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.

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; SaO₂ = oxygen saturation; SDB = sleep-disordered breathing

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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 ≥ 5/h with daytime sleepiness) in middle-aged (30-60 years) men and women has been traditionally described as 4% and 2%, respectively. However, these numbers soar if we consider asymptomatic patients with an AHI ≥ 5/h: up to 24% in men and 9% in women. Prevalence rates rise in association with male sex, increasing age, and postmenopausal status. 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. 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. In fact, a more recent look at the Wisconsin Sleep Cohort by Peppard et al finds the prevalence of asymptomatic AHI ≥ 5/h: up to 24% in middle-aged (30-60 years) men and women. However, these numbers soar if we consider asymptomatic patients with an AHI ≥ 5/h: up to 24% in men and 9% in women.

Prevalence of PH in Patients With OSA
The reported prevalence of PH among patients with OSA has varied between 17% and 70% (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 ≥ 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, 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 ± 6 mm Hg. PH strongly correlated with a higher daytime PaCO₂, lower daytime PaO₂, obstructive dysfunction on spirometry, and lower mean nocturnal oxygen saturation (SaO₂). 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 found PH in 27%. The mPAP in the PH group was 28.5 ± 6 mm Hg. Once again, PH was strongly linked to a higher mean BMI and a lower daytime PaO₂.

In a more recent retrospective study by Minai et al, 83 subjects with OSA underwent RHC within 6 months of polysomnography (PSG). The occurrence of PH was 70% (mPAP, 40.3 ± 11 mm Hg). Correlates of PH included female sex, age < 49 years, BMI ≥ 26, and RVSP ≥ 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 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 found that although apneas and hypopneas measured during PSG were rare, 10 of the 13 patients with severe idiopathic
<table>
<thead>
<tr>
<th>Study/Year (Type)</th>
<th>No.</th>
<th>Diagnosis of OSA</th>
<th>Diagnosis of PH</th>
<th>Prevalence of PH, No./Total (%)</th>
<th>BMI, kg/m² (PH Status)</th>
<th>Evaluation of Pulmonary Function</th>
<th>Evaluation of LV Dysfunction</th>
<th>Statistically Significant Variables Associated With PH (P Value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minai et al 2009 (retrospective)</td>
<td>83</td>
<td>AHI &gt; 5</td>
<td>mPAP &gt; 25 mm Hg</td>
<td>58/83 (70)</td>
<td>35.6 ± 9.3 (PH) 31.2 ± 6.9 (without PH)</td>
<td>Not excluded for obstructive lung disease (PFTs only available in 51/83)</td>
<td>RHC PCWP &gt; 15 in 40 of 58 patients (69%) PCWP &lt; 15 in 18/58 (31%)</td>
<td>Higher BMI (.026); female sex (.01); longer duration of nocturnal desaturation (.018); lower FVC (.042)</td>
</tr>
<tr>
<td>Bady et al 2000 (retrospective)</td>
<td>44</td>
<td>A1 &gt; 20 or AHI &gt; 30</td>
<td>mPAP &gt; 20 mm Hg</td>
<td>12/44 (27)</td>
<td>37.4 ± 6 (PH) 30.3 ± 6.7 (without PH)</td>
<td>Excluded if FEV₁ &lt; 70% and FEV₁/VC &lt; 60%</td>
<td>RHC Excluded for PCWP &gt; 15 mm Hg</td>
<td>Higher BMI (.002); lower daytime PaO₂ (.006); higher daytime Paco₂ (.002); lower TST-Sao₂ &lt; 80% (.002); lower FVC, FEV₁, TLC (.005, .001, .048, respectively)</td>
</tr>
<tr>
<td>Niijima et al 1999 (prospective)</td>
<td>19</td>
<td>AHI &gt; 10</td>
<td>mPAP &gt; 20 mm Hg</td>
<td>10/19 (52.6)</td>
<td>39.9 ± 6.8 (PH) 29.8 ± 4.4 (without PH)</td>
<td>Mean VC%, 76 (PH) Mean VC%, 95 (without PH)</td>
<td>RHC Mean PCWP 9.5 ± 2.7 (PH) Mean PCWP 5.6 ± 2.8 (without PH)</td>
<td>Higher BMI (&lt;.01); lower daytime pH (&lt;.05); higher Pco₂ (&lt;.05); %VC (&lt;.01)</td>
</tr>
<tr>
<td>Sajkov et al 1999 (prospective)</td>
<td>32</td>
<td>AHI &gt; 10</td>
<td>Doppler-estimated mean Ppa &gt; 20 mm Hg</td>
<td>11/32 (34)</td>
<td>30.5 ± 1.3 (PH) 31.7 ± 0.8 (without PH)</td>
<td>Excluded if FEV₁/FVC &lt; 80%; or FEV₁/FVC &lt; 75%</td>
<td>TTE No suspicion of LV dysfunction, and no valvular disease</td>
<td>Increased small airways closure during tidal breathing (&lt;.05); more ventilation/perfusion mismatch (.08); lower sleep efficiency on PSG (&lt;.05)</td>
</tr>
</tbody>
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(Continued)
<table>
<thead>
<tr>
<th>Study/Year (Type)</th>
<th>No.</th>
<th>Diagnosis of OSA</th>
<th>Diagnosis of PH</th>
<th>Prevalence of PH, No./Total (%)</th>
<th>BMI, kg/m² (PH Status)</th>
<th>Evaluation of Pulmonary Function</th>
<th>Evaluation of LV Dysfunction</th>
<th>Statistically Significant Variables Associated With PH (P Value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sanner et al 1997</td>
<td>92</td>
<td>AHI &gt; 10</td>
<td>mPAP &gt; 20 mm Hg</td>
<td>18/92 (20)</td>
<td>32.1 ± 5.2 (PH)</td>
<td>FEV₁/FVC, %, 78.3 ± 14.9 (PH)</td>
<td>RHC, PCWP &gt; 13 mm Hg in 8 of 18 patients (44%)</td>
<td>Higher PCWP (&lt;.0001); higher percentage sleep with Sao₂ &lt; 90% (.003)</td>
</tr>
<tr>
<td>Chaouat et al 1996</td>
<td>220</td>
<td>AHI &gt; 20</td>
<td>mPAP &gt; 20 mm Hg</td>
<td>37/220 (17)</td>
<td>31.2 ± 5.1 (without PH)</td>
<td>FEV₁/FVC, %, 64 ± 13 (PH)</td>
<td>RHC, Resting PCWP, when recorded, was always &lt; 13 mm Hg.</td>
<td>Higher BMI (&lt;.01); higher AHI (&lt;.001); lower Pao₂ (&lt;.001); higher Paco₂ (&lt;.001); lower FEV₁, FVC, FEV₁/FVC (&lt;.001); lower mean nocturnal Sao₂ (&lt;.001)</td>
</tr>
<tr>
<td>Laks et al 1995</td>
<td>100</td>
<td>RDI &gt; 20</td>
<td>mPAP &gt; 20 mm Hg</td>
<td>42/100 (42)</td>
<td>38 (range, 24-54) (PH)</td>
<td>FEV₁/FVC, %, 73 (range, 48-91) (PH)</td>
<td>RHC, PCWP not reported, but patients with isolated LV failure were excluded.</td>
<td>Lower Pao₂ (&lt;.001); higher Paco₂ (&lt;.001); lower FEV₁, FEV₁/FVC (&lt;.001, 03, respectively); lower minimum Sao₂ (&lt;.01)</td>
</tr>
<tr>
<td>Krieger et al 1989</td>
<td>114</td>
<td>AI &gt; 5</td>
<td>mPAP &gt; 20 mm Hg</td>
<td>19/100 (19)</td>
<td>31.7 ± 0.54</td>
<td>Mean FEV₁/FVC, %, 71.10 ± 0.99</td>
<td>RHC, PCWP not reported.</td>
<td>Lower Pao₂ (&lt;.001); higher Paco₂ (&lt;.001); lower daytime Sao₂ (&lt;.001); lower TLC, FEV₁, FEV₁/FVC, FVC, %FVC (&lt;.001); higher AI, AHI (&lt;.001)</td>
</tr>
</tbody>
</table>

AHI = apnea-hypopnea index; AI = apnea index; LV = left ventricular; mPAP = mean pulmonary artery pressure; PCWP = pulmonary capillary wedge pressure; PFT = pulmonary function test; PH = pulmonary hypertension; PSG = polysomnography; RDI = respiratory disturbance index; RHC = right-sided heart catheterization; Sao₂ = arterial oxygen saturation; TTE = transthoracic echocardiogram; VC = vital capacity.
## TABLE 2 | Prevalence of SDB Among Patients With Established PH

<table>
<thead>
<tr>
<th>Study/Year (Type)</th>
<th>No.</th>
<th>Diagnosis of PH</th>
<th>Type of SDB</th>
<th>Prevalence of SDB (%)</th>
<th>BMI, kg/m²</th>
<th>Evaluation of Ventilatory Function</th>
<th>Evaluation of LV Dysfunction</th>
<th>Statistically Significant Variables Associated With SDB (P Value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jilwan et al²/2013 (prospective)</td>
<td>46</td>
<td>mPAP &gt; 25 mm Hg, PCWP &lt; 15 mm Hg Patients with IPAH or CTEPH</td>
<td>AHI &gt; 5/h Nocturnal hypoxemia (time SaO₂ &lt; 90%) &gt; 60 min</td>
<td>OSA: 41 of 46 patients (89) CSA: 4 of 46 patients (8) Nocturnal hypoxemia: 38 of 46 patients (82.6)</td>
<td>24.6 ± 4.2</td>
<td>Excluded if FEV₁, FVC &lt; 60% predicted</td>
<td>PCWP &gt; 15 mm Hg excluded from study</td>
<td>Nocturnal desaturators: lower PaO₂ (.006), lower resting SpO₂ (.019); higher A-a gradient (.039); lower FEV 25%-75% (.003); higher AHI (.05)</td>
</tr>
<tr>
<td>Prisco et al²/2011 (prospective)</td>
<td>28</td>
<td>mPAP &gt; 25 mm Hg, PCWP &lt; 18 mm Hg IPAH, or WHO Groups IV, V</td>
<td>AHI &gt; 5/h Nocturnal hypoxemia (%TST SaO₂ &lt; 90%)</td>
<td>OSA (AHI &gt; 5) 14 of 28 patients (50) CSA: 0 of 28 patients %TST &lt; 90%: SaO₂ 30.6 ± 36</td>
<td>31.3 ± 9.3</td>
<td>FEV₁, % 72.7 ± 20.8</td>
<td>PCWP &gt; 18 mm Hg, evidence of LV dysfunction on TTE, excluded from analysis</td>
<td>OSA: higher mPAP (.005) Nocturnal desaturators: higher mPAP (.038)</td>
</tr>
<tr>
<td>Ulrich et al²/2008 (prospective)</td>
<td>38</td>
<td>mPAP &gt; 25 mm Hg, PCWP &lt; 15 mm Hg</td>
<td>AHI &gt; 10/h Nocturnal hypoxemia (&gt;10% TST-Sao₂ &lt; 90%)</td>
<td>CSR/CSA: 15 of 38 patients (39) OSA: 4 of 38 patients (11) Nocturnal hypoxemia (68)</td>
<td>25 (range, 22-29)</td>
<td>NR</td>
<td>PCWP &gt; 15 excluded from analysis</td>
<td>CSR/CSA: lower quality of life by MLHF, SF-36 questionnaires</td>
</tr>
<tr>
<td>Schulz et al²/2002</td>
<td>20</td>
<td>NR (mPAP 56 ± 2.7 mm Hg)</td>
<td>CSR AHI &gt; 5/h</td>
<td>Cheyne-Stokes respiration 6 of 20 patients (30) OSA: 0 of 20 patients</td>
<td>23.5 ± 1.1</td>
<td>FEV₁, % 88.0 ± 3.3</td>
<td>PCWP (mean 5 ± 0.4 mm Hg)</td>
<td>Periodic breathing: lower resting PaO₂ (.05); lower Dco (.05); higher PAP, PVR (.05); lower CO, CI, RVEF (.01)</td>
</tr>
<tr>
<td>Rafanan et al²/2001 (retrospective)</td>
<td>13</td>
<td>mPAP &gt; 25 mm Hg (rest); mPAP &gt; 30 mm Hg (exercise)</td>
<td>AI &gt; 5 Nocturnal hypoxemia &gt; 10% TST-Spo₂ &lt; 90%</td>
<td>0 of 13 patients with AI &gt; 5 10 of 13 patients (77) nocturnal hypoxemia</td>
<td>30.1 ± 7.3</td>
<td>FEV₁, % 76.5 ± 83.5</td>
<td>NR</td>
<td>Nocturnal desaturators: lower resting PaO₂ (.048); lower SpO₂ (.038); higher P(A-a)O₂ (.002); lower FEV₁ (.002)</td>
</tr>
</tbody>
</table>

CI = cardiac index; CO = cardiac output; CSA = central sleep apnea; CSR = Cheyne-Stokes respiration; IPAH = idiopathic pulmonary arterial hypertension; NR = not reported; PVR = pulmonary vascular resistance; RVEF = right ventricular ejection fraction; SDB = sleep-disordered breathing; TST = total sleep time; WHO = World Health Organization. See Table 1 legend for expansion of other abbreviations.
PAH (IPAH) (mPAP, 60.8 ± 15 mm Hg) had nocturnal oxygen desaturations. In addition, Schulz et al. observed no OSA among 20 patients with IPAH, but six had Cheyne-Stokes respiration (CSR), associated with higher mPAP and reduced right ventricular function. In a more recent study including 23 patients with PAH and 15 with chronic thromboembolic pulmonary hypertension (CTEPH), 45% had CSA/CSR, while OSA was present in 11%.

In contrast, among 46 patients with IPAH or CTEPH, Jilwan et al. found OSA in 89% of patients, while only four patients had CSA. These results are in agreement with those of Prisco et al. on 28 patients with varying etiologies of PH (World Health Organization groups I, IV, and V) among whom obstructive events predominated over central. However, these latter studies included older patients who were predominantly male and had higher BMIs, likely predisposing to a higher prevalence of OSA.

In summary, despite scarce data, it appears that SDB is common in patients with PH. CSA/CSR prevails in younger patients with severe PH and right-sided heart failure, while OSA predominates in older patients with PH, especially if studied populations include more men with higher BMI. Clearly, larger and better defined studies are needed to more accurately describe the prevalence of SDB in different subtypes of patients with PH.

Pathophysiology

Hemodynamic Changes Associated With OSA

In 1971, the Bologna Sleep Laboratory (University of Bologna, Italy) was the first to directly measure systemic and pulmonary arterial (PA) pressures and alveolar ventilation in normal subjects during different stages of sleep. They demonstrated a significant rise in mPAP during sleep compared with wakefulness, but without significant change from one sleep stage to the next. At the same time, alveolar ventilation fell significantly during sleep compared with wakefulness, with diminished ventilatory responses to hypoxic and hypercapnic stimuli.

Unlike normal subjects, patients with OSA experience progressive PA pressure increases throughout sleep stages 1 to 3, with an upswing during rapid eye-movement sleep. Alveolar ventilation follows an opposite pattern, declining in slow-wave sleep and dropping even further during rapid eye-movement sleep. Tracheostomy (the only effective treatment of OSA at the time) was associated with a decrease in PA pressure and return of alveolar ventilation to normal (Fig 1).

Recurrent upper airway obstruction with accompanying apneas presents a distinct physiologic challenge to the cardiovascular system (Fig 2). Pulmonary vasoconstriction occurs in response to alveolar hypoxia, increasing pulmonary vascular resistance and contributing to an increase in precapillary PA pressure. Simultaneously, intrathoracic pressure swings intensify with increasing respiratory efforts against a closed upper airway. Negative intrathoracic pressure during obstructive events can reach −80 cm H2O. The associated increase in venous return leads to increased right ventricular preload and stroke volume, in turn increasing pulmonary blood flow.

Increased venous return also shifts the interventricular septum to the left, which reduces left ventricular (LV) compliance. In addition, negative intrathoracic pressure, by increasing LV transmural pressure, elevates LV afterload. Both factors impede LV function and contribute to a relative increase in pulmonary venous pressure. Pulmonary systolic pressures as high as 80 mm Hg and diastolic pressures as high as 54 mm Hg have been reported toward the end of an apneic event.

Given these pathophysiologic changes, one would expect daytime PH to be universally present in patients with OSA. However, individuals vary considerably in their pulmonary vasoconstrictor responses to hypoxia. In their Doppler echocardiogram study on 32 patients with severe OSA (mean AHI, 36/h), Sajkov et al. found an exaggerated increase in pulmonary artery pressure (Ppa) in response to hypoxia, and a marked rise in Ppa during dobutamine-induced increase in blood flow in patients with PH compared with control subjects. This suggests that a subset of patients with OSA may be more susceptible to vascular remodeling, another area in need of further research.

Vascular Endothelial Dysfunction Associated With OSA

In addition to the discussed hemodynamic changes, accumulating evidence indicates that endothelial dysfunction, oxidative stress, heightened inflammation, as well as a procoagulant state also contribute to OSA-induced PH (Fig 2). Impaired vasodilation to endothelium-dependent vasodilators such as acetylcholine has been observed in systemic vessels of patients with OSA. Ip et al. demonstrated that 4 weeks of CPAP reverses that process. Further, endothelin-1, the potent long-acting vasoconstrictor peptide synthetized by endothelium, is elevated in OSA and decreases with
CPAP therapy. Vascular endothelial growth factor expression is also increased in relation to the degree of nocturnal oxygen desaturation with OSA. Other mediators that have been linked to endothelial dysfunction, including leukocyte adhesion molecules, are also elevated in patients with OSA.

In addition, a heightened inflammatory state exists, as suggested by elevated levels of C-reactive protein (CRP) and IL-6 levels, both of which decrease with CPAP therapy. Increased release of oxygen free radicals similar to that seen in hypoxia/reperfusion injury has also been detected, to the extent that some believe OSA to be an "oxidative stress disorder." Finally, the occurrence of a procoagulant state is well documented. Elevated hypoxia-induced erythropoietin production has been observed by Cahan et al. CPAP treatment lowered erythropoietin levels in these patients. Serum fibrinogen levels are elevated and fibrinolytic activity is reduced secondary to elevated plasminogen activator inhibitor. In addition, patients with OSA have increased platelet activation and aggregation, and both return to normal with CPAP treatment.

Weak but growing evidence has also implicated OSA as a risk factor for DVT and pulmonary embolism, even after correcting for other risk factors like obesity. To our knowledge, OSA has not been linked to CTEPH, but additional research is needed to explore the possibility.

**PH as a Cause for OSA**

An equally interesting but even less researched aspect of the OSA/PH interaction is how PH and, eventually, right-sided heart failure, can contribute to the development of OSA. Fluid retention and rostral redistribution have been suggested to worsen OSA in patients with end-stage renal disease. In a cohort of 40 patients with hypertension, Friedman et al. studied rostral fluid shifts by measuring calf and neck circumference before and after sleep during PSG. AHI strongly correlated with the amount of leg fluid volume displaced. These findings were reproduced by Jafari and Mohsenin in a cohort of patients with OSA. Patients with PH, especially those with right-sided heart failure, are frequently fluid overloaded and one can expect similar redistributive changes during sleep that could exacerbate upper airway edema and OSA. This possible relationship, as well as potential therapeutic effect of fluid removal and treatment of right-sided heart failure on OSA, has not been specifically studied.

**Screening and Diagnosis**

**Screening for PH in Patients With OSA**

Typically, even patients with severe sleep apnea are not routinely screened for PH. In fact, American College of Chest Physicians (CHEST) evidence-based guidelines recommend against routine evaluation for PH in patients with OSA. PH can be suspected clinically, but
signs and symptoms are neither sensitive nor specific. Evidence of increased pulmonary artery diameter on chest radiographs, or right ventricular strain on ECG would support a diagnosis of PH or right-sided heart dysfunction, but are not routinely obtained in patients with OSA.

B-type natriuretic peptide (BNP) level, which correlates with left or right ventricular dysfunction and a cardio- genic etiology of dyspnea, can also be helpful in detecting PH and right-sided heart failure. In one study, plasma BNP levels correlated with mPAP, right atrial pressure, right ventricular end-diastolic pressure, and pulmonary vascular resistance. In another study, elevated BNP levels seemed to reflect an increased likelihood of LV hypertrophy in patients with severe sleep apnea. Therefore, plasma BNP may be elevated in patients with OSA but without PH and its sensitivity and specificity for detection of PH have not been established.

Suspicion of PH or right-sided heart failure in a patient with SDB should lead to a trans-thoracic echocardiogram. However, echocardiography, especially in the obese or those with concomitant lung disease, has its limitations. Fisher et al prospectively tested the accuracy of Doppler echocardiography in estimating PA pressure in 65 consecutive patients with various forms of PH (the majority had PAH) referred for RHC. Only 48% of the echocardiographic estimates were within 10 mm Hg of catheterization values. Moreover, 38% of pressure overestimates and 80% of pressure underestimates exceeded 20 mm Hg. Other studies also questioned the accuracy of echocardiography for estimation of PA pressure in patients with advanced lung disease, especially emphysema.

In summary, because symptoms of PH are not specific, and tools used to detect PH have not been validated in the OSA population, specific recommendations cannot be made on screening patients with OSA for PH.
Nevertheless, the lack of accurate screening tools should not be interpreted as a lack of necessity to screen for PH in patients with OSA, as will be discussed later.

**Screening for SDB in Patients With PH**

Current CHEST evidence-based guidelines endorse assessment of SDB when evaluating patients with PH and, if suspected, PSG is recommended. In practice, this raises a vital question: How is SDB assessed in patients with PH? Even in non-PH populations undergoing sleep evaluation, the answer is not straightforward. Snoring, in a retrospective analysis of 250 consecutive patients referred to a sleep center, had a positive predictive value (PPV) and negative predictive value (NPV) for OSA of only 0.63 and 0.56, respectively. In another study of 380 patients referred for PSG, witnessed apneas with hypersomnia had a PPV and NPV for OSA in the range of 0.40 and 0.60. The Epworth Sleepiness Scale is a notoriously poor discriminative tool for OSA. Even overall clinical impression of experienced clinicians appears to have a sensitivity and specificity of 52% and 70%, respectively.

In the PH population, several studies suggest that even typical symptoms like snoring and excessive daytime sleepiness, are not reliable in the evaluation of SDB. Sleep questionnaires developed to help overcome some of these uncertainties include the Berlin questionnaire, which assesses risk factors for OSA, wake-time sleepiness or fatigue, and the presence of obesity or hypertension. An evaluation of its accuracy in identifying patients with OSA in the primary care setting revealed a sensitivity of 0.86, specificity of 0.77, PPV of 0.89, and a likelihood ratio of 3.79. To our knowledge, sleep questionnaires have not been validated for use in the PH population.

Clinical prediction models combining clinical data with objective measurements like craniofacial measurements, BMI, and oximetry also hold some promise to identify patients at risk for OSA more accurately. One study tested a model using upper airway and body measurements in 300 patients, and showed a PPV of 100% and a NPV of 88.5%. Thus, in summary, sleep questionnaires and prediction models seem to perform better than single clinical predictors in identifying patients with OSA, but a standardized screening method awaits validation in the PH population.

**Specific OSA/PH-Associated Syndromes**

Certain disorders have a strong predilection for both OSA and PH, and the presence of one disease should be a signal to screen for the other.

**Obesity Hypoventilation Syndrome**

Obesity hypoventilation syndrome (OHS) is the combination of obesity (BMI > 30 kg/m²) and hypoventilation (awake Paco₂ > 45 mm Hg), after the exclusion of other disorders associated with hypoventilation. The majority of patients also have associated OSA (up to 90%). The typical patient is middle aged, extremely obese (BMI > 40 kg/m²), and a hyperventilating loud snorer with dyspnea, lower extremity edema, oxygen desaturation, and elevated serum bicarbonate.

Cohort studies show a remarkably high occurrence of PH in OHS. In two different studies, the prevalence of PH was 58% and 88% (mPAP > 20 mm Hg). The prevalence of severe PH (mPAP > 40 mm Hg) was 31%. If OHS is left untreated, cor pulmonale usually develops. The prevalence of OHS is almost certainly underestimated in the general population, as arterial blood gases are not routinely analyzed in obese patients, but in patients with OSA, available epidemiologic data suggest a prevalence of OHS in the range of 10% to 20%, and even higher in patients with extreme obesity (BMI > 40 kg/m²). There is currently no recommendation for intensified screening of patients with OHS for OSA or PH, although the strong concurrence of both would seem to justify it.

**Overlap Syndrome**

Coined by Flenley to describe the association of COPD and OSA, the Overlap Syndrome has an estimated prevalence of 11% to 15% in consecutive patients with OSA. This coexistence was initially thought to be based on a common pathophysiologic linkage, but is now thought to occur by chance, according to epidemiologic evidence from the Sleep Heart Health Study database, since both are relatively common disorders in the adult population.

Characteristically, patients with Overlap Syndrome have more daytime hypoxemia, hypercapnea, and PH than expected with either disease alone. Furthermore, these changes develop in patients with milder airway obstruction and less severe OSA than would be expected. Again, there is currently no recommendation to screen for PH in patients with the Overlap Syndrome.

**The Bariatric Patient**

Morbidly obese patients being evaluated for bariatric surgery present a unique opportunity for screening. Obesity, by far, is the strongest risk factor for OSA. It has also been suggested as a strong predictor of PH in patients...
with OSA.\textsuperscript{13-15} Nocturnal oxygen desaturation related to apneic events can be more prolonged and severe in the morbidly obese,\textsuperscript{73} mainly due to reduction in expiratory reserve volume, especially when lying supine.\textsuperscript{74}

In addition to the large percentage of patients with OHS who appear to be underdiagnosed, there is also a higher prevalence of the cardiomyopathy of obesity, chronic thromboembolic disease, and prior anorexigen use, that may contribute to the increased incidence of PH.\textsuperscript{75} The additional burden of PH on morbid obesity can greatly impair the functional capacity of these patients and increase their risk for perioperative complications. Some bariatric surgery programs routinely screen every patient for OSA, but few routinely screen for PH. Presently, evidence does not support more aggressive screening, but the question has not been adequately investigated.

Management Dilemmas

Clinical Implications of the Diagnosis of PH in Patients With OSA

Should we be more determined to diagnose PH in patients with OSA? Would it impact relevant clinical outcomes? In the previously described study by Minai et al,\textsuperscript{13} patients with OSA and PH showed trends toward a shorter 6-min walk distance and greater Borg dyspnea and fatigue scores. In addition, and for the first time, they showed increased mortality in patients with OSA and PH at 1, 4, and 8 years (Fig 3).\textsuperscript{13}

The knowledge that PH is present would enable us to intensify the focus on controlling reversible factors, such as optimal therapy of OSA, systemic hypertension, fluid overload, and diabetes mellitus. It would also address the potential causal role PH might play in the development of upper airway edema and obstruction. However, current data do not answer the question of whether specific PH therapy improves outcomes in PH associated with OSA.

Clinical Implication of the Diagnosis of OSA in Patients With PH

Should we be more conscientious about excluding OSA as a cause or comorbidity in a patient with PH? Does it impact quality of life? Can undiagnosed OSA hinder the response to advanced PH therapy? The evidence to address these questions has been scant.

Ulrich et al,\textsuperscript{23} in their cohort of 38 patients with PH, found that the 50% of patients with SDB reported a worse quality of life in physical domains assessed by different questionnaires. Another unanswered question is whether CSR/CSA in patients with PH translates into a poorer prognosis, as it does in left-sided heart failure.\textsuperscript{76}

CPAP is a well-established treatment of patients with OSA and can reverse the pathophysiology that ultimately may lead to the development of PH. By eliminating recurrent episodes of upper airway obstruction, positive pressure therapy dampens the swings in intrathoracic pressure and their effects on right ventricular function. Hypoxemia, for the most part, is corrected.
<table>
<thead>
<tr>
<th>Study/Year (Type)</th>
<th>No.</th>
<th>Patient Characteristics</th>
<th>Dependent Variable</th>
<th>Severity or Prevalence of Dependent Variable</th>
<th>CPAP Compliance</th>
<th>Duration of Treatment</th>
<th>Effects of CPAP Treatment on Dependent Variable (P Value)</th>
</tr>
</thead>
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<tr>
<td>Colish et al17/2012 (prospective)</td>
<td>47</td>
<td>AHI &gt;15 (mean AHI, 63 ± 30/h)</td>
<td>RVSP estimated by TTE</td>
<td>Mean RVSP 54 ± 6 mm Hg</td>
<td>&gt;4.5 h/night (100%)</td>
<td>12 mo</td>
<td>RVSP decreased from 54 ± 6 mm Hg to 39 ± 5 mm Hg (.05)</td>
</tr>
<tr>
<td>Arias et al18/2006 (RCT, crossover)</td>
<td>33</td>
<td>AHI &gt;10/h, with control group AHI &lt;10/h</td>
<td>PASP &gt; 30 mm Hg by TTE</td>
<td>10 of 23 patients (43%)</td>
<td>6.2 ± 1.1 h/night (CPAP group)</td>
<td>3 mo, crossover</td>
<td>PASP decreased from 28.9 ± 8.6 mm Hg to 24.0 ± 5.8 mm Hg (.0001)</td>
</tr>
<tr>
<td>Sajkov et al19/2002 (prospective)</td>
<td>20</td>
<td>AHI &gt;10/h</td>
<td>Doppler-estimated mPAP &gt; 20 mm Hg by TTE</td>
<td>5 of 20 patients (25%)</td>
<td>5.1 ± 0.3 h/night</td>
<td>4 mo</td>
<td>mPAP decreased from 16.8 ± 1.2 mm Hg to 13.9 ± 0.6 mm Hg (.05)</td>
</tr>
<tr>
<td>Alchanatis et al20/2001 (prospective)</td>
<td>41</td>
<td>Patients: AHI &gt; 15 (n = 29) Control subjects: AHI &lt; 15/h (n = 12)</td>
<td>Doppler-estimated mPAP &gt; 20 mm Hg by TTE, confirmed by RHC</td>
<td>OSA: 6 of 29 patients (21%) No OSA: 0 of 12 patients</td>
<td>5.4 (range: 4.2-7.5) h/night</td>
<td>6 mo</td>
<td>mPAP decreased from 17.2 ± 5.4 mm Hg to 13.2 ± 3.8 mm Hg after CPAP (.001)</td>
</tr>
<tr>
<td>Phillips et al21/1999 (prospective)</td>
<td>34</td>
<td>Patients: mean AHI 74 ± 22 per h (n = 22) Control subjects: AHI &lt; 5/h (n = 12)</td>
<td>Endothelin-1</td>
<td>OSA: 13.7 ± 2.7 pg/mL Control subjects: 7.3 ± 0.5 pg/mL</td>
<td>5.4 ± 0.4 h</td>
<td>Single night</td>
<td>Endothelin-1 decreased from 13.7 ± 2.7 pg/mL to 8.3 ± 0.6 pg/mL (.05)</td>
</tr>
<tr>
<td>Ip et al22/2000 (prospective)</td>
<td>70</td>
<td>Patients: mean AHI 48.0 ± 18.1 per h (n = 30) Control subjects: AHI &lt; 5/h (n = 40)</td>
<td>Nitric oxide level measured as serum nitrite and nitrate</td>
<td>OSA: 38.9 ± 22.9 μM Control subjects: 63.1 ± 47.5 μM</td>
<td>8.6 ± 1.1 h</td>
<td>Single night</td>
<td>Serum nitrate/nitrite increased from 30.5 ± 14.4 μM to 81.0 ± 82.1 μM (.01)</td>
</tr>
<tr>
<td>Yokoe et al23/2003 (prospective)</td>
<td>44</td>
<td>Patients: AHI &gt; 5/h (n = 30) Control subjects: AHI &lt; 5/h (n = 14)</td>
<td>CRP IL-6</td>
<td>CRP levels in OSA: 0.21 ± 0.02 mg/dL vs control subjects 0.07 ± 0.01 mg/dL, P &lt; .0001 IL-6 levels in OSA: 0.89 ± 0.11 pg/mL vs control subjects: 0.44 ± 0.07 pg/mL, P = .05</td>
<td>NR</td>
<td>1 mo</td>
<td>CRP decreased from 0.29 ± 0.02 to 0.11 ± 0.03 (.0001) IL-6 decreased from 1.20 ± 0.15 to 0.45 ± 0.08 (.001)</td>
</tr>
</tbody>
</table>

CRP = C-reactive protein; PASP = systolic pulmonary artery pressure; RVSP = right ventricular systolic pressure. See Table 1 legend for expansion of other abbreviations.
at the optimum CPAP level. In addition, positive pressure, as has been well documented, reduces LV afterload and improves LV function.

Several studies have reported improvements in pulmonary hemodynamics after initiation of CPAP therapy in patients with OSA (Table 3). Sajkov et al \(^79\) used Doppler echocardiography before and after CPAP treatment in 20 patients with OSA, after excluding patients with cardiac disease, systemic hypertension, and abnormal lung functions. After 4 months of CPAP, estimated mPAPs decreased from 16.8 ± 1.2 mm Hg to 13.9 ± 0.6 mm Hg (\(P < .05\)), with the greatest decline seen in the five patients with PH at baseline. Interestingly, the pulmonary vascular response to hypoxia also decreased after CPAP, possibly related to improved pulmonary endothelial function.

In another trial by Alchanatis et al \(^80\) consisting of 29 patients with OSA and PH but no other cardiac or lung dysfunction, and 12 patients with OSA but without PH, Doppler-estimated mPAP decreased in both the PH and the non-PH groups after 6 months of CPAP therapy.

Last, Arias et al \(^78\) randomized 23 otherwise healthy patients with OSA and 10 healthy control subjects to receive either sham or effective CPAP therapy for 6 months with crossover at the end of 3 months. Ten of the 23 patients with OSA and none of the control subjects had PH at baseline, as determined by echocardiography (PA systolic pressure > 30 mm Hg). CPAP significantly reduced PA systolic pressure in the OSA group, with the greatest reduction occurring in patients with PH or LV diastolic dysfunction at baseline (Fig 4)\(^78\).

A separate but equally important benefit of CPAP therapy is its effect on pathways of vascular endothelial injury and platelet dysfunction. As mentioned, endothelin-1 is elevated in OSA and decreases with CPAP therapy. \(^36\) Patients with OSA have lower levels of circulating metabolites of nitric oxide compared with healthy subjects; these levels readily return to normal with CPAP. \(^81\) Elevated markers of inflammation are observed in OSA, namely CRP and IL-6, and both decrease with CPAP therapy. \(^40\) Finally, increased platelet activation and aggregation normalize with CPAP treatment. \(^46\)

The universal concern with CPAP nonadherence, which may discourage a more aggressive screening or treatment approach to OSA, seems to be unfounded in the PH population, at least based on the interventional trials discussed here. Adherence ranged from 77% (5.1 ± 0.3 h/night) in the Sajkov trial, \(^79\) to 87% (mean, 5.4 h/night) in the Alchanatis trial, \(^80\) and 91% (mean, 6 ± 1.4 h/night) in the Arias trial. \(^78\) Perhaps knowledge of underlying PH promotes enhanced adherence, or possibly the clinical response is more consistently positive in this patient population, encouraging routine use of CPAP.

![Figure 4 – Individual values for the PASP after both sham and effective CPAP treatment in patients with OSA. Black bar represents mean PASP, changing from baseline 28.9 ± 6.6 mm Hg to 24.0 ± 5.8 mm Hg after 12 wk of CPAP (\(P = .0001\)). PASP = pulmonary artery systolic pressure. (Reprinted with permission from Arias et al.\(^78\))](http://journal.publications.chestnet.org/)
In summary, despite the paucity of clinical trials, available evidence supports an ameliorative effect of CPAP therapy on PA pressure. It appears that patients who stand to gain the most are the ones with more significant PH with already compromised vascular endothelial function. These findings support a more aggressive approach to the detection of OSA in patients with PH, and institution of effective CPAP therapy as early as possible.

Conclusions
As emphasized in this review, it is difficult to draw firm conclusions about the interplay between OSA and PH as far as prevalence, causation, and response to therapy, especially specific PAH regimens. Nevertheless, this discussion highlights the need for further research to more accurately characterize the interaction between these two entities. In patients with OSA, we need to better define and predict who is at risk for clinically significant PH, create better screening tools, understand the impact PH has on quality of life and other outcomes, and develop more effective therapeutic approaches.

Similarly, perhaps before a diagnosis of idiopathic PH is made, we need to develop a standard evaluation for OSA, recognize the consequences of untreated disease, and establish the additional benefits CPAP might offer to the management of this patient population.

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References

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