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Review Article: Obstructive Sleep Apnea In Patients With Interstitial Lung Diseases : Links To Pulmonary Hypertension

Hoda Ali[1], Alaa Rashad[2], Mohamed S. Badawy[3], Eptehal M. Dongol[4]

[1,2,4]Chest diseases and tuberculosis Department, Faculty of Medicine, South Valley University, Qena, Egypt
[3]Chest diseases and tuberculosis Department, Faculty of Medicine, Luxor university, Luxor, Egypt
correspond to hodaali@med.svu.edu.eg

Abstract: *OSA is a common but frequently underrecognized comorbidity in patients with ILDs, particularly IPF, with prevalence estimates ranging from 22% to 90%. The coexistence of OSA in ILD patients is associated with worsened quality of life, accelerated clinical decline, and increased risk of cardiovascular complications and IPF. Pathophysiologically, reduced lung volumes and traction forces in ILD may promote upper airway collapsibility, especially during REM sleep, while intermittent hypoxia from OSA contributes to systemic inflammation, oxidative stress, and vascular remodeling. Pulmonary hypertension in ILD results from a complex interplay of hypoxia, endothelial dysfunction, and fibrotic processes, further compounding morbidity. CPAP therapy remains the gold standard treatment for moderate-to-severe OSA and has demonstrated beneficial effects on sleep quality, daytime functioning, pulmonary hemodynamics, and potentially on survival in ILD patients with OSA. This review highlights the epidemiology, pathophysiology, clinical impact, and therapeutic implications of OSA in ILD—with or without PH—and emphasizes the importance of early diagnosis and CPAP adherence in improving patient-centered outcomes.*

Keywords: *Obstructive sleep apnea (OSA), interstitial lung disease (ILD), idiopathic pulmonary fibrosis (IPF), pulmonary hypertension (PH).*

INTRODUCTION:

The broad category of diffuse parenchymal lung disorders known as ILD is distinguished by a wide range of clinical manifestations and outcomes. With a median lifespan of three to four years, IPF is the most common kind of idiopathic interstitial pneumonia among ILDs. Comorbidities are common in ILD patients and have a significant impact on their clinical results**(1)**.

ILDs are frequently associated with a number of comorbidities, including depression, pulmonary hypertension, OSA, and gastroesophageal reflux syndrome. International recommendations from the American Thoracic Society, European Respiratory Society, Japanese Respiratory Society, and Latin American Thoracic Association have recognized the significance of comorbidities, particularly in patients with EPF **(2)**.

The prevalence of OSA, a kind of sleep disordered breathing, is increasing, in part because of increased public awareness and growing obesity rates. **(3)**.

It is estimated that between 2 and 4% of healthy people suffer from OSA. OSA has a high morbidity and death rate, especially when it coexists with other respiratory disorders such ILD. It has been reported that between 17% and 88% of these people have OSA **(4)**.

Among patients with ILD, the identification of Pulmonary hypertension (PH) typically is a finding of grave consequence. PH-ILD portends increased morbidity with decreased functional capacity, more frequent hospitalizations, higher supplemental oxygen requirements, and reduced quality of life when compared to

patients with ILD without PH. This negative relationship additionally holds true for mortality, where patients with PH-ILD may experience as much as a five-fold increase **(5)**.

Epidemiology and clinical associations of OSA in ILD

Accurately determining the precise incidence of OSA in individuals with ILD is hard. Prior research has mostly assessed the prevalence of obstructive sleep apnea in individuals with idiopathic pulmonary fibrosis, with seven of these cohorts additionally included other interstitial lung disease subgroups. The majority of studies were conducted at a single site and involved less than 100 participants **(6,19)**. In individuals with ILD, the reported prevalence of OSA, which is characterized as an AHI of ≥5, varies fourfold, from 22% to 90%. Up to two-thirds of these people may have moderate to severe OSA, according to certain research. Variations in the diagnostic criteria for OSA and the polysomnographic evaluation of hypopnea episodes, as well as the exclusion of patients with a prior diagnosis and/or those at elevated risk for OSA in certain studies, are likely to contribute to the disparities in reported prevalence. Furthermore, as OSA is more common in patients with IPF than in patients with other ILDs, especially in men, disparities in ILD diagnosis and the demographic composition of the research groups might contribute to the explanation of the noted disparities **(14, 15, 20, 21)**. Because the diagnostic criteria for IPF have changed over the past several decades, there is a large difference in the diagnosis of IPF between investigations. The diagnosis criteria for OSA and ILD varies in terms of methodology, and polysomnographic examinations, differences in patient comorbidities, and the definitions of age and BMI subgroups limit the direct comparison of OSA prevalence between ILD patients and the general population. In contrast, most studies show that the prevalence of OSA in ILD is much higher than in a normal population that is matched for age or BMI. According to a recent population-based study, up to 72% of the whole cohort—which had a mean BMI of 25.6 kg/m² and a median age of 57 years—had sleep-disordered breathing, which is defined by an AHI of ≥5. The prevalence of OSA keeps increasing with age, which is especially relevant for people with ILD, who frequently exhibit symptoms beyond the age of 60 **(10,24)**. Due mostly to differences in the features of the research population and a small sample size, the relationship between the severity of ILD and the incidence and severity of OSA produces contradictory results. DLCO, a measure of gas exchange efficiency, is correlated with polysomnographic measurements of oxygen desaturation in patients with ILD. These measurements include the oxygen desaturation index, SpO2, and total sleep duration with SpO2 < 90% **(7, 17)**. The degree of obstructive sleep apnea is somewhat correlated in conjunction with spirometry and lung volume in interstitial lung disease **(17, 25)**. According to preliminary research, individuals with interstitial lung disease may have negative health consequences from underlying obstructive sleep apnea. How bad OSA is and how it affects people's health status, as measured by the St George's Respiratory Questionnaire, were clearly correlated, according to a case-control study including 34 IPF patients **(26)**. A recent study indicated that obstructive sleep apnea may serve as a predictor of cognitive impairment in individuals with idiopathic pulmonary fibrosis **(27)**. In ILD, the degree of nocturnal desaturation and OSA are prognostic markers of disease progression and death. A significant consequence of ILD is pulmonary hypertension, which has been linked to nocturnal hypoxemia with or without OSA **(11, 17)**.

Pathophysiology of OSA

The failure of the muscles that dilate the airways to offset the negative pressure that is generated while breathing is the fundamental fault in the intricate pathophysiology of obstructive sleep apnea (OSA and its associated conditions). The muscles that dilate the airway contract in a coordinated manner with each inhale, which is generally done in order to counterbalance the negative pressure that is created in the upper airway during inspiration. When this negative pressure becomes more pronounced or when the effectiveness of

relaxing muscles is impaired, this equilibrium is disrupted, and individuals become more prone to upper airway blockage. This is because of either of these two variables. Constriction of the upper airway causes an increase in the negative pressure that occurs after inhalation, which makes it simpler for the patient to collapse. The craniofacial bone structure, the buildup of soft tissue, and temporary variables such as fluid retention that transfers to the neck when the patient is supine are all factors that might cause constriction at the same time **(9,28)**.

- **Upper airway narrowing**

Most patients suffering from obstructive sleep apnea exhibit a constricted oropharyngeal airway, which may be clinically evaluated using the Mallampati score, with hereditary factors significantly influencing the condition. Cephalometric and CT analyses reveal skeletal measurements in the lower face and neck that lead to upper airway constriction, while clinical evaluations indicate micrognathia or retrognathia in several cases. Treacher-Collins syndrome and Robin sequence children are more susceptible to obstructive sleep apnea because to bone alterations in the lower face and/or jaw, leading to structural constriction of the oropharyngeal airway **(29,31,32)**. Obesity and adenotonsillar hypertrophy are two conditions that can cause soft tissue accumulation in and around the upper airway, which can narrow the oropharyngeal lumen and make people more susceptible to obstructive sleep apnea. While abdominal obesity increases vulnerability to collapsibility by reducing tension on the upper airway, cervical obesity causes oropharyngeal constriction. Pediatric obstructive sleep apnea is further exacerbated by adenotonsillar hypertrophy, which often coexists with obesity **(22,28)**. Because nocturnal fluid redistribution in the supine position heightens the difficulty of opening and maintaining an airway, patients with CHF and end-stage renal failure are more susceptible to OSA when they accumulate fluid **(33, 34)**. There is evidence that nasal obstruction, and more specifically variable occlusion as observed in rhinitis, plays a role in the development of OSA. Additionally, it has been demonstrated that intranasal corticosteroids can reduce the AHI in persons who suffer from rhinitis and mild to severe OSA. The supine posture has a detrimental effect on the patency of the upper airway, mostly because of the stresses exerted by gravity **(28)**.

- **Upper airway dilator muscle function**

During inspiration, the genioglossus and other pharyngeal dilator muscles are crucial for maintaining the patency of the oropharyngeal airway. This is accomplished by providing reinforcement to the collapsible segment for additional support. In synchrony with the process of inspiration, these muscles have a phasic contraction that occurs milliseconds before the diaphragmatic contraction. The degree to which the muscles in the upper airways are engaged is influenced by a number of factors, including chemical signals, vagal feedback, fluctuations in airway pressure, and baroreceptor activity **(28)**. Obstructive sleep apnea is characterized by a restricted upper airway, which results in an elevated inspiratory collapse force. This force requires a more forceful contraction of dilating muscles in order to maintain airway patency that is necessary for breathing. after wakefulness, dilating muscular activity is substantially more than it is in normal people, but it drops significantly more after sleep, hence increasing the risk of blockage, particularly in REM sleep. The deficit in OSA is mostly due to insufficient compensation for heightened inspiratory negative pressure, rather than a fundamental lack in muscle performance. This issue is exacerbated by the involvement of skeletal muscles, leading to a more significant decline during sleep compared to the diaphragm **(35)**.

- **Respiratory control**

At the time in the cycle when the inspiratory EMG activity of the diaphragm and genioglossus is at its lowest, upper airway blockage is most likely to occur. This pattern of recurrent apnea, which is frequently observed in OSA, suggests a lack of consistency in the regulation of the ventilator, comparable to periodic breathing. The last stages of apnea cause an increase in EMG activity, which is followed by hyperventilation for a number of breaths. Both EMG activities then decrease, making the person more susceptible to obstruction in the future **(36)**.

Apnea threshold

Normal individuals exhibit variations in ventilation during the shift from alertness to non-REM sleep, attributable to a decrease in the CO2stimulus for respiration and the discovery of an acute threshold for apnea that is crucially reliant on CO2 levels. In obstructive sleep apnea, this threshold is heightened by post-apnea hyperventilation, leading to a decrease in CO2 levels and increasing the likelihood of further apnea episodes. Further mechanisms that may lead to subsequent apnea during hyperventilation include activation of lung stretch receptors and baroreceptors **(36)**.

- **Loop gain**

The susceptibility to apnea linked to alternating episodes of Loop gain influences both hyper- and hypoventilation when sleeping, which denotes the amplification of the negative feedback mechanism that modulates ventilation in reaction to a ventilatory disruption. A high degree of ventilation augmentation following an apnea results in a significant loop gain, hence elevating the probability of recurrent apnea episodes and rendering the ventilatory system more unstable. Plant gain, associated with the fundamental necessity of respiration, and controller gain, linked to chemoreceptive sensitivity, represent the two primary categories of respiratory control system gains. Minimal, temporary ventilatory overshoots are necessary to attain the apneic threshold (augmented plant gain); hence, hypoventilation and diminished ventilatory drive heighten the risk of apnea. An elevated slope of the ventilatory response gradient to CO2 (controller gain) heightens the likelihood of apnea, even when both background hyperventilation and plant gain are diminished **(28, 36)**.

- **Arousal**

Although brain activation is frequently associated with apnea cessation, and that might be a crucial safeguard, it may also worsen the pathophysiology of OSA by raising the risk of upper airway collapse as a result of increased post-apneic hyperventilation. There seems to be a clear pathophysiological relationship between the severity of OSA and the degree of respiratory cortical arousals in patients. The main arousal trigger appears to be increasing ventilatory effort **(28, 37)**. Each person with OSA has a different arousal response, which may be quantified by the arousal threshold, which can be evaluated noninvasively using PSG. One important possible factor in the pathophysiology of obstructive sleep apnea is a low arousal threshold, which some patients may benefit from therapy for **(38, 39)**.

OSA and ILD

ILDs are a diverse and extensive category of restrictive pulmonary illnesses that lead to diminished lung volumes and compliance. IPF, a distinct kind of ILD of uncertain etiology, is associated with low survival rates and predominantly affects elderly persons. Contrary to previous studies that identified IPF as a singular

organ disease, it appears that other concomitant diseases, such as OSA, coexist. It has also been found that obstructive sleep apnea, regardless of the severity of idiopathic pulmonary fibrosis, is linked to a faster clinical decline **(8, 40,41)**.

Clinical presentation and PSG characteristics

Just 20% of patients with IPF OSA experience severe daytime somnolence, which is an unusual symptom. Moreover, only 13–29% and 38–48% of these people, respectively, reported having other common symptoms such snoring and witnessed apneas. Clinical symptoms such as nocturnal cough (48–56%), insomnia associated with sleep initiation and maintenance (52–67%), and daytime fatigue (43–75%) are frequently observed. Compared to OSA patients in the general population, OSA patients with IPF seem to have a lower BMI. For appropriate referral to sleep clinics for further evaluation, treating physicians must identify IPF patients presenting OSA with this clinical profile. These people have altered sleep architecture, which includes decreased REM sleep and efficiency as well as increased stage 1, frequent arousals, and fragmented sleep. Additionally, SpO2 levels significantly drop as you sleep, especially during REM sleep **(13,23,42)**.

Pathophysiological relationship between OSA and ILDs

Reduced lung capacity can make obstructive sleep apnea and ILD worse by compromising the integrity of the upper airway and increasing resistance as a result of decreased traction on the airway. These modifications may make it easier for the upper airway to collapse during REM sleep, which occurs when the activity of the intercostal muscles is at its lowest. Continuous hypoxia is not as effective as the periodic hypoxia that is associated with obstructive sleep apnea. Periodic hypoxia is a more potent catalyst for causing oxidative stress, systemic inflammation, and tissue damage, all of which can result in lung fibrosis. The GOR illness, which is rather common in IPF, need to be considered as a potential mechanism **(16,43,44)**.

Clinical consequences

It seems that obstructive sleep apnea is associated with a worse outcome in patients with idiopathic pulmonary fibrosis, shown by a decline in clinical condition and increased death. Recent findings indicate that untreated obstructive sleep apnea in individuals with idiopathic pulmonary fibrosis may result in modified sleep architecture and intensified nocturnal desaturation, forecasting worse survival outcomes. A significant correlation was identified between ischemic heart disease and patients with proven pulmonary fibrosis exhibiting severe obstructive sleep apnea, in contrast to those with low or mild-to-moderate OSA. Moreover, high-resolution computed tomography demonstrated a correlation between moderate-to-severe coronary artery calcifications and severe obstructive sleep apnea. Pulmonary hypertension, perhaps evidenced by elevated right ventricular systolic pressure, appears to be correlated with OSA. It is advised that individuals with idiopathic pulmonary fibrosis undergo evaluation for sleep apnea **(12, 27)**.

Pathogenesis of ILD-PH

The significant correlation between ILD and PH can be elucidated by their same pathophysiological mechanisms related to parenchymal and vascular remodeling. While epithelial damage has traditionally been viewed as the primary factor in the onset of lung fibrosis, with vascular dysfunction regarded as a subsequent consequence, growing evidence suggests that the vasculature itself may play a pathogenic role in the initiation of lung disorders. Alveolar hypoxia is recognized for inducing reactive vasoconstriction (the Euler-Liljestrand

response) and redistributing blood to areas with improved ventilation. A sequence of mediators and cellular alterations facilitates vascular remodeling following this event, resulting in elevated pressure, wall tension, and shear forces. Nonetheless, pulmonary hypertension can manifest in the absence of resting hypoxemia or significant pulmonary pathology, and there exists no link between mean pulmonary arterial pressure and the extent of pulmonary function test abnormalities. Pulmonary hypertension in interstitial lung disease may also arise from endothelial dysfunction, oxidative stress, dysregulated immunological pathways, perivascular fibrosis, or hereditary susceptibility **(45, 46)**. Endothelial dysfunction is the primary culprit, as the pulmonary vascular endothelium generates many crucial vasoactive mediators that regulate tone, smooth muscle cell proliferation, and vascular remodeling. The most potent pulmonary vasoconstrictor is ET-1, which also functions as a co-mitogen for fibroblasts and smooth muscle cells. IPF was related with increased endothelial production of ET-1, particularly in individuals with concomitant pulmonary hypertension. Additionally, studies show that ET-1 stimulates fibrogenesis by interacting with matrix metalloproteinases (pro-fibrotic) and initiates the epithelial-to-mesenchymal transition by increasing TGF-β1 through an ET type A receptor. The latter belongs to the TGF-β1 class of cytokines, which are very potent pro-fibrotic growth factors that control a number of physiological processes, such as inflammation and cell division and proliferation **(45, 47)**. The BMPR-2 is responsible for regulating the signaling pathway of TGF-β, which in turn restricts the expansion of smooth muscle tissue in the vascular system and enhances the lifespan of the endothelium in the pulmonary artery. BMPR2 levels and mPAP exhibit a connection that is inversely proportional in individuals who have IPF. Hereditary PAH is mostly induced by a mutation in the BMPR2 gene that results in its inactivation. In rat models of pulmonary fibrosis, endothelin receptor antagonists, such as bosentan and macitentan, have demonstrated the ability to reduce fibroproliferative injury and pulmonary hypertension. The pathogenic score was shown to have a negative correlation with a decrease in NO synthase inside the lungs of patients who were diagnosed with ILD by the utilization of procedures that were similar to those of the previous study. Additionally to its role as a powerful vasodilator, nitric oxide also inhibits the aggregation of platelets, restricts the remodeling of blood vessels, and safeguards against reactive oxygen species **(45, 47, 48)**. IPF originates from recurring, unidentified injuries that compromise basement membranes and alveolar epithelial cells, leading to fibrin exudation and localized fibroblast activation, finally culminating in fibrotic remodeling of lung parenchyma. A notable underlying mechanism is oxidative stress imbalance, particularly a deficit in the antioxidant glutathione. This may lead to anti-vasodilatory effects and fibroproliferation (smooth muscle cell proliferation and enhanced extracellular matrix component synthesis), hence elucidating a further link to PH. Moreover, oxidative stress inactivates soluble guanylyl cyclase, which subsequently re-associates with antioxidants **(46)**. Pulmonary hypertension can develop as a result of vascular inflammation and pulmonary thromboembolism in individuals with connective tissue disease-related interstitial lung disease generated by autoimmune mechanisms (e.g., anti-endothelial antibodies). There is an increased likelihood of ILD and/or PH in patients with diffuse SScl. There is an increased chance of developing pulmonary arterial hypertension in SScl patients who have anticentromere antibodies (group 1), whereas those with antiscleroderma 70 antibodies demonstrate a greater prevalence of interstitial lung disease and interstitial lung disease-associated pulmonary hypertension (group 3) **(49, 50)**. A major inducer of fibrosis, the pleiotropic cytokine IL-6 has broad pro-inflammatory and immunological effects. An important function of IL-6 signaling in bleomycin-induced lung fibrosis in rats has been identified, and patients with pulmonary hypertension also have an increased pathway. Through proliferative and anti-apoptotic mechanisms, IL-6 is directly linked to increased pulmonary pressures, vascular remodeling, and right ventricular remodeling. In interstitial lung disease, tissue injury, inflammation, fibrosis, and hypoxia interact intricately to cause pulmonary hypertension. These factors exacerbate one another and lead to pulmonary vascular remodeling through a variety of processes **(47, 50)**.

Treatment

At present, there is no sanctioned medical treatment for ILD-PH. The fundamental pulmonary condition must be managed according to established criteria, including the provision of long-term supplemental oxygen treatment if necessary. Persistent thromboembolic pulmonary hypertension and sleep-disordered breathing are two reversible etiologies necessitating prompt intervention and management. Due to age and various medical factors, only a limited proportion of persons with ILD qualify for lung transplantation. Patients require referral for pulmonary rehabilitation, and diuretics are necessary to enhance fluid equilibrium. Nintedanib and pirfenidone, two antifibrotic agents newly sanctioned for IPF and COPD, have demonstrated enhancements in FVC and diminished disease development; nevertheless, their effects on PH remain unexamined **(52-54)**. Three different pathways can be used to categorize pharmacological agents for patients with group 1 PAH into five groups: the prostacyclin pathway, which includes prostacyclins and prostacyclin receptor agonists; the NO pathway, which includes NO-cGMP enhancers and PDE -5 inhibitors; and endothelin receptor antagonists. Exclusion criteria for pulmonary function tests were defined by the crucial trials (e.g., total lung capacity <60–70% of predicted values). However, a number of drugs have been tested in people with ILD-PH, mostly using registry data or unblinded case series, with varying degrees of success **(46)**. The first study was using phosphodiesterase-5 inhibitors to modify the nitric oxide pathway in pulmonary hypertension linked to interstitial lung disease. During a 12-week period, 180 participants in the randomized controlled STEP-IPF trial received sildenafil, a PDE-5 inhibitor, or a placebo. Although there was no discernible change in functional outcomes, there was a little improvement in quality of life and shortness of breath, and no significant adverse effects were recorded **(53-55)**. The INSTAGE study evaluated the efficacy of sildenafil in conjunction with the antifibrotic agent nintedanib in individuals with IPF. Patients receiving nintedanib in conjunction with sildenafil exhibited a diminished likelihood of reaching the specified composite endpoint of an absolute decline in FVC of ≥5% predicted value or mortality compared to those treated solely with nintedanib, despite this combination not enhancing quality of life (hazard ratio 0.56, 95% CI 0.38–0.82) (**18,55, 56)**. Unfortunately, the recently published experiment by Behr et al. did not support these positive results **Behr et al. (57)** assessing the effects of sildenafil as a supplement to pirfenidone over a 52-week period by looking at changes in exercise capacity, pulmonary function tests, and health-related quality of life. Riociguat, a soluble guanylate cyclase stimulator, was evaluated in patients with group 3 pulmonary hypertension brought on by idiopathic interstitial pneumonia in the largest trial to date on NO-cGMP enhancers, RISE-IIP. Significant damage, including increased rates of major adverse events and death, led to the trial's early termination. Therefore, riociguat is contraindicated for those with pulmonary hypertension linked to idiopathic interstitial pneumonia, according to the researchers of this phase 2b experiment **(58)**.

Continuous Positive Airway Pressure (CPAP)

CPAP is listed as the gold standard therapy for OSA in the treatment guidelines created by the European Respiratory Society and the American Academy of Sleep Medicine. In order to improve alertness, quality of life, and lower blood pressure, patients who have been diagnosed with moderate-to-severe obstructive sleep apnea after a home sleep apnea test or an in-laboratory sleep study should start CPAP therapy right away. As a flow generator, CPAP has the potential to produce air pressure higher than that of the surrounding environment. Through a tube, the device is connected to a nasal, intranasal, or oronasal facemask. The excess pressure it produces helps maintain airway patency, hence reducing the OSA patient's apnea or hypopnea. Patients who use the nasal facemask show the best adherence to CPAP treatment, making it the most recommended alternative. The OSA patient's symptoms will be lessened if their sleep is less fragmented. It is advised that people with obstructive sleep apnea lose weight, stop smoking, and abstain from alcohol in

addition to CPAP therapy **(30,59)**. Alternative approaches and equipment are available for the treatment of OSA. This involves augmenting the pharyngeal space using oral appliances for patients with obstructive sleep apnea who are refractory to CPAP treatment. **(60,61)**.

CONCLUSION:

OSA is a highly prevalent and clinically significant comorbidity in patients with ILD, particularly IPF, and its presence is associated with worsened prognosis, increased risk of PH. The complex interplay between OSA-induced intermittent hypoxia, systemic inflammation, and vascular remodeling may accelerate disease progression and contribute to right heart dysfunction. Despite often being underdiagnosed due to atypical symptoms in this population, timely recognition and treatment of OSA, especially through CPAP therapy can lead to substantial improvements in sleep quality, daytime function, cardiovascular status, and possibly survival.

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