CHEST

Growing Evidence Linking OSA During Rapid Eye Movement Sleep to Systemic Hypertension

Babak Mokhlesi, MD, FCCP
Chicago, IL
Jason R. Carter, PhD
Houghton, MI

It was nearly six decades ago when two University of Chicago investigators, Nathaniel Kleitman and Eugene Aserinsky, discovered rapid eye movement (REM) sleep, a stage of sleep that accounts for approximately one-quarter of total sleep time in healthy adults.[1] To date, the preponderance of research on REM sleep has focused on memory, affect, and cognition. In the last few years, however, there has been a growing interest in understanding the consequences of OSA during the two main stages of sleep (REM and non-REM sleep). Although OSA during REM sleep has not been associated with excessive daytime sleepiness or reduced quality of life,[2,3] it is important to recognize that there are important autonomic nervous system and cardiorespiratory changes during REM sleep supporting the notion that REM OSA may have worse cardiometabolic consequences than non-REM OSA.[4] From a pathophysiologic point of view, cholinergic-mediated inhibition of the hypoglossal nerve results in the suppression of genioglossus muscle tone and thus substantially increases propensity for upper airway collapse during REM sleep. This scenario in turn can lead to either REM-predominant OSA or simply OSA that becomes more severe during REM sleep. Moreover, REM sleep is associated with greater sympathetic activity, lower vagal tone, and more cardiovascular instability compared with non-REM sleep.[5] REM sleep is also characterized by a reduction in the hypoxic and hypercapnic ventilatory drive. These physiologic phenomena may in part explain why obstructive apneas and hypopneas during REM sleep are longer in duration, associated with significantly greater oxygen desaturation, and lead to greater fluctuations in BP compared with obstructive events in non-REM sleep.[5,6]

FOR RELATED ARTICLE SEE PAGE 495

Recent analysis of the Wisconsin Sleep Cohort has shown that OSA during REM sleep is independently associated with prevalent and incident systemic hypertension as well as with incident nondipping of nocturnal BP.[7,8] In this population-based cohort, the REM apnea-hypopnea index (AHI) $\geq$ 15 events/h had a clinically significant threshold effect. Interestingly, the non-REM AHI was not associated with hypertension. From a metabolic standpoint, elevated REM AHI has been independently associated with worse glycemic control in patients with type 2 diabetes[9] and with insulin resistance in the community-based Sleep Heart Health Study.[10] Despite these important associations between REM OSA and cardiometabolic health, additional evidence is needed.

Consequently, the recent study by Appleton et al[11] in this issue of *CHEST* is a welcome addition to the growing evidence that REM OSA is a clinically important entity and not just an epiphenomenon. These investigators examined the association between OSA during REM sleep and systemic hypertension in 739 middle-aged and elderly community-dwelling men enrolled in the Men Androgen Inflammation Lifestyle Environment and Stress (MAILES) Study, a population-based longitudinal cohort from Adelaide, Australia. In contrast to the Wisconsin Sleep Cohort and the Sleep Heart Health

AFFILIATIONS: From the Department of Medicine (Dr Mokhlesi), Section of Pulmonary and Critical Care, Sleep Disorders Center, University of Chicago; Sleep, Metabolism and Health Center (Drs Mokhlesi and Carter), University of Chicago; and the Department of Kinesiology and Integrative Physiology (Dr Carter), Michigan Technological University.

FINANCIAL/NONFINANCIAL DISCLOSURES: The authors have reported to *CHEST* the following: B. M. is supported by National Institutes of Health [Grant R01HL119161] and has served as a consultant to Philips Respironics and has received research support from Philips Respironics; he has also received honorarium from Zephyr Medical Technologies and has served on the advisory board of Itamar Medical. J. R. C. is supported by the National Heart, Lung, and Blood Institute (Grant HL-122919-01). Both authors are supported by the Merck Investigator Studies Program.

CORRESPONDENCE TO: Babak Mokhlesi, MD, FCCP, Section of Pulmonary and Critical Medicine, Department of Medicine, University of Chicago, 5841 S Maryland Ave, MC6076/Room M630, Chicago, IL 60637; e-mail: bmokhles@medicine.bsd.uchicago.edu

DOI: http://dx.doi.org/10.1016/j.chest.2016.03.047

Study (which scored hypopneas based on 4% oxygen desaturation), hypopneas were scored by using 3% oxygen desaturation and/or microarousal. This study found that moderate to severe OSA in REM sleep, defined by REM AHI $\geq$ 20, was independently associated with prevalent as well as recent-onset hypertension. When the analysis was limited to men without "clinically significant OSA" (defined as AHI $<$ 10), REM AHI $\geq$ 20 remained significantly associated with prevalent hypertension in the fully adjusted models. These associations were not attenuated by the addition of non-REM AHI to the statistical models. Importantly, and similar to the analysis of the Wisconsin Sleep Cohort,[7] the non-REM AHI was not independently associated with prevalent and incident hypertension.[11]

The strong association between REM OSA and hypertension is of significant relevance because REM OSA is prevalent. In clinical cohorts, the prevalence of REM OSA fluctuates widely based on how it is defined, varying from 10% to 36% of patients with OSA.[12] The prevalence of OSA during REM sleep is also high in community-based cohorts. For instance, in the Wisconsin Sleep Cohort, 18% of the sleep studies that had no evidence of OSA (ie, AHI $<$ 5) demonstrated moderate or severe OSA during REM sleep (ie, REM AHI $\geq$ 15).[7] Moreover, 70% of the sleep studies with an overall AHI $<$ 15 (ie, no OSA and mild OSA) had an REM AHI $\geq$ 15. Likewise, in the Sleep Heart Health Study, 25% of individuals with a non-REM AHI $<$ 8 had an REM AHI $\geq$ 13.[2] In both of these studies, hypopneas were conservatively scored by using 4% oxygen desaturation.[2,7] In the study by Appleton et al,[11] 15% of the community-dwelling men without "clinically significant" OSA (ie, AHI $<$ 10) had an REM AHI $\geq$ 20, a threshold that is likely similar to REM AHI $\geq$ 15 used in the Wisconsin Sleep Cohort given the 3% oxygen desaturation and/or microarousal definition used to score hypopneas in the MAILES study. These findings suggest that REM OSA, defined by using REM AHI thresholds that are strongly associated with hypertension, is prevalent in the community at large and in individuals who would not be considered as having OSA according to current clinical definitions.

Undoubtedly, further research is needed to establish whether treatment can decrease the cardiovascular and metabolic risks associated with REM OSA. In this context, it is important to note common therapeutic patterns and implications of OSA during REM sleep. In clinical practice, 4 h of nightly CPAP use for 70% of the nights is considered adequate adherence to therapy. This approach translates into an average CPAP use of 2.8 h every night.[7] 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 effects of CPAP therapy on BP control in randomized clinical trials. Indeed, using CPAP for 3 or 4 h from the time lights are turned off will cover only 25% or 40% of REM sleep, respectively, and will leave most obstructive events during REM sleep untreated.[7,9]

As correctly acknowledged by Appleton et al,[11] there are a few limitations to this study. First and foremost, the findings cannot be extended to women. This limitation is relevant because REM OSA tends to be more prevalent in women.[12] Moreover, similar to the Wisconsin Sleep Cohort, the majority of the participants were non-Hispanic white individuals of European ancestry, thus limiting generalizations to others races and ethnicities. In contrast to the Wisconsin Sleep Cohort, the MAILES study was not designed to longitudinally assess sleep-disordered breathing, and therefore the direction of causality is limited. It also lacks a more robust measure of BP such as ambulatory BP monitoring (ABPM).

An important question that remains to be elucidated is how sleep-disordered breathing during only 1 to 2 h of REM sleep leads to daytime hypertension. Although studies using 24-h ABPM have provided useful insight into the relationship between OSA and hypertension, this monitoring technique has inherent limitations because it typically measures BP in snapshots of 15- to 30-min intervals. Obstructive apneas and hypopneas can cause temporary and significant elevations of BP (ie, $\geq$ 30-40 mm Hg lasting 20-30 s) that might be misrepresented using ABPM.[5] Continuous beat-to-beat BP monitoring via finger plethysmography, conversely, offers a reliable noninvasive approach that can capture rapid oscillations and surges in BP that often occur during obstructive apneas and hypopneas.[13] It is plausible that obstructive apneas and hypopneas during REM sleep lead to greater and more prolonged surges in BP than obstructive events during non-REM sleep. We believe that the frequent surges in BP in patients with OSA, which are not captured by ABPM, are clinically relevant. Using noninvasive beat-to-beat monitoring of BP may shed further light on whether obstructive events during REM sleep are more deleterious to BP regulation than obstructive events during non-REM sleep. It is possible that repeated bouts of sympathetic activation

prevent complete normalization of BP in the time between apneas and hypopneas, preventing a normal and healthy nocturnal BP dip. This nocturnal sympathetic activation, particularly during untreated REM OSA, may eventually carry over to the daytime period.

While the sleep medicine community awaits more definitive studies, Appleton et al[11] have provided incremental evidence that moderate to severe OSA during REM sleep is clinically relevant regardless of the overall severity of OSA.

References

1. Aserinsky E, Kleitman N. Regularly occurring periods of eye motility, and concomitant phenomena, during sleep. *Science*. 1953;118(3062):273-274.
2. Chami HA, Baldwin CM, Silverman A, et al. Sleepiness, quality of life, and sleep maintenance in REM versus non-REM sleep-disordered breathing. *Am J Respir Crit Care Med*. 2010;181(9):997-1002.
3. Pamidi S, Knutson KL, Ghods F, Mokhlesi B. Depressive symptoms and obesity as predictors of sleepiness and quality of life in patients with REM-related obstructive sleep apnea: cross-sectional analysis of a large clinical population. *Sleep Med*. 2011;12(9):827-831.
4. Mokhlesi B, Punjabi NM. "REM-related" obstructive sleep apnea: an epiphenomenon or a clinically important entity? *Sleep*. 2012;35(1):5-7.
5. Somers VK, Dyken ME, Clary MP, Abboud FM. Sympathetic neural mechanisms in obstructive sleep apnea. *J Clin Invest*. 1995;96(4):1897-1904.
6. Peppard PE, Ward NR, Morrell MJ. The impact of obesity on oxygen desaturation during sleep-disordered breathing. *Am J Respir Crit Care Med*. 2009;180(8):788-793.
7. Mokhlesi B, Finn LA, Hagen EW, et al. Obstructive sleep apnea during REM sleep and hypertension. Results of the Wisconsin Sleep Cohort. *Am J Respir Crit Care Med*. 2014;190(10):1158-1167.
8. Mokhlesi B, Hagen EW, Finn LA, Hla KM, Carter JR, Peppard PE. Obstructive sleep apnoea during REM sleep and incident non-dipping of nocturnal blood pressure: a longitudinal analysis of the Wisconsin Sleep Cohort. *Thorax*. 2015;70(11):1062-1069.
9. Grimaldi D, Beccuti G, Touma C, Van Cauter E, Mokhlesi B. Association of obstructive sleep apnea in rapid eye movement sleep with reduced glycemic control in type 2 diabetes: therapeutic implications. *Diabetes Care*. 2014;37(2):355-363.
10. Chami HA, Gottlieb DJ, Redline S, Punjabi NM. Association between glucose metabolism and sleep-disordered breathing during REM sleep. *Am J Respir Crit Care Med*. 2015;192(9):1118-1126.
11. Appleton SL, Vakulin A, Martin SA, et al. Hypertension is associated with undiagnosed OSA during rapid eye movement sleep. *Chest*. 2016;150(3):495-505.
12. Conwell W, Patel B, Doeing D, 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(2):519-526.
13. Carter JR, Fonkoue IT, Grimaldi D, et al. Positive airway pressure improves nocturnal beat-to-beat blood pressure surges in obesity hypoventilation syndrome with obstructive sleep apnea. *Am J Physiol Regul Integr Comp Physiol*. 2016;310(7):R602-R611.