The “silent threat” of nocturnal hypoxia remains unresolved for patients with fibrotic interstitial lung diseases

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Sleep is an inherent and vital state of rest for both the body and mind. While it is recommended that adults get 7–8 h of sleep, patients with fibrotic interstitial lung disease (ILD) often experience poor sleep quality and shorter sleep duration [1–4]. Notably, nocturnal hypoxia is widely recognised as a comorbidity that occurs during sleep [5]. The most significant issue with nocturnal hypoxia is not only its impact on worsening sleep quality but also its contribution to the deterioration of pulmonary hypertension and the resulting poor prognosis [5]. Despite the acknowledgement of this issue by many clinicians and researchers, the management still lacks large-scale clinical trials, resulting in a lack of clear recommendations [6].

In this issue of *ERJ Open Research*, Margaritopoulos *et al.* [7] demonstrated that nocturnal hypoxia is present in more than a quarter of patients with both idiopathic pulmonary fibrosis (IPF) and those with non-IPF fibrotic ILD (retrospectively collected data from 2010 to 2013). It was associated with several noninvasive indicators of pulmonary hypertension and had a significant impact on prognosis. This is the largest study examining nocturnal hypoxia in the population of ILD to date, providing new evidence in this area. A recent prospective observational cohort study from the UK (recruited from 2018 to 2020, mainly IPF) also found that nocturnal hypoxia is associated with a more rapid decline in the quality of life and increased 1-year all-cause mortality [8]. These studies underscore the urgent need for intervention in nocturnal hypoxia.

Nocturnal hypoxia is generally thought to result from hypoventilation, sleep-related breathing disorders and cardiopulmonary vascular changes [9–11]. However, it occurs even in ILD patients with preserved pulmonary function and without obstructive sleep apnoea (OSA). Corte *et al.* [12] reported that ∼30% of ILD patients without exertional hypoxia experienced nocturnal hypoxia. Mermigkis *et al.* [13] reported that IPF patients with no evidence of OSA showed a significant nocturnal hypoxia (mean sleep time with oxygen saturation measured by pulse oximetry <90% was 12.6% of the total). Systematic review of nocturnal hypoxia in ILD has reported that the association between nocturnal hypoxia and forced vital capacity was not significant [5]. Although these intriguing data may underestimate hypoventilation due to supine positioning, it is possible that nocturnal hypoxia is not only associated with disease severity but also independently linked to feedback from cardiopulmonary vascular changes.

Our subsequent objective is to devise strategies for addressing nocturnal hypoxia in individuals with ILD. The points to be discussed include whether to administer oxygen alone or in combination with positive airway pressure (PAP). PAP treatment is a common and well-known effective therapy for OSA, also recognised for its potential to improve pulmonary haemodynamics [14, 15]. In patients with IPF and OSA, good compliance with PAP showed statistically significant improvement in multiple quality-of-life measurements after 1 year [16, 17]. However, a meta-analysis of randomised controlled trials demonstrated that supplemental oxygen therapy can be cautiously considered for improving nocturnal hypoxia and

symptoms of depression for patients with OSA when PAP is not tolerated [18]. There is no evidence regarding whether PAP improves pulmonary haemodynamics and quality of life in patients with ILD without OSA. The question of whether PAP should be used in all ILD patients with nocturnal hypoxia or only in those with both nocturnal hypoxia and OSA is an important topic for future investigation.

Another point of discussion is the duration of oxygen administration. A 1980 clinical trial in patients with COPD showed that continuous oxygen therapy was associated with lower mortality than nocturnal oxygen therapy [19]. In a landmark crossover randomised controlled trial in the UK, ambulatory oxygen was associated with an improvement in quality of life in ILD patients with isolated exertional hypoxia (no hypoxia at rest) [20]. These findings appear to suggest that many patients with ILD and nocturnal hypoxia may benefit from both daytime and nocturnal oxygen administration. Meanwhile, Ramadurai *et al*. [21] demonstrated that wearing the backpack containing oxygen led to a decrease in walk distance and increased dyspnoea in patients with ILD. The use of oxygen may hinder travel by aeroplane and could potentially lead to a decrease in outdoor activities due to concerns about others' attention. It is also necessary to consider whether the cost-effectiveness is adequate [22]. Even if future clinical studies show the benefits of long-duration oxygen therapy, physicians should alert patients to these effects and help them decide on the best way to meet their needs.

Given the high impact of this silent threat, it is time to conduct clinical trials on patients with ILD and nocturnal hypoxia. An international collaborative study is needed, taking into account differences in physique and the frequency of OSA.

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