Overlaps between obstructive sleep apnoea and other respiratory diseases, including COPD, asthma and interstitial lung disease

Izolde Bouloukaki[1], Michail Fanaridis[1], Dries Testelmans[2], Athanasia Pataka[3] and Sophia Schiza[1]

[1]Sleep Disorders Center, Department of Respiratory Medicine, School of Medicine, University of Crete, Heraklion, Greece. [2]Department of Pneumology, UZ Leuven, Leuven, Belgium. [3]Respiratory Failure Unit, G. Papanikolaou Hospital Medical School, Aristotle University of Thessaloniki, Thessaloniki, Greece.

Corresponding author: Sophia Schiza (schiza@med.uoc.gr)

Shareable abstract (@ERSpublications)
Obstructive sleep apnoea seems to be a common disorder in patients with respiratory disease, affecting the clinical outcomes of both diseases. Early detection and management are essential to improve morbidity and mortality in these patients. https://bit.ly/3SiuJH8

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Abstract

In the past, there was limited research relating to the role of sleep in respiratory diseases. Physicians treating these patients tended to focus mainly on the daily disabling symptoms, overlooking the possible significant role of coexisting sleep disorders such as obstructive sleep apnoea (OSA).

Nowadays, OSA has been recognised as an important, highly prevalent comorbidity for respiratory diseases such as COPD, asthma and interstitial lung diseases (ILDs). Overlap syndrome refers to the coexistence of chronic respiratory disease and OSA in the same patient. Although, in the past, overlap syndromes have been poorly studied, recent data underline that they result in increased morbidity and mortality compared with either underlying disorder alone. OSA and respiratory disease may be of different severity, and this, along with the existence of various clinical phenotypes, points to the necessity of an individualised therapeutic plan. Early recognition and OSA management could offer key benefits, such as improved sleep, quality of life and disease outcomes.

Educational aims

- Describe pathophysiological aspects of OSA in chronic respiratory diseases such as COPD, asthma and ILDs.
- Understand the bidirectional clinical importance when OSA coexists in chronic respiratory diseases.
- Review current knowledge of treatment strategies towards an individualised therapeutic plan resulting in patient-centric outcomes.

Introduction

Obstructive sleep apnoea (OSA) is as a major and under-recognised public health problem, with an increasing prevalence over time. It is widely recognised as an independent risk factor for cardiovascular and metabolic diseases, leading to significant increases in health and social costs. Therefore, healthcare providers should be familiar with clinical manifestations of OSA, from subtle intrusion into daily life, to excessive sleepiness, neurocognitive deficiency and low quality of life, in order to accurately identify high-risk patients and refer them to a sleep specialist for accurate diagnosis and effective treatment.

There are specific chronic respiratory disorders, such as COPD, asthma and interstitial lung diseases (ILDs), that may coexist with OSA and exacerbate sleep-related breathing disturbances. In particular, a synergistic relationship between OSA and these respiratory disorders has been described and is often referred to as overlap

syndrome (figure 1), leading to increased morbidity and mortality compared with either underlying disorder alone. Additionally, as the underlying disorders in overlap syndrome may vary in severity, there is a substantial inter-individual variability in heterogeneity and prognosis of the disease.

The purpose of this review is to summarise the current knowledge regarding overlap syndromes and reveal the role of OSA management in improving sleep, quality of life and disease outcome in these patients.

OSA and COPD

Prevalence

COPD and OSA are common pulmonary diseases. The prevalence of COPD or OSA in the general adult population is ∼10% [1]. The coexistence of these two diseases, referred to as overlap syndrome (OS), was first described by Flenley [2] in 1985. Although the term "overlap syndrome" also applies to the coexistence of OSA and any chronic respiratory disease, such as idiopathic pulmonary fibrosis (IPF), the use of this term is generally limited to the association of OSA and COPD. Given the high prevalence of these conditions, it is expected that many patients are affected by both diseases. However, this is not the case in the general population in which the coexistence of the two diseases due to chance alone can yield a prevalence of 1–3.6%. Nevertheless, the prevalence of OS may be higher in patients already diagnosed with either OSA (7.6–55.7%) or COPD (2.9–65.9%) [3]. These discrepancies in prevalence may be attributed to differences in the studied populations and in the methods used for OSA and COPD diagnosis between studies, as well as the low clinical suspicion for OSA coexistence among respiratory physicians. Specifically, previous studies were heterogeneous in terms of design and method, including not only different definitions of COPD and OSA but also COPD and OSA patients with different degrees of disease severity to determine accurate prevalence estimates.

Respiration during sleep in COPD

Sleep normally induces changes in breathing, including alterations in lung mechanics, diminished respiratory drive and reduced respiratory muscle activity [4]. Changes in lung mechanics include decreased ventilation–perfusion matching, decreased end-expiratory volume and functional residual capacity (FRC). Diminished respiratory drive during normal sleep is associated with blunted chemoreceptor sensitivity (decreased hypoxaemic and hypercapnic response) and increased upper airway resistance. During sleep there is hypotonia of skeletal muscles including the accessory respiratory muscles with relative preservation of diaphragmatic contraction. In particular, during rapid eye movement (REM) sleep, these changes are more prominent and alveolar ventilation is based only on the diaphragm and to a lesser degree on parasternal intercostal muscles [5]. Consequently, these disturbances result in alveolar hypoventilation, hypoxaemia and hypercapnia. Although this effect is mild and easily compensated in normal subjects, in COPD patients this may result in significant nocturnal oxygen desaturations during sleep due to a combination of ventilation–perfusion mismatch and hypoventilation. As a result, COPD patients may experience frequent awakenings, reduced sleep efficiency and quality, reduced REM sleep, and increased nocturnal hypoxic burden, with potential major clinical consequences, including increased risk of exacerbations, hospitalisations, cardiovascular events, reduced survival and poorer quality of life.

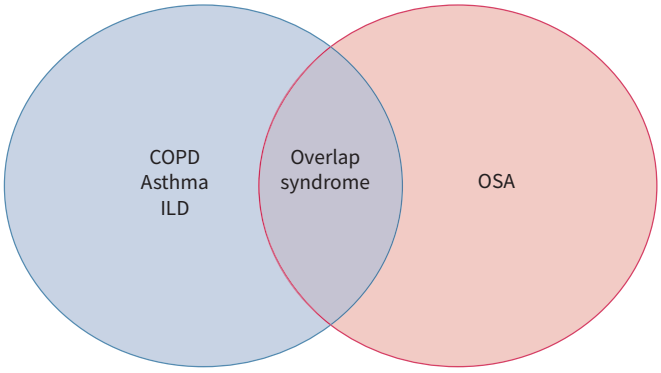

FIGURE 1 The overlap syndrome as a synergistic relationship between coexisting respiratory disease and obstructive sleep apnoea (OSA). ILD: interstitial lung disease.

Risk factors

COPD is a heterogeneous disease with multiple phenotypes ranging from patients with predominant emphysema to patients with predominant chronic bronchitis. The clinical phenotype of COPD and other patient-related factors may contribute to OSA development [4]. Promoting factors for OSA development are oral or inhaled steroids leading to fat deposition in the neck, rostral fluid shift in the supine position due to right heart failure and muscle weakness with consequent pharyngeal muscle weakness. Smoking, a major risk factor for COPD, also promotes and increases OSA severity through upper airway inflammation (figure 2). Patients with relatively mild COPD who have a higher body mass index (BMI) tend to develop OSA, and subsequently OS at a younger age. By contrast, lung hyperinflation, older age, low BMI, reduced REM sleep and treatment with theophylline can be protective factors against OSA [6].

Pathophysiology

In recent years knowledge regarding OSA pathophysiological traits has increased, including anatomical factors (*i.e.* upper airway collapsibility), as well as non-anatomical factors (upper airway muscle responsiveness, arousal threshold and loop gain). Although a recent study did not find differences in anatomical and non-anatomical traits between OSA and OS patients, a strong relationship between several important OSA traits and lung function parameters was noted [7]. Specifically, the authors found reduced upper airway response in those with indicators of air trapping and increased loop gain in those with airflow obstruction [7]. By contrast, another recent trial showed that the majority of OS patients had multiple altered pathophysiological traits (mostly high loop gain and low arousal threshold), with only two out of 10 with high upper airway collapsibility as a sole trait. Moreover, low arousal threshold was associated with lung hyperinflation and air trapping [8]. The authors concluded that clinicians should consider the interaction between traits contributing to OSA and pulmonary function test (PFT) abnormalities in OS patients with the potential to provide personalised treatment and ensure better patient care.

Clinical presentation and polysomnography characteristics

Patients with COPD often complain about sleep disturbances like difficulty in initiating and/or maintaining sleep, and frequent awakenings from sleep resulting in sleep architecture disturbances, decreased sleep efficiency and diminished REM sleep. These sleep alterations may be due to COPD-related night-time symptoms, lung hyperinflation and use of stimulants like theophylline. Impaired sleep quality has an impact on quality of life and it may also contribute to increased COPD exacerbation rate and potentially mortality.

The clinical presentation of OS compared with OSA alone remains poorly identified. It seems that the burden of OSA symptoms, such as snoring, witnessed apnoeas, unrefreshed sleep, daytime sleepiness, poor sleep quality and fatigue, is significantly reduced in OS compared with OSA alone [9]. More specifically,

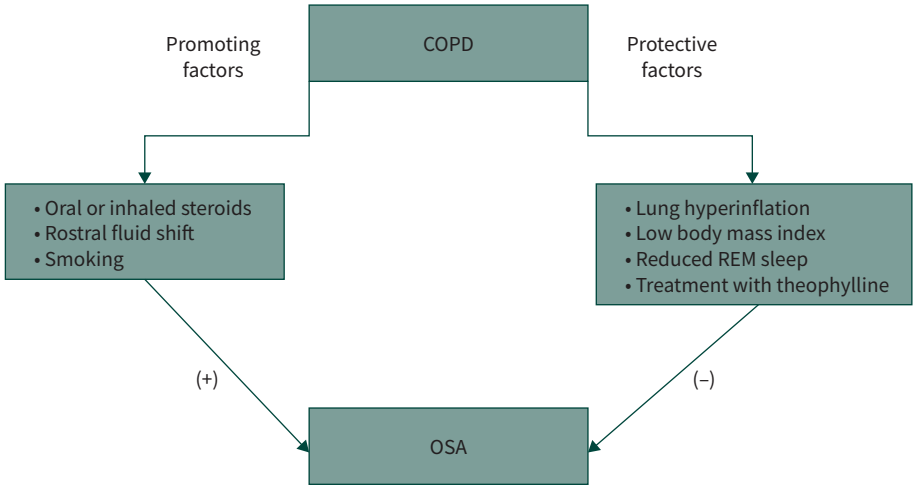

FIGURE 2 Protective and promoting factors for overlap syndrome development. REM: rapid eye movement; OSA: obstructive sleep apnoea.

OS patients report less excessive daytime sleepiness and higher prevalence of nocturia compared with OSA patients; symptoms of fatigue and dyspnoea appeared to be comparable between groups [9]. In any case, clinicians should be aware of mild symptoms in OS and be highly suspicious in patients with severe COPD (table 1).

OS patients seem to have worse polysomnography (PSG) parameters and report worse sleep quality than either condition alone, probably due to an increase in sleep disturbances and arousals which lead to a fragmented sleep pattern. It is noteworthy that the decrease in sleep efficiency noted in OS patients correlated better with the degree of hyperinflation rather than the apnoea–hypopnoea index (AHI) or nocturnal hypoxaemia [10].

Complications

Both COPD and OSA are independently associated with increased cardiovascular disease (CVD). Therefore, it can be expected that CVDs are more prevalent in patients with OS compared with OSA or COPD alone. Indeed, OS is associated with higher prevalence of comorbidities, such as hypertension, peripheral vascular disease, diabetes mellitus and obesity, compared with COPD or OSA alone [1, 6, 11]. However, a recent review underlines that although patients with OS have a high prevalence of CVD there is some suggestion but no valid evidence of an increased risk compared with patients with either condition alone [11]. OS patients also have a higher incidence of pulmonary hypertension and right ventricular remodelling and increased risk of arrhythmias like atrial fibrillation [3], leading to higher hospitalisation rate and worse mortality [10]. Furthermore, untreated OS is associated with severe exacerbation risk, prolonged hospital stay and invasive mechanical ventilation, and higher mortality compared with OSA alone.

The pathophysiological mechanisms in patients with either OSA, COPD or OS for the development of CVD are not clearly defined (figure 3) [1]. The hallmark of OSA is intermittent nocturnal hypoxia that results in chronic systemic inflammation, endothelial dysfunction, oxidative stress and higher sympathetic activity [12]. COPD is also associated with nocturnal oxygen desaturation, resulting in systemic inflammation, oxidative stress, sympathetic excitation and vascular dysfunction [13]. However, patterns of nocturnal desaturation are different between OSA, COPD and OS. In OSA, there are episodes of hypoxia (intermittent hypoxia) with normal saturation levels between apnoeas/hypopnoeas. In COPD, the pattern is modest sustained oxygen desaturation with deterioration during REM sleep. In OS there is a combination of these two patterns, with intermittent hypoxia but the patient remains hypoxic between episodes of apnoea [1, 4]. OS patients with lower baseline oxygen saturation have greater nocturnal hypoxaemia resulting in oxidative stress, sympathetic hyperactivity, and inflammation through increased inflammatory mediators such as tumour necrosis factor-1, interleukin (IL)-6, IL-8 and C-reactive protein [1, 10]. Finally, inflammation results in endothelial dysfunction and atherosclerotic plaque formation [1, 10].

TABLE 1 Clinical characteristics and parameters resulting in high clinical suspicion for obstructive sleep apnoea (OSA) in patients with COPD

Symptoms compatible with OSA, such as snoring, witnessed apnoeas, unrefreshed sleep, daytime sleepiness and nocturia
Obesity as measured by:
Body mass index (>30 kg·m^{-2} in males and >35 kg·m^{-2} in females)
Neck circumference (>43 cm in males and >41 cm in females)
Deranged blood gases
Persistent daytime hypoxaemia
Hypercapnia
Signs of pulmonary hypertension or right heart failure, such as peripheral oedema
Polycythaemia
Use of opioids and/or hypnotic medications
Comorbidities such as:
Resistant hypertension
Atrial fibrillation
Heart failure
Type 2 diabetes
Stroke
End-stage renal disease

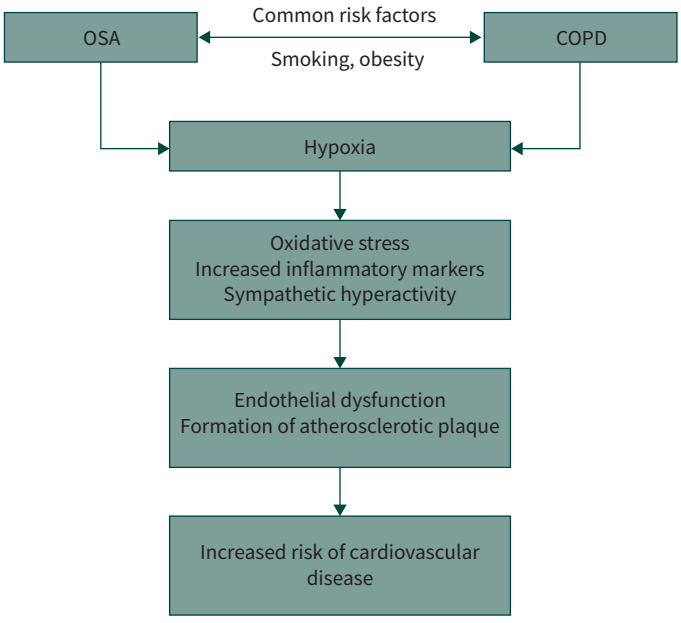

FIGURE 3 Pathophysiological interactions between COPD and obstructive sleep apnoea (OSA) predisposing to cardiovascular disease.

Screening and diagnosis

Screening questionnaires, used in everyday clinical practice to predict the presence of OSA, such as the STOP-Bang questionnaire, Berlin questionnaire (BQ) and Epworth Sleepiness Scale (ESS), may be used, although direct evidence for their performance in OS is limited. Furthermore, as the finding of daytime sleepiness is not common in OS patients, questionnaires which assess sleepiness, such as ESS and the BQ, may not be accurate in predicting OSA in COPD patients.

The American Thoracic Society (ATS) has suggested the use of the STOP-Bang questionnaire to screen for OSA in COPD patients with chronic hypercapnic respiratory failure [14]. However, one should keep in mind that its use is not without limitations since lung function influences BMI and neck circumference, parameters used in this questionnaire and consequently the efficiency of its diagnostic accuracy. Soler *et al*. [15] showed that high BMI, the presence of CVD, and to a lesser extent the STOP-Bang questionnaire, were good predictors of OSA, whereas the ESS was not.

Important clinical features in COPD patients suggestive of OSA (table 1) should always be taken into account [4]. Conversely, suspicion of OS in OSA patients should be considered in patients with significant smoking history and prominent respiratory symptoms. Additionally, OS patients have greater nocturnal hypoxaemia compared to those with OSA alone; therefore, OS should be suspected in patients who require either unanticipated oxygen during positive airway pressure (PAP) titration or a bilevel PAP (BPAP) therapy [16].

The gold standard method for detection of OSA or other sleep disorders in COPD patients is in-laboratory PSG with the ability to noninvasively monitor carbon dioxide tension (P_{CO_2}). In-laboratory titration is also superior to automatic continuous positive airway pressure (CPAP) titration. Although there is an interest of using home sleep tests as a cheaper and more convenient method to diagnose OSA in COPD patients, it is not validated and not recommend in these patients, especially in patients with chronic respiratory failure. Overnight pulse oximetry may be used, but only as a screening device. A study comparing home nocturnal oximetry and PSG in patients with moderate-to-severe COPD showed that OSA was diagnosed by PSG only in 50% of patients with highly suggestive tracings (significant desaturation associated with a sawtooth pattern in saturation) on overnight oximetry and none of the patients' characteristics could predict OSA diagnosis [17]. It is worth noting that, although readily available, nocturnal oximetry does not record sleep duration and arousals, and therefore underestimates the frequency of breathing events such as hypopnoea, potentially underdiagnosing OSA. This effect could be more prominent in patients undergoing long-term oxygen therapy (LTOT) [18].

Therapy

The goals of OS treatment include improvement in sleep quality, indices from the sleep study, arterial blood gases, quality of life, morbidity and mortality. Currently, there are no formal guidelines for treatment of OS patients.

The first step in treatment is optimal medical therapy for COPD according to current guidelines [19]. First-line inhaled drug treatment (long-acting β_2-agonist and long-acting muscarinic antagonist) can improve nocturnal oxygen saturation without improvement in sleep quality [6]. Theophylline has shown improvement in nocturnal oxygenation and AHI, although its use is limited due to side-effects. Pulmonary rehabilitation is also recommended in moderate-to-severe COPD patients (Global Initiative for Chronic Obstructive Lung Disease groups B–D) [19]. Structured exercise programmes have shown improvement not only in quality of life, dyspnoea index, hospital readmissions and mortality, but also in sleep quality, daytime sleepiness and AHI in OSA patients [20].

PAP is the cornerstone of treatment in moderate and severe OSA. However, the optimal treatment with PAP in OS remains unclear. Data regarding the impact of PAP treatment in OS patients are limited to large observational studies with an absence of well-designed randomised controlled trials. The choice of PAP mode is of high importance and depends on OS phenotype. When OSA predominates, PAP is the most appropriate treatment to prevent upper airway collapse. When severe emphysema is prominent resulting in hypoventilation (which could also be caused or exacerbated by coexisting obesity), noninvasive ventilation in BPAP mode is the treatment of choice to augment minute ventilation [6]. The clinician should be careful about positive end-expiratory pressure (PEEP) levels. Modest levels of applied PEEP counteract auto-PEEP due to expiratory flow limitation in severe emphysema thus reducing work of breathing and hyperinflation; however, increasing PEEP levels, more than the auto-PEEP, may worsen hyperinflation. PAP therapy in OS patients has been found to improve admission-free survival, hospitalisation rates, arterial blood gases, 6-minute walk distance, forced expiratory volume in 1 s (FEV_1), exercise capacity and mean pulmonary artery pressure, and to reduce pro-inflammatory markers implicated in CVD [6]. Despite these promising results, treatment adherence is an important parameter that should be taken into account. Increased hours of PAP usage were associated with reduced COPD exacerbations, hospitalisations, cardiovascular events and mortality [6], leading to improvement in health status and a reduction in healthcare costs. Predictors of poor adherence and lower treatment response are dyspnoea and nocturia.

LTOT is also a well-established treatment with improvement in survival in COPD patients with daytime respiratory failure [19]. However, in isolated nocturnal hypoxaemia, oxygen supplementation failed to decrease mortality [4]. Additionally, inappropriate LTOT in patients with borderline hypoxaemia and OS may increase mortality, hospitalisations and acute exacerbations [6]. In patients with OS, supplementary oxygen therapy during sleep may be used only in patients who continue to have hypoxaemia despite PAP therapy with a target oxygen saturation measured by pulse oximetry (S_{pO_2}) of 88–92%. Finally, there are no data comparing BPAP *versus* PAP with supplementary oxygen. However, the presence of hypoventilation during a titration study may be in favour of BPAP therapy over supplementary oxygen [6].

OSA and asthma

Asthma is a heterogeneous disease, usually characterised by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, along with variable expiratory airflow limitation.

Prevalence

Coexistence of OSA and asthma is common and could be explained by the high prevalence of both disorders and shared risk factors such as rhinitis, gastro-oesophageal reflux (GOR) and obesity. However, a growing body of evidence suggests a bidirectional relationship between both disorders and a mutual impact on disease severity [21]. A recent meta-analysis showed a prevalence of objectively confirmed OSA in asthma patients of 50%, which was 2.6 times higher than in non-asthma patients [22]. Teodorescu *et al.* [23] reported an increased 4-year incidence of OSA among subjects with asthma in the Wisconsin Sleep Cohort Study, while asthma duration increased the OSA risk in a dose-dependent manner. OSA prevalence also increased with asthma severity. Besides, higher asthma severity was associated with worse sleep quality and daytime sleepiness [23].

Data about asthma prevalence in OSA populations are scarce with variable results. In the large European Sleep Apnea Database (ESADA) cohort, overall physician-diagnosed asthma prevalence was 5%, with a higher prevalence in women (8%) compared to men (4%) [24]. A much higher prevalence may exist in severely obese women with OSA.

Clinical presentation

Symptoms of OSA are heterogeneous and sometimes difficult to separate from asthma-related symptoms. A higher BMI and worse daytime sleepiness were demonstrated in asthmatic subjects with OSA. In addition, frequent exacerbations or difficult-to-control asthma should raise suspicion for OSA presence [22, 25]. The majority of respiratory events in asthmatic subjects are obstructive hypopnoeas with arousals, which suggests that respiratory polygraphy (without electroencephalography and without the possibility of arousal scoring) may underestimate OSA severity in these patients.

Risk factors

Common risk factors, such as rhinitis, GOR and obesity, contribute to the increased OSA risk in asthma while also modulating the effects of OSA on asthma. A significant independent association of diagnosed GOR with OSA risk was reported in patients with asthma [26]. Obesity is a well-known risk factor for both OSA and asthma, potentially mediated by alterations in lung mechanics, airway hyperresponsiveness, inflammation and adipokines released by adipose tissue [27].

Other asthma related features possibly contribute to an increased OSA risk. Recent results from basic and animal studies suggest that airway and systemic inflammation could affect neural breathing control and chemoreception while also having an impact on upper airway patency [28]. Patients with asthma treated with inhaled corticosteroids seem to have an increased risk to develop OSA mediated by an impact on upper airway collapsibility through direct muscle effects and fat redistribution to the neck [29].

Pathophysiology

In patients with severe asthma, a higher proportion of neutrophils and higher IL-8 levels in the sputum and a thinner reticular basement membrane was demonstrated in patients with OSA compared with patients without OSA [30]. These findings suggest that OSA could induce a specific phenotype of neutrophilic asthma and airway remodelling, being poorly responsive to steroid therapy.

On the other hand, specific OSA features could have an impact on the distal airway. Animal studies showed that repetitive upper airway collapse and reopening induced a neutrophilic-dominant response, while sleep fragmentation led to neutrophil migration into extravascular lung tissue, consistent with tissue injury [31]. Also, chronic intermittent hypoxia was shown to induce a T-helper cell (Th)1 pattern of inflammation leading to collagen deposition, matrix degradation and airflow limitation [32]. These findings of irreversible airway remodelling may explain the earlier reported absence of effect of CPAP on lung function measures in asthmatic patients.

Consequences

OSA seems to be associated with increased exacerbation risk, reduced quality of life and accelerated FEV_1 decline in patients with asthma [25]. An impact of OSA on asthma can also be inferred from studies evaluating the effect of OSA treatment in patients with both OSA and asthma. Davies *et al*. [32] performed a meta-analysis, including observational and prospective studies, on the effect of PAP in patients with OSA and asthma. PAP significantly improved asthma-related quality of life with effects being more pronounced in severe OSA or poorly controlled asthma. PAP did not improve lung function.

Hence, accumulating data suggest a bidirectional interaction between asthma and OSA, mediated by shared risk factors and asthma- and OSA-related features, that contributes to worsening disease severity. Several studies suggest that asthma patients have an increased risk for OSA. Likewise, OSA could impact quality of life in asthma patients.

Therapy

Treatment of OSA can improve quality of life and treatment of severe asthma. The effects of asthma treatment on OSA in patients suffering from both diseases are less clear. There is a need for well-designed longitudinal studies on well-characterised populations to further evaluate the mutual impact of OSA and asthma, and optimal treatment in patients with both diseases.

OSA and ILDs

ILDs are a large and heterogeneous group of lung restrictive disorders resulting in reduction in lung volumes and compliance. IPF, a characteristic form of ILDs of unknown cause, has poor survival and appears mainly in older adults. In contrast to earlier findings characterising IPF as a single-organ disease, it seems that many comorbid conditions coexist, like OSA [33–35]. In addition, it has been shown that coexistence of OSA in IPF was linked to accelerated clinical decline regardless of IPF severity [36].

Prevalence of OSA in ILDs

OSA seems to be a prevalent condition in ILD patients [37], ranging from 50% to 90% in patients with IPF [33–40]. The variability in reported frequency could be attributed to differences in the design of studies and the methods used for OSA diagnosis, as well as differences in sample size. A majority of patients with OSA and ILDs have moderate-to-severe OSA [34, 35, 38], while central events accounted for less than 5% of all respiratory events [34, 35, 38]. Nevertheless, larger studies are needed to estimate the accurate OSA prevalence in these patients, and for this reason it is improper to define this as an "overlap" syndrome. Aside from IPF populations, studies estimating OSA prevalence in mixed ILD populations, such as scleroderma-ILD, ankylosing spondylitis, chronic hypersensitivity pneumonitis and sarcoidosis, demonstrated similar findings (44–83%) [37, 41–43]. Despite the variable prevalence reported, it seems to be disproportionately high, even when compared against an age- or BMI-matched population without ILD [44].

Clinical presentation and PSG characteristics

Patients with OSA and IPF frequently present with no typical symptoms, such as excessive daytime somnolence which appeared in only 20% of these patients [33]. Moreover, other typical symptoms such as witnessed apnoeas and snoring presented only in 13–29% and 38–48% of these patients, respectively [34]. Frequent reported clinical symptoms are daytime fatigue (43–75%), sleep onset and maintenance insomnia (52–67%) and nocturnal cough (48–56%) [35]. It is also noteworthy that BMI seems to be lower in OSA patients with IPF compared with OSA patients in the general population. Therefore, treating physicians need to identify these IPF patients with OSA with this clinical phenotype for appropriate referral in sleep centres for further evaluation.

Sleep architecture is also altered in these patients, who exhibit increased stage 1, arousals and sleep fragmentation as well as diminished sleep efficiency and REM sleep [45]. Furthermore, S_{pO_2} levels are significantly reduced during sleep, more notably in REM sleep.

Pathophysiological relationship between OSA and ILDs

The mechanism underlying OSA and ILDs is potentially related to reduced lung volumes, which may reduce upper airway stability and increase resistance due to reducing traction on the upper airway. These alterations may promote upper airway collapse, especially during REM sleep as FRC is further reduced, which is attributable to the decreased intercostal muscle activity. The characteristic intermittent hypoxia of OSA is a stronger stimulus compared with continuous hypoxia for inducing oxidative stress, systemic inflammation and tissue damage that may lead to pulmonary fibrosis [46]. GOR disease, which is frequent in IPF, should also be considered as another potential mechanism. Figure 4 illustrates proposed pathophysiological relationships between OSA and IPF.

Risk factors

Potential predictors for OSA include obesity [35, 41] and PFT impairments [34, 39]. However, Lancaster *et al.* [35] failed to demonstrate an association between OSA severity and PFT measurements. One likely explanation is that PFTs were performed in an upright position but not in a supine position, which could not accurately reflect PFTs during sleep [35].

Clinical consequences

OSA in patients with IPF seems to be associated with poor prognosis as expressed by deterioration in clinical status and mortality [36]. More specifically, it was recently shown that untreated OSA in patients with IPF may lead to altered sleep architecture and exacerbation of nocturnal desaturation, predicting worse survival. A strong association was also observed with ischaemic heart disease in diagnosed IPF patients with severe OSA in comparison to patients with no or mild-to-moderate OSA [38]. Moreover, another association was noted between moderate-to-severe coronary artery calcifications on high-resolution computed tomography and severe OSA [38]. OSA also seems to be associated with increased right ventricular systolic pressure [40], which may reflect pulmonary hypertension. All these observations imply that OSA should be investigated in IPF patients.

Recent research has revealed that patients with OSA and IPF frequently present with mild cognitive impairment, related to the areas of visuospatial abilities, language and working memory [40]. These results suggest that OSA could predict cognition deficit in IPF patients. Moreover, questionnaire-based quality of life in patients with IPF and sarcoidosis was also affected, particularly in the domains concerning physical health and the level of independence, compared with a control group [42].

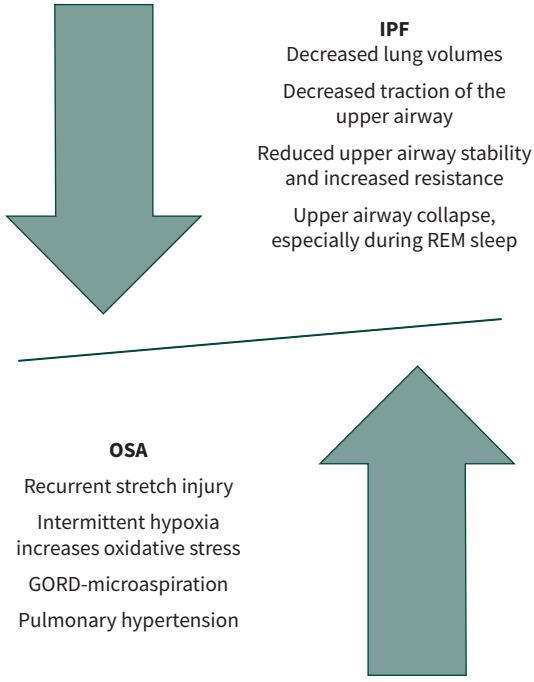

FIGURE 4 Proposed pathophysiological relationships between obstructive sleep apnoea (OSA) and idiopathic pulmonary fibrosis (IPF). REM: rapid eye movement; GORD: gastro-oesophageal reflux disease.

Screening and diagnostic considerations

Although OSA seems to be a common disease in the IPF population, few of these patients undergo OSA screening. Currently, there are no clear guidelines for clinicians for screening for OSA in IPF patients. In a previous study, clinically known questionnaires developed for OSA screening, such as the ESS and Sleep Apnea Scale of the Sleep Disorders Questionnaire, did not distinguish IPF patients with and without OSA [35]. More recently [38], tools that exhibited the best accuracy in identifying OSA were the STOP-Bang questionnaire and oxygen desaturation index from the oximetry recording. However, the ideal tool for OSA screening in patients with IPF has not yet been found and overnight PSG, the gold standard diagnostic test for OSA, remains inevitable for evaluation of these patients. Noteworthy, accurate OSA diagnosis requires formal PSG for accurate characterisation of hypopnoeas, since the main respiratory events noted in these patients are hypopnoeas and not apnoeas [34, 35, 37, 41].

OSA therapy in IPF

CPAP is the treatment of choice in patients with moderate-to-severe OSA not only in the general population, but also in IPF patients. It has been associated with improved quality of life and sleep-related outcomes in these patients [33]. Despite the potential benefits of CPAP therapy, there are specific challenges, including claustrophobia, irritating cough during sleep, insomnia, and depression [44]. Nevertheless, intense follow-up is suggested for CPAP non-acceptance or poor compliance to maximise tolerance and potential benefits of treatment [33].

In cases of effective CPAP treatment a meaningful improvement in activities of daily living is observed [33]. Patients with 1-year good CPAP adherence appeared with significant improvement in all quality-of-life and sleep instruments used. Changes of smaller strength were noted only in a minority of the used instruments in patients with poor CPAP adherence. Throughout the follow-up period, three patients from the poor CPAP adherence group died, whereas all patients from the good CPAP adherence group remained alive, providing the first evidence that effective treatment of comorbid diseases like OSA appear to influence mortality. In a more recent study, effective PAP treatment in 45 patients with newly diagnosed IPF resulted in a significant improvement in sleepiness, fatigue, sleep quality, and life expectancy at a 7-year follow-up period [47].

As a rule, a formal in-laboratory CPAP titration is required in patients with OSA and comorbidities, including ILDs. The role of automatic-PAP (APAP) titration was investigated in 25 patients with fibrotic

ILD and moderate-to-severe OSA and in patients with mild OSA with daytime sleepiness and/or CVD [48]. Four out of 25 patients refused APAP treatment, two patients died before starting treatment, and two others reported APAP intolerance due to claustrophobia and/or insomnia and were excluded after 1 week of unsuccessful attempts. In the remaining 17 patients, good APAP adherence was noted 1 month after APAP initiation with no need for supplemental oxygen. Eight patients with previous sleep time with S_{pO_2} below 90% of >20%, while on APAP, presented with resolved desaturation [48].

Other therapies, such as positional therapy, supplemental oxygen and oral appliances, have not yet been studied in ILDs and IPF patients, in cases of denial of CPAP therapy or poor compliance.

Conclusion

Recognition and treatment of comorbidities, like OSA, in patients with respiratory disease is of great importance for their overall management. Although recent data demonstrate an increased OSA prevalence in these patients, it is too early to define it as an "overlap" syndrome in all respiratory diseases and further research is required. However, clinicians need to have high awareness of OSA and monitor the appropriate therapy in these patients. Studies with larger numbers of newly diagnosed patients with lung disease are essential for evaluation of accurate OSA prevalence, adverse consequences of OSA and the effectiveness of CPAP therapy on survival and lung disease exacerbations.

Key points

- OSA seems to be a common disorder in patients with respiratory disease.
- There is accumulating evidence suggesting that the presence of OSA results in worse disease control, increased frequency of exacerbations, increased cardiovascular risk and reduced quality of life.
- The optimal tool for OSA screening in these patients has yet to be determined, necessitating a holistic patient approach and an evaluation with overnight PSG.
- Management of OSA in patients with respiratory disease is very important due to the impact of OSA on disease control, quality of life, exacerbation rate and cardiovascular risk.

Self-evaluation questions

1. Which of the following seems to be a protective factor for OSA in COPD patients?
    a) Cigarette smoking
    b) Fluid retention
    c) Lung hyperinflation
    d) Oral corticosteroids
2. What is the gold standard method of diagnosis for overlap syndrome?
    a) Overnight oximetry
    b) Actigraphy
    c) Home sleep study
    d) PSG with end-tidal P_{CO_2} monitoring
3. Which comorbidities are associated with OS compared with OSA alone?
    a) Arterial hypertension
    b) Stroke
    c) Heart failure
    d) Chronic kidney disease
4. Which statement about OSA in asthma patients is not correct?
    a) Patients with asthma treated with inhaled corticosteroids seem to have an increased risk of developing OSA
    b) The majority of respiratory events in asthmatic subjects are obstructive hypopnoeas with arousals
    c) Frequent exacerbations or difficult-to-control asthma should raise suspicion of OSA presence
    d) Gastro-oesophageal reflux is not considered a risk factor of OSA in asthma patients
5. Which of the following options is not considered a common symptom of OSA in IPF patients?
    a) Fatigue
    b) Excessive daytime sleepiness
    c) Insomnia
    d) Nocturnal cough

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Suggested answers

1. c.
2. d.
3. a.
4. d.
5. b.