Obstructive Sleep Apnea, Obesity Hypoventilation Syndrome, and Pulmonary Hypertension

A State-of-the-Art Review

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KEYWORDS

• Pulmonary hypertension • Obstructive sleep apnea • Obesity hypoventilation syndrome
• Positive airway pressure therapy • CPAP • Noninvasive ventilation • Bilevel PAP
• Pulmonary arterial hypertension • Right heart catheterization • Echocardiogram
• Pulmonary artery systolic pressure • Right ventricular systolic pressure • Hypoxemia • Hypercapnia
• Sleep disordered breathing

KEY POINTS

- Sleep-disordered breathing (SDB) is a common disease that can lead to pulmonary hypertension (PH).
- There are several mechanisms by which SDB can lead to or worsen PH, including intrathoracic pressure swings, sustained and intermittent hypoxemia, hypercapnia, and obesity.
- Treatment of SDB can improve hypoxemia and pulmonary vascular hemodynamics as well as symptoms of patients with PH.
- Further research is needed to establish better screening approaches as well as developing a multidisciplinary approach to PH that includes providers with expertise in not only PH but also in cardiology, sleep medicine, and weight management/bariatric surgery.

INTRODUCTION

Pulmonary hypertension (PH) is a heterogeneous disorder with varying outcomes across different PH groups. The prevalence of sleep-disordered breathing (SDB) and obstructive sleep apnea (OSA) varies among PH groups, and its impact on survival differs, whether by intrinsic injury or by comorbidity metabolic profile. There is a complex pathophysiological interplay between SDB and PH. In this review, we explore the impact of SDB and its downstream consequences (ie, intrathoracic pressure changes, sustained and intermittent hypoxemia, hypercapnia, and obesity) on the pulmonary artery (PA) vasculature in the context of PH. We also discuss challenges in diagnosing PH in patients with SDB, particularly in the severely obese population, underscore the need for refined diagnostic criteria and screening approaches. Lastly, we will review treatment strategies in patients with PH and comorbid SDB, including obesity hypoventilation syndrome (OHS).

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EPIDEMIOLOGY

SDB includes multiple distinct disorders. The most prevalent form of SDB is OSA. Other important forms of SDB include central sleep apnea (CSA) with and without Cheyne–Stokes breathing pattern, sleep-related hypoventilation, sleep-related hypoxemia, and OHS. The prevalence of OSA varies widely based on how hypopneas are classified and what threshold of the apnea–hypopnea index (AHI) is considered pathologic. Population-based studies suggest that the prevalence of OSA is increasing in the United States.[1,2] In 2015, a Swiss population-based study reported a prevalence of moderate-to-severe OSA (AHI $\geq$15/h) of 23.4% in women and 49.7% in men.[3] This high prevalence of moderate-to-severe OSA could be in part attributable to the increased sensitivity of current polysomnographic technology and hypopnea scoring criteria when compared to prior population-based studies such as the Wisconsin Sleep Cohort. The global burden of OSA has been estimated at 936 million men and women aged 30 to 69 years having any OSA (AHI >5/h) and 425 million people estimated to have moderate-to-severe OSA (AHI $\geq$15/h).[4]

Two important risk factors for SDB include aging and obesity. As the global prevalence of obesity continues to increase in an aging population, the prevalence of SDB is bound to increase.[1,5–7] SDB, particularly severe OSA, is independently associated with increased likelihood of developing systemic hypertension,[8] heart failure,[9] coronary artery disease,[10] stroke,[11–13] arrhythmias,[14] and overall mortality.[10,15–17]

Although the precise prevalence of PH is unknown, it has been estimated that 1% of the global population or 80 million people have PH.[18] Cardiac disorders (group 2 PH) and pulmonary disorders/hypoxia (group 3 PH) are the leading causes of PH with a significantly higher prevalence in persons aged above 65 years.[18] Individuals with group 2 and group 3 PH are more likely to have comorbid OSA and/or obesity given that they are more likely to be older and male. In contrast, the prevalence of OSA in patients with pulmonary arterial hypertension (PAH) is lower as these patients are younger, less obese, and predominantly female.[19] Despite the lower risk, on average OSA was present in 23.5% of patients with PAH (**Table 1**). As multimodal therapeutic approaches improve patient survival in PAH,[20] the prevalence of OSA is bound to increase due to aging and increased prevalence of obesity.[21]

Prevalence of PH in OSA and OHS

A few studies have investigated the prevalence of PH in patients with OSA. Smaller studies that were limited by selection bias reported a prevalence ranging from 19% to 42%.[22–24] However, larger studies have reported higher prevalence. One of the largest studies had a cohort of 220 patients with diagnosed severe OSA who underwent right heart catheterization (RHC) regardless of underlying clinical suspicion of comorbid PH.[25] Seventeen percent of these patients had a mean pulmonary artery pressure (mPAP) greater than 20 mm Hg and therefore met the definition of PH. In this cohort, patients with PH had significantly higher body mass index (BMI; 34 vs 31 kg/m^2), higher prevalence of obstructive lung disease and lower daytime Pa_{O_2} (64.4 vs 74.7 mm Hg). They also had a higher mean AHI (100 vs 73/h) and higher percentage of sleep time with oxygen saturation less than 90 (T90; 38.4 vs 11.9 min/h). In univariate and multivariate analyses, higher mPAP was associated with lower mean nocturnal oxygen saturation, higher BMI, and higher AHI.

In a smaller study of 83 patients with OSA who underwent RHC, 58 (70%) had PH defined by mPAP greater than 25 mm Hg; 18 out of 58 (31%) had precapillary PH.[26] In contrast to the earlier, larger study,[25] there was no difference in AHI between patients with and without PH (29.1 vs 34.6, respectively). However, patients with PH and OSA had a significantly higher T90 (20.5% vs 7.4% of total sleep time, respectively).[26]

Studies have also shown a high prevalence of exercise-induced PH in patients with OSA.[27–29] In one study, patients diagnosed with OSA (AHI >5/h) underwent RHC at rest and during exercise. PH at rest was present in 13 out of 65 (20%) patients. Exercise-induced PH was present in an additional 31 patients.[28]

The prevalence of PH in patients with OHS has been described in a large, randomized controlled trial as well as in smaller observational studies, and it ranges between 50% and 69%.[30–33] In the Pickwick study, which enrolled 246 patients with a diagnosis of OHS, over 50% of patients had echocardiographic evidence of PH (right ventricular systolic pressure or RVSP $\geq$40 mm Hg) at the time of study enrollment. Patients with comorbid OHS and PH had significantly higher BMI (43.6 vs 39.1 kg/m^2) at baseline. In multivariate analysis, higher BMI and lower daytime Pa_{O_2} were predictors for PH. AHI and Pa_{CO_2} were not predictors for PH.[34]

PATHOPHYSIOLOGY

The pathophysiology of SDB and PH is complex. For the purposes of this review, we will focus on 4 mechanistic pathways by which the downstream consequences of SDB can impact PA hemodynamics: (1) intrathoracic pressure swings during

Table 1
Prevalence of obstructive sleep apnea in precapillary/group 1 pulmonary hypertension diagnosed by right heart catheterization

	N	Age (years)	% Female	BMI or Obesity Prevalence	OSA Dx Criteria	OSA Prevalence (%)
REVEAL 2013[111] US Cohort	2959	52.7	79	32%	Medical record	599/2959 (20)
Dumitrascu et al,[112] 2013 German Cohort	28	51.1 ± 17.2	75	25.9 ± 5.6	RP AHI >10	2/28 (7)
PVDOMICS 2022[19] US Cohort	185	48.4	70	27.4[a] [23.7–32.9]	RP AHI ≥5	92/185 (49.7)
Huang et al,[84] 2023 Chinese Cohort	394	44[a] [33.0–62.2]	55	23.6 ± 8.5	RP AHI3% ≥5	114/394 (29)
Murta et al,[113] 2022 Brazilian Cohort	36	38.2[a] [38.2–57.0]	69.4	25.5[a] [20.7–28.9]	RP AHI4% ≥5	26/36 (75)
Nagaoka, et al,[114] 2018 Japanese Cohort	151	44 ± 16	75.5	21.7 ± 4.5	RP AHI3% ≥5	29/151(19.2)
Minic,[115] 2014 Canadian Cohort	52	53 ± 15	57.7	29.6 ± 9.2	AHI ≥5	29/52 (55.7)
Simonson et al,[116] 2022 US Cohort	49	56[a] [42–65]	78	30 (26–33)	AHI ≥5	13/37 (35)
OSA prevalence for all cohorts combined						904/3842 (23.5)

Abbreviations: AHI, apnea hypopnea index; OSA, obstructive sleep apnea; RP, respiratory polygraphy.
[a] Median [25–75 percentile].

obstructive apneas and hypopneas, (2) sustained and intermittent hypoxemia, (3) hypercapnia and acidosis, and (4) obesity. Fig. 1 illustrates this complex relationship.

PH is defined by an mPAP of greater than 20 mm Hg on assessment by RHC. Precapillary PH is further defined as mPAP greater than 20 mm Hg, pulmonary artery wedge pressure (PAWP) 15 mm Hg or lesser, and pulmonary vascular resistance (PVR) greater than 2 Wood units. Combined precapillary and postcapillary PH includes patients with a PAWP greater than 15 mm Hg and PVR greater than 2 Wood units.[18]

Intrathoracic Pressure Swings

Obstructive events cause large swings in intrathoracic pressure. During obstructive apneas and hypopneas, thoracic pressure becomes more negative, which can cause an increase in right ventricular (RV) filling pressures, leftward septal deviation, reduced left ventricular function, and increased PAWP. Measuring changes in mPAP in human subjects during sleep when obstructive apneic events occur is challenging.[35] For an accurate assessment of changes in mPAP, concomitant esophageal manometry becomes critically

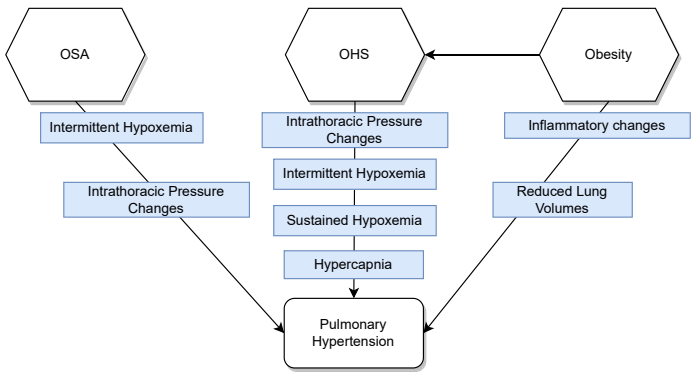

Fig. 1. Proposed pathophysiological mechanisms by which SDB can lead to PH. OHS, obesity hypoventilation syndrome; OSA, obstructive sleep apnea.

important since swings in intrapleural pressures will need to be quantified to accurately measure transmural PA pressures.[36]

Although the long-term effect of frequent and profound intrathoracic pressure swings on the pulmonary vasculature has not been fully elucidated, canine and primate models have attempted to dissect the impact of intrathoracic pressure swings versus intermittent hypoxemia on pulmonary hemodynamics. These studies are limited by the fact that they last only a few hours. Notwithstanding this important limitation, the data suggest that intermittent hypoxemia, not swings in intrathoracic pressure, lead to an acute increase in mPAP. Correction of hypoxemia with supplemental oxygen led to normalization of mPAP despite recurrent obstructive apneas with large swings in intrathoracic pressures.[37] Moreover, repetitive exposure to hypoxic gas lasting 45 to 60 seconds (4%–6% Fio_2 with 5% CO_2) without any upper airway obstruction led to similar increases in PA pressure.[37] In a primate model, central apneas that led to no changes in intrathoracic pressure also led to an increase in PA pressures due to ensuing hypoxemia.[38] The data in humans are even more limited. In one study of spontaneously breathing subjects with OSA undergoing simultaneous esophageal manometry and measurement of pulmonary hemodynamics using RHC, the degree of hypoxemia from recurrent obstructive apneas and hypopneas had a stronger relationship with the rise in transmural pulmonary artery systolic pressure (PASP) than the swings in intrathoracic pressure.[36] Collectively, these animal models and the limited human studies suggest that hypoxemia, and not intrathoracic pressure swings, is the larger driving factor in SDB leading to an acute increase in PA pressure. However, it remains unclear whether years of untreated OSA with repetitive swings in intrathoracic pressure plays an active role in the development of PH.

Hypoxemia

The impact of hypoxemia on PA pressures and RV dysfunction has been extensively studied. Animal models have explored both intermittent and sustained hypoxia to mimic the patterns of hypoxemia in human disease and its subsequent effects on PA hemodynamics. Chronic sustained hypoxia has consistently led to increased pulmonary vasoconstriction causing acute and chronic PH in various animal models. In fact, chronic sustained hypoxia has served as a reliable way to create an animal model to study PH.[39]

One of the primary proposed mechanisms for vascular remodeling is due to hypoxia-induced production of oxygen radicals such as superoxide and increased nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, leading to smooth muscle proliferation and endothelial dysfunction by reduced nitric oxide bioavailability. More so, these changes were shown in mice models that were subjected to chronic intermittent hypoxia (CIH), which was defined as fractional oxygen concentration (Fio_2) cycling between 21% and 10%, 45 times per hour in a closed chamber for 8 hours per day, 5 days per week for 8 weeks.[40] This closely resembles SDB with cycling hypoxemia, and yet, it does not account for intermittent rise in CO_2 levels during apneas or the hemodynamic effects related to physiologic pressure swings due to breathing against increased upper airway resistance during obstructive apneas and hypopneas. When comparing normoxia to CIH settings, this led to modest increases in RVSP from 26.3 to 32.4 mm Hg. Interestingly, knockout mice lacking gp91phox, a NADPH oxidase subunit, showed attenuated RV hypertrophy changes under CIH compared to the wild-type mice.[40]

Hypoxic-driven NADPH oxidase-dependent regulated changes in pulmonary vasculature have also been shown in murine models under sustained hypoxic conditions (Fio_2% 10 for 3 weeks).[41] In another murine model of intermittent hypoxia, mice were exposed to 3 experimental conditions: normoxia, continuous hypoxia, and intermittent hypoxia. In the intermittent hypoxia condition, mice were exposed to air with 10% oxygen for 2 minute intervals for 9 hours a day for 28 days. RVSP and RV mass was highest in mice exposed to continuous hypoxia (44.2 mm Hg and 0.34 g, respectively) compared to normoxia (29.5 mm Hg and 0.22 g, respectively). Compared to normoxia, mice exposed to intermittent hypoxia had significantly higher RVSP (36 mm Hg) and RV mass (0.27 g).[42] Similar findings were replicated in a rat model, although this model included hypercapnia to better simulate blood gas changes that occur in OSA. Rats were exposed to 2 conditions: a control group and CIH and hypercapnia group. In the CIH and hypercapnia group, rats were exposed to air with an Fio_2 of 6% to 8% and an increased $FiCO_2$ of 10% to 14% for 30 second intervals, 8 hours per day, 5 days per week for 5 weeks. Rats exposed to CIH and hypercapnia had a significantly higher mPAP than controls (31.3 ± 7.2 mm Hg vs 20.7 ± 6.8 mm Hg). This study was limited in that it did not include a sustained hypoxia model to compare the effects of intermittent versus continuous exposure or intermittent hypoxia without hypercapnia to dissect the independent contribution of hypercapnia to increase in PA hemodynamics.[43]

Murine models have also been developed to study the effect of intermittent plus sustained hypoxia, or the so-called overlap hypoxia. In a series of experiments, mice were exposed to 4 conditions: sustained hypoxia (constant Fio_2 of 10%), intermittent hypoxia (1 minute bursts of 6% Fio_2 alternating with Fio_2 of 21% for 12 hours), overlap hypoxia, and room air. Overlap hypoxia was unique in this study and was a combination of sustained and intermittent hypoxia (Fio_2 fluctuating between 13% and 6% once per minute, for 12 hours and Fio_2 of 13% for 12 hours). The investigators found that RVSP did not change in mice exposed to intermittent hypoxia. However, a significant increase in the RVSP was noted with sustained hypoxia and overlap hypoxia when compared to mice exposed to room air. There was a 52% increase in the RVSP in the sustained hypoxia group and a 20% increase in the overlap hypoxia group.[44]

The overlap hypoxia model can be used for human conditions in which both sustained and intermittent hypoxemia coexist: that is, chronic obstructive pulmonary disease with comorbid OSA, PH with comorbid SDB, and OHS with comorbid OSA. Sustained hypoxemia during sleep can occur due to hypoventilation or PH. The addition of intermittent hypoxemia due to OSA leads to an overlap phenomenon. Patients with OSA and comorbid PH have a heightened pulmonary vasoconstrictor response to hypoxia when compared to patients without comorbid PH.[45] Therefore, the presence of SDB may lead to worsening right-sided pressures in existing PH or could lead to PH over time if untreated.

The relationship between hypoxia, OSA and PH has also been explored in canine models as well as in primates and human subjects. By its complex nature, these physiologic studies are limited by small sample sizes and duration of only a few hours. In the primate and canine models, animals were endotracheally intubated under anesthesia. Under these conditions, obstructive and central apneas were induced during RHC. These studies have consistently shown that hypoxemia induced by both central and obstructive apneas increase transmural PA pressures without any change in PAWP, and the degree of PH was directly related to the extent of hypoxemia.[37,38,46] The mPAP increased by approximately 200% when dogs were exposed to recurrent apneas lasting 45 to 60 seconds leading to intermittent drops in arterial oxygen saturation (SaO_2) from above 95% to 50%.[37] Similar increases in PASP were observed in baboons exposed to obstructive and central apneas lasting 30 to 60 seconds leading to reductions in SaO_2 from above 90% to approximately 60%.[38] When supplemental oxygen was provided to blunt the hypoxemia during recurrent obstructive apneas in the canine model, PA hemodynamics remained normal, providing additional evidence that intermittent hypoxemia is the main driver of worsening PA hemodynamics.[37]

Although animal models have been criticized for long apneas leading to profound hypoxemia, in clinical practice, patients with very severe OSA and/or with OHS can experience similar durations of apneas leading to similar levels of intermittent hypoxemia. In one study of 4 patients with severe OSA undergoing simultaneous esophageal manometry and measurement of pulmonary hemodynamics using RHC, obstructive apneas that lasted on average 40 seconds and led to a greater degree of hypoxemia (from an average oxygen saturation by pulse oximetry (SpO_2) of 96% to 64%) led to a significant rise in transmural PASP, from an average baseline of 26 mm Hg to nearly 50 mm Hg.[47] This finding suggests that similar to animal models, patients with severe OSA (or OHS) can also experience obstructive apneas that are similar in duration leading to significant hypoxemia.

Obesity

The basic mechanisms by which obesity can lead to PH is an area of active investigation and remains to be fully elucidated. There are several noteworthy pathophysiological mechanisms by which obesity could worsen pulmonary hemodynamics, independent of SDB.

Excess adiposity increases the risk of cardiovascular disease independent of other cardiovascular risk factors such as type 2 diabetes, dyslipidemia, and SDB. Obesity leads to increased blood volume and hyperdynamic circulation, thereby exerting excess load on the cardiovascular system. Obesity can increase preload as well as left ventricular afterload. This increase in left ventricular afterload can eventually lead to concentric left ventricular hypertrophy and left ventricular diastolic dysfunction and over time to postcapillary PH and RV dysfunction.[48,49] In a study of 3790 echocardiographically normal individuals studied over a decade, there was a significant linear association between higher BMI and higher PASP. In subjects with BMI less than 25 kg/m^2, the mean PASP was 27 to 28 mm Hg. In contrast, in subjects with BMI greater than 35 kg/m^2, the mean PASP was 30 to 31 mm Hg.[50]

Another proposed mechanism by which obesity can worsen pulmonary hemodynamics is the accumulation of fat in the perivascular tissue. Although the complex pathophysiology of perivascular fat-induced microvascular dysfunction is not fully understood, a few mechanisms have been proposed and studied. Perivascular fat deposition can

mechanically decrease the size of the vasculature.[51] Indirectly, this perivascular fat can induce an inflammatory cascade leading to endothelial dysfunction. Studies have reported that an increase in tumor necrosis factor-α by perivascular adipose tissue in small arteries leads to an increase in vascular endothelin-1 and endothelin-1 A receptor expression. Adipocytes also secrete inflammatory molecules that impair healthy endothelial function with diminished generation of nitric oxide, a known vasodilator with anti-inflammatory properties.[52] The interaction of hypoxia with adipose tissue further complicates the pathophysiological mechanisms. In-vitro cultures of human adipocytes exposed to hypoxic conditions (Fio_2 1%, 2.5%, and 5%) induces an upregulation of proinflammatory cytokines including IL-1.[53] In rat models, IL-1 has been shown to be a mediator of PH.[54] Furthermore, aggressive treatment of obesity with bariatric surgery has been shown to reduce perivascular adipose tissue after weight loss to the level similar to nonobese controls.[55]

Another mechanism by which obesity can worsen pulmonary hemodynamics is related to reduction in lung volumes due to body habitus with a U-shaped relationship between lung volumes and PVR, with PVR being at its lowest at functional residual capacity. However, with increasing body mass, the expiratory reserve volume decreases and resting lung volume moves toward residual volume. This leads to an increase in PVR since lower lung volumes progressively decrease the caliber of the pulmonary arteries. Given that vascular resistance is inversely proportional to the radius of a vessel to the power of 4, slight changes in the radius of extra-alveolar vessels can lead to an exponential increase in PVR.[56,57]

Histopathological studies have reported that severe obesity and untreated comorbid OHS can lead to PA muscularization, presumably due to chronic hypoxemia, and biventricular cardiac dysfunction that can ultimately lead to a combination of group 2 and group 3 PH.[58] Whether obesity leads to histopathological changes observed in group 1 PA hypertension was assessed in an autopsy study of 76 obese subjects (46 with class III obesity or BMI $\geq$40 kg/m^2) compared to 46 age-matched nonobese controls. Pulmonary hypertensive disease was present in 72% of obese subjects compared to 6% of the nonobese controls. Strikingly, pulmonary capillary hemangiomatosis (defined as diffuse or localized proliferation of alveolar capillaries on both sides of the alveolar walls, with formation of glomeruloid tufts or nodules), a histologic feature that is typically seen in patients with group 1 PAH was present in 2% of nonobese, 39% of those with BMI between 30 and 40 kg/m^2, and 61% of severely obese subjects with a BMI of 40 kg/m^2 or greater.[59] It remains unclear whether the high prevalence of pulmonary capillary hemangiomatosis observed in the severely obese was due to chronic hypoxemia or some other angiogenic stimulus. Importantly, none of these subjects had a premortem history of pulmonary vascular disease suggesting that pulmonary vascular histologic changes may precede clinical recognition and diagnosis of PH.

Evidence shows that obesity plays an intrinsic role in the development of PH. This role is not exclusively related to mechanical load of excess body fat causing restrictive ventilatory limitations with subsequent hypoventilation and hypoxemia. In a study of obesity-prone rats that were subjected to a high-fat diet, there was evidence of oxidative stress in the PA wall, leading to subsequent PA wall remodeling and thickening when compared to low-fat-fed rats.[60] In a different rat model, where PH was induced with single subcutaneous injection of monocrotaline, calorie restriction resulted in a lower mPAP and reduced vascular remodeling and RV hypertrophy.[61]

Further evidence linking obesity to PH comes from the post hoc, cross-sectional analysis of the Pickwick trial that included 246 patients with OHS with a prevalence of PH of 50%. In this cohort, the severity of obesity, measured by the BMI, and daytime hypoxemia were independently associated with PH.[34] Collectively, the murine model studies and the analysis of the Pickwick study suggest that obesity per se is implicated in the pathogenesis of PH. These findings provide incremental evidence that obesity can be implicated in the causal pathway of PH independent of hypoxemia and SDB.

Hypercapnia

Much like obesity, the role of hypercapnia in PH has not been fully elucidated. Part of the challenge in assessing the independent contribution of hypercapnia to the development of PH is that hypoventilation in disease states also leads to hypoxemia. Rats develop a rise in pulmonary arterial pressure and RV hypertrophy as early as 1 week after exposure to chronic hypoxia with Fio_2 of 10%. However, rats exposed to 3 weeks of hypercapnia alone (without hypoxia) did not experience any significant changes in pulmonary hemodynamics compared to control. Interestingly, when hypercapnia was added to the hypoxic condition (Fio_2 10% and $FiCO_2$ 10%), the deleterious effect of hypoxia on the pulmonary vasculature was attenuated compared to hypoxia alone.[62] Similarly, in newborn rats that were chronically exposed to hypoxic conditions (Fio_2 13%), higher concentrations of CO_2

($FiCO_2$ 10%) normalized RV performance, limited oxidant stress, and prevented upregulation of endothelin-1.[63] These animal studies demonstrate that hypercapnia in isolation may not lead to PH. This is consistent with human data demonstrating that in patients with OHS, hypercapnia was not independently associated with PH after adjusting for hypoxemia and obesity.[34]

In a large, retrospective single-center study of 491 patients with compensated hypercapnia, there was an association between hypercapnia and worse outcomes, including mortality.[64] However, the limitation of this study was that the association of hypercapnia with outcomes was not adjusted for concomitant hypoxemia. Hypercapnia may have other downstream deleterious effects unrelated to its effect on the pulmonary vasculature. Accumulating evidence in various animal models suggests that hypercapnia without concomitant hypoxemia leads to a reduction in innate immune response.[65–67] In summary, although hypercapnia may not be pathophysiologically linked to PH, it may have other deleterious effects and should be treated accordingly.

CHALLENGES

Challenges with Echocardiography

There are several technical challenges in correctly diagnosing and classifying PH in patients with OHS and/or severe OSA who are severely obese. Transthoracic echocardiography is an excellent screening tool and the recommended first step to assess for PH.[18] RVSP is considered a reasonable surrogate of PASP in the absence of pulmonic stenosis or RV tract obstruction. RVSP is calculated by the modified Bernoulli formula: RVSP = 4(peak tricuspid regurgitation velocity)^2 + right atrial pressure.[68] However, it is not possible to obtain a reliable tricuspid regurgitation (TR) velocity to estimate the RVSP in up to 40% to 50% of patients.[69–73] This technical challenge is even more prevalent in severely obese patients due to difficulty obtaining adequate views during echocardiography. Additionally, in high-output cardiac states, the TR velocity may overestimate pressure gradients. Conversely, TR can underestimate pressure gradients. Both these scenarios lead to inaccuracies of RVSP estimation.[18]

Another limitation of echocardiography is that the echocardiographer must estimate the right atrial pressure by determining the diameter of the inferior vena cava and the percentage of collapse during inspiration. This partly subjective estimation of right atrial pressure adds to inaccuracies of calculating RVSP or PASP by echocardiography. Most commonly, the right atrial pressure is assumed to be 5 to 10 mm Hg.[69] Although guidelines caution against relying solely on RVSP as described above,[18] accumulating evidence suggest that RVSP measured by echocardiography is strongly associated with mortality.[69,70,74] Additional echocardiographic parameters of such as RV outflow tract acceleration time less than 105 milliseconds and tricuspid annular plane systolic excursion (TAPSE)/PASP ratio less than 0.55 mm/mm Hg can provide further confirmation of PH.[18] In summary, even though echocardiography is considered to be an extremely useful screening tool for PH, RHC remains the gold standard to accurately diagnose and classify PH.

Significance of Elevated Pulmonary Artery Systolic Pressure on Echocardiography

It is important to note that despite the above-mentioned limitations of echocardiography in assessing PH, elevated RVSP (or PASP) has a strong association with patient outcomes. In the National Echocardiography Database of Australia cohort (n = 313,492), RVSP could be calculated in 50% of patients. In this subgroup, 19% had elevated PASP defined as 40 mm Hg or greater. Adjusted 5 year all-cause mortality incrementally increased with higher PASP, from 20% in those with PASP less than 40 mm Hg to 55.6% in mild PH (PASP 40–49.9 mm Hg), 69% in moderate PH (50–59.9 mm Hg) to 78% in severe PH (PASP $\geq$60 mm Hg).[69] In fact, even mildly elevated PASP on echocardiography, defined as 30 to less than 40 mm Hg, has been associated with increased mortality.[69,70,74] Therefore, patients with SDB who are found to have mild PH on echocardiography may benefit from additional evaluation and treatment of PH. This is particularly relevant in patients with OHS because of persistent PH despite positive airway pressure therapy.[31,75] In the Pickwick trial, the prevalence of PH, defined as PASP greater than or equal to 40 mm Hg, decreased significantly after 3 years of positive airway pressure therapy. However, despite improvements in pulmonary hemodynamics, nearly a quarter of patients had PASP greater than 40 mm Hg.[31] In a smaller study of 21 patients with successfully treated OHS after 3 months of home noninvasive ventilation, 9 patients (43%) had persistent PH on RHC, with 6 out of these 9 patients having only precapillary PH.[75] Consequently, clinicians should consider additional evaluation and treatment of PH in patients with SDB/OHS who continue to have elevated PASP despite initial improvement with adherent positive airway pressure therapy. It is important to ascertain whether this residual PH is precapillary in nature and would benefit from pharmacotherapy.

Challenges with Right Heart Catheterization

RHC also has limitations, particularly in the severely obese patients. In this patient population, respiratory effort and swings in pleural pressure while in the supine position can be significant and can make the interpretation of pressure waveforms quite challenging. Moreover, in severely obese patients, there can be a clinically significant level of intrinsic positive end expiratory pressure (PEEP) while in the supine position.[76] Without concomitant esophageal manometry, the interpretation of cardiac waveforms can become very challenging. Clinicians performing RHC in patients who have significant respiratory excursion due to obesity and/or dyspnea use a variety of techniques to try to obtain reliable PA pressures and PAWP. One of these maneuvers consists of averaging pressures measured across several respiratory cycles. Another approach is to ask the patient to momentarily hold their breath at functional residual capacity in order to measure mPAP and PAWP while there is no respiratory effort. However, these approaches do not take into account the intrinsic PEEP and/or significant swings in pleural pressure that is frequently present in spontaneously breathing severely obese patients while in the supine position. These oversights can lead to misclassification of PH, potentially delaying or preventing appropriate treatment.

To more accurately assess and overcome these limitations, Khirfan and colleagues examined 53 severely obese patients with mPAP greater than 20 mm Hg and PAWP greater than or equal to 12 mm Hg.[77] Esophageal manometry was performed to account for dynamic respiratory fluctuations in intrathoracic pressures and intrinsic PEEP at end expiration in the supine position. Accurate transmural pressures were obtained by subtracting esophageal pressure from mPAP and PAWP and these values were compared to measurements obtained at the end of exhalation or obtained by averaging pressures across several respiratory cycles. Assessment of pulmonary hemodynamics using esophageal manometry was superior to the other 2 methods. Postcapillary PH decreased from 32 out of 53 (60%) to 4 out of 53 (7.5%) patients. At the same time, precapillary PH increased from 1 out of 53 (2%) to 13 out of 53 (24.5%) patients. Notably, 12 out of 53 (23%) patients no longer classified as having PH following this adjustment.[77]

Performing measurements in the sitting position can significantly decrease intrinsic PEEP and reduce intrathoracic pressure swings in severely obese subjects.[76] When patients undergoing RHC were transitioned from supine to the sitting position, there was a significant decrease in right atrial pressure, mPAP, PAWP, and cardiac output. In fact, the accuracy of pulmonary hemodynamics with the head of the bed elevated was very similar to adjusted measurements using esophageal manometry.[77] These findings underscore the potential for misclassification and misdirected treatment strategies in symptomatic patients with PH due to inaccurate PH phenotyping. As such, it is important for clinicians caring for severely obese patients with SDB/OHS to recognize that RHC has significant limitations. It is our opinion that pulmonologists and sleep specialists need to discuss RHC techniques with experts who perform RHC to ensure a more accurate diagnosis and classification of PH and not assume that all patients with SDB/OHS have group 3 PH.

Pulmonary Hemodynamic Assessment During Wake Versus Sleep

Another important limitation of RHC (or echocardiography) is that it is performed during wakefulness when patients with SDB are not experiencing repetitive apneas and/or hypopneas, hypoxemia/hypercapnia, and significant intrathoracic pleural pressure swings while breathing against an occluded upper airway. This might be more relevant when dynamic, reversible, and treatable changes can occur before actual PA remodeling takes place, which ultimately leads to less-reversible RV failure.

A few studies have investigated performing pulmonary hemodynamics in patients with SBD during sleep.[35,36,78,79] Kang and colleagues performed awake and sleep RHC in 6 patients with known OSA and PH. The rise in mPAP was significantly higher in rapid eye movement (REM) vs non-REM sleep (11.6 vs 6.9 mm Hg). However, the degree of oxygen desaturation with apneic events was also greater during REM sleep (23% vs 14%).[78] In a follow-up study by the same group, they were able to demonstrate that for the same level of hypoxemia, obstructive events during REM sleep led to a larger increase in mPAP than non-REM sleep.[79] This phenomenon has also been described in the context of systemic hypertension.[80,81] Therefore, it is plausible that similar to systemic blood pressure, PA vascular tone is more elevated in REM sleep, and therefore, any degree of hypoxemia leads to a higher increase in PA pressures compared to non-REM sleep.

Exercise-induced Pulmonary Hypertension

In addition to proper patient positioning, incorporating an exercise component into RHC can lead to a more accurate diagnosis of PH in patients

with SDB. Studies have shown that adding exercise RHC can increase the detection rate of PH in OSA by up to 55%.[27–29] This highlights the importance of exercise RHC in identifying occult PH that may be missed during a resting RHC procedure—especially in a population where the contribution of SDB to PH development is being debated as negligible. A pathologic increase in PA pressure with exertion has been associated with impaired prognosis in patients with unexplained exercise dyspnea.[18] It remains unclear whether more aggressive treatment of SDB will improve outcomes in patients with exercise-induced PH.

TREATMENT

The effective treatment of PH in the setting of SDB and OHS involves (1) screening of patients with diagnosed PH for SDB; (2) screening of patients with SDB and obesity for PH; (3) utilization of positive airway pressure therapy for patients with PH and OSA/OHS and supplemental oxygen for patients who only have sleep hypoxemia; and (4) multidisciplinary efforts to address obesity and optimize left heart disease, if present (**Fig. 2**).

Screening Patients with PH for SDB and Nocturnal Hypoxemia

Several studies have reported a prevalence of OSA ranging from 7% to 55% in patients with precapillary PH (see **Table 1**). There are also studies to suggest that in patients with PH, comorbid OSA leads to worsening PA pressures, likely mediated by nocturnal hypoxemia. In patients diagnosed with PAH, nocturnal hypoxemia can be present despite normoxia during daytime and even with exertion. In a cross-sectional study of 43 patients with PAH, 69.7% had significant nocturnal hypoxemia (T90 > 10%) and of those with nocturnal oxygen desaturation, 87% had a T90 of greater than 20%. These patients, however, did not consistently have concomitant daytime hypoxemia. Patients experiencing nocturnal hypoxemia had higher mPAP on RHC compared to those who did not (53.7 ± 16.5 vs 45 ± 13.6 mm Hg, respectively).[82] This brings to light the population of patients with PAH with a missed diagnosis of SDB and/or nocturnal hypoxemia.

In patients with precapillary group 1 PH, pulmonary vascular disease phenomics (PVDOMICS) data suggest there is a significant burden of OSA and nocturnal hypoxemia in patients with group 1 PH.[19] Out of 186 participants who underwent home respiratory polygraphy, the prevalence of OSA defined as AHI of greater than or equal to 5/h was 49.7%. Moderate-or-severe OSA (AHI ≥15/h) was 22%.[83] Even though 39.8% of these patients underwent home respiratory polygraphy while on therapy (ie, oxygen, positive airway pressure therapy, or both), the median T90 was 37% of the total recording time, consistent with a significant burden of hypoxemia.[19,83] It remains unclear whether such high burden of hypoxemia was due to OSA or PH. A large, single-center, retrospective study from China was able to address this question.[84] These investigators obtained respiratory polygraphy in 627

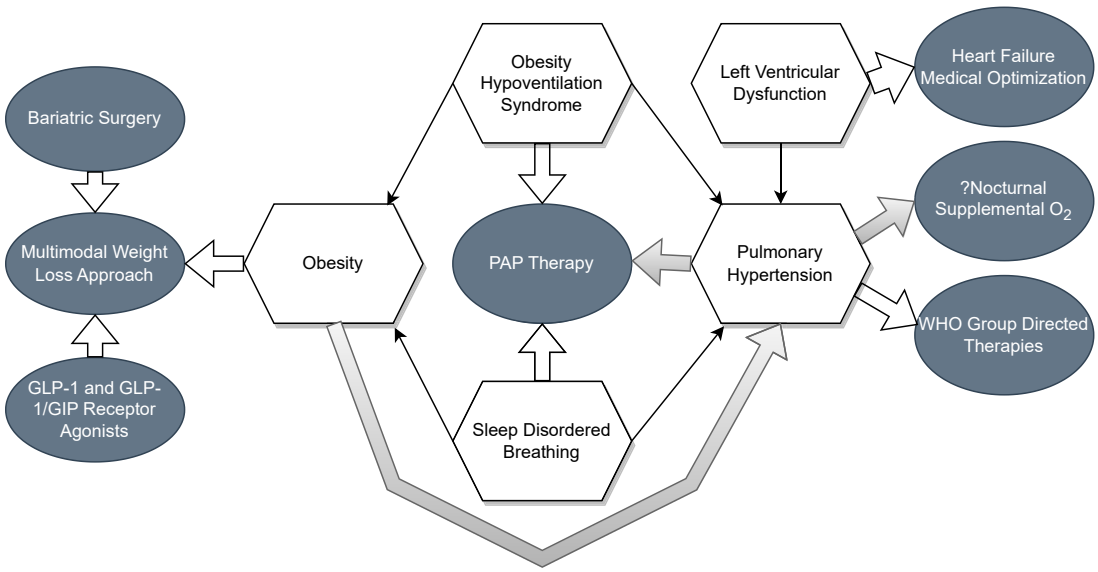

Fig. 2. Treatment approach algorithm for SDB and PH. GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide 1; PAP, positive airway pressure; WHO, World Health Organization; Gray arrow, proposed mechanism and treatment pathway; White arrow, accepted treatment pathway.

patients undergoing evaluation for PH with RHC. Of these, 434 had PH and 90% were classified as precapillary in nature. PH with comorbid OSA was present in 134 (30%) of the patients. Nocturnal hypoxemia was assessed by T90. In this cohort, patients with PH and comorbid OSA experienced significantly greater degree of nocturnal hypoxemia compared to patients with only PH (median T90 of 9.4% vs 0.3%, respectively) despite having less severe elevation of PH (median mPAP of 43 vs 51 mm Hg, respectively).[84] Despite its retrospective nature, a major strength of this study is that it provides data on patients with PH without OSA to address the chicken and egg conundrum: is hypoxemia in patients with PH predominantly due to PH or to comorbid SDB? The data suggest that SDB is an important contributor to nocturnal hypoxia in patients with precapillary PH, and as such, it is appropriate to screen all patients with precapillary PH for SDB and nocturnal hypoxemia.[85]

Screening of Patients with SDB and Obesity for PH

Current PH or SDB guidelines do not provide specific recommendations on whether patients with SDB should be screened for PH. Screening all patients with SDB for PH would be impractical. However, there may be a subset of patients with SDB who would benefit from being screened for PH with echocardiography. These include those who have significant burden of hypoxemia during sleep, have evidence of daytime hypoxemia or hypercapnia, have unexplained dyspnea, and are severely obese. In patients enrolled in the Registry to Evaluate Early and Long-term PAH Disease Management (REVEAL), OSA and obesity were associated with delays in diagnosing PAH.[86] In a retrospective analysis of 8940 patients undergoing RHC, obesity was associated with greater prevalence of postcapillary, mixed, and precapillary PH.[87] For every 5 unit increment in the BMI, the odds ratio for precapillary PH increased significantly by 1.18. In fact, the cohort included 659 severely obese patients, and this group was at highest risk for PH, with a prevalence of precapillary PH of 14%.[87] As such, in severely obese who are symptomatic, it is important to consider PH as a diagnosis and not attribute all symptoms to severe obesity and/or SDB, particularly that a proportion of these patients may have group 1 PH and may benefit from pharmacotherapy.[88]

Positive Airway Pressure Therapy in PH with Comorbid OSA or OHS

Despite the high prevalence of comorbid SDB in patients with PH and the extensive pathophysiologic mechanisms linking SDB and nocturnal hypoxemia with PH, there are limited data examining the impact of positive airway pressure therapy on pulmonary hemodynamics. Most studies are limited by being observational in nature, having small sample sizes with various follow-up periods, and using different techniques to measure pulmonary hemodynamics. It is important to note that to more accurately assess the effect of positive airway pressure therapy on pulmonary hemodynamics, it is imperative to examine studies that only include patients who have PH at baseline. This approach can explain the discrepancy between 2 meta-analyses, one that included all patients (including those who did not have PH at baseline) leading to a very small effect size of positive airway pressure therapy in reducing PA pressures (1.34 mm Hg, 95% CI 0.34–2.33)[89] versus another meta-analysis that only included patients with PH at baseline (13.3 mm Hg, 95% CI 12.7–14.0).[90] Importantly, both these meta-analyses did not include patients with OHS. In **Table 2**, we summarize 11 studies that include patients with predominantly severe OSA or OHS and PH at baseline, were treated with positive airway pressure therapy, and had adequate adherence to therapy (n = 262). The improvement in PA pressures ranged from 4 to 17.6 mm Hg, with a weighted average of 10.5 mm Hg. The effect of positive airway pressure therapy was similar in OSA and OHS. Moreover, in the Pickwick trial, there was no significant difference between noninvasive ventilation (NIV) and continuous positive airway pressure (CPAP) in the degree of improvement of PH in patients with OHS who had comorbid severe OSA.[31]

As illustrated in **Table 2**, persistent PH is not an uncommon finding despite initial improvements in pulmonary hemodynamics with adherent positive airway pressure therapy, particularly in patients with OHS.[31,75] Even mildly elevated PASP on echocardiography is associated with increased mortality.[69,70,74] As such, we recommend that if patients with OSA and/or OHS have persistently elevated PASP on echocardiography after 6 to 12 months of adherent positive airway pressure therapy, clinicians should consider referring these patients to multidisciplinary PH clinics for consideration of RHC. It is important to determine if the residual PH is precapillary in nature and whether it would benefit from medications for PAH.

Potential Adverse Effects of Positive Airway Pressure Therapy in Pulmonary Hypertension

One area of concern is whether positive airway pressure therapy can adversely affect RV function

Table 2
Effect of positive airway pressure therapy on right-sided heart pressures in patients with pulmonary hypertension at baseline

Author	Study Design	Total Sample (n)	PH Treated with PAP (n)	SDB Type	BMI (kg/m^2)	OSA Severity (AHI)	PAP Usage (h/night)	Therapy Duration (months)	Baseline Right-sided Pressure	Follow-up Right-sided Pressure
Chaouat et al,[117] 1997	Obs RHC	65	11	OSA	33±6[a]	87 ± 33[a]	CPAP 5.2[a,f]	64 ± 6	24±5[b]	20±7[b]
Alchanatis et al,[118] 2001	CC TTE	29	6	OSA	41 ± 7	63 ± 18	CPAP 5.4[a,f]	6	25.6 ± 4.0[c]	19.5 ± 1.5[c]
Sajkov et al,[119] 2002	Obs RHC	20	5	OSA	32 ± 3.6[a]	48.6 ± 23.3[a]	CPAP 5.1[a,f]	4	24.4 ± 5.0[b,g]	15.2 ± 2.8[b,g]
Arias et al,[120] 2006	RCT-CO TTE	21	11	OSA	33.6 ± 4.4	68.7 ± 24.9	CPAP 6.2[a,f]	3	38.3 ± 5.4[c,g]	29.8 ± 2.6[c,g]
Colish et al,[121] 2012	Obs TTE	47	47	OSA	38 ± 9	63 ± 30	CPAP >4.5[a]	12	54±6[d]	39±5[d]
Shehata et al,[122] 2013	CC TTE	24	10	OSA	32.2 ± 4	84[e]	CPAP >6[a]	6	35[c,e]	26[c,e]
Marvisi et al,[123] 2015	CC TTE	25	17	OSA	32 ± 6	59.3 ± 24	CPAP >4[a]	9	39.8 ± 4.1[c]	22.2±3[c]
Sharma et al,[124] 2019	RCT TTE	21	10	OSA	28.8 ± 5.8[a]	31.8 ± 8.0	AutoPAP *Total 29.7 h*[f]	*48 h*	58.6 ± 2.5[d]	42.8 ± 2.7[d]
Chu et al,[125] 2020	CC TTE	71	45 *High altitude*	OSA	26.0 ± 2.4[a]	44.3 ± 17.2[e]	CPAP *"compliant"*	6	44.6 ± 8.0[d]	37.9 ± 6.9[d]

(*continued on next page*)

Table 2
(*continued*)

Author	Study Design	Total Sample (n)	PH Treated with PAP (n)	SDB Type	BMI (kg/m^2)	OSA Severity (AHI)	PAP Usage (h/night)	Therapy Duration (months)	Baseline Right-sided Pressure	Follow-up Right-sided Pressure
Castro-Añón et al,[126] 2012	CC TTE	30	13	OHS + OSA	43.3 ± 9.8	37.1 ± 23.0	NIV ≥4[a]	6	58 ± 11[d]	44 ± 12[d]
Masa et al,[31] 2020	RCT/post-hoc TTE	94	49	OHS + OSA	43.1[a,e]	69.3[a,e]	NIV 6[a,e]	36	48.8 ± 10.5[d]	40.0 ± 9.5[d]
Masa et al,[31] 2020	RCT/post-hoc TTE	102	38	OHS + OSA	42.5[a,e]	69[a,e]	CPAP 6[a,e]	36	53.9 ± 10.5[d]	43.2 ± 8.7[d]
Improvement in right-sided pressures[h]									10.5 mm Hg	

Abbreviations: Obs, observational; CC, case control; NIV, noninvasive ventilation; RCT-CO, randomized controlled trial crossover; RHC, right heart catheterization; TTE, transthoracic echocardiogram.

Patients with PH alone.

[a] Entire cohort.

[b] mPAP via RHC.

[c] mPAP via TTE Doppler.

[d] RVSP via TTE Doppler.

[e] Median.

[f] Mean.

[g] Calculated from raw data provided in the article.

[h] Weighted average excluding study by Sharma given that duration of therapy was short.

by decreasing preload in patients with PH, particularly in those with milder forms of OSA who do not experience significant sleep hypoxemia. Although more research is needed in this area, one small study found an improvement in RV ejection fraction measured by cardiac magnetic resonance after 6 months of adherent CPAP therapy in 15 patients with mild-to-moderate OSA (right ventricular ejection fraction increased from 52.8 ± 4.1–59.4 ± 8.3, $P = .014$).[91]

Another area of concern is whether positive airway pressure therapy can lead to excessive increase in lung volumes and thereby adversely impacting endothelial function. In one study, investigators measured levels of several biomarkers, including circulating angiopoietin-2 at baseline and after 3 months of adherent CPAP therapy in 77 participants with moderate-to-severe OSA and no parenchymal lung disease.[92] Angiopoietin-2 is a biomarker of lung injury and an amplifier of inflammation and endothelial injury and its level correlates with the severity of OSA and sleep hypoxemia. Surprisingly, there was a slight, yet statistically significant increase in angiopoietin-2 with CPAP therapy. Even though CPAP resolved intermittent hypoxemia, it may have led to endothelial injury by a different mechanism. The authors speculated that it could be related to excess lung inflation with CPAP.[92] Although the effect of CPAP on functional residual capacity has not been tested during sleep in obese persons with OSA, CPAP of 5 to 10 cm H_2O pressure can increase the functional residual capacity by more than 1000 cc in healthy adults.[93] However, in an obese subject with a low expiratory reserve volume while supine, CPAP levels typically used to treat OSA may simply raise the expiratory lung volume and functional residual capacity to normal levels, without leading to lung overdistention. Clearly, further research is needed to ensure CPAP can be safely used in patients with PH and comorbid OSA, particularly those with milder forms of SDB.

Treatment of Obesity

As obesity plays a significant role in SDB and PH, an aggressive and multimodal approach to weight loss should be pursued. Bariatric surgery has been shown to improve pulmonary hemodynamics in severely obese patients with PH, with resolution of PH in some patients.[94–97] Bariatric surgery in patients with OHS can also lead to significant improvement in PA pressures, although it is unclear if this improvement is due to improvement in gas exchange, OSA, lung mechanics or a combination of these changes. In 17 patients with OHS and PH, a mean weight loss of 42% led to a significant decrease in mPAP by RHC from 36 ± 14 to 23 ± 7 mm Hg. However, PH persisted in 10 out of 17 (59%) patients.[97,98]

Randomized controlled trials of subcutaneous glucagon-like peptide-1 (GLP-1) receptor agonists (semaglutide 2.4 mg/wk) for 68 weeks or GLP-1/glucose-dependent insulinotropic polypeptide (GIP) receptor agonists (tirzepatide 15 mg/wk) for 72 weeks have shown significant reductions in body weight of 15% (~16 kg) and 21% (~22 kg), respectively.[99,100] This degree of weight loss, if sustained, can lead to significant improvement in SDB/hypoxemia in patients with OSA or OHS.[101,102] Weight loss induced by semaglutide can also lead to improvements quality of life and exercise capacity in obese patients with heart failure with preserved ejection fraction.[103] It remains unclear whether these medications improve pulmonary hemodynamics by mechanisms other than weight loss, such as reducing inflammation, vascular remodeling, and metabolic improvements.[104,105]

Supplemental Oxygen in Pulmonary Hypertension and Nocturnal Hypoxemia

There is accumulating evidence that sleep-related hypoxemia is a more important contributor to patient outcomes in PH than the AHI.[106] In the PVDOMICS cohort of patients with PAH who completed home respiratory polygraphy, elevated T90 was associated with elevated mPAP on RHC and RVSP on echocardiogram. For every 10% increment in T90, mPAP increased by 1.86 mm Hg and RVSP increased by 2.49 mm Hg. In contrast, AHI was not associated with mPAP or RVSP.[83] A median T90 threshold greater than 37% and mean SpO_2 less than 90% were associated with decreased transplant-free survival. For each 10% increase in T90, the risk for transplantation or death increased by 12%.[83]

Despite the association between sleep hypoxemia and patient outcomes, there is a paucity of data on whether the treatment of sleep hypoxemia with supplemental oxygen improves outcomes in patients with PH with or without comorbid SDB. In the REVEAL registry study, group 1 patients with PAH were categorized into two groups: those receiving supplemental oxygen and those who did not.[107] Only patients with severe reduction in diffusing capacity for carbon monoxide (DLCO) had a survival benefit with supplemental oxygen therapy. The limitation of this study is that it did not assess oxygen supplementation during sleep. In a randomized, cross-over trial that assessed 23 patients with precapillary PH and SDB (mean nocturnal SpO_2 <90% or 3% oxygen saturation index >10/h) but without

significant daytime hypoxemia, treatment with 3 L/min nocturnal oxygen led to improvements in certain RV parameters, nocturnal O_2 saturation, and 6 minute walk distance.[108]

Further studies are needed to assess whether treatment should focus only on treating nocturnal hypoxemia with supplemental oxygen during sleep versus treatment of comorbid SDB with positive airway pressure therapy.

Multidisciplinary Clinics to Treat PH and SDB

Current PH guidelines recommend that PH centers provide care by a multidisciplinary team with providers from a broad spectrum of medical disciplines (pulmonologists, cardiologists, radiologists, and rheumatologists), as well as those with an expertise in providing psychological and social support.[18] Studies that describe an established multidisciplinary approach in a health system suggest that this approach leads to a more efficient and comprehensive diagnostic workup for patients with PH.[109,110] We propose that multidisciplinary clinics that include medical experts in sleep and weight loss, in addition to the more traditional disciplines involved in the management of patients with PH, may improve outcomes. However, further studies are needed to assess whether multidisciplinary PH clinics lead to improved patient-centered outcomes.

GAPS OF KNOWLEDGE

Despite advances in the field, important gaps of knowledge persist. Here, we list a few areas that in our opinion require further investigation.

1. What is the contribution of untreated sleep hypoxemia due to SDB in PAH (group 1 PH) and does it worsen patient outcomes?
2. Should hypoxemia due to SDB be treated with oxygen or positive airway pressure therapy?
3. Does treatment of sleep hypoxemia in PAH improve patient-centric outcomes?
4. Does untreated SDB diminish response to approved pharmacotherapy in patients with PAH or pulmonary hypertension associated with interstitial lung disease (PH-ILD)?
5. What is the contribution of obesity to PAH, independent of SDB?
6. Does treatment of obesity with GLP-1 receptor agonists and GLP-1/GIP receptor agonists (eg, semaglutide and tirzepatide) improve pulmonary hemodynamics in obese patients with PH or PAH?
7. Does echocardiographic improvement in PASP/RVSP with positive airway pressure therapy (or oxygen) lead to improvement in patient-centered outcomes?
8. What are the best practices for RHC in severely obese patients to avoid misclassification of PH?
9. Should severely obese patients with SDB who have persistent PH despite positive airway pressure therapy be evaluated for precapillary PH by RHC?
10. Do patients with OSA or OHS who are adherent to positive airway pressure therapy and are found to have comorbid precapillary PH benefit from PAH-specific pharmacotherapy?

CLINICS CARE POINTS

- Sleep-disordered breathing and sleep hypoxemia are prevalent in patients with pulmonary hypertension.
- In patients with pulmonary hypertension, sleep hypoxemia is associated with worse outcomes.
- Patients with pulmonary hypertension should be screened for sleep-disordered breathing and sleep hypoxemia.
- Positive airway pressure therapy (CPAP or NIV) during sleep improves sleep hypoxemia due to sleep-disordered breathing.
- Limited data suggests that treatment of obstructive sleep apnea and obesity hypoventilation syndrome with positive airway pressure therapy improves pulmonary hypertension.

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DISCLOSURE

None of the authors have any conflicts of interest to declare.

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