CHEST™

OSA and Pulmonary Hypertension
Time for a New Look

Khalid Ismail, MD; Kari Roberts, MD; Patrick Manning, MD; Christopher Manley, MD; and Nicholas S. Hill, MD, FCCP

OSA is a common yet underdiagnosed disorder encountered in everyday practice. The disease is a unique physiologic stressor that contributes to the development or progression of many other disorders, particularly cardiovascular conditions. The pulmonary circulation is specifically affected by the intermittent hypoxic apneas associated with OSA. The general consensus has been that OSA is associated with pulmonary hypertension (PH), but only in a minority of OSA patients and generally of a mild degree. Consequently, there has been no sense of urgency to screen for either condition when evaluating the other. In this review, we explore available evidence describing the interaction between OSA and PH and seek to better understand underlying pathophysiology. We describe certain groups of patients who have a particular preponderance of OSA and PH. Failure to recognize the mutual additive effects of these disorders can lead to suboptimal patient outcomes. Among patients with PH and OSA, CPAP, the mainstay treatment for OSA, may ameliorate pulmonary pressure elevations, but has not been studied adequately. Conversely, among patients with OSA, PH significantly limits functional capacity and potentially shortens survival; yet, there is no routine screening for PH in patients with OSA. We think it is time to study the interaction between OSA and PH more carefully to identify high-risk subgroups. These would be screened for the presence of combined disorders, facilitating earlier institution of therapy and improving outcomes.

CHEST 2015; 147(3):847-861

ABBREVIATIONS: AHI = apnea-hypopnea index; BNP = B-type natriuretic peptide; CRP = C-reactive protein; CSA = central sleep apnea; CSR = Cheyne-Stokes respiration; CTEPH = chronic thromboembolic pulmonary hypertension; IPAH = idiopathic pulmonary arterial hypertension; LV = left ventricular; mPAP = mean pulmonary artery pressure; NPV = negative predictive value; OHS = obesity hypoventilation syndrome; PA = pulmonary arterial; PAH = pulmonary arterial hypertension; PCWP = pulmonary capillary wedge pressure; PH = pulmonary hypertension; Ppa = pulmonary artery pressure; PPV = positive predictive value; PSG = polysomnography; RHC = right-sided heart catheterization; RVSP = right ventricular systolic pressure; Sao_2 = oxygen saturation; SDB = sleep-disordered breathing

OSA, defined as intermittent upper-airway obstructions that result in an apnea/hypopnea index (AHI) $\geq$ 5/h, has been linked to multiple comorbidities, including cardiovascular disease, metabolic derangements, and neurocognitive impairment.[1-3] Pulmonary hypertension (PH) frequently coexists with OSA and may sometimes be a direct consequence of the disease.[4] Despite efforts to better define this interaction, it remains elusive. Studies consisting of small and diverse patient populations, as well as variable definitions of sleep apnea and PH preclude firm conclusions. In this review, we discuss the currently available evidence on the prevalence, proposed pathophysiologic

Manuscript received March 13, 2014; revision accepted September 15, 2014.

AFFILIATIONS: From Tufts Medical Center, Boston, MA.

CORRESPONDENCE TO: Khalid Ismail, MD, Tufts Medical Center, 800 Washington St, Box #369, Boston, MA 02111; e-mail: kismail@tuftsmedicalcenter.org

DOI: 10.1378/chest.14-0614

mechanisms, and diagnostic approaches associated with OSA and PH, and suggest areas for future research.

Search Methods

In preparation for this narrative review, we searched the medical literature using Medline and PubMed, using obstructive sleep apnea, sleep-disordered breathing, obesity hypoventilation, pulmonary hypertension and pulmonary arterial hypertension as key words. We selected articles in English published over the past 2 decades that had a specific definition of PH with clearly defined diagnostic methods and a well-described studied patient population.

Magnitude of the Problem

Prevalence of OSA in Adults

The prevalence of OSA syndrome (AHI $\geq$ 5/h with daytime sleepiness) in middle-aged (30-60 years) men and women has been traditionally described as 4% and 2%, respectively.[5] However, these numbers soar if we consider asymptomatic patients with an AHI $\geq$ 5/h: up to 24% in men and 9% in women.[5] Prevalence rates rise in association with male sex, increasing age, and postmenopausal status.[6,7] The problem is further magnified by the estimated 80% of individuals with moderate to severe OSA who remain undiagnosed or untreated despite adequate access to health care.[8,9] With the ongoing obesity epidemic and the known association between obesity and OSA, there is reason to believe that these numbers will continue to rise for the foreseeable future.[10] In fact, a more recent look at the Wisconsin Sleep Cohort by Peppard et al[11] finds the prevalence of asymptomatic AHI $\geq$ 5/h in men and women 30 to 70 years old to be 34% and 17%, respectively.

Prevalence of PH in Patients With OSA

The reported prevalence of PH among patients with OSA has varied between 17% and 70%[12,13] (Table 1). This remarkably broad range can be attributed to the different patient populations studied, the retrospective nature of some studies, the definition of PH as a mean pulmonary artery pressure (mPAP) $>$ 20 mm Hg (as opposed to the current definition of mPAP $\geq$ 25 mm Hg) and the failure to control for the presence of concurrent heart and lung disease.

In one of the larger prospective trials by Chaouat et al,[14] 220 consecutive patients diagnosed with OSA underwent right-sided heart catheterization (RHC). PH was diagnosed in 17%, but the mPAP in the PH group was only mildly elevated at 26 $\pm$ 6 mm Hg. PH strongly correlated with a higher daytime $Paco_2$, lower daytime Pao_2, obstructive dysfunction on spirometry, and lower mean nocturnal oxygen saturation (Sao_2). BMI was significantly higher in the PH group compared with the non-PH group.

In another prospective cohort of 44 patients with OSA that excluded obstructive airway dysfunction but included heavier patients than the Chaouat cohort, Bady et al[15] found PH in 27%. The mPAP in the PH group was 28.5 $\pm$ 6 mm Hg. Once again, PH was strongly linked to a higher mean BMI and a lower daytime Pao_2.

In a more recent retrospective study by Minai et al,[13] 83 subjects with OSA underwent RHC within 6 months of polysomnography (PSG). The occurrence of PH was 70% (mPAP, 40.3 $\pm$ 11 mm Hg). Correlates of PH included female sex, age $<$ 49 years, BMI $\geq$ 26, and RVSP $\geq$ 30 mm Hg on echocardiogram. The strikingly high prevalence of PH in this study may have reflected referral bias (all patients were referred for a RHC because of high clinical suspicion for PH), inclusion of patients with elevated pulmonary capillary wedge pressure (PCWP) $>$ 15 mm Hg (if excluded, prevalence drops from 70% to 22%), and incomplete exclusion of patients with other pulmonary disorders.

The higher prevalence of PH in women with OSA is intriguing and reflects the female preponderance in various other forms of pulmonary arterial hypertension (PAH), including idiopathic and that associated with collagen vascular diseases such as scleroderma. Potential explanations include genetic predisposition, the role of estrogen, and the increased prevalence of autoimmune disease in women.

In summary, available evidence indicates that in patients with OSA, the presence of obesity, daytime hypoxia and hypercapnia, abnormal pulmonary function testing, and nocturnal oxygen desaturation strongly correlate with PH. When present, PH is usually mild but can be severe, as suggested by the Minai et al[13] study. Given the wide variations between studies, large prospective trials are still needed to tease out the effects of specific risk factors and more accurately define the prevalence of PH in patients with isolated OSA.

Prevalence of OSA in Patients With PH

Sleep-disordered breathing (SDB), which comprises not only OSA, but also central sleep apnea (CSA), periodic breathing, and oxygen desaturation related to sleep, is associated with PH (Table 2). Rafanan et al[25] found that although apneas and hypopneas measured during PSG were rare, 10 of the 13 patients with severe idiopathic