Incidence of Sleep Disordered Breathing in ILD Patients: Review Article

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Abstract

Patients with interstitial lung disease commonly exhibit abnormal sleep architecture and increased sleep fragmentation on polysomnography. Fatigue is a frequent complaint, and it is likely that poor sleep quality is a significant contributor. A number of studies have shown that sleep disordered breathing is prevalent in this population, particularly in the idiopathic pulmonary fibrosis subgroup. Sleep fragmentation, arousals, and Stage N1 sleep are all increased in patients with ILD. Sleep disordered breathing, in the form of nocturnal hypoxia and obstructive sleep apnea, is common in these patients as well.

These sleep disorders are associated with indices of poor quality of life and excessive daytime sleepiness, and may be targets of therapy for the overall management of patients with ILD.

The aim of the present review is to summarize what is currently known about sleep and sleep disordered breathing in patients with ILD.

KeyWords: Interstitial lung disease, Sleep disordered breathing, Nocturnal hypoxemia, Obstructive sleep apnea.

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Introduction:

The interstitial lung diseases (ILD) are a heterogeneous group of disorders characterized by varying degrees of fibrosis and inflammation of lung parenchyma. These diseases typically cause restrictive lung disease and oxygenation impairment. ILD patients suffer from daytime symptoms, including dyspnea, cough, fatigue, and poor overall quality of life. In addition, ILD can result in severe hypoxemia and pulmonary hypertension with corpulmonale, which contribute to a high mortality in these patients [1]. Independent of the presence of daytime hypoxia, many individuals with ILD are observed to desaturate during sleep, with or without associated apnea. Sleep disorders can cause a wide range of symptoms and co-morbidities, including daytime sleepiness, fatigue, poor quality of life, pulmonary hypertension and higher mortality features similar to the manifestations of ILD. Sleep-related breathing disorders (SRBDs) represent a group of physio-pathological conditions that are characterized by an abnormal respiratory pattern during sleep that can be isolated or can coexist with other respiratory, nervous, cardiovascular, or endocrine diseases. SRBDs are now known to be widely prevalent in the general population and contribute to numerous problems resulting from the underlying fragmented sleep patterns.

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The sleep-related breathing disorders (SBD) classification of the American Academy of Sleep

Medicine describes obstructive sleep apnea (OSA), central sleep apnea (CSA) with or without Cheyne-Stokes breathing pattern and sleep-related hypoventilation [2]. An apnea is defined by a cessation of airflow for at least 10 seconds. The obstructive nature of apnea is evidenced by increased inspiratory effort. The definition of hypopnea can be summarized by a decrease in airflow for at least 10 seconds associated with an oxygen desaturation and / or an electro-encephalographic arousal and it requires a continuous measurement of thoraco-abdominal respiratory movements or a surrogate of intra-thoracic pressure [3]. Obstructive sleep apnea syndrome (OSAS) is an extremely common condition in the general adult population [4]; Obstructive sleep apnea (OSA) is a subtype of SRBDs, which is characterized by a repetitive pattern of upper airway collapsibility, airflow obstruction, and resultant arousals, it requires the presence of symptoms and an apnea hypopnea index (AHI) greater than five events per hour mainly consisting of obstructive respiratory events [5]. CSA is defined by a cession of airflow due to lack of inspiratory effort for at least 10 seconds. In contrast to obstructive apnea, there is no significant variation in intrathoracic pressure during central apnea. They are infrequent in the general population [6] but are commonly seen in patients with congestive heart failure and possibly associated with Cheyne-Stokes respiration. Sleep-related hypoventilation is characterized by a significant increase in nocturnal arterial carbon dioxide tension ($PaCO_2$) to 45 mmHg or more or by abnormally increased in $PaCO_2$ values compared to those of the waking state [7].

Patients with ILD are likely to be at risk for sleep-disordered breathing (SDB) due to limitations in their gas exchange and the ventilator impairment. This SDB in ILD can encompass a broad spectrum ranging from nocturnal oxygen desaturation (NOD) alone or NOD associated with OSA of varying intensity [8]. ILD patients are at additional risk for sleep disorders due to the stresses of chronic illness, respiratory abnormalities, and treatment effects. Sleep disorders contribute to the morbidity and mortality of ILD and treatment of these sleep disorders may improve outcomes. Particularly in the face of the limited treatment options directed at ILD, management of sleep disorders deserves particular attention in these patients [9].

Why are ILD patients at risk for sleep disorders?

Symptom overlap is likely common in patients with ILD and sleep disorders. Fatigue is a common complaint among patients with ILD. Although it is a relatively nonspecific symptom, sleep disorders often manifest with symptoms of fatigue [10]. Additional symptoms, such as daytime sleepiness and night time respiratory complaints may be typical manifestations of both illnesses. ILD is a chronic pulmonary illness that may predispose to a number of sleep disorders. Chronic medical illnesses are associated with self-reported insomnia and disturbed sleep. The emotional stress of the medical illness, as well as the stresses associated with medical procedures and treatments, will also contribute to psychological pressure that can contribute to insomnia. Some underlying diseases, such as scleroderma or other autoimmune disorders that are associated with ILD may increase the risk of iron deficiency anemia, which can contribute to restless legs syndrome. Scleroderma may result in esophageal dyskinesia and reflux, which are known to disrupt sleep. In addition, the infiltrative nature of scleroderma may also affect the anatomy of the upper airway, and predispose to upper airway collapse, although this has not been studied. Treatment of interstitial lung diseases is limited, but in cases of active alveolitis, corticosteroid therapy may be given to patients, and can increase the risk of obstructive sleep apnea [11].

Patients with ILD are likely to be at risk for sleep disordered breathing due to limitations in their gas exchange. Daytime hypoxemia is more common in patients with ILD compared to patients with healthy lungs. **Midgren and colleagues** showed that in 16 patients with moderate to severe ILD, nocturnal hypoxemia was related to the degree of daytime oxygenation [12], but not to lung mechanics. That is, the gas exchange impairment, and not necessarily the degree of restrictive ventilatory impairment, determines nocturnal hypoxemia. The nocturnal hypoxemia, if not treated, can cause further deleterious effects on oxygenation. Muscle weakness and fatigue may result from nocturnal hypoxemia, and these conditions can contribute to nocturnal hypoventilation [13]. The ventilatory impairment of ILD also put these patients at risk for sleep disordered breathing. Respiratory patterns of ILD

patients differ from normal patients, with ILD patients having a higher resting respiratory rate and higher alveolar ventilation. This pattern of breathing during wakefulness can predispose to hypoventilation during sleep [14].

Sleep architecture in interstitial lung disease

Numerous studies have demonstrated the fragmentation of sleep in patients with ILD by using polysomnography.

In 1985, **Perez-Padilla et al.** [15] provided the first comparison of sleep architecture between patients with ILD and age and sex matched controls. Six men and five women with clinical, radiographic and pulmonary functions compatible with ILD (10 also had lung biopsies) as well as a matched control group underwent standard overnight polysomnogram (PSG). The sleep architecture showed that Stage 1 sleep was increased while REM sleep was reduced and REM sleep latency was prolonged in the patient group compared with control subjects. The patients had more arousals per hour and more sleep stage changes per hour. Slow wave sleep was absent in seven patients and four control subjects. They noted that ILD patients with lower oxygen saturations during wakefulness had increased sleep fragmentation [15].

In 2002, **Prado et al.** [16] reported that a group of 27 patients with systemic sclerosis (48% of who had documented PFT abnormalities) similarly had reduction in REM sleep and an increase in arousal index and slow wave sleep in comparison with age-adjusted published norms. The role of sleep disorders in patients with ILD was supported by a 2005 study comparing nocturnal PSGs of patients awaiting lung transplantation with those of a healthy control group [17]. The study group consisted of 17 patients, six undergoing lung transplantation for pulmonary fibrosis. Although the study did not report the results separately for patients with ILD, for the group as a whole, there was an increase of Stage 1 and 2 sleep, more fragmented sleep patterns with more stage changes per hour, and a greater average time of wakefulness between sleep stages.

In assessing potential etiologies of sleep disruption among patients with ILD, **Hira and Sharma** [18] used actigraphy to evaluate the motor activity of subjects during sleep. Based on the percent activity during sleep, ILD patients (n = 20) were reported to have slightly more disturbed sleep than the controls (n = 20). ILD patients spent 0.18% of total sleep time (TST) in activity as compared to 0.12% of TST spent in activity among controls. Bye and colleagues cited a number of other mechanisms that potentially contribute to arousal including hypoxemia, hypercapnia, cough, and several respiratory reflexes [19].

In 2006, **Aydogdu M et al.** [20] thirty seven ILD patients were examined in the study and whole night standard polysomnography was performed to all. Polysomnography results revealed that, total sleep time, time spent in NREM sleep stage III and IV, and in REM sleep were decreased. The patients had poor sleep efficiency and they spent more time as wake after sleep onset (WASO). Severe oxygen desaturations were detected during sleep and statistically significant positive correlations were found between mean awake O2 saturation and mean and lowest sleep O2 saturations. Another recent study of similar design have shown reduced sleep efficiency, reduced slow wave sleep, and increased wake after sleep onset, which are all indices of sleep fragmentation [21].

In addition, **Schiza S et al. and Bosi M et al.** [8&22] studied sleep disorders in idiopathic pulmonary fibrosis patients, they found that sleep fragmentation (WASO) are increased, and sleep efficiency are decreased, and patients also have an increased incidence of periodic limb movement disorder.

In a study by **Vazquez and colleagues** in 2001, the authors sought to determine whether treatment of nocturnal hypoxemia would improve the sleep architecture [23]. They studied 19 patients with ILD and 14 control patients. In ILD patients, supplemental oxygen was shown to significantly reduce heart rate and respiratory rate during sleep, but had no effect on sleep efficiency or arousal index. This suggests that the nocturnal hypoxia may be a marker for other sleep disordered breathing that is inadequately treated by supplemental oxygen.

Respiratory disturbances during sleep

- Nocturnal Hypoxemia and Hypoventilation

Nocturnal hypoxemia can play a central role in the progression of disease in patients with ILD. Nocturnal hypoxemia can result in progressive pulmonary hypertension and corpulmonale if left untreated. Predicting and preventing nocturnal

oxygen desaturation among patients with PF is of significant clinical concern. Even this fairly straight forward aspect of sleep remains unclear. **Perez-Padilla et al.** [15] reported lower mean SpO2 during sleep among ILD patients as compared to age- and gender-matched controls. As might have been anticipated, patients with awake SpO2 below 90%, especially those with more severe awake hypoxemia, experienced oxygen desaturation during REM sleep. The patients with lowest awake SpO2 were reported to have greatest desaturation.

By contrast, **McNicholas et al.** [24] reported, ''Although oxygen desaturation does occur in patients with ILD; this desaturation is minor and unlikely to be of clinical importance." The authors studied seven patients with severe ILD, five with fibrosing alveolitis and two with Farmer's Lung. None of the patients had a history of loud snoring or daytime somnolence or clinically significant airflow obstruction. During the study, two of the patients were unexpectedly found to have apneas but neither patient had more than 2–3% oxygen desaturation during these apneic episodes. These patients had only transient desaturation and showed only slightly decreased mean SpO2 between wakefulness and sleep (both NREM and REM phases). The authors concluded that their results were significantly different from those of Perez-Padilla and Bye because of the confounding effect of including patients with snoring and

Sleep apnea in earlier studies.

In 1990, **Midgren** [25] investigated oxygen desaturation during sleep as a function of underlying respiratory disease. In this study, 14 patients with ILD were compared to 29 patients with COPD and 10 patients with scoliosis. Similar to other studies, a significantly greater reduction in mean SpO2 was observed during REM sleep as compared to the NREM sleep in all three groups, although the decline was least in the ILD patient population. The study was carried out with the intent of confining the investigations to conditions with ''reasonably high probability of clinically important desaturations during sleep." It was reported that the fall in SpO2 with sleep in ILD patients was minimal and the authors hypothesized that ILD patients are better oxygenated while resting supine than during exercise. **Midgren and Hansson** [26] had previously reported that the transcutaneous PCO2 (PtcCO2) was lower in ILD patients compared to controls; the increase in PtcCO2 with sleep was not significantly different than controls.

Miyahara et al. [27] studied the relationship between the degree of nocturnal desaturation (NOD) and pulmonary hemodynamics, pulmonary function tests and resting awake blood gases in patients with Chronic Pulmonary Diseases (CPD) in a Japanese population. The group of patients with CPD consisted of 16 patients with Restrictive Lung Disease, 11 patients with emphysema and 3 patients with Chronic Bronchitis. In this study population, NOD could not be accurately predicted from the pulmonary function tests or resting awake arterial blood gases (representing parameters of the severity of CPD). The study, however, was severely limited by the heterogeneity of the study population.

Hira and Sharma [18] reported a mean decline in SpO2 of 8.6% during sleep as compared to 3.6% among normal controls. They observed a maximum decline of 13.1% (10–16%) in the ILD patients as compared to 4.8% (3–6%) in the healthy controls. It was observed that ILD patients spent 16.9% of the mean TST with SaO2 below 85% while none of the controls has such degree of desaturation during sleep. They draw a parallel between their results of oxygen desaturation with the results obtained by **Bye et al.** [28]. Although they do not report information about the snoring data on their patient population, they report that the AHI was 0.56 in patients as compared to 0.58 in controls (not statistically significant).

In a study of 31 patients newly diagnosed with IPF, the maximal difference in SpO2 between wakefulness and sleep, as well as the nadir of oxygenation during sleep correlated with percent predicted total lung capacity and percent predicted diffusion capacity (DLCO) [29] and desaturations seen during sleep are thought to be greater than those at peak exercise, although studies of mixed ILD populations have not shown this association [26, 30].

- **Sleep Disordered Breathing**

Obstructive Sleep Apnea (OSA)

In the 1980s **Bye et al.** [28] unexpectedly identified two patients with OSA in their study of oxygenation during sleep, although other studies from the same time period reported a normal apnea-hypopnea index (AHI) in their cohort [15]. More recently, OSA has been identified as a potentially important comorbidity in patients with ILD in a retrospective analysis of IPF patients with symptoms suggestive

of sleep disordered breathing referred for polysomnography.

Eleven of 18 patients (61%) were diagnosed with OSA, with the remainder having upper airway resistance syndrome or snoring [31]. However, 875 patients with IPF had been seen during the period of the study, with only 18 referred to the sleep center and the authors speculated that treating physicians may not recognize the true incidence of sleep disorders in IPF or consider that the rapidly progressive course of the disease means that it is not relevant. Further prospective work from the same group in newly diagnosed patients with IPF showed 15% had at least moderate OSA, and 44% had mild disease [21]. In another study, **Lancaster et al.** found a prevalence of at least moderate OSA of 68% in a prospective study of 50 patients with newly diagnosed IPF [32], and subsequent studies in other cohorts have shown similarly high rates of moderate-to-severe OSA of between 51 and 72% in patients with incident IPF [22,29,33].

Mavroudi et al. [34] evaluate the frequency of sleep disorders in idiopathic pulmonary fibrosis (IPF) and sarcoidosis and to assess patients' quality of life in relation to these disorders. They found that Of the IPF patients, 68% were diagnosed with mild obstructive sleep apnea (OSA), 5.2% with moderate to severe, 5.2% with severe OSA and 21% with no OSA. Of patients with sarcoidosis, 52.4% were diagnosed with mild OSA and 4.8% with moderate severity OSA. The remaining 42.8% did not have OSA.

Troy LK et al. [35] A total of 92 ILD patients (including 44 with IPF) underwent PSG. At least mild obstructive sleep apnea (OSA) was observed in 65.2%.

Utpat K et al. [36] evaluate prevalence of SDB in ILD patients and found 28 case (28%) had OSA. The 28 cases of OSA were distributed as 15 mild OSA (53.57%), 10 moderate OSA (35.71%), and 3 severe OSA (10.71%).

CONCLUSIONS

The relationship of sleep with fibrotic interstitial lung disease is clearly complex. Sleep disorders play a substantial role in the morbidity and mortality of interstitial lung disease.

The sleep architecture is disrupted in patients with interstitial lung disease. The existing review on sleep in patients with ILD offers only a few consistent insights. ILD is associated with marked alterations in sleep architecture including decreased sleep efficiency, more arousals, decreased time in REM sleep and a higher degree of sleep fragmentation. Not only is sleep architecture effected by ILD, elements of respiratory mechanics are also affected.

Altered breathing patterns observed during sleep have been different across studies. Much larger studies with more robust methods are needed to document with certainty the actual changes in breathing patterns in ILD patients during sleep. A number of studies reported a significant reduction in SpO2 levels during sleep (especially REM sleep) in these patients. However, even these findings have not been reproduced in all studies. In addition to nocturnal desaturation, ILD patients may also have disordered breathing events, OSA is more common especially in IPF patients, which may independently contribute to reduction in sleep quality and affect quality of life.

Future directions

The review of existing literature reveals many areas of research in sleep in patients with ILD. Although there are a number of studies documenting alteration in sleep architecture in ILD patients, little is known about the etiology of sleep fragmentation. This may result from the interplay of nocturnal desaturation, altered respiratory physiology and sleep disordered breathing such as OSA in some patients. However, there may be contribution from additional factors such as chronic cough, which is common in ILD, and is not typically evaluated during PSG. Further, inflammatory cytokines produced as a result of ILD may independently effect sleep quality and contribute to sleep disorders. More fully evaluating the contributors to altered sleep in ILD is of particular importance in terms of potential for improving quality of life in these patients.

Systematic evaluation of sleep-in patients with ILD will also provide a starting point to determine the efficacy of currently available interventions in improving the quality of sleep in these patients. Moreover, given the occurrence of significant nocturnal oxygen desaturation in ILD, it is imperative to study the role of oxygen in modifying sleep characteristics in these patients.

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