REVIEW ARTICLE

Effect of Oxygen on Obstructive Sleep Apnoea with Interstitial Lung Disease

Ketaki Utpat and Jyotsna. M. Joshi

Department of Pulmonary Medicine, T. N. Medical College and B. Y. L. Nair Hospital, Mumbai, India

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Introduction

Interstitial lung disease (ILD) describes the group of lung diseases of diverse etiologies that involve inflammation and fibrosis of the interstitium of the lung. This heterogeneous group of disease causes limitation in oxygen diffusion and ventilatory impairment thereby leading to a restrictive lung disease. ILD patients suffer from daytime symptoms, including dyspnoea, cough, fatigue, and poor overall quality of life. Sleep-related breathing disorders (SRBD) represents a group of physiopathological 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. SRBD are now known to be widely prevalent in the general population and contribute to numerous problems resulting from the underlying fragmented sleep patterns. Obstructive sleep apnoea (OSA) is a subtype of SRBDs which is characterized by a repetitive pattern of upper airway collapsibility, airflow obstruction, and resultant arousals. It is associated with repeated episodes of partial or full cessation of breathing during sleep, usually accompanied by oxyhemoglobin desaturation. Patients with ILD are likely to be at risk for sleep-disordered breathing due to limitations in their gas exchange and the ventilatory impairment. The medical literature on the actual prevalence of sleep disorders in ILD is sparse. Independent of the presence of daytime hypoxia, many individuals with ILD are observed to desaturate during sleep, with or without associated apnoeas. There is mounting evidence that nocturnal hypoxia and sleep-disordered breathing (SDB) may contribute to adverse outcomes in ILDs. Apart from resulting in poor sleep quality and daytime fatigue, transient repetitive desaturation and associated sympathetic nervous system activation may play a role in the development of pulmonary hypertension and contribute to increased mortality[1, 2, 3].

Address for correspondence:

Dr. J. M. Joshi,
Professor and Head
Department of Respiratory Medicine,
T. N. Medical College and B. Y. L. Nair Hospital,
Mumbai-400008;
Tel: 022 23027643
Fax : 022 23003095
Email: drjoshijm@gmail.com

Sleep Architecture in ILD

In 1985, Perez-Padilla et al.[4] provided the first comparison of sleep architecture between patients with ILD and age and sex matched controls. The sleep architecture in patients with interstitial lung disease was noted to be significantly altered in comparison to controls. Stage 1 sleep was increased (33% of TST) while REM sleep was reduced (11.9%) and REM sleep latency was prolonged in the patient group. The patients had more arousals and more sleep stage changes per hour. Slow wave sleep was absent in seven patients and four control subjects. Further, one patient did not exhibit REM sleep. Among the ILD patients, those with awake oxyhemoglobin saturation (SpO2) below 90% had a higher percentage of Stage 1; more sleep state changes, more fragmentation of sleep and longer awake time than patients with awake SpO2 above 90%. Similar abnormalities had been previously reported in patients with Chronic Obstructive Pulmonary Disease (COPD) leading the authors to hypothesize that these alterations of sleep architecture might occur in most acute and chronic lung diseases and that poor sleep quality might be a nonspecific consequence of illness. While the cause

of sleep disturbance was not elucidated in this study, the fact the sleep disturbances were present and may have contributed to daytime morbidity illustrates a potential role of sleep disorders as a factor for poor quality of life in patients with ILD. There have been a number of conflicting observations reported regarding alterations in respiratory physiology during sleep in patients with ILD. Perez-Padilla et al.[4] also reported a higher breathing frequency and a shorter respiratory cycle duration in ILD patients compared to control subjects, during both wakefulness and sleep. During sleep, respiratory frequency decreased in normal controls; in ILD patients, by contrast, there was no significant change in respiratory frequency or respiratory cycle duration. The authors hypothesized that this lack of change might be due to the maintenance of reflexes causing rapid shallow breathing during sleep. The authors also reported lower mean SpO2 during sleep among ILD patients as compared to age and gender-matched controls Three patterns of SDB have been reported in patients with ILD, i) oxygen desaturation occurring primarily during rapid eye movement (REM) sleep, ii) a sustained fall in saturation during both non-REM (NREM) and REM sleep and iii) snorers, some of whom have the classic obstructive sleep apnoea (OSA).[5]

Obstructive sleep apnoea has been described in patients with disorders that may cause ILD, including rheumatoid arthritis[6] and sarcoidosis.[7] Nocturnal oxygen therapy is recommended for ILD with nocturnal hypoxemia, while the use of continuous positive airway pressure (CPAP) is now the established treatment for OSA.

Obstructive sleep apnoea in ILD

Pihtili et al.[8] presented polysomnographic data in patients with ILDs including 17 patients with idiopathic pulmonary fibrosis (IPF), 15 patients with stage II–III sarcoidosis, and 18 patients with pulmonary fibrosis due to scleroderma. The study revealed a high prevalence of 68% OSA in this population. The prevalence of OSA was 82.3% in the IPF patients, 66.6% in the sarcoidosis patients, and 55.5% in the scleroderma patients. The OSA severity was mostly mild, while the scored respiratory events were predominantly hypopnoeas. An interesting feature of this study is that an increased incidence of OSA was observed after the exclusion of patients with well-known predisposing factors for OSA such as obesity and/or significant upper airway pathologies causing obstruction. The authors used a disease severity index consisting of body mass index, carbon monoxide diffusion capacity, the Modified Medical Research Council (MMRC) dyspnea scale, and the 6-minute walk distance (6MWD), with scores ranging between 0 and 10. The OSA diagnosis rate was higher in the patients who had severity index $\geq$3.

CPAP Therapy in OSA with ILD

CPAP therapy has an inveterate role in the management of OSA. It acts by the virtue of its action of dynamically splinting the redundant upper airways thereby intercepting the airway collapsibility. However, the role of CPAP therapy in OSA associated with ILD is an uncertain domain. There is a deficiency of data pertaining to the utility of CPAP therapy in OSA associated with ILD with respect to its impact on the sleep, quality of life and disease progression. A recent study conducted by Mermigkis et al. concluded that effective treatment with CPAP therapy in patients with IPF results in significant improvements in daily activities and quality of life[9]. In addition CPAP therapy has also displayed a beneficial effect on pulmonary hemodynamics in patients with OSA by decreasing the pulmonary artery pressures[10]. These grounds rationalize the institution of CPAP therapy in OSA associated with ILD. However, CPAP commencement in this subgroup can be difficult due to several reasons. These include unacceptance or poor compliance due to a cough, claustrophobia or insomnia[11]. These factors are rectifiable to a certain extent by measures such as meticulous counseling, heated humidification and initiation of CPAP at an early stage of the disease when the rate of acceptance is relatively better. However, there is a dire need for further studies to address this issue.

Oxygen Therapy in OSA

Oxygen supplementation has been believed to have a deleterious effect on OSA by prolonging the apnoeas and hypopneas perhaps by removal of the hypoxic ventilatory drive. Gold et al.[12] found a reduction in central and mixed apnoea with nasal oxygen in nine patients, but the frequency of obstructive apnoeas doubled. However, Breitenbucher et al.[13] studied the effect of nocturnal low-flow oxygen administration in 10 consecutive patients with obstructive sleep apnoea and in 5 patients the clinical symptoms disappeared

completely with nasal oxygen administration. In the remaining 4 of 5 patients, insertion of a transtracheal catheter for nocturnal oxygen delivery resulted in a favorable outcome.

Oxygen Therapy in OSA with ILD

In a study[14] on patients of interstitial lung disease with associated obstructive sleep apnoea, we showed that nocturnal oxygen therapy has a beneficial effect on oxyhemoglobin saturation as well as the obstructive events. All patients had a restrictive abnormality on spirometry. The mean partial pressure of oxygen was 71.88 (+/- 12.44) in the awake state. None except one patient was hypercapnic, mean daytime partial pressure of carbon dioxide was 36.39 (+/- 8.27). The mean AHI was 23.33 (+/- 6.27), which showed significant improvement ($p<0.001$) in the AHI to 8 (+/- 8.03) on breathing 2 liters per minute of supplemental oxygen.

McNicholas et al.[15] have suggested that hypoxemia might be a critical factor in the pathogenesis of sleep-related breathing disorders, by resulting in hypoxia-induced brainstem depression. Low oxygen saturation during sleep in ILD is related to awake PaO2, age, and lung compliance, predicted by the equation:

Predicted SaO2=75+0.23(PaO2)-0.2(age).

Patients with SaO_2 less than 90% are reported to have more disrupted sleep than those with SaO_2 above 90%. The mean partial pressure of oxygen in this study was 71.88 (+/- 12.44) in the awake state and all patients had a low SaO_2 during sleep.

Arterial $PaCO_2$ is another factor, which has a dominant influence on breathing. Data on patients with heart failure show that low $PaCO_2$ results in sleep apnoea during sleep.[16] A carefully performed study[17] done during sleep in normal humans showed that central apnoea may be induced when the $PaCO_2$ is experimentally lowered by 1 to 3 mm Hg below the resting $PaCO_2$ while patients are awake. Patients with interstitial lung disease characteristically exhibit increased ventilation and breathing frequency when awake and these increases persist during deep non-REM sleep[18]. The resultant level of ventilation is usually excessive for the level of carbon dioxide (CO2) production leading to hypocapnea. Therefore, a low $PaCO_2$ while awake may predispose to ventilatory instability and development of sleep apnoea.

Both central and obstructive apnoeas may result, depending on the propensity of the upper airways to collapse, when cyclical output to respiratory muscles occurs during sleep in response to the stimuli (i.e. hypoxia or hypercapnia). The mechanism of apnoea elimination by nasal oxygen could be either by relieving the hypoxic brain stem suppression or by restoring a normal breathing pattern in hypercapnic patients by reducing the hypoxic influence on ventilation[19].

Conclusion

The diagnosis of OSA in cases with ILD would require careful consideration regarding treatment options, nocturnal oxygen desaturation requiring supplemental oxygen and OSA requiring CPAP therapy. In a subgroup of patients, oxygen supplementation is effective in reversing both apnoeas and oxygen desaturation.

The coexistence of Chronic Obstructive Pulmonary Disease (COPD) and Obstructive Sleep Apnoea (OSA) is known as the "Overlap Syndrome" and is explained by the high prevalence of both disorders.

Similar risk factors such as male gender, age, cigarette smoking and defective control of breathing predisposing to OSA.

The same could be applicable to ILD and OSA. Larger studies are required to study the frequency of sleep-disordered breathing in ILD and also the role of supplemental oxygen in treating "the overlap of ILD and OSA".

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