To breathe, per chance not to wake?

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In the present issue of the Journal of Applied Physiology, Younes et al. (10) provide direct support for their hypothesis that “in most OSA [obstructive sleep apnea] patients non-arousal mechanisms are capable of restoring upper airway patency if given the chance.” They show that in up to 40% of cases the genioglossus (GG) muscle can be recruited during obstruction enough to open the airway without arousal and that in many cases only a small reflex increase in activity is needed to unobstruct the airway. Importantly, they demonstrate that the increase in activity needed to open the airway is much less than the increase in activity that is part of the electrophysiology of arousal. This challenges the traditional thinking first articulated byPhillipson et al. (5) and Remmers et al. (6) more than 30 years ago that the physiological sequence ending each individual obstructive sleep event requires arousal.

According to the Remmers hypothesis, obstruction occurs during sleep because of an imbalance between abnormal upper airway anatomy and diminished stabilizing/dilating forces exerted by upper airway muscles that occur as a result of sleep (6). Ending obstruction requires reactivation of the upper airway due primarily to arousal. Multiple studies have in fact shown that reflexes responding to upper airway obstruction and asphyxia are impaired during sleep (3), and until recently it was generally believed that airway patency (end of obstruction) was only possible when some degree of central nervous system arousal caused return of full tone in the upper airway muscles. Recent data has challenged this conceptualization (4, 8). Not infrequently patients with OSA have long periods of partially obstructed but stable breathing without arousal. This implies that, at least sometimes, reflex upper airway muscle responses are sufficient to compensate for the anatomic causes of obstruction.

In the present article, Younes et al. provide direct measurement of the genioglossal EMG recruitment concurrent with the end of obstructive events with and without arousal. The data were collected in patients with OSA who were placed on optimal continuous positive airway pressure (CPAP) and in whom the obstructive events were initiated by dropping the CPAP acutely after stable sleep had been established. The results clearly show that arousal is not needed to end an obstructive event. In fact, only small increases in GG activity, occurring spontaneously after the onset of obstruction, are often sufficient to allow resumption of flow through the upper airway independent of and prior to arousal. Furthermore, these increases are much smaller than the large increases of upper airway muscle tone seen with arousal itself, yet sufficient to reestablish airway patency. The authors introduce the term “GG opening threshold” to define the level of tone needed and show that it appears to be characteristic of a patient. Furthermore, the increase of GG muscle activity as it rises to this opening threshold is nonlinear and in about half the patients has an inflection beyond which it accelerates sharply. Contributing factors to this nonlinearity are suggested in another article from the same authors (9) where it was shown that the response of the GG to negative airway pressure was strongly increased as chemical stimuli rose.

Respiratory stimulation was also manipulated by giving either CO2 or hypoxia and examining the temporal relationship of airflow to arousal. While the relationship between the threshold GG activity for opening the airway, as well as the “suitability” of the upper airway muscles, to the level of general respiratory stimulation producing an arousal was variable across individuals, the authors describe the pattern of this response as stable within a single subject. This opens the door to calling this a physiological “trait” as has been done by others examining the components of obstruction in individual patients (7, 9).

These observations represent an important shift in our understanding of the physiological mechanisms responsible for ending obstructive events induced by sleep. The clinical significance is less clear, but as pointed out by the authors, they do raise interesting possible avenues for exploring therapeutic manipulations. If arousal and airway opening are no longer obligatorily linked, the oscillatory nature of breathing once obstruction occurs (the essential finding in OSA) becomes a consequence of the interaction between the time at which the GG opening threshold is achieved and the ease with which arousal occurs. Three potential therapeutic strategies emerge: delaying arousal, increasing the slope of the GG response, and decreasing opening threshold. Delaying arousal may be therapeutic in some subjects (1, 2), and zopiclone was in fact used in the present studies for this purpose. However, it carries risk of increasing hypoxia if it is not successful and its use may be limited to a small number of patients. The lack of correlation that Younes et al. show between the opening threshold and the Pcrit of the airway show that the value of opening threshold is independent of passive anatomy and thus an independent factor in OSA, whose determinants need to be further investigated. Manipulation of either the actual opening threshold or the rate of rise in response to stimuli would seem worth pursuing.

There are some caveats to this approach however. The data presented did show that opening of the airway occurred before arousal in 40% of events. However, of these, half were rapidly followed by an arousal. This raises the question of whether it will be possible to accomplish changes in stimulation of the upper airway while not simultaneously activating arousal mechanisms. This might be a place for a combined therapeutic approach. An additional caution is that while an increase in genioglossal tone without arousal may result in a stable open airway, this could be at the expense of sympathetic stimulation from the elevated CO2. It is not clear if the gain in stability and lack of arousals will offset any long-term health detriment from such chronic autonomic stimulation. Overall, the concept advanced by the authors of lowering the opening threshold...
is more attractive—in fact it could be argued that mechanical manipulation of the upper airway (as with mandibular advancement devices and upper airway surgery) works through this mechanism.

The clinical questions deserve further investigation, but the present paper helps by providing a new framework in which to view them. The work reported emphasizes the need to understand the determinants of opening threshold of genioglossal activation and its response pattern to respiratory stimulation. It is to be hoped that these new perspectives, which go beyond the assessment of passive mechanics of the upper airway, will help in the goal of defining “phenotypes” of obstructions that may lead to new therapeutic paradigms.

DISCLOSURES


AUTHOR CONTRIBUTIONS

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REFERENCES