

The importance of arousal in obstructive sleep apnea—updates from the American Thoracic Society 2016

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The mechanism underlying obstructive sleep apnea (OSA) is thought to vary across individuals (1). OSA patients are anatomically predisposed to airway collapse but pharyngeal dilator muscle reflexes can help to protect pharyngeal patency (2). Studies suggest that the degree of anatomical compromise in OSA is highly variable, as is the robustness of the upper airway dilator muscle reflexes. The accumulation of respiratory stimuli during sleep can help to activate the upper airway dilator muscles and thus prevent repetitive pharyngeal collapse (3). One factor thought to be important is the arousal threshold i.e., the propensity to wake up from sleep (4). Some individuals have a low arousal threshold i.e., wake up easily whereas others have a high arousal threshold i.e., hard to wake up. The importance of arousal was discussed extensively at the American Thoracic Society (ATS) 2016 meeting in San Francisco. Several concepts emerged from this meeting and from the recent literature:

(I) Control of breathing is thought to be important in OSA pathogenesis, although the impact of state instability (wake to sleep to wake transitions) has been less clear (5,6). Some believe that repetitive arousal from sleep will lead to hypocapnia and subsequent dilator muscle hypotonia. Proponents of this theory suggest that repetitive arousals in and of themselves can lead to apneas, based on the CO₂ fluctuations which occur (7). However, current experimental studies have not demonstrated low upper airway dilator muscle activity following arousal-induced hypocapnia. In fact, many prior studies did not measure ETCO₂ in this context and assumed hypocapnia to be present. Cori

et al. examined spontaneous respiratory-event induced arousals in OSA patients and did observe hypocapnia to be present in the majority of cases. However, genioglossus EMG was not suppressed below baseline (8,9). Instead, genioglossus activity was typically high despite hypocapnia perhaps reflecting prolonged after-discharge i.e., a type of neural memory in the motor control of the upper airway. Thus, the role of state instability and arousal-induced hypocapnia in OSA pathogenesis could be questioned (10);

(II) Arousal from sleep is although thought to be important in some OSA complications. Indeed, arousal from sleep is associated with catecholamine surges which may be critical to some of the observed OSA cardiometabolic complications. Djonlagic *et al.* have observed that arousal frequency is indeed the best predictor of impairment in sleep dependent memory consolidation in OSA (11). Thus, although hypoxemia is clearly important in OSA complications, recurrent arousal also has an important role in this context;

(III) The arousal threshold can be manipulated pharmacologically using sedative/hypnotic agents. In theory agents which raise the arousal threshold could allow the accumulation of respiratory stimuli during stable sleep which could activate pharyngeal dilator muscles and in turn stabilize the upper airway. Indeed, Heinzer *et al.* showed that trazodone led to consistent increases in the arousal threshold (12). Subsequently, several authors have assessed various sedative hypnotic agents including

eszopiclone, and trazodone, all showing modest increases in the arousal threshold (13,14). In theory, such agents could be used to treat a subset of OSA patients in whom a low arousal threshold was critical in OSA pathogenesis. Some improvements in AHI have been observed in this context, although the observed improvements have been rather modest and primarily from single night studies. On the other hand, sedative/hypnotic agents could theoretically be deleterious for some patients if they lead to prolonged apneas and profound hypoxemia prior to arousal. Thus, any such interventions must be done cautiously. Edwards *et al.* have recently reported that the arousal threshold can be estimated using clinically available data such as the severity of OSA (4), the nadir oxygen saturation, the predominance of apneas *vs.* hypopneas and perhaps the arousal index itself. Efforts are also ongoing to use plasma biomarkers to estimate the arousal threshold, although further work is clearly needed in this area. Robust clinical trials examining outcomes of patients will be required before clinical recommendations can be provided;

- (IV) Some OSA patients who are treated with continuous positive airway pressure (CPAP) have difficulty adhering to therapy. Some clinical data support the use of sedative hypnotic agents to improve CPAP adherence (15). In theory these agents help to improve sleep quality such that individuals who are prone to repeated awakenings on CPAP may tolerate therapy better following hypnotic treatment. Indeed Lettieri *et al.* showed improved CPAP adherence in a randomized placebo controlled trial using eszopiclone to improve sleep quality (15). Of note, both groups were receiving CPAP therapy in this study but adherence was better with eszopiclone compared to placebo;
- (V) Some OSA patients, particularly the elderly, can present with insomnia (16). In such cases, recurrent arousal from sleep occurs from repetitive respiratory events, but the presenting complaint in some individuals is inability to sleep. Indeed in clinical practice, elderly individuals with insomnia frequently have underlying sleep disorders. The optimal treatment of people with both sleep apnea and insomnia is unclear. We occasionally use sedative/hypnotic agents in such cases to improve

sleep quality. Behavioral interventions such as cognitive behavioral therapy can also be helpful in insomnia cases, although its impact on comorbid OSA has not been assessed to our knowledge. Long-term clinical outcome studies will be required to determine the optimal recommendations for such cases.

In summary, OSA has a myriad of different causes. A personalized medicine approach to OSA has been suggested whereby treatments could be targeted to the underlying mechanism of disease (17). In some individuals multiple mechanisms are likely underlying OSA and thus combination therapy may be required to eliminate apnea. Such approaches will require robust clinical trials to assess important neurocognitive and cardiometabolic outcomes. The role of arousal in OSA pathogenesis and the pathophysiology of its complications is being clarified. Recurrent arousals and the arousal threshold may well be an important therapeutic target in a subset of patients, although clearly careful studies investigating outcomes will be required before such approaches can be recommended clinically.

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Footnote

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