COMMENTARY

The Chicken-or-Egg Debate in OSA Pathogenesis

Commentary on Loewen et al. Determinants of ventilatory instability in obstructive sleep apnea: inherent or acquired? Sleep 2009;32:1355-65.

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SEVERAL CONCEPTS HAVE RECENTLY EMERGED REGARDING OUR THINKING ABOUT THE PATHOGENESIS OF OBSTRUCTIVE SLEEP APNEA (OSA).

First, considerable evidence now suggests that several variables may interactively contribute to the development of OSA.[1] Although some patients have primarily an anatomical problem, with little contribution from other factors, others may have dysfunction of upper airway dilator muscles or instability in ventilatory control that exacerbates otherwise minor anatomical deficits. Some patients clearly have combinations of abnormalities that yield repetitive obstructive apnea. As such, measuring a single variable in isolation, as has been done historically, is unlikely to be illuminating.

Second, the concept of tailored therapy suggests that measures to influence underlying pathophysiology are likely to be successful in some, but not all, patients with OSA. For example, the subgroup of patients with OSA that responds well to uvulopalatopharyngoplasty is likely to have primarily velopharyngeal anatomical compromise. Additionally, the subgroup of patients that responds well to oxygen is likely to have unstable ventilatory control as a major contributing factor.[2] Similarly, a theoretic agent to augment hypoglossal motor output[3,4] may benefit some patients with OSA (with dysfunctional upper airway muscles) but may be deleterious in others (with unstable ventilatory control in whom airway dilation may promote important hypocapnia[5]). Given the need for therapeutic advances in OSA, an individualized approach that targets underlying mechanism (or combination of mechanisms) would seem worthwhile.

Third, Younes[6] has recently emphasized that even patients with severe OSA have some periods of stable breathing during sleep. Jordan et al[7] have observed that these stable breathing periods are associated with marked genioglossus muscle activity. These data suggest that the upper airway dilator muscles are necessary and sufficient to stabilize breathing spontaneously in patients with OSA. Although these dilator muscles are known to have robust recruitment with respiratory stimuli during wakefulness, more marked or prolonged stimulation (or combinations of stimuli) are required for muscle activation during sleep.[8] As a result, the arousal threshold becomes a critical factor, since individuals who wake up easily (low arousal threshold) will have unstable airway mechanics due to an inability to accumulate adequate respiratory stimuli to activate dilator muscles.[9-11] Conversely a very high arousal threshold (hard to wake up) would be predicted to be deleterious in some patients, since profound hypoxemia or hypercapnia may occur prior to arousal (see Figure 1). Thus, strategies to manipulate arousal threshold (or any other variable) must be carefully individualized since a "one-size-fits-all" approach is unlikely to be fruitful in OSA.

In this issue of *SLEEP*, Loewen and colleagues[12] have characterized critical pathophysiological variables in patients with OSA before and after therapy. The authors have helped to move us beyond the simple AHI by demonstrating the feasibility of a comprehensive assessment of multiple pathophysiological variables in one overnight study to determine important factors critical to the presence or absence of apnea. Ultimately, simplification or automation of these measurements would be useful to define the mechanisms underlying apnea in a given individual. Alternatively, demographic variables, polysomnography characteristics, or biomarkers may help to predict mechanistic variables with sufficient accuracy to determine why an individual does or does not have disease. The authors define an important *conceptual* model of the interactions among various respiratory parameters in a particular individual. However, it is unclear how "abnormal" a particular variable must be, or even whether an increase or decrease in a particular factor might be favorable. For example, an increase in the arousal threshold may be good or bad (depending on the upper airway recruitment threshold), or a significant reduction in the dynamic ventilator response (chemoresponsiveness) might be undesirable if chemical drive fails to recruit upper airway dilators. To answer these sorts of questions, *quantitative* models are needed to define more precisely how the different pathophysiologic factors interact in a particular individual.[13] Such an approach would seem crucial given the lack of utility of a single variable (eg, arousal threshold) in isolation.

These experiments[12] provide insight into the question regarding whether observed abnormalities are intrinsic or acquired in patients with OSA. Although a change in a variable following continuous positive airway pressure (CPAP) is consistent with OSA causing the abnormality, a stable value of a variable following CPAP might suggest that the observed value is either intrinsic to these patients (eg, genetically determined or not directly OSA related) or perhaps an irreversible consequence of disease. A repeat assessment of the AHI in the Loewen study[12] may have provided insight into the pathophysiologic importance of the observed changes with CPAP. For example, if a marked fall in dynamic ventilatory response were observed (as documented by the authors) despite a stable AHI, one could argue

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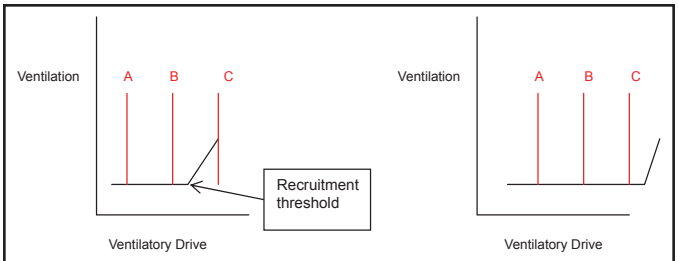

Figure 1—Schematic figure to illustrate the potential variability in response to a manipulation. The black lines illustrate the changes in ventilation which occur with increasing ventilatory drive. On the left is an individual with a relatively low recruitment threshold, implying that the upper airway muscles can respond to drive and open the pharynx sufficiently to raise ventilation. The individual depicted on the right has a very high recruitment threshold, implying an unresponsive upper airway. The vertical red lines represent various levels of arousal threshold. For the individual on the left, an agent which raised arousal threshold to level C may well benefit from the intervention since ventilation will have increased considerably prior to arousal. For the individual on the right, an increase in arousal threshold to level C is likely to be deleterious due to the prolonged respiratory event which is likely to occur prior to arousal accompanied by no major improvement in ventilation. On the other hand, neither individual would benefit from shifting the arousal threshold from A to B since ventilation would remain unchanged. For clarity, the impact of each individual's ventilatory control and metabolic production of CO2 have not been depicted, but can add further complexity to the above scenarios. As such, a comprehensive evaluation of multiple variables must be integrated into a working model to understand the impact of a given manipulation.

that this measure of dynamic ventilatory response is not a major factor in predicting AHI, at least in that individual. Thus, the authors have raised important questions that are worth pursuing.

Of note, the authors[12] demonstrate that the arousal threshold to respiratory stimuli decreases (patients wake up more easily) following CPAP therapy, suggesting that the observed elevation in arousal threshold in OSA[10] maybe a disease consequence (rather than a cause), ostensibly due to sleep fragmentation. This finding is interesting, since a high arousal threshold should protect against apnea in those with robust upper airway muscle responsiveness. In theory, the arousal threshold may change over time adaptively to stabilize breathing. Clearly, excessive elevations in arousal threshold may become maladaptive if profound hypoxemia occurs prior to arousal. Another new finding[12] is the observation that dynamic ventilatory response (a surrogate for ventilatory control instability) is markedly suppressed following CPAP therapy as compared with before CPAP. Because chemosensitivity may be blunted by sleep deprivation,[14] the finding of increased dynamic ventilatory response in untreated OSA is somewhat surprising. The mechanism underlying this observation is unclear but may represent a form of long-term facilitation—that is, alterations in blood gases have sustained effects on control of breathing,[15] a phenomenon that has been questioned in humans. Thus, further study is required.

We applaud the authors and would advocate for further work using a comprehensive analysis of multiple pathophysiological variables integrated into a patient-specific quantitative model to identify mechanisms underlying apnea. Such individualized approaches should pave the way to targeted OSA therapy based on underlying mechanism.

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REFERENCES

1. Eckert DJ, Malhotra A. Pathophysiology of adult obstructive sleep apnea. Proc Am Thorac Soc 2008;5:144-53.
2. Wellman A, Malhotra A, Jordan AS, Stevenson KE, Gautam S, White DP. Effect of oxygen in obstructive sleep apnea: Role of loop gain. Respir Physiol Neurobiol 2008.
3. Horner RL. Motor control of the pharyngeal musculature and implications for the pathogenesis of obstructive sleep apnea. Sleep 1996;19:827-53.
4. Kubin L, Tojima H, Davies RO, Pack AI. Serotonergic excitatory drive to hypoglossal motoneuron in the decerebrate cat. Neurosci Lett 1992;139:243-8.
5. Dempsey J. Crossing the apnoeic threshold: causes and consequences. Exp Physiol 2004;90:13-24.
6. Younes M. Role of respiratory control mechanisms in the pathogenesis of obstructive sleep disorders. J Appl Physiol 2008;105:1389-405.
7. Jordan AS, White DP, Lo YL, et al. Airway dilator muscle activity and lung volume during stable breathing in obstructive sleep apnea. Sleep 2009;32:361-8.
8. Stanchina ML, Malhotra A, Fogel RB, et al. Genioglossus muscle responsiveness to chemical and mechanical stimuli during non-rapid eye movement sleep. Am J Respir Crit Care Med 2002;165:945-9.
9. Younes M. Role of arousals in the pathogenesis of obstructive sleep apnea. Am J Respir Crit Care Med 2004;169:623-33.
10. Berry RB, Gleeson K. Respiratory arousal from sleep: mechanisms and significance. Sleep 1997;20:654-75.
11. Horner RL. Arousal from sleep—perspectives relating to autonomic function. Sleep 2003;26:644-5.
12. Loewen A, Ostrowski M, Laprairie J, et al. Determinants of ventilatory instability in OSA: inherent or acquired. Sleep 2009;32:1355-65.
13. Huang Y, White DP, Malhotra A. Use of computational modeling to predict responses to upper airway surgery in obstructive sleep apnea. Laryngoscope 2007;117:648-53.
14. White DP, Douglas NJ, Pickett CK, Weil JV, Zwillich CW. Sleep deprivation and the control of ventilation. Am Rev Respir Dis 1983;128:984-6.
15. Ling L, Fuller DD, Bach KB, Kinkead R, Olson EB, Mitchell GS. Chronic intermittent hypoxia elicits serotonin-dependent plasticity in the central neural control of breathing. J Neurosci 2001;21:5381-8.