REM-Related Obstructive Sleep Apnea: To Treat or Not to Treat?

Commentary on Su et al. Functional outcomes in patients with REM-related obstructive sleep apnea treated with positive airway pressure therapy. *J Clin Sleep Med* 2012;8:243-247.

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The term REM-related obstructive sleep apnea (OSA) is used loosely by sleep clinicians when the polysomnogram (PSG) reveals obstructive apneas and hypopneas that occur predominantly or exclusively during REM sleep. In addition to being poorly characterized, various set of criteria have been used to describe REM-related OSA.¹ It is therefore not surprising that the reported prevalence of REM-related OSA is quite variable, ranging from as little as 10% to as much as 36% of the patient population with OSA undergoing PSG.¹⁻⁵ Despite the wide variation in prevalence, studies have consistently shown that REM-related OSA occurs more commonly in younger individuals, women, children, and in patients with mild or moderate OSA.¹⁻⁶ More importantly, the clinical significance of REM-related OSA remains controversial.⁷ Although a few studies have reported a link between obstructive respiratory events during REM sleep and hypersomnolence,^{2,8} several large cross-sectional clinic-based and prospective epidemiologic studies have suggested that only obstructive events during NREM sleep are associated with excessive daytime sleepiness (EDS).⁹⁻¹² The Sleep Heart Health Study investigators reported that in a large community-based sample of middle-aged and older adults, REM_{AHI} was not independently associated with daytime sleepiness or quality of life after adjusting for NREM_{AHI}.¹¹ These findings were also confirmed in a large clinical cohort.¹²

Patients with REM-related OSA tend to have an overall low AHI by virtue of the disproportionately lower percent of REM sleep as a function of total sleep duration. However, it remains unknown whether obstructive respiratory events that are isolated to REM sleep have a differential neurocognitive and cardiometabolic impact compared to events that occur in NREM sleep. It is now well established that compared to NREM sleep, REM sleep is associated with greater sympathetic activity and cardiovascular instability in healthy human subjects and patients with OSA.^{13,14} The hemodynamic and sympathetic changes during REM sleep cause a surge in the blood pressure and heart rate. These acute hemodynamic changes could play a part in triggering ischemic events in patients with cardiovascular disease.¹⁴⁻¹⁷ Indeed, obstructive apneas and hypopneas during REM sleep lead to greater degrees of hypoxemia^{18,19} and higher levels of sympathetic activity compared to events in NREM sleep.¹³ While numerous studies have established a robust association between OSA and adverse neurocognitive and cardiometabolic outcomes, there is a major gap of knowledge

on the risks associated with untreated REM-related OSA. To date it remains a clinical conundrum whether asymptomatic or minimally symptomatic patients with REM-related OSA—who typically have an overall low severity of disease as measured by the AHI—should be treated and whether they would derive any benefit from CPAP therapy.

Given the paucity of clinical research in REM-related OSA, the study by Su and colleagues in this issue of the *Journal* is an important and timely contribution to the field and may help shed some light to the uncertainty faced by clinicians. In a retrospective observational study the authors evaluated a cohort of patients with REM-related OSA and compared them to non-stage specific OSA. They found that symptomatic patients with REM predominant—but not REM exclusive—OSA benefited equally from CPAP therapy compared to patients with non-stage specific OSA as it relates to sleepiness, fatigue, and quality of life. The authors measured relevant outcomes with several validated questionnaires. Moreover, an attempt was made to obtain objective CPAP adherence in a large proportion of patients. The authors are to be commended for providing the first line of evidence that symptomatic patients with REM-related OSA can achieve similar degree of improvement in functional outcomes with CPAP therapy compared to patients with non-stage specific OSA.

Notwithstanding the strengths and novelty of the study, there are several limitations that are noteworthy. The definition used for classifying REM-related OSA was fairly permissive with regards to the NREM_{AHI} (NREM_{AHI} < 15 events per hour).^{1,7} Therefore, some patients with clinically significant OSA in NREM sleep were included in the REM-related OSA group. It is quite plausible that the CPAP benefit experienced by patients labeled as REM-related OSA may have been related to the treatment of mild OSA and upper airway resistance present during NREM sleep. Similarly, one could argue that the study merely compared treatment response between patients with mild OSA vs. moderate-to-severe OSA. Therefore, given the criteria used to define REM-related OSA in this study, it remains an open question whether CPAP therapy leads to any measurable benefit in patients with OSA that is almost exclusively limited to REM sleep.

In addition, as correctly recognized by the authors, there is a significant component of selection bias. The investigators enrolled patients with REM-related OSA that were quite symptomatic and were actively seeking therapy. This cohort

of REM-related OSA is most likely not representative of the larger population of patients identified with REM-related OSA. The enrolment of only 330 patients over a 2-year period from a large tertiary-care clinical sleep laboratory most likely represents a small fraction of patients seen at that institution. While it is tempting to conclude that patients with REM-related OSA benefit equally from CPAP therapy compared to those with non-stage specific OSA, it is difficult given the very selective nature of the cohort. The study, however, confirms the findings of a prior report that CPAP adherence is no worse in patients with REM predominant disease despite an overall significantly lower severity of OSA.¹ Due to the selection bias mentioned above, the findings of the current study are not applicable to the less sleepy and less symptomatic patients found to have REM-related OSA on diagnostic PSGs, therefore limiting its generalizability. Although there was no difference in percent of days with > 4 hours of CPAP use per night, this measure of adherence is less informative. It is important to elucidate whether patients with REM-related OSA use CPAP in the early morning hours when REM sleep is most prevalent. If most patients were starting their sleep period using CPAP and the mean adherence to therapy was 5 hours per night, then it is very likely that a significant proportion of REM sleep remained untreated. It is therefore unclear whether OSA during REM sleep was effectively treated or whether the authors noted a benefit that was independent of treating REM-related OSA and more related to treating mild NREM disease or even a placebo effect. Although rigorously designed studies would undoubtedly address these limitations and provide superior evidence, Su et al. have just provided incremental evidence warranting such studies in the near future.

CITATION

Mokhlesi B. REM-related obstructive sleep apnea: to treat or not to treat? *J Clin Sleep Med* 2012;8(3):249-250.

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SUBMISSION & CORRESPONDENCE INFORMATION

Submitted for publication March, 2012

Accepted for publication March, 2012

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DISCLOSURE STATEMENT

Dr. Mokhlesi has received research support from, has consulted for, and has participated in speaking engagements for Philips/Respironics.