varies between individuals, generally mechanisms that increase activation of upper airway dilator muscles are considered to help protect the airway from collapse.

Sleep itself reduces excitatory stimulation to the upper airway dilator muscles (2) in addition to reducing chemosensitivity (3,4). Therefore despite increased arterial CO_2, stable NREM sleep is characterized by low upper airway dilator muscle electromyogram (EMG) activity and reduced minute ventilation compared to wakefulness (2,5). During sleep ventilatory control is dominated by the level of arterial CO_2 and O_2. Arterial CO_2 has a major influence and unlike during wakefulness, during sleep reductions in arterial CO_2 will reduce ventilatory drive until ventilation ceases—when the apneic threshold is reached (several mmHg below eupnea). Central ventilatory drive not only determines the level of activity of the thoracic pump muscles, but also the upper airway dilator muscles. Consequently hypocapnia during sleep is thought to render the airway susceptible to collapse due to hypotonia of upper airway dilator muscles. Indeed, mechanical hyperventilation induced hypocapnia during stable sleep will induce passive pharyngeal collapse even in healthy persons not normally exhibiting OSA (6).

Although obstructive events will invariably be followed by hyperventilation due to accumulated chemical drive, a low arousal threshold (wake easily) is considered a key pathological mechanism in OSA as arousal is thought to increase the magnitude of post-occlusion hyperventilation (and consequently hypocapnia) due both to arousal associated sympathetic activation and the state dependent differences in eupneic CO_2 and sensitivity. This theory is based on the founding work by Iber and colleagues in 1986 (7) who studied tracheostomized OSA patients following experimental tracheal occlusion during stable NREM sleep. They found that tracheal occlusion yielded arousal and pharyngeal opening which resulted in hyperventilation and hypocapnia, followed by a reduction in minute ventilation and prolongation of expiratory time. The magnitude of hypocapnia correlated with expiratory prolongation and ventilatory depression was attenuated with administration of a hypercapnic hyperoxic gas mixture prior to occlusion. Thus, the data supported the role of hyperventilation induced hypocapnia in the induction of the subsequent ventilatory depression. Additionally, in one patient in whom tracheal occlusion was terminated prior to arousal, although hyperventilation, hypocapnia and ventilatory depression still occurred the magnitude was reduced compared to those terminated by arousals (7). This finding led the authors to conclude that arousals exacerbate the post-obstruction hyperventilation and because pharyngeal dilator activation is insufficient in relation to diaphragm activation in OSA, the increased magnitude of ensuing hypocapnia may predispose the airway to subsequent collapse (7). This theory has since been supported by findings that obstructive events terminated by arousals resulted in more severe hyperventilation and successive hypoventilation (8). Moreover some but not all studies of sedatives which increase the arousal threshold show that the apnea-hypopnea index is reduced (9-11). However, a major limitation of these studies is that few if any analyzed upper airway dilator muscle EMG activities to confirm that arousal and the ensuing hypocapnia do in fact attenuate upper airway muscle activity.

Cori *et al.* presented two papers at the 2016 ATS meeting in San Francisco which suggest the prevailing theory that arousal promotes subsequent obstructive events due to hypocapnia induced hypotonia of the upper airway dilator muscles is, in fact, wrong. In two separate studies the authors investigated the effects of both auditory arousals and spontaneous arousals on end tidal CO_2, minute ventilation and genioglossal EMG activity. Interestingly they report that although arousal induced hyperventilation produces significant hypocapnia yielding hypoventilation, genioglossal EMG activity is not depressed following resumption of sleep, but rather it is elevated. The findings are attributed to the phenomenon of short-term potentiation, a form of neural memory previously reported following obstruction and hyperventilation, but thought to be specifically inhibited by arousal (12). While these recent findings by Cori *et al.* do not refute that arousals may contribute to promoting obstructive events, they do challenge the mechanism by which arousals may promote airway collapse. These findings suggest arousal itself may in fact provide a protective stimulus to the upper airway dilator muscles which persists following resumption of sleep and which over-rides the inhibitory effects of hypocapnia.

The field of clinical sleep medicine is currently pursuing a goal of developing methods to individualize OSA treatments. A cornerstone of this approach would be allowing measurements of each of the four traits thought to contribute to OSA pathogenesis in each patient and predicting how modulation of each trait could improve the patient's disease. In order to apply this approach, models are being developed to integrate how each trait interacts and impacts on airway patency. The post-arousal period is currently considered to promote airway obstruction and treatments to inhibit arousal are being investigated. However these new data suggest the role of arousals in OSA pathogenesis is possibly not all bad and needs to be revisited, especially with regard to modeling the effects of arousals on airway patency.

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None.

Footnote

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References

1. Wellman A, Eckert DJ, Jordan AS, et al. A method for measuring and modeling the physiological traits causing obstructive sleep apnea. J Appl Physiol (1985) 2011;110:1627-37.
2. Lo YL, Jordan AS, Malhotra A, et al. Influence of wakefulness on pharyngeal airway muscle activity. Thorax 2007;62:799-805.
3. Douglas NJ, White DP, Weil JV, et al. Hypoxic ventilatory response decreases during sleep in normal men. Am Rev Respir Dis 1982;125:286-9.
4. Douglas NJ, White DP, Weil JV, et al. Hypercapnic ventilatory response in sleeping adults. Am Rev Respir Dis 1982;126:758-62.
5. Henke KG, Dempsey JA, Kowitz JM, et al. Effects of sleep-induced increases in upper airway resistance on ventilation. J Appl Physiol (1985) 1990;69:617-24.
6. Sankri-Tarbichi AG, Rowley JA, Badr MS. Expiratory pharyngeal narrowing during central hypocapnic hypopnea. Am J Respir Crit Care Med 2009;179:313-9.
7. Iber C, Davies SF, Chapman RC, et al. A possible mechanism for mixed apnea in obstructive sleep apnea. Chest 1986;89:800-5.
8. Younes M. Role of arousals in the pathogenesis of obstructive sleep apnea. Am J Respir Crit Care Med 2004;169:623-33.
9. Eckert DJ, Owens RL, Kehlmann GB, et al. Eszopiclone increases the respiratory arousal threshold and lowers the apnoea/hypopnoea index in obstructive sleep apnoea patients with a low arousal threshold. Clin Sci (Lond) 2011;120:505-14.
10. Heinzer RC, White DP, Jordan AS, et al. Trazodone increases arousal threshold in obstructive sleep apnoea. Eur Respir J 2008;31:1308-12.
11. Smales ET, Edwards BA, Deyoung PN, et al. Trazodone Effects on Obstructive Sleep Apnea and Non-REM Arousal Threshold. Ann Am Thorac Soc 2015;12:758-64.
12. Younes M, Loewen A, Ostrowski M, et al. Short-term potentiation in the control of pharyngeal muscles in obstructive apnea patients. Sleep 2014;37:1833-49.

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