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Adaptive Responses Using Obstructive Sleep Apnea as the Paradigm

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Adaptive Responses Using Obstructive Sleep Apnea as the Paradigm

For practicing clinicians, obstructive sleep apnea (OSA) represents an excellent illustration of how understanding adaptive physiological principles are required for optimal patient care. Clinically important OSA is estimated to affect roughly 13% of North American men, 6% of North American women, and 2% of children based on current criteria (11). The disease is characterized by repetitive collapse of the pharyngeal airway, which occurs during sleep, resulting in hypoxemia, hypercapnia, and sleep fragmentation, leading to adverse metabolic, neurocognitive, and cardiovascular consequences. Nasal continuous positive airway pressure (CPAP) is the treatment of choice for OSA in adults, but long-term adherence is unsuccessful in ~50% of patients (8), leading to a requirement for further research to develop new therapies.

Traditionally OSA was considered a result of abnormalities in craniofacial structure and/or parapharyngeal soft tissues, which rendered the airway collapsible (8). Recently, it has become increasingly recognized that OSA is a multifactorial condition where several physiological determinants of airway patency, including neuromuscular activation, arousal threshold, and ventilatory control stability (8), are abnormal in OSA and contribute to differing degrees in each patient to propagate airway collapse. This concept has led to a personalized medicine approach being developed, whereby OSA patients might be treated in an individualized manner based on an underlying physiological mechanism (3, 9). However, the question remains whether these traits, which are abnormal in OSA patients, are inherent and contribute to the onset of disease, or whether they are acquired as an adaptation to OSA. Then, if they are acquired, are they adaptive or maladaptive?

At sleep onset, excitatory drives to upper airway dilator muscles associated with wakefulness are abruptly lost, and protective reflexes are dramatically blunted, yielding collapse of the vulnerable airway (6). During obstructed breathing, the ability to recruit upper airway dilator muscle activity is highly dependent on responsiveness to negative (subatmospheric) intrapharyngeal pressure and carbon dioxide. Both are respiratory stimuli that activate pharyngeal dilator muscles, particularly when the stimuli are provided in combination (8,6). Thus the arousal threshold becomes an important factor in determining whether apnea will occur. Patients with a high arousal threshold (hard to wake up) allow for the accumulation of negative intrapharyngeal pressure and CO_2 during stable sleep, thus permitting sufficient neuromuscular compensation to maintain airway patency. By contrast, patients with a low arousal threshold (wake up easily) are at risk for repetitive apnea in part due to inadequate tolerance of sufficient respiratory stimuli to activate pharyngeal dilator muscles. Unstable ventilatory control (high loop gain) also has been implicated in OSA (15), whereby fluctuations in output from the central pattern generator in the brain stem can lead to upper airway collapse when output to the upper airway dilator muscles (and diaphragm) is at its nadir.

Arousal Threshold

OSA patients exhibit an increased arousal threshold compared with controls, and this threshold is reduced by OSA therapy (2, 5), indicating increased arousal threshold is induced by OSA. Elevation in arousal threshold is likely an adaptive phenomenon that helps to reduce the severity of OSA, whereby gradual elevation in arousal threshold would allow accumulation of respiratory stimuli and activation of pharyngeal dilator muscles to stabilize the upper airway. However, roughly one-third of OSA patients lack this adaptive increase in arousal threshold, and

several studies investigating pharmacological strategies, e.g., using sedative/hypnotic agents to increase arousal threshold, have already shown promise in a subset of OSA patients with a low arousal threshold (2, 5). Although there is controversy over the benefits vs. dangers of raising the arousal threshold since a higher arousal threshold may theoretically cause longer apneas, resulting in more profound desaturations and greater accumulation of respiratory stimuli before arousal, yielding end-organ consequences. For this reason, pharmacological approaches to raise the arousal threshold must be done cautiously, but in theory non-myorelaxant hypnotic agents could be used to restore this adaptive response for patients in whom it is lacking (5, 8).

Negative Effort Dependence

The upper airway has been classically modeled as a Starling resistor, such that, during inspiration, airflow is said to be constant over a range of driving pressures beyond a "critical closing pressure (Pcrit)" (13). However, recent literature has emphasized a reduction in airflow seen with increasing inspiratory efforts [negative effort dependence (NED)], which is not characteristic of classic Starling behavior but may be clinically important (10, 14). The mechanism of inspiratory NED is unknown (10, 14), although theories have been proposed based on the complexity of upper airway anatomy, i.e., the tongue and soft palate do not behave as a simple floppy tube. Of note, the magnitude of the reduction in airflow can be substantial, and thus NED may contribute to unsustainably low levels of minute ventilation. Adaptive responses are also important in this regard, since robust upper airway dilator muscles would be predicted to stiffen the upper airway and prevent progressive reductions in inspiratory airflow, which occur over time. The observed variability in NED may thus be a function of upper airway dilator muscle responsiveness, such that individuals with robust dilator muscle reflexes may preserve inspiratory airflow, whereas those with minimal reflexes may progressively

reduce inspiratory airflow as a result of deteriorating pharyngeal mechanics over time. These relationships are complex, however, since negative intrathoracic pressures generated by strong diaphragmatic activity may contribute to inspiratory airflow reduction in predisposed individuals. Thus paradoxically high ventilatory drive (as seen in those with high loop gain) may predispose one to inspiratory airflow reductions if upper airway dilator muscle responsiveness is inadequate. The augmented pharyngeal dilator muscle activity seen during wakefulness in OSA may be an adaptive phenomenon to protect pharyngeal patency, and the loss of this mechanism during sleep may be an important factor predisposing one to OSA (15).

Elevated Loop Gain

Loop gain is a term adapted from engineering that describes the propensity for instability in a negative feedback control system (1, 7, 8, 12, 15). A system with a high loop gain is prone to instability, even with minor perturbations, whereas a system with low loop gain remains stable, even with major applied stimuli. OSA have less stable ventilatory control than non-OSA and loop gain correlates with the frequency of apneas in OSA. High loop gain may also contribute to pharyngeal compromise in patients with NED, since high drive to the diaphragm may create a major collapsing influence on the upper airway. Some patients have OSA, with high loop gain a major contributing factor, and, in such individuals, agents to lower loop gain, such as oxygen or acetazolamide, may have utility (4).

Recent studies have shown that OSA patients have unstable ventilatory control (high loop gain), largely due to increased chemoreflex responses, which appear to be an acquired condition as chemoreflex control is seen to normalize after OSA therapy (12, 15). The interpretation of this finding is that loop gain elevation occurs as a result of OSA, and thus CPAP treatment leads to lowering of loop gain in OSA patients. However, high loop gain is also felt to be a mechanism underlying apnea (via fluctuating output from the central pattern generator to the upper airway and diaphragm), such that high loop

gain may be both a cause and a consequence of OSA.

Why loop gain elevates over time in OSA is unclear, but we would offer some speculation in this regard. In both humans and animal models, intermittent hypoxia has been shown to induce long-term facilitation of ventilatory motoneurons and carotid body activity, resulting in a sustained increase in neural output. Motoneuron long-term facilitation may augment both upper airway dilator muscle activity as well as pump muscle activity. Controversy persists regarding the importance of these effects in humans, since long-term facilitation of upper airway dilator muscle activity has been suggested to be a potential benefit of the intermittent hypoxia seen in OSA. Alternatively, intermittent hypoxia may contribute to worsening of OSA by increasing loop gain via increasing chemoreflex gain. Additionally, carotid body long-term facilitation results in increased sympathetic neural activity, which is thought to contribute to baroreflex dysfunction and elevation of blood pressure in OSA (1). Consequently, adaptive responses to intermittent hypoxia may both increase the severity of OSA by increasing loop gain and also contribute to the sequelae of cardiovascular comorbidities characteristic of OSA.

Given the elevation in arousal threshold seen in OSA, gradual elevation in loop gain may be protective at some level. That is, elevation in loop gain may yield brief repetitive apneas without major desaturation rather than profound desaturations, which could occur under conditions of low ventilatory drive. This potential interaction between the adaptive increase in loop gain, and the adaptive increase in arousal threshold has received minimal attention but may well be a fruitful area for investigation.

In summary, we would offer several unanswered questions that could be addressed by the physiologist with potential direct benefits for patient care. First, is the low arousal threshold a viable therapeutic target for a subset of OSA patients, or is the adaptive increase in arousal threshold only present in some OSA patients for a reason? Second, what is the mechanism underlying negative effort

dependence, and could strategies to increase upper airway dilator muscle tone be used to mitigate against the observed reductions in airflow in select patients (9). Third, should the subset of OSA patients with elevated loop gain be targeted pharmacologically only in those with a low arousal threshold? In other words, perhaps the high loop gain is protective for those with a high arousal threshold. We would emphasize two strategies in answering these questions. *1*) Techniques to define pathophysiological mechanisms of OSA without the need for invasive physiology would clearly be desirable. The use of demographic variables, polysomnographic recordings, signal processing methods, and other biomarkers should be carefully explored to identify underlying mechanisms. *2*) Given the subtleties of OSA pathogenesis, the study of interactions between variables is paramount, since the manipulation of a single variable in isolation is likely to be complex. Only by understanding the complexity of the various adaptive responses and their interactions are new insights and therapeutic strategies likely to emerge. ∎

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