CLINICAL REVIEW

Sleep and respiratory sleep disorders in idiopathic pulmonary fibrosis

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SUMMARY

Idiopathic pulmonary fibrosis (IPF) is an interstitial lung disease (ILD) characterized by inflammation and progressive scarring of the lung parenchyma. IPF profoundly affects the quality of life (QoL) and fatigue is a frequently disabling symptom. The cause of fatigue is not well understood but patients with IPF often report extremely poor sleep quality and sleep-related breathing disorders (SRBD) that correlate with QoL. IPF patients present alterations in sleep architecture, including decreased sleep efficiency, slow wave sleep and rapid eye movement (REM) sleep, and increased sleep fragmentation. Moreover, sleep related hypoventilation during the vulnerable REM sleep period and obstructive sleep apnea-hypopnea syndrome (OSAHS) are frequent, but remain usually underdiagnosed. These SRBD in IPF are associated with alterations of the sleep structure, reduction of QoL and increased risk of mortality.

In the absence of an effective therapy for IPF, optimizing the QoL could become the primary therapeutic goal. In this perspective the diagnosis and treatment of SRBD could significantly improve the QoL of IPF patients.

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Introduction

Idiopathic pulmonary fibrosis (IPF) is defined as a specific form of chronic and progressive fibrosing interstitial pneumonia of unknown cause, which occurs primarily in older adults and is associated with the histopathologic and/or radiologic pattern of usual interstitial pneumonia [1].

IPF is the most common form of interstitial lung disease (ILD) with a poor prognosis (median survival 2–5 y) [2,3]. Despite remarkable improvement in understanding IPF, the pathogenesis of this disease needs to be further explored. The interaction between environmental stressors and genetic predisposition determines the activation of multiple pathogenetic pathways leading to the development of fibrosis [4]. IPF is characterized by heterogeneous clinical features and a highly variable course with inter-individual variability that impairs our ability to predict prognosis. The clinical spectrum of this disease, its morbidity and mortality, are influenced also by the coexistence of multiple comorbidities that are now better recognized [5–7]. The identification and treatment of these pathologies may improve morbidity and potentially impact mortality.

Sleep related disorders are increasingly recognized as important features in IPF [6–10]. In the last official guidelines for the diagnosis and management of IPF [1], obstructive sleep apnea-hypopnea syndrome (OSAHS) is recognized for the first time as an important comorbidity.

Recent studies have focused on quality of life (QoL) in IPF patients. Fatigue is a common and frequently disabling complaint in these patients [7]. The cause of fatigue in IPF is multifactorial (the disease itself, comorbidities, medications, sleep quality, depression etc). Poor sleep quality may be another potential underestimated cause of fatigue. The patients with IPF report extremely poor sleep quality and symptoms consistent with sleep-related breathing disorders (SRBD) that correlate with poor QoL. Moreover, recent studies show an increased incidence of OSAHS in patients with interstitial lung diseases and particularly IPF [9]. IPF shares with other respiratory diseases (i.e., chronic obstructive pulmonary disease, COPD) some pathogenic factors (in particular rapid eye movement related hypoventilation and ventilation/perfusion mismatch) in the development of nocturnal desaturations and OSAHS (overlap syndrome) [11]. However, IPF is a rare disease and the role of SRBD in this pathology has been investigated only in a limited number of studies, compared to the ones conducted on COPD.

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Published studies related to sleep in IPF (Table 1) should be divided into those performed before and after the introduction of American Thoracic Society and European Respiratory Society International Multidisciplinary criteria for the classification of the idiopathic interstitial pneumonias [12]. The limited number of studies from the mid-eighties and nineties includes small numbers of patients with a variety of restrictive lung disease that, unlike IPF, occurs on a background of systemic disease, affecting multiple organs/systems which may themselves influence sleep quality and/or SRBD. By contrast, studies performed after the 2002 guidelines, have mostly included only patients with confirmed diagnosis of IPF and this may clarify the reasons for some different results between previous and more recent studies.

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

Sleep architecture

A significant number of studies have demonstrated a sleep disruption and consequent impairment of physical and social functioning in patients with IPF. A first description of sleep alteration in ILD patients was provided by Bye at al. who highlighted a decrease or disappearance of rapid eye movement (REM) sleep in these patients [13]. The comparison of sleep architecture between patients with ILD and age and sex matched controls is described by Perez-Padilla et al. [10]. In this polysomnographic study the authors showed a worsening in sleep quality in ILD group, with increase in non rapid eye movement (NREM) stage 1 (33.7% of total sleep time versus 13.5%) and in sleep fragmentation (13.7 ± 3.1 arousals/h and 24.3 ± 6.0 sleep stage changes/h versus 6.9 ± 1.0 and 12.7 ± 1.4, respectively). A decrease of REM sleep (11.8% versus 19.9% total sleep time (TST)) was also found. Moreover patients with ILD with awake SaO2 less than 90% had greater abnormalities in sleep structure than those with SaO2 exceeding 90%. Similar results were reported by Mermigkis et al. [8] in 15 patients with IPF and by McNicholas et al. in seven subjects with severe ILD [14]. Reduction in sleep efficiency, slow wave sleep and REM sleep were found also in patients with stable moderate ILD (diffuse fibrosis on X-ray examination, reduced lung volumes, and low lung compliance) and daytime hypoxemia [15]. These sleep alterations were confirmed by Pihtili et al. [16] in a recent study carried out in 50 patients with ILD (17 IPF, 15 sarcoidosis stage II–III and 18 scleroderma).

Sleep quality and quality of life (QoL)

It is known that poor sleep quality is extremely common in patients with IPF and it is associated with poor QoL. In a cross-sectional controlled study, using validated measurements of self-reported sleep quality (Pittsburgh sleep index), daytime sleepiness (Epworth sleepiness scale) and medical outcomes (short form health survey (SF36)), sleep quality was significantly worse in patients with IPF compared to normal control subjects [17]. Poor sleep quality was not associated with pulmonary function test parameters, but sleep quality was correlated with daytime sleepiness and poor health-related QoL, as assessed by the SF-36. These findings suggest that poor sleep quality may adversely impact both the emotional well-being and the physical functioning of patients with IPF, contributing to the decreased health-related QoL experienced by these individuals in comparison to the general population.

Clark et al. [18] demonstrated that within the SF-36 scores, the physical functioning, social functioning, and energy domains were associated with lower overnight SaO2 mean and sleep alterations...
normal subjects, during sleep, respiratory frequency and PtcCO2 were increased, TE was shortened, and ventilation was unchanged. In ILD patients, respiratory frequency and TE decreased, while the rise in PtcCO2 observed in normal subjects during sleep did not occur. The authors hypothesized that the increased drive to breathe in patients with ILD during wakefulness may be a behavioral phenomenon dependent upon cortical perception of afferent information from the respiratory apparatus, which disappears during NREM sleep.

Respiratory disorders in sleep

Sleep related hypoventilation in REM

In the International Classification of Sleep Disorders (ICSD 3) [20] the REM-related respiratory disorders in ILD patients are included in the “Sleep related hypoventilation due to a medical disorder”.

ILD is characterized by reduced lung volumes, ventilation/perfusion (V/Q) mismatch, and gas diffusing capacity impairment. During wakefulness, compensatory mechanisms associated with ventilator chemosensitivity and elastic load responses provide augmented activation of ventilatory muscles with compensation of alveolar ventilation and initially maintenance of PaCO2 and Pao2 homeostasis or development of mild hypoxemia with normocapnia. From NREM to REM sleep, there is a progressive decrease of compensatory mechanisms, with consequent reduction of alveolar ventilation and appearance of hypoxic and hypercapnic respiratory failure. These signs occur primarily in REM sleep when there is a reduced activation of other ventilatory muscles and the diaphragm is not able to support alveolar ventilation.

The combination of the decreased lung volume, resulting in reduced oxygen reserve, the alteration of V/Q and the condition of being closer to, or on, the steep portion of the oxyhemoglobin dissociation curve increase the severity of oxyhemoglobin desaturation in the hypoventilation phases of REM sleep. This REM related hypoventilation has been also recognized as a significant abnormality in patients with COPD, neuromuscular and chest wall disorders [11,21,22].

Between 1984 and 2014, nine studies explored the prevalence and the severity of sleep related hypoxemia and REM related sleep disordered breathing in ILD patients (Table 1).

Bye et al. showed that patients with ILD often develop marked fall in SaO2% during REM sleep [13]. In a cross-sectional study performed in a group of seven patients with moderate ILD (mean vital capacity 50%, mean diffusing capacity 46% predicted) McNicholas demonstrated that all subjects had episodes of oxygen desaturation during sleep but the SaO2 presented only a slight fall in REM sleep. [14]. These data suggest that nocturnal oxygen treatment need not be considered in patients with ILD unless the level of oxygenation, during wakefulness, indicates the need for such treatment. However the results could be conditioned by the small sample size and the heterogeneity of the patient group (1 Cheyne Stokes respiration, 1 OSAHS, 1 severe respiratory failure and 4 without SRBD or severe respiratory failure).

Similar results were shown by Midgren et al. in a cross-sectional study conducted on 16 IPF patients with total lung capacity (TLC) 65.6% predicted and slight hypoxemia during wakefulness (PaO2 68.2 mmHg) [15].

Different results were shown by Perez-Padilla et al. [10] in 11 ILD patients in whom cumulative percentage time at SaO2 < 90% (CT90) was much lower than in healthy controls (43.3 ± 14.9% vs 0.2 ± 0.1%) and oxygen saturation dropped during slow wave sleep with lower values in REM sleep.

In a retrospective study in 134 patients with moderate-severe (TLC 68.8% and diffusion lung CO, DLCO, 37.4% predicted) ILD (IPF, idiopathic non-specific interstitial pneumonia, pulmonary hypertension) Corte et al. [23] showed that a significant nocturnal...
desaturation (>-10% of sleep with SpO2 < 90%) occurred in 49 (37%) out of 134 patients. Significant nocturnal desaturation was present also in 21 (32%) out of the 65 patients with limited fibrosis (DLCO > 35%). When the authors assessed the extent of nocturnal hypoxemia 66% of patients met the criteria for moderate-severe CT90 (CT90 > 21%) and 32% of patients met the criteria for moderate-severe desaturation (>10% of sleep time with saturation <85%).

In a cross-sectional study all 38 ILD patients analyzed by Trakada et al. [24], fell below a baseline sleep saturation of 90% for 5 min or more, reaching a nadir saturation of at least 85%. In a group of 15 patients with moderate IPF (TLC 65%, FVC 77%, DLCO 56.3% predicted), Mermigkis et al. [8] noted significant differences comparing IPF patients and controls in mean and nadir oxygen saturation during sleep and CT90 (O2 saturation mean 91.6 ± 3.8 vs 95.3 ± 1.9, O2 saturation nadir 81 ± 6.2 vs 91.3 ± 2.9, CT90 34.3 ± 37.3 vs 0.9 ± 1.2) despite no differences in the apnea-hypopnea index.

Applying an arbitrary definition of nocturnal hypoxemia (CT90 > 2%) on 67 ILD patients (60 IPF, seven connective tissue diseases) with mild impairment (FVC 80% and PaO2 89 mmHg) Clark et al. [18] showed that mean overnight oxygen saturation was 92.5% but decreased in 45% of patients (18%) had a CT90 of more than 30% of TST.

In a cross-sectional study Tatsumi et al. [25] analyzed 14 patients with moderate-severe ILD (TLC 72.5%, FVC 67.9% and DLCO 29.6% predicted). During sleep, 71.4% of these subjects showed hypoxic episodes for more than 4% of TST, and five patients had episodes for more than 10%. Almost all desaturations occurred in REM sleep and were associated with decreased excursions of the chest wall and abdomen. Only 3% of these hypoxic episodes were due to obstructive sleep apnea. The severity of desaturation both in REM and NREM sleep was negatively correlated with ventilatory responses to CO2, but was not related to ventilatory responses to hypoxia and pulmonary function parameters such as FVC, functional residual capacity (FRC), and DLCO. Only in REM sleep the severity of desaturation was inversely correlated with the value of baseline SaO2 during wakefulness.

The association of depressed CO2 drives and sleep desaturation suggests that chemical control of breathing is another important factor in determining the severity of desaturation during sleep in ILD. Depressed CO2 drives and sleep desaturation are additional mechanisms responsible for desaturation during REM sleep in patients with ILD similar to what is observed in patients with COPD and neuromuscular/chest wall diseases [11,21,22].

REM-related sleep disordered breathing, resulting from alveolar hypoventilation in ILD and IPF, is therefore frequent and often severe. The development of shared criteria for REM-related hypoventilation in IPF will allow the collection of more homogeneous and comparable data [26].

Obstructive sleep disordered breathing

OSAHS is one of the most common SRBD, affecting up to 9% of men and 4% of women [27]. Excessive sleepiness [28,29], neuro-cognitive deficiency [28,30,31] and low QoL [32,33] represent the most frequent symptoms patients complain about. Car crashes [34], increase of cardiovascular morbidity and heart mortality [35,36] are the worst complications reported, with significant increase of health and social costs as a consequence [28].

Although the increase of central respiratory drive is considered a protective factor, OSAHS is a common disorder in ILD patients [16]. This high frequency was not reported in the past and only the REM related hypoventilation was considered in patients with ILD. Underestimation of SRBD in ILD could be due to the techniques of recording: previous studies, dating back 10–20 y, used only thermal sensors and not nasal pressure transducers, which are recognized as more sensitive devices for hypopnea detection, that represent the majority of the respiratory events observed in IPF patients [37].

In a recent retrospective study by Mermigkis et al. [38], SRBD were reported in 18 patients with moderate IPF (TLC 66.3%, DLCO 49.9% predicted). OSAHS was confirmed in 11 patients while other seven subjects were diagnosed as upper airway resistance syndrome (3/18) or primary snoring (4/18). Oxygen saturation below 90% was observed during 17.7% of TST. The periodic limb movement index was elevated in seven patients and two patients were diagnosed as restless legs syndrome (RLS). An interesting feature of this study was a reduction in sleep efficiency, slow wave sleep and REM sleep as well as marked sleep fragmentation due to increased arousals in all 18 patients. The apnea hypopnea index (AHI) was positively correlated with body mass index (BMI) values: OSAHS was observed in 11 moderately to severely obese IPF patients (BMI = 38.4 ± 3.1, range = 35.3–44.3 kg/m²), while upper airway resistance syndrome and primary snoring were observed in those patients with BMI values in the normal or overweight range. REM AHI and total AHI were negatively correlated with forced expiratory volume in the first second (FEV1) and with FVC percentages. These data suggest that the decreased lung volumes in ILD patients can reduce the upper airway stability and increase resistance due to a decreased traction on the upper airway. These changes can facilitate the upper airway collapse, especially during REM sleep when FRC is further reduced due to the inactivity of the intercostal muscles. Therefore, obese IPF patients with significantly decreased pulmonary function may be at increased risk for OSAHS, particularly during REM sleep [38].

Moreover, the authors highlight that despite growing OSAHS awareness among healthcare providers, treating physicians may defer sleep testing due to more acute problems such as dyspnea and limitations in daily activities. However, the data of this study suggest that OSAHS is often observed in patients with IPF and these patients should be asked for possible sleep problems and referred to sleep physicians for further evaluation.

In a cross-sectional study on 34 patients with moderate IPF (TLC 68.1%, DLCO 53.6% predicted) without pharmacological or oxygen treatment, Mermigkis et al. [39] showed a high incidence of OSAHS (59%, 44% mild and 15% moderate-severe OSAHS). Sleep structure showed a decrease in sleep efficiency and REM sleep (10.1 ± 4.8%) and an increase in stage 1, arousal index and wake time after sleep onset. REM sleep appeared as the most vulnerable period for SRBD in IPF patients (REM AHI was ≥ 5 even in patients with a normal total AHI). In addition, REM AHI was significantly correlated with TLC. These data confirm the hypothesis that decreased lung volumes facilitate the upper airway instability especially during REM sleep.

Similar results are reported by Lancaster et al. [40] in a polysomnographic study carried out in 50 patients with moderate IPF. 88% of these subjects had an AHI of ≥5 events per hour, 10 subjects (20%) had mild OSAHS (AHI > 5 and <15 events per hour), and 34 subjects (68%) had moderate-to-severe OSAHS (AHI >15 events per hour). Spironometry, lung volumes, and DLCO showed no correlation with the AHI or severity of SRBD. The lack of correlation between the pulmonary function test and the severity of sleep apnea could be related to the upright or standing position of the patients when performing the pulmonary function test. Neither ESS nor sleep apnea score of sleep disorders questionnaire (SA-SDQ) alone or in combination was a strong screening tool.

A possible confounding factor was the inclusion of patients under corticosteroids or other treatments for IPF which may have influenced sleep and/or SRBD.

Applying the American Academy Sleep Medicine guidelines [41] for the scoring of hypopnea, Mermigkis et al. [42] demonstrated...
that five out of 23 patients (22%) with moderate IPF (TLC 68%, DLCO 59.5% predicted) had an AHI within the normal range, six patients (26%) had an AHI compatible with mild OSAHS, and 12 patients (52%) had moderate to severe OSAHS. The subjects in the latter group were included in the study and were started on continuous positive airway pressure (CPAP).

In the studies carried out by Lancaster et al. [40] and Mermigkis et al. [42] the majority of scored respiratory events were hypopneas.

In 50 patients with diagnoses of ILD (17 IPF, 15 sarcoidosis stage II–III, 18 scleroderma), without important risk factors for SRBD (BM ≤ 30 and no upper airway pathologies that could cause OSAHS) Pihtili et al. [16] showed a diagnosis of OSAHS in 68% of the subjects (19 mild, 11 moderate, and four severe). The prevalence of OSAHS was 82.3% in the IPF patients, 66.6% in the sarcoidosis patients, and 55.5% in the scleroderma patients. The AHI was 11.41 ± 12.52 and most of the respiratory events were hypopneas. REM-related sleep apnea was present in 52.9% of the patients. The frequency of OSAHS was higher in patients with severe disease and in patients with diffuse radiological involvement.

An interesting field of research is the study of the interrelationship between OSAHS and gastroesophageal reflux disease (GERD) in IPF patients. Some studies strongly suggest that GERD or occult and repetitive microaspiration play a key role in the pathogenesis of IPF [43]. It is known that the lung fibrosis alters intrathoracic pressure and this results in morphologic or mechanistic effects on the diaphragm’s esophageal hiatus and the lower esophageal sphincter (LES). This alteration of LES can promote GERD. Creating a transdiaphragmatic differential pressure, OSAHS can also promote a dysfunction of LES and worsen the severity of GERD.

Pihtili et al. [44] examined the putative link between OSAHS and GERD in 54 patients with moderate IPF (FVC 64%, DLCO 43% predicted); 90% patients showed GERD, 64% had a diagnosis of OSAHS and 50% presented both diseases. Subjects with IPF had a risk of GERD seven-fold greater than subjects with other forms of ILD but GERD was not more frequent or severe among subjects with OSAHS vs. those without OSAHS. These results suggest that OSAHS is not a risk factor for GERD in IPF.

Since SRBD are frequent even in the initial phase of ILD, sleep evaluation and polysomnographic study should be considered in all patients with IPF and a high percentage of these subjects could be treated with positive air pressure also for the improvement of QoL (see paragraph Therapy of SRBD).

Mortality and mechanisms of mortality

REM related sleep disordered breathing in ILD patients seems to play a role not only in the quality of sleep and life but also in the severity and mortality of the disease.

Pulmonary hypertension (PH) is a common complication of IPF with a reported incidence ranging from 32 to 85% [45]. The development of PH during the course of the disease has a negative impact on functional status and QoL of IPF patients and it is associated with a poor survival. The pathogenesis of PH in IPF is incompletely understood but hypoxic pulmonary vasoconstriction, leading to remodeling of the vessel wall, is a mechanism of PH both in idiopathic and in secondary chronic lung disease [46].

In a cross-sectional study in 33 patients with IPF, Pitsiou et al. [45] showed that PH was present in 57% of the subjects. Nocturnal hypoxemia was correlated with advanced PH and right ventricular dysfunction. There was also a correlation between pulmonary arterial pressure and exercise parameters especially the recovery time of SpO2 after the end of the exercise. These data lead the authors to conclude that intermittent nocturnal hypoxemia, common in IPF patients, is an important risk factor for PH.

The sleep-related desaturation in ILD patients is linked to pulmonary vascular disease and therefore it is a risk factor for increased mortality. Corte et al. [23] demonstrated that increased mortality risk was associated with elevated nocturnal oxygen desaturation index (ODI), number of SpO2 dips <90%, cardiovascular non-invasive biomarkers (brain natriuretic peptide) and moderate to severe PH, but there was no link with severity markers of the underlying ILD (including FVC and composite physiologic index, CPI). In a group of ILD patients (DLCO > 35% predicted) the authors retrospectively compared sleep desaturation, PH severity and degree of fibrosis, defined by CPI [47], and observed that nocturnal desaturation was related more to PH severity than to degree of fibrosis. These results suggest that in ILD, intermittent nocturnal hypoxia may play a role in the development of PH. The possible links between nocturnal hypoxia and PH could be the increase of endothelin 1, the hypoxia-mediated endothelial dysfunction, and a concomitant OSAHS. However, in this study, the use of oximetry did not permit to distinguish those patients who desaturated due to concomitant OSAHS.

In a polysomnographic study, Kolilekas et al. [48] showed that intermittent sleep oxygen desaturation exceeds significantly that of maximal exercise and is associated with survival. Among SRBD parameters, the lowest saturation during sleep correlates best with clinical, functional and physiological parameters of disease severity and outcome. The sleep oxygen desaturation variables studied were related to lung damage, sleep apnea events, exercise oxygen desaturation, dyspnea, and right ventricular systolic pressure. These data imply the existence of a link between lung damage and apnea events in the induction and severity of intermittent sleep oxygen desaturation that aggravate pulmonary arterial hypertension and influence IPF survival. Evidence that treatment of comorbidities such as OSAHS may influence mortality in IPF patients with a difference in survival rates between good and poor CPAP compliant patients was described in a recent published multicenter study by Mermigkis et al. [49]. Two years after CPAP initiation, all good CPAP compliance patients were alive, and only one case of hospitalization due to acute IPF exacerbation was reported. By contrast, three patients from the poor CPAP compliance group died during the first 24 mo and six needed hospitalization for acute exacerbation of IPF in the same time period.

Therapy of SRBD

In the absence of an effective therapy for IPF, optimizing the QoL could become a primary therapeutic goal. In this perspective the diagnosis and treatment of SRBD could significantly improve the QoL of IPF patients [16,37,38,40,42,45,50]. Available tools are O2 therapy for REM-related sleep disordered breathing and positive pressure in the upper airway for the overlap of IPF and OSAHS.

The administration of O2 is not particularly difficult and it is mostly recommended for advanced forms of ILD. However, in a Cochrane review analyzing the effect of long-term home oxygen therapy in patients with a diagnosis of IPF and hypoxemia there was evidence that oxygen therapy did not improve survival when respiratory insufficiency had developed [51].

Only one study has been carried out to analyze the use of positive airway pressure in the overlap of IPF and OSAHS. Mermigkis et al. [42] demonstrated that if IPF patients with OSAHS showed a significant improvement in daily living activities based on the FOSQ, at 1, 3, and 6 mo after CPAP initiation. Improvement was also noted in other questionnaires assessing QoL (PSQI, FSS, SF-36), daytime sleepiness (ESS), and depression (Beck depression.
inventory), though not to a statistically significant degree, probably because of the multifactorial influences of IPF on physical and mental health. In a more recent multi-center study, Mermigkis [49] showed that effective CPAP treatment in IPF patients with comorbid moderate to severe OSAHS resulted in a significant improvement in daily living activities, and quality of sleep and life, based on questionnaires assessing QoL (FOSQ, ESS, PSQI, FSS, SF-36) used during the first year of the follow-up period.

For multiple reasons (cough, claustrophobia, or insomnia) the possibility of non-acceptance or poor compliance with CPAP is high, and may be eliminated when these patients are followed up thoroughly and the staff of the sleep laboratory is aware of all the potential difficulties that must be overcome [52].

**Predictors of SRBD**

If the SRBD in ILD patients are associated with poor QoL, alteration of sleep and increase of mortality, it is reasonable to consider the identification of effective clinical and functional predictors of SRBD. This issue has already been addressed in the literature for patients with neuromuscular diseases [53] and for COPD with nocturnal desaturation [54–56].

In ILD patients Perez-Padilla et al. [10] showed that subjects with awake SaO2 less than 90% had greater abnormalities in sleep structure than those with SaO2 greater than 90%. Moreover, sleep SaO2, both during NREM and REM sleep, is correlated with SaO2 during wakefulness [14,25].

In the study conducted by Clark et al. [18] the best physiological predictor of nocturnal hypoxemia (CTsao > 2% of study time) was resting daytime oxygen level while, in contrast, FVC was a poor predictor. Similarly, Midgren et al. [15] showed that the SaO2 value in sleep was highly correlated with PaO2 at rest and during moderate and maximum exercise and with SaO2 in nocturnal wakefulness. There was no significant relation with PaCO2 during wakefulness, airway resistance or lung volume.

In light of these findings, normal PaO2 and SaO2 during wakefulness (at rest and during exercise) cannot exclude the presence of REM related sleep disordered breathing, but alterations of these parameters during wakefulness seem to be the predictors of an increased risk of SRBD in IPF. However, other studies exclude a correlation between PaO2 during wakefulness and desaturation during sleep [23,45].

**Conclusion**

In the past, a high frequency of OSAHS in IPF was not reported and only the REM related hypoventilation was considered in patients with ILD. This different interpretation of SRBD in ILD could be due to the new techniques of recording.

The REM-related sleep disordered breathing is associated with alteration of sleep structure, reduction of QoL and increased risk of mortality. On the other hand in IPF patients OSAHS is a prevalent disorder, frequently moderate to severe [16].

In other chronic pulmonary diseases (COPD, obesity hypoventilation syndrome) the overlap with OSAHS is a factor of increased severity that worsens sleep quality, QoL, gas exchange, and increases exacerbations, and mortality [57,58].

Physicians should dedicate greater attention to IPF patients with suspected OSAHS. Following diagnosis of OSAHS these patients should be referred to experienced centers capable of managing an effective therapy with CPAP and able to overcome interfering clinical problems (especially cough, claustrophobia, insomnia). The minimum target of the therapy will be to improve the symptoms and the QoL.

In the future well-designed studies will be mandatory to investigate all sleep disorders in IPF.

### Practice points

1. There is evidence that IPF patients present alterations in sleep architecture, sleep related hypoventilation and OSAHS.
2. Sleep alteration and SRBD are associated with reduction of QoL and increased risk of mortality.
3. Since SRBD are frequent, sleep evaluation and polysomnographic study should be considered in patients with IPF.
4. A high percentage of IPF patients with SRBD could be treated with positive air pressure for the improvement of QoL.
5. In the absence of an effective therapy for IPF the therapeutic goal should be to improve the symptoms and the QoL.

### Research agenda

**Impact of ILD on sleep architecture**

- effects on sleep macrostructure (efficiency, duration, depth)
- effects on sleep microstructure (stability and instability)

**Identification of reliable wakefulness predictors of sleep related desaturation**

- test of lung function at rest
- test of lung function during exercise

**Prevalence of sleep disorders**

- REM related alveolar hypoventilation
- OSAHS
- Periodic limb movements
- other sleep disorders

**Impact of SRBD on symptoms and QoL**

**Impact of SRBD on the progression and mortality of IPF**

**Impact of SRBD treatment on symptoms, QoL, progression and mortality, social and health costs**

### Conflicts of interest

This was not an industry supported study. The authors have indicated no financial conflict of interest.

### References


* The most important references are denoted by an asterisk.


Dudley KA, Owens RL, Malhotra A. Pulmonary overlap syndromes, with a focus on COPD and IBD. Sleep Med Clin. 2013;8:363–79.


