Dreaming of New Obstructive Sleep Apnea Treatments

It is estimated that almost 1 billion adults have obstructive sleep apnea (OSA) worldwide (1). Somewhere around 130–370 million of these patients experience OSA either only during or at a greater severity while in REM as opposed to non-REM sleep (2). REM-related OSA has been linked in epidemiological studies to an increase in the risk of hypertension, cardiovascular disease, metabolic disease, and poor neurocognitive outcomes (3). These clinical consequences highlight the importance of understanding the pathogenesis of airway obstruction in REM to develop more targeted therapeutic approaches. Continuous positive airway pressure (CPAP) is the first-line therapy for OSA, but adherence to CPAP is lower in REM-related than non–stage-specific OSA (4). This likely results in less effective treatment of REM-related OSA, particularly considering the increased distribution of REM toward the latter part of the night requiring whole night compliance for adequate treatment. Similarly, mandibular advancement devices are less effective at dealing with obstructive events in REM than non-REM (3). Thus, OSA in REM is common and less well treated than non–stage-specific OSA. Understanding the contributors to increased airway obstruction in REM is of interest and may improve treatment.

Current concepts of OSA pathophysiology incorporate four main factors contributing to the presence and severity of OSA: airway anatomical compromise, upper airway dilator muscle effectiveness, arousal threshold, and respiratory stability. Given that gross anatomical change between non-REM and REM is unlikely, research to understand the increased frequency of airway obstruction in REM has focused on nonanatomical traits. Although the arousal threshold has been recognized to be lower (individuals awaken more easily) in REM for some time (5), how much this contributes to REM-related airway obstruction is uncertain. Respiratory control is *more* stable in REM than non-REM sleep (6, 7) and therefore unlikely to contribute to increased event frequency in REM. Meanwhile, upper airway collapsibility has been shown in several studies to be increased in REM (7, 8), a result attributed to a preferential reduction in neural drive to upper airway dilator muscles in REM sleep, resulting in an imbalance of drive between pharyngeal and diaphragm muscles. Animal models have demonstrated this imbalance, as well as a reduced responsiveness to carbon dioxide in REM of the largest airway dilator, the genioglossus (9). Accordingly, considerable work has focused on understanding the preferential hypotonia of upper airway dilator muscles in REM sleep, with cholinergic inhibition via muscarinic receptors (10) as well as a possible contribution from removal of noradrenergic drive (11) to the hypoglossal motor nucleus considered key.

In this issue of the *Journal*, Messineo and colleagues (pp. 219–232) propose a new model for upper airway closure during REM sleep (12). The authors propose a reduction in common respiratory drive to *both* respiratory pump and genioglossus muscles during REM sleep, resulting in increased upper airway closure. This novel hypothesis is based on interpretation of their experimental findings. Specifically, Messineo and colleagues studied 25 patients with obstructive events present in both REM and non-REM, during a portion of the night without CPAP. Using breath-by-breath measures (averaged into deciles), they created plots of respiratory drive against $\dot{V}_E$ and genioglossus muscle activity to investigate the causes of REM-related increases in obstructive event frequency. Contrary to the proposal that upper airway dilator muscles are preferentially inhibited in REM (where they would expect a parallel downward shift in genioglossus muscle activity for any given level of drive), they reported an unchanged relationship between peak inspiratory genioglossus activity and ventilatory drive. They did note, however, a shift in drive to lower levels across all deciles in REM sleep. Notably, tonic (minimum expiratory) genioglossus activity did show the expected reduction in activity for a given level of drive, as proposed by the preferential dilator muscle hypotonia model. The authors are to be congratulated on their extensive and careful experimental methods, including the use of intraesophageal diaphragmatic EMG to measure respiratory drive and intramuscular genioglossus EMG recordings, although the evidence for their model is not extensive and there are some limitations, such as the recording of only one airway dilator muscle that may or may not be representative of all dilators.

Perhaps more importantly, there are other explanations of their results. During REM sleep in humans, there are well-documented changes in patterns of breathing with a reduction in overall ventilation, marked variability in breathing, a reduction in V_T, and increased breathing frequency, all resulting in a higher end tidal CO_2 during REM sleep than in non-REM sleep or wakefulness (13). Quantification of common eupneic ventilation, as used by Messineo and colleagues to justify their conclusions, necessitate measurement of alveolar ventilation. Breath-by-breath measurements of airflow, as used by Messineo (12) and colleagues, are unlikely to be equivalent to alveolar ventilation in REM sleep due to patterns of breathing and increased dead space ventilation. In addition, reduction in ventilatory drive in REM results in well-documented reductions in intrapharyngeal pressures (14), decreasing transmural pressures acting to collapse the pharynx (15). The increased obstructive frequency during REM sleep as observed by Messineo and colleagues (12) appears unlikely to be explained by an equal reduction in ventilatory and pharyngeal muscle drive alone, as collapse requires an imbalance between collapsing and dilating forces. However, the documented reduction in tonic genioglossus muscle activity observed may be an important contributor to REM-related obstruction given that airway collapse typically occurs during expiration. This reduction in tonic genioglossus activity in REM sleep relative to phasic genioglossus activity is similar to findings in animals (9). Likewise, the reduction in arousal threshold observed in the study of Messineo and colleagues (12) and others (5) may be important.

A final consideration is that if the model proposed by Messineo and colleagues (12) was the sole explanation of increased obstructive event frequency in REM, then approaches directed at increasing upper

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airway muscle activity may be less effective in REM sleep. However, hypoglossal nerve stimulators are equally effective during REM and non-REM obstruction (16), although this is not necessarily evidence against their model. Thus, although the findings of Messineo and colleagues are certainly interesting and have potentially identified another mechanism by which obstructive frequency increases in REM sleep, it may be premature to dismiss animal literature explaining preferential dilator muscle hypotonia in REM and their own tonic genioglossus activity reductions in REM sleep as being unimportant. ■

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References

1. Benjafield AV, Ayas NT, Eastwood PR, Heinzer R, Ip MSM, Morrell MJ, *et al.* Estimation of the global prevalence and burden of obstructive sleep apnoea: a literature-based analysis. *Lancet Respir Med* 2019;7:687–698.
2. Conwell W, Patel B, Doeing D, Pamidi S, Knutson KL, Ghods F, *et al.* Prevalence, clinical features, and CPAP adherence in REM-related sleep-disordered breathing: a cross-sectional analysis of a large clinical population. *Sleep Breath* 2012;16:519–526.
3. Varga AW, Mokhlesi B. REM obstructive sleep apnea: risk for adverse health outcomes and novel treatments. *Sleep Breath* 2019; 23:413–423.
4. Almeneessier AS, Almousa Y, Hammad O, Olaish AH, ALAnbay ET, BaHammam AS. Long-term adherence to continuous positive airway pressure in patients with rapid eye movement-only obstructive sleep apnea: a prospective cohort study. *J Thorac Dis* 2017;9:3755–3765.
5. Berry RB, Kouchi KG, Der DE, Dickel MJ, Light RW. Sleep apnea impairs the arousal response to airway occlusion. *Chest* 1996;109:1490–1496.
6. Landry SA, Andara C, Terrill PI, Joosten SA, Leong P, Mann DL, *et al.* Ventilatory control sensitivity in patients with obstructive sleep apnea is sleep stage dependent. *Sleep (Basel)* 2018;41:zsy040.
7. Joosten SA, Landry SA, Wong AM, Mann DL, Terrill PI, Sands SA, *et al.* Assessing the physiologic endotypes responsible for REM- and non-REM-based OSA. *Chest* 2021;159:1998–2007.
8. Carberry JC, Jordan AS, White DP, Wellman A, Eckert DJ. Upper airway collapsibility (Pcrit) and pharyngeal dilator muscle activity are sleep stage dependent. *Sleep (Basel)* 2016;39:511–521.
9. Horner RL, Liu X, Gill H, Nolan P, Liu H, Sood S. Effects of sleep-wake state on the genioglossus vs.diaphragm muscle response to CO(2) in rats. *J Appl Physiol (1985)* 2002;92:878–887.
10. Grace KP, Hughes SW, Horner RL. Identification of the mechanism mediating genioglossus muscle suppression in REM sleep. *Am J Respir Crit Care Med* 2013;187:311–319.
11. Chan E, Steenland HW, Liu H, Horner RL. Endogenous excitatory drive modulating respiratory muscle activity across sleep-wake states. *Am J Respir Crit Care Med* 2006;174:1264–1273.
12. Messineo L, Eckert DJ, Taranto-Montemurro L, Vena D, Azarbarzin A, Hess LB, *et al.* Ventilatory drive withdrawal rather than reduced genioglossus compensation as a mechanism of obstructive sleep apnea in REM sleep. *Am J Respir Crit Care Med* 2022;205:219–232.
13. Douglas NJ, White DP, Pickett CK, Weil JV, Zwillich CW. Respiration during sleep in normal man. *Thorax* 1982;37:840–844.
14. Eckert DJ, Malhotra A, Lo YL, White DP, Jordan AS. The influence of obstructive sleep apnea and gender on genioglossus activity during rapid eye movement sleep. *Chest* 2009;135:957–964.
15. Kairaitis K, Byth K, Parikh R, Stavrinou R, Wheatley JR, Amis TC. Tracheal traction effects on upper airway patency in rabbits: the role of tissue pressure. *Sleep* 2007;30:179–186.
16. Strollo PJ Jr, Soose RJ, Maurer JT, de Vries N, Cornelius J, Froymovich O, *et al.*; STAR Trial Group. Upper-airway stimulation for obstructive sleep apnea. *N Engl J Med* 2014;370:139–149.

Expanding the Tuberculosis Cascade of Care to Treat Undiagnosed and Subclinical Tuberculosis in High-Burden Settings

Globally, more than 25% of all incident cases of tuberculosis (TB) occur in India, which is more TB cases than in any other country in the world (1). In excess of 2.6 million new cases of TB and approximately 500,000 TB-related deaths occurred in India in 2020. Although India has made strides in TB control, progress has been incremental, and acceleration of progress has been limited in part by systemic delays in diagnosis and initiation of TB therapy.

It has long been appreciated that early TB diagnosis and treatment in India are hampered by the vast and unregulated private healthcare sector (2–4). The scale of this sector cannot be overstated, as nearly half of patients with TB in India may initially seek care from private practitioners (2), where diagnosis, treatment, and reporting practices often do not meet national or

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