Archivos de Bronconeumología xxx (xxxx) xxx–xxx

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Sociedad Española de Neumología y Cirugía Torácica

ARCHIVOS DE
Bronconeumología

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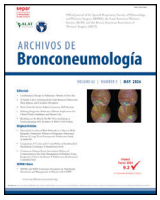

Editorial

# Positive Airway Pressure Therapy for Pulmonary Hypertension Associated with Sleep-disordered Breathing

During normal sleep, the cardiovascular system enters a relative state of quiescence, characterized by a 10%–15% reduction in heart rate and blood pressure. This physiologic decline, known as nocturnal dipping, is most pronounced during non-rapid eye movement (non-REM) sleep, which accounts for approximately 75% of total sleep time in healthy adolescents and adults. The autonomic and hemodynamic stability of non-REM sleep, marked by progressive reductions in central sympathetic outflow and increased parasympathetic tone, leads to a corresponding decrease in cardiac workload [1]. In contrast, REM sleep is associated with intermittent surges in sympathetic activity and abrupt increases in heart rate and blood pressure. However, in a small study of five healthy individuals, mean pulmonary artery pressure did not differ significantly between the first and second halves of the night, suggesting that pulmonary hemodynamics are unlikely to worsen during normal REM sleep [2].

Sleep-disordered breathing (SDB) encompasses several clinical entities, of which obstructive sleep apnea (OSA) is the most common. At the severe end of the spectrum is obesity hypoventilation syndrome (OHS), defined by the presence of obesity (typically class 3 obesity/body mass index $\geq$40 kg/m$^2$), sleep-disordered breathing, and daytime hypercapnia in the absence of an alternative neuromuscular, mechanical, or metabolic cause of hypoventilation [3]. Importantly, approximately 90% of patients with OHS have concomitant OSA, and nearly 70% have severe OSA [4]. Although the cardiovascular effects of SDB have been extensively studied and are beyond the scope of this commentary, several mechanistic considerations are particularly relevant. During REM sleep, physiologic muscle hypotonia increases upper airway collapsibility, thereby worsening obstructive events such as apneas and hypopneas, resulting in more profound hypoxemia and hypercapnia than events occurring during non-REM sleep [5]. These observations have important clinical implications for understanding both the downstream cardiovascular consequences of OSA and the impact of suboptimal adherence to positive airway pressure (PAP) therapy, particularly because REM sleep predominates during the second half of the night. As a result, patients who use CPAP for only the first 3–4 h of sleep may leave much of their REM-related OSA untreated [6]. The associated surges in blood pressure and heart rate increase left ventricular afterload and myocardial oxygen demand. With respect to pulmonary hemodynamics, limited experimental data suggest that the mean pulmonary artery pressure becomes more labile and may rise during REM sleep compared with non-REM sleep in patients with OSA, particularly when hypoxemia is more severe [7,8]. Sleep hypoxemia tends to be more severe in patients with OHS. Patients with OHS are known to have higher cardiovascular and respiratory morbidity as compared to eucapnic OSA.

Pulmonary hypertension (PH) is highly prevalent in patients with OHS [4,9]. In the largest clinical trial to date, approximately 50% of participants with OHS had echocardiographic evidence of PH, defined as a pulmonary artery systolic pressure $\geq$40 mmHg [9]. PH can be moderate to severe in patients with OHS. Although PH can occur in patients with eucapnic OSA, it tends to occur in patients with severe OSA, and the degree of PH tends to be mild [10]. SDB was previously recognized as a cause of group 3 PH. However, in the 2022 ESC/ERS guidelines for PH, the broad category of SDB was removed from the classification scheme and hypoventilation syndromes were specifically identified as a cause of group 3 PH [11]. Thus, although OSA has been reclassified from a cause of PH to a comorbidity, the pulmonary hemodynamic effects of severe OSA remain clinically important.

Multiple pathophysiologic mechanisms are likely to contribute to the development of PH in patients with OSA or OHS. The most studied and with the strongest evidence is hypoxemia, emanating from multiple animal models (murine, canine, feline) and limited human studies. Hypercapnia, intrathoracic pressure swings, and obesity can also contribute to worsening pulmonary hemodynamics [10]. These mechanisms can also induce left ventricular dysfunction and activate inflammatory pathways, further worsening systemic and pulmonary hypertension. On the other hand, pre-capillary PH associated with right ventricular failure may promote instability of the ventilatory control system leading to SDB through mechanisms similar to left ventricular failure with Cheyne–Stokes respiration/central sleep apnea [12].

There is limited data on the impact of PAP therapy on PH in patients with OSA or OHS. In fact, many studies are observational in nature with limited sample size and not all of them included patients with OHS. The largest meta-analysis to date exploring the effect of PAP therapy on pulmonary artery pressures in SDB included 518 patients OSA (mostly severe OSA) and 215 patients with OHS from a total of 23 studies, of which only 3 with randomized controlled trials [13]. In addition to exploring the impact of PAP therapy in OSA and OHS, the meta-analysis also assessed the benefits of PAP therapy according to the method used to assess pulmonary arterial pressure and included a separate analysis of patients with and without evidence of PH at baseline [13]. Not surprisingly, the impact of PAP therapy was more pronounced in patients with pre-existing PH. However, the effect size was

https://doi.org/10.1016/j.arbres.2026.04.018
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Please cite this article as: A. Kohli and B. Mokhlesi, Positive Airway Pressure Therapy for Pulmonary Hypertension Associated with Sleep-disordered Breathing, Archivos de Bronconeumología, https://doi.org/10.1016/j.arbres.2026.04.018

similar in OSA and OHS who had preexisting PH. Despite substantial heterogeneity, patients with PH at baseline experienced mean reductions in pulmonary artery systolic pressure and mean pulmonary artery pressure of 12.9 mmHg and 8.4 mmHg, respectively. This meta-analysis provides robust evidence that PAP therapy has significant salutary effects on pulmonary hemodynamics in patients with severe OSA or OHS, especially in patients with preexisting PH [13].

The effect of PAP therapy on the right ventricle has long been a concern, particularly in patients with pulmonary hypertension, because of the possibility that PAP-induced increases in intrathoracic pressure could adversely affect right ventricular function. Given the inverse relationship between intrathoracic pressure and net right ventricular filling pressure and cardiac output, PAP therapy may meaningfully alter right ventricular hemodynamics. In a small observational study of patients with mild to moderate OSA, CPAP therapy improved right ventricular function in those with lower baseline right ventricular ejection fraction and higher end-diastolic volume index, as measured by cardiac magnetic resonance imaging [14]. In another study of patients with pulmonary arterial hypertension, CPAP significantly reduced right ventricular end-diastolic pressure without a significant effect on resistive right ventricular afterload during wakefulness while undergoing right heart catheterization [15]. The limited data suggests that treatment of OSA with PAP therapy is unlikely to worsen PH, even in patients with pulmonary arterial hypertension. Although larger, methodologically robust studies are needed to more fully characterize the effects of PAP therapy of SDB on pulmonary vascular and right ventricular hemodynamics, particularly in patients with pulmonary arterial hypertension with mild OSA, current data indicate that PAP is generally well tolerated and has not been associated with adverse effects on right ventricular hemodynamics.

Taken together, the available evidence underscores the important intersection between SDB and pulmonary vascular disease. Severe OSA and OHS can both contribute to adverse pulmonary hemodynamics through recurrent nocturnal hypoxemia, hypercapnia, exaggerated intrathoracic pressure swings, and secondary cardiac and inflammatory effects, with OHS generally associated with a greater burden of PH. Although the current literature remains limited by small sample sizes, heterogeneous study designs, and a relative paucity of randomized data, the overall signal is reassuring in that PAP therapy appears to be well tolerated and, particularly in patients with established PH, and may improve pulmonary vascular pressures without clear evidence of harm to right ventricular function. Future prospective studies are needed to better define the magnitude of benefit, identify the patients most likely to respond, and clarify the effects of PAP across the spectrum of OSA, OHS, and coexisting pulmonary vascular disease. For now, the existing data supports careful recognition and treatment of SDB as an important component of comprehensive care in patients with PH.

## Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work Babak Mokhlesi used a generative AI tool (Chat GPT version 5.2) for language and grammatic editing. After using this tool/service, the author reviewed and edited the content as needed and takes full responsibility for the content of the published article.

## Conflicts of interest

B. Mokhlesi reports a role as deputy editor of the Journal of Clinical Sleep Medicine published by the American Academy of Sleep Medicine and payment for legal expert testimony. A. Kohli does not have any conflicts of interest.

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