on group-level data and estimates of MCID are applied with caution to individual patients when making treatment or funding decisions, and to ensure that trial-derived metrics do not become a barrier to accessing emerging therapies for uncommon life-threatening diseases with few management options. ■

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Obstructive Sleep Apnea and Cardiovascular Disease
REM Sleep Matters!

REM sleep accounts for approximately a quarter of total sleep time in healthy adults. During REM sleep, several factors coalesce to result in longer duration and greater severity of oxygen desaturation during obstructive apneas and hypopneas versus non-REM sleep (1), including cholinergic-mediated inhibition of the hypoglossal nerve, resulting in suppression of genioglossus muscle tone and increased propensity for upper airway collapse (2), as well as a reduction in the hypoxic and hypercapnic ventilatory drive (3). Such physiological features of REM sleep can lead to obstructive sleep apnea (OSA) that occurs predominantly or exclusively during REM sleep in a third of patients presenting to clinical sleep laboratories (4). It is well established that compared with non-REM sleep, REM sleep is associated with greater sympathetic activity, lower vagal tone and more cardiovascular instability (5). Hemodynamic and sympathetic changes observed with obstructive events during REM sleep cause a surge in blood pressure and heart rate and may even alter glucose metabolism (6, 7). The above-mentioned pathophysiologic differences between REM and non-REM sleep support the notion that obstructive events during

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REM sleep may be disproportionately toxic from a cardiometabolic standpoint versus obstructive events occurring during non-REM sleep.

Indeed, extended follow-up from the Wisconsin Sleep Cohort demonstrated that OSA isolated to REM sleep (REM apnea hypopnea index [AHI] >15 events/h with non-REM AHI <5 events/h) was independently associated with prevalent and incident hypertension, as well as with nondipping of the nocturnal blood pressure (8, 9). Similarly, in the MAILES (Men Androgens Inflammation Lifestyle Environment and Stress) study, REM OSA (REM AHI ⩾30 events/h) was independently associated with hypertension (10). Of note, in both these epidemiologic studies, non-REM AHI was not associated with hypertension.

It remains unclear whether the increased risk for hypertension and alterations in glucose metabolism resulting from REM OSA could promote atherosclerosis and play a part in triggering ischemic events in patients with cardiovascular disease. To that end, the analysis of the Sleep Heart Health Study cohort in this issue of the *Journal*, by Aurora and colleagues (pp. 653–660), is an important and timely contribution to the growing evidence that REM OSA is clinically relevant (11). These investigators examined the association between OSA during REM sleep and composite fatal and nonfatal cardiovascular endpoints including myocardial infarction, coronary artery revascularization, congestive heart failure, and stroke. The cohort consisted of 3,265 community-dwelling men and women (mean [± SD] age, 62 ± 10.7 yr; body mass index, 27.8 ± 5.0 kg/m^2; 63.1% women) with no significant OSA during non-REM sleep (non-REM AHI <5 events/h) who were followed for an average of 9.5 years. To obtain more precise estimates of REM AHI, the authors included participants who had at least 30 minutes of recorded REM sleep on home polysomnography (12). The AHI was defined as the number of apneas and hypopneas associated with at least a 4% decrease in oxygen saturation per hour of sleep. The severity of OSA during REM sleep was categorized as normal (REM AHI <5 events/h; 53.8% of the cohort), mild (REM AHI 5.0–14.9 events/h; 27.7% of the cohort), moderate (REM AHI 15.0–29.9 events/h; 13% of the cohort), and severe (REM AHI ⩾30.0 events/h; 5.5% of the cohort). The analysis revealed that in participants with prevalent cardiovascular disease at baseline, the hazard ratio for the composite cardiovascular endpoint was 2.56 (95% confidence interval, 1.46–4.47) for severe REM OSA compared with no OSA during REM sleep (REM AHI <5 events/h), after adjusting for age, sex, race, body mass index, smoking status, prevalent hypertension, and diabetes. The association was much weaker in participants without prevalent cardiovascular disease. The study by Aurora and colleagues suggests that in patients who have cardiovascular disease at baseline (i.e., prior myocardial infarction, coronary revascularization, stroke, and heart failure), severe OSA isolated to REM sleep more than doubles the risk for recurrent cardiovascular events.

The study has several strengths including a large sample size recruited from the community, full polysomnographic assessments, robust method of ascertaining cardiovascular end points, and a long follow-up period. Notwithstanding the strengths, there are several noteworthy limitations. As acknowledged by the authors, there were only 33 participants who had both cardiovascular disease at baseline and severe OSA during REM sleep. Although we appreciate lumping of the cardiovascular endpoints to increase statistical power, it is important to point out that these outcomes do not necessarily have the same underlying pathophysiology, and therefore limits the ability to get at a mechanistic understanding of the role of OSA during REM sleep in increasing cardiovascular risk. Certainly hypertension is a common thread, but the OSA-driven sympathetic surges associated with paroxysmal arrhythmias and atrial embolus generation leading to stroke are mechanistically distinct from OSA-associated endothelial dysfunction and local thrombus generation leading to atherosclerosis.

Given the strong and independent association between OSA during REM sleep and cardiometabolic disorders (6–10), it is disappointing to see that large randomized clinical trials of continuous positive airway pressure (CPAP) have yielded ambiguous or negative results (13–15). In these trials, however, CPAP adherence was low and likely covered only the first half of the sleep period. Indeed, it is plausible that reduced CPAP adherence and the predominantly untreated OSA during REM sleep (which prevails during the latter hours of normal nocturnal sleep) may explain the negative or modest cardiometabolic benefits of CPAP therapy in several randomized clinical trials.

To date, it remains unclear whether the adverse outcomes associated with REM OSA are a specific product of the physiology of REM sleep, or whether they are a product of intermittently severe disease during sleep, as would also be seen, for example, in positional OSA. Such individuals typically have an overall low severity of disease, as measured by the total AHI, and questions remain about whether they would derive any benefit from CPAP therapy, particularly in the face of minimal symptomatology. Nonetheless, Aurora and colleagues have provided incremental evidence that severe OSA during REM sleep is not to be ignored, particularly in individuals with prevalent cardiovascular disease. Although the sleep medicine community awaits more definitive interventional studies, we believe there is also a need for better-tolerated and novel treatment options so that patients with REM-related OSA can tolerate therapy during the entire sleep period. ■

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