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Obstructive sleep apnea and pulmonary hypertension: a bidirectional relationship.

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COMMENTARY

Obstructive sleep apnea and pulmonary hypertension: a bidirectional relationship

Commentary on Samhouri B, Venkatasaburamini M, Paz Y Mar H, Li M, Mehra R, Chaisson NF. Pulmonary artery hemodynamics are associated with duration of nocturnal desaturation but not apnea-hypopnea index. *J Clin Sleep Med*. 2020;16(8):1231–1239. doi:10.5664/jcsm.8468

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Obstructive sleep apnea (OSA) is a highly prevalent syndrome, affecting up to 1 billion people worldwide.[1] Dickens wrote classic literature describing Fat Boy Joe with "dropsy," a form of right heart failure, implying that some of the early descriptions of OSA ostensibly were complicated by pulmonary hypertension (PH). In a landmark French study, OSA did not seem to be independently associated with significant PH.[2] This dogma stuck for some time; however, Sajkov et al[3,4] published studies approximately 20 years ago that seemed to show an important link between OSA and elevated pulmonary artery pressure when patients with pulmonary parenchymal disease and hypoventilation were excluded from analysis. The authors drew 3 major conclusions about the link between OSA and PH. First, OSA is associated with only mild to moderate PH. Second, patients with OSA and PH had marked hypoxic vasoreactivity, such that small changes in inspired FiO_2 caused large elevations in pulmonary arterial pressures. Third, elevated pulmonary arterial pressures associated with OSA were reversible with positive airway pressure (PAP) therapy. These studies and others revived interest in the connection between OSA and PH.

Such findings in human patients with OSA parallel years of studies in animal models. Decades ago, canine models were used to demonstrate increases in pulmonary arterial pressures in response to intermittent hypoxia,[5] and more recently, rodent models of more realistic OSA—with cycle times on the order of seconds to minutes instead of hours—have shown that chronic intermittent hypoxia in awake animals may be capable of elevating right ventricular systolic pressure.[6,7]

Mechanistic data linking OSA to PH are relatively sparse, although a bidirectional causal relationship is proposed. Loop gain refers to the instability in the ventilatory control system; one component is sometimes referred to as mixing gain and includes circulatory delay. Classic studies by Guyton et al[8] demonstrated the development of Cheyne-Stokes breathing, a manifestation of high loop gain, with prolonged circulation in animals. Some human studies have supported the improvement in sleep-disordered breathing with reduced circulatory time.[9] In addition, edema formation, as commonly observed in PH, has been implicated in the pathogenesis of OSA. Rostral fluid shift in patients with marked elevations in extracellular fluid volume may contribute to upper airway and perhaps lung edema.[10] Conversely, OSA may contribute to the development of PH via intermittent hypoxia, catecholamine surges, and other molecular mechanisms. Thus, there are plausible mechanistic links between OSA and PH, although further research is clearly required.

In this issue of the *Journal of Clinical Sleep Medicine*, Samhouri et al[11] examined retrospective data from a large clinical cohort of patients with PH. The authors identified 493 clinic patients over 13 years, who had both a diagnostic polysomnogram and right heart catheterization within 2 years of the sleep study. Polysomnographic parameters (apnea-hypopnea index [AHI] and sleep time with peripheral saturation below 90% [T90]) were compared among those with various etiologies of PH, and sensitivity analyses were performed to better understand the associations between polysomnographic measures and right heart catheterization parameters.

Perhaps unsurprisingly, the cohort had a high prevalence of nocturnal hypoxemia (74% in the entire group, as defined by a T90 of at least 1% of total sleep time). T90 was higher among those with PH, but T90 was not different among the various PH subgroups. Several PH indices on the right heart catheterization were associated with increased T90 (higher mean pulmonary artery pressure, pulmonary vascular resistance, and right atrial pressure). The authors report that exclusion of those patients on supplemental oxygen during polysomnogram, or those on PH therapy, did not significantly impact the results. When those patients who had a polysomnogram before right heart catheterization were excluded, in an effort to minimize the potential effect of PAP therapy on right heart catheterization data, there was also minimal effect. Interestingly, there was little to no association between AHI and various markers of PH severity.

There are some intriguing findings and potential implications here. First, sleep-disordered breathing and PH have not been commonly coinvestigated in a cohort of this size and containing patients from a wide spectrum of PH classes.

Second, these findings suggest a possible role for supplemental oxygen in patients with PH with or without superimposed OSA. As is clear from other large cohorts, the acceptance of nasal PAP therapy in OSA is frustratingly low.[12] An imperfect solution (supplemental oxygen) may have a part to play in addressing nocturnal hypoxemia, in particular, among those who cannot or will not tolerate PAP. Indeed, 1 recent trial suggested the promise of supplemental oxygen alone at improving blood pressure after PAP withdrawal.[13] Could similar results be shown in PH?

However, there are some opportunities for further investigation as well. The main limitation is that, although the authors used polysomnography to characterize sleep, it may not have been used to full effect. Oxyhemoglobin desaturation indices were not presented, nor were nadir, mean, or baseline saturations. Compelling recent data have pointed to the need for more advanced metrics of hypoxic burden in OSA in relating to major cardiovascular outcomes.[14,15] Without further analyses, it remains unclear whether T90 is a marker of PH severity or a manifestation of OSA severity. Moreover, respiratory events that made up the AHI—even central vs obstructive—similarly were not delineated. Sleep quality is often poor in patients with PH[16]; therefore, the lack of association between AHI and PH severity may reflect that the AHI here is driven primarily by a low arousal threshold in these patients. Questions remain without a deeper dive into the polysomnographic data and further mechanistic research.

The authors provide a useful substrate for further discussion. Three remaining questions are emphasized. First, should patients with PH be screened routinely for OSA? We currently recommend a sleep evaluation for these patients based on our clinical experience and some anecdotes of severe PH improving markedly with PAP therapy. Second, should patients with OSA be screened for PH? We currently perform a history and physical in this context but do not perform routine exercise testing or echocardiography. Third, in light of emerging data showing possible improvements in World Health Organization group 3 PH (in interstitial lung disease),[17] should pharmacotherapy also be considered for OSA-associated PH? We applaud the authors for encouraging this discussion.

CITATION

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REFERENCES

1. Benjafield AV, Ayas NT, Eastwood PR, et al. Estimation of the global prevalence and burden of obstructive sleep apnoea: a literature-based analysis. *Lancet Respir Med.* 2019;7(8):687–698.
2. Chaouat A, Weitzenblum E, Krieger J, Oswald M, Kessler R. Pulmonary hemodynamics in the obstructive sleep apnea syndrome. Results in 220 consecutive patients. *Chest.* 1996;109(2):380–386.
3. Sajkov D, Wang T, Saunders NA, Bune AJ, Neill AM, Douglas Mcevoy R. Daytime pulmonary hemodynamics in patients with obstructive sleep apnea without lung disease. *Am J Respir Crit Care Med.* 1999;159(5 Pt 1):1518–1526.
4. Sajkov D, Wang T, Saunders NA, Bune AJ, Mcevoy RD. Continuous positive airway pressure treatment improves pulmonary hemodynamics in patients with obstructive sleep apnea. *Am J Respir Crit Care Med.* 2002;165(2):152–158.
5. Unger M, Atkins M, Briscoe WA, King TK. Potentiation of pulmonary vasoconstrictor response with repeated intermittent hypoxia. *J Appl Physiol.* 1977;43(4):662–667.
6. Campen MJ, Shimoda LA, O'Donnell CP. Acute and chronic cardiovascular effects of intermittent hypoxia in C57BL/6J mice. *J Appl Physiol.* 2005;99(5):2028–2035.
7. Nisbet RE, Graves AS, Kleinhenz DJ, et al. The role of NADPH oxidase in chronic intermittent hypoxia-induced pulmonary hypertension in mice. *Am J Respir Cell Mol Biol.* 2009;40(5):601–609.
8. Crowell JW, Guyton AC, Moore JW. Basic oscillating mechanism of Cheyne-Stokes breathing. *Am J Physiol.* 1956;187(2):395–398.
9. Stanchina ML, Ellison K, Malhotra A, et al. The impact of cardiac resynchronization therapy on obstructive sleep apnea in heart failure patients: a pilot study. *Chest.* 2007;132(2):433–439.
10. White LH, Bradley TD. Role of nocturnal rostral fluid shift in the pathogenesis of obstructive and central sleep apnoea. *J Physiol Lond.* 2013;591(5):1179–1193.
11. Samhouri B, Venkatasaburamini M, Paz Y Mar H, Li M, Mehra R, Chaisson NF, Chaisson NF. Pulmonary artery hemodynamics are associated with duration of nocturnal desaturation but not apnea-hypopnea index. *J Clin Sleep Med.* 2020;16(8):1231–1239.
12. Sawyer AM, Gooneratne NS, Marcus CL, Ofer D, Richards KC, Weaver TE. A systematic review of CPAP adherence across age groups: clinical and empiric insights for developing CPAP adherence interventions. *Sleep Med Rev.* 2011;15(6):343–356.
13. Turnbull CD, Sen D, Kohler M, Petousi N, Stradling JR. Effect of supplemental oxygen on blood pressure in obstructive sleep apnea (SOX). A randomized continuous positive airway pressure withdrawal trial. *Am J Respir Crit Care Med.* 2019;199(2):211–219.
14. Azarbarzin A, Sands SA, Stone KL, et al. The hypoxic burden of sleep apnoea predicts cardiovascular disease-related mortality: the Osteoporotic Fractures in Men Study and the Sleep Heart Health Study. *Eur Heart J.* 2019;40(14):1149–1157.
15. Aurora RN, Crainiceanu C, Gottlieb DJ, Kim JS, Punjabi NM. Obstructive sleep apnea during REM sleep and cardiovascular disease. *Am J Respir Crit Care Med.* 2018;197(5):653–660.
16. Batal O, Khatib OF, Bair N, Aboussouan LS, Minai OA. Sleep quality, depression, and quality of life in patients with pulmonary hypertension. *Lung.* 2011;189(2):141–149.
17. NIH U.S. National Library of Medicine. Safety and Efficacy of Inhaled Treprostinil in Adult PH With ILD Including CPFE. https://clinicaltrials.gov/ct2/show/NCT02630316. Accessed June 16, 2020.

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