

Review Article

Overlap Syndrome – the Coexistence of Sleep Disordered Breathing (SDB) and Chronic Obstructive Pulmonary Disease (COPD)

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Abstract

COPD is amongst the most common pulmonary disease and with the increasing diagnosis of SDB; it is prudent to give attention to their co-existence which is denominated as "Overlap Syndrome". Recent epidemiological data suggest prevalence of Sleep Apnea Hypopnea Syndrome (SAHS) is not higher in COPD than in general population, and that the coexistence of the two conditions is due to chance and not via any genetic-patho-physiologic linkage. This combination has important implications for diagnosis, treatment and outcome. Patients with overlap have more profound sleep related oxygen desaturation events; have an increased risk of developing hypercapnic respiratory insufficiency and pulmonary arterial hypertension as compared to COPD patients alone. Therapy of overlap syndrome consists of Positive Airway Pressure ventilation (PAP) or Non Invasive Ventilation (NIV), with or without associated nocturnal oxygen. Patients who are markedly hypoxemic during daytime (PaO₂ < 55 -60 mmHg) benefit with long term oxygen therapy (LTOT) in addition to NIV.

Key Words: Overlap syndrome, Chronic obstructive pulmonary disease, Sleep apnea hypopnea syndrome, Sleep related oxygen desaturation, Non invasive ventilation.

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Definitions and Epidemiology

Chronic Obstructive Pulmonary Disease (COPD), a common preventable and treatable disease, is characterized by persistent airflow obstruction that is usually progressive and associated with enhanced chronic inflammatory response in the airways and lungs to noxious particles and gases. Exacerbations and co morbidities contribute to the overall severity in individual patients.

COPD is a leading cause of morbidity and mortality worldwide and results in an economic and social burden that is both substantial and increasing^{1,2}. COPD prevalence, morbidity and mortality vary across countries and across different groups within the countries. The Global Burden of Disease Study projected that COPD which ranked as the 6th leading cause of death in 1990 will become the 3rd leading cause by 2020; a newer projection estimated COPD will be the 4th leading cause in 2030².

Sleep Apnea Hypopnea Syndrome (SAHS):

There is no standardized definition of SAHS. Obstructive Sleep Apnea (OSA) is characterized by repetitive episodes of complete (apnea) or partial (Hypopnea) upper airway obstruction occurring during sleep. These events often result in reductions in blood

oxygen saturation and are usually terminated by brief arousals from sleep. By definition apneic and hypopneic events last a minimum of 10 seconds.

OSA can occur in any age group. When OSA is defined as an AHI greater than 5 with a complaint of excessive daytime sleepiness, the prevalence was estimated to be 4% in men and 2% in women. The ratio of OSA in men compared to women is approximately two to one.

Overlap Syndrome:

The combination of COPD and SAHS has been denominated "Overlap Syndrome" by the late David Flenley³. In his opinion the term "overlap syndrome" could apply as well to the coexistence of SAHS and any chronic respiratory disease³, but the use of this term is generally limited to the association of SAHS and COPD.

Prevalence data are not available for the overlap syndrome, probably as a consequence of the lack of a standardized definition along with the lack of a unique diagnostic code.

The earliest reports from Guilleminault and co-workers found 22 out of 26 patients in a case series suffered from sleep apneas. This might have been due to methodological bias as they had been referred to the

sleep clinic because they complained of excessive daytime sleepiness.⁴ Conversely in studies by Bradley and colleagues^{6,7} and by Chaouat and coworkers⁵ in which consecutive patients with SAHS were investigated the prevalence of an associated COPD was respectively 14%⁷ and 11%⁵.

Data was analyzed from the Sleep Heart Health Study, a prospective multicenter cohort study⁸. In this study no increased association was found between (generally mild) obstructive airways disease and OSA. Furthermore, the presence of airway obstruction did not seem to affect the respiratory disturbance index.

It is worth emphasizing that, although there may be no causative association between COPD and OSA, but because of the rising prevalence of these diseases, a patient with one of the disorders has a high chance of coexistence of the other. Thus when evaluating a patient with either OSA or COPD, it is reasonable to screen for the other, based on history, review of symptoms and questionnaires whenever possible.

Clinical consequences of overlap

Quality of Sleep

Many patients with COPD complain of poor quality sleep with more difficulty both initiating and maintaining sleep than controls, and also complain of excessive daytime sleepiness⁹. Objective evidence of disturbed sleep in COPD has been demonstrated by adequate EEG studies¹⁰⁻¹⁴; sleep efficiency is reduced, sleep onset is delayed, total sleep time is reduced and period of wakefulness are frequent and sometimes prolonged. The cause of this poor quality sleep is probably multifactorial, and includes nocturnal cough, nocturnal dyspnea, and use of drugs and effects of ageing on sleep. Sanders and colleagues¹⁵ observed that after stratification for BMI quartile, RDI values were similar in participants with or without OAD. On comparing sleep variables and sleepiness they found subjects with overlap had lower sleep efficiency and % Total Sleep Time (TST) in Stage 1 as compared to subjects with SAHS alone & subjects with overlap as compared to those with OAD alone had lower sleep efficiency, lower TST, lower %TST in Stage Rapid Eye Movement Sleep, Stage 3/4 sleep, higher %TST Stage 2 sleep, higher sleepiness on Epworth Sleepiness Score, and higher arousal index.¹⁵ Thus the quality of sleep in COPD is influenced by the presence of SAHS but not by the severity of airway obstruction.

Nocturnal desaturation

The most significant sleep abnormality associated with COPD is nocturnal oxygen desaturation^{27, 28} Chaouat and coworkers⁵ have found that nocturnal hypoxemia was more important in patients with overlap than in patients with SAHS alone. Sanders et al have reported that after adjusting for age, sex, height, race, smoking status and awake SpO₂ the Odds Ratio for oxyhemoglobin saturation below levels of 85% for more than 5% of total sleep time was 20 fold greater in participants with SAHS alone compared with those who had neither disorder and 30 fold greater in participants with both disorders (subjects with overlap)¹⁵

Perhaps most clinically relevant as observed by Fletcher et al, nocturnal oxygen desaturation in a patient of COPD with daytime SpO₂ > 60 mmHg is associated with decreased survival.¹⁶ Acutely, nocturnal oxygen desaturation causes surges in both systemic and pulmonary blood pressure¹⁷. It now seems likely that repetitive, transient oxygen desaturation can cause pulmonary hypertension¹⁸. Various arrhythmias are also reported during episodes of nocturnal desaturation¹⁹

Pulmonary functions and Arterial Blood Gases

Chaouat A et al, in a series of 30 patients compared the spirometric and arterial blood gases results of patients with overlap to those of patients with SAHS alone and also to a series of patients with obesity hypoventilation.^{5,20} Patients with overlap have lower pulmonary volumes and lower FEV₁/FVC ratio than do subjects with SAHS alone. The coexistence of COPD and SAHS favors the presence of hypoxemia, which is rarely observed in patients with SAHS alone. Hypoxemia and hypercapnia are more severe in patients with obesity-hypoventilation than in patients with overlap.

Pulmonary Hypertension

Patients with overlap are at risk of developing pulmonary hypertension (PAH) even though their obstructive defect is not severe. Chaouat and colleagues⁵ have observed that among the 26 patients with overlap who underwent right heart catheterization 11 patients had PAH defined by a mean pulmonary artery pressure (Ppa) greater than 20 mm Hg. The prevalence of PAH was 36% in patients with overlap, much higher than in usual SAHS (9%), but somewhat lower than in the obesity-hypoventilation syndrome²⁰. In patients with COPD, PAH is generally observed when daytime PaO₂ is less than 55 to 60 mm Hg²¹, Chaouat et al have demonstrated that the average daytime PaO₂ in patients with overlap is higher (66 ± 10 mmHg) and only 8/30 evaluated cases had PaO₂ less than 60 mm Hg. In SAHS/overlap, the mean PaO₂ during sleep is certainly lower because of the repetition of apneas and hypopneas. Patients with overlap can develop PAH even if they do not exhibit a marked degree of bronchial obstruction Thus the combination of marked nocturnal hypoxemia with a mild to moderate diurnal hypoxemia could explain the occurrence of pulmonary hypertension.²²

Treatment

The goal of treatment is to maintain adequate oxygenation at all times and to prevent sleep disordered breathing events.

Weight Loss

Weight loss can clearly be of benefit to those with OSA and Obesity²³. Conversely in COPD since cachexia sets in with increasing disease severity, weight loss is generally associated with increased mortality. Thus, there is no data to recommend weight loss as a therapeutic option in overlap syndrome; however it seems reasonable to deduce that those with less severe

COPD would benefit from a diet and exercise program.

Bronchodilators and Corticosteroids

Data suggests that the treatment of the underlying obstructive airway diseases in COPD with anticholinergics, β_2 agonists and systemic steroids will prevent or ameliorate nocturnal oxygen desaturation,. Whether treatment of COPD in the overlap syndrome also improves OSA is not known.

Oxygen

Supplemental oxygen is the mainstay of treatment for those with daytime and nocturnal hypoxemia, and has been shown to improve overall mortality if used for more than 18 hours per day, including during sleep^{24, 25} Alford and colleagues administered 4l/min supplemental oxygen to 20 men with both OSA and COPD. While nocturnal oxygenation improved, the duration of obstructive events increased from 25.7 seconds to 31.4 seconds, resulting in an end-apneic pCO₂ increase from 52.9 mm Hg to 62.3 mm Hg, with corresponding decrease in pH²⁶. Thus oxygen alone should not be used for treatment of the Overlap Syndrome.²⁷

Continuous Positive Airway Pressure

Continuous positive airway pressure (CPAP) is the first line of treatment of SAHS²⁸. This treatment is efficient in suppressing apneas and hypopneas and sleep-related hypoxemia in patients with SAHS. CPAP may be inefficient for correcting nighttime hypoxemia in patients with associated COPD^{29, 30}. In these patients some degree of sleep related hypoxemia may persist, particularly during REM sleep. Consequently, it is necessary to add supplementary O₂ to CPAP when the mean nocturnal SaO₂ under CPAP alone is < 90%. It is also possible in these cases to shift to bilevel positive airway pressure (BiPAP). The effect of therapy by CPAP or BiPAP in terms of reducing or preventing episodes of apnea, hypopnea and nocturnal oxygen desaturation events should periodically be assessed by nocturnal oximetry and whenever possible by polysomnography.

Finally in the most severe overlap patients, a marked daytime hypoxemia may persist in spite of the efficient treatment of nocturnal apneas – hypopneas. These patients require conventional long term oxygen therapy (LTOT) in addition to CPAP or NIV, when the standard criteria for oxygen therapy are fulfilled³¹ – namely a daytime PaO₂ regularly less than 55–60 mm Hg. These patients are the most likely to develop PAH³² and LTOT may help to decrease or at least stabilize PAP³³

Conclusion

Overlap Syndrome is not a rare condition due to high prevalence of both COPD and SAHS. A recent epidemiologic study has clearly shown that the presence of COPD does not increase the concurrence of SAHS and vice versa. The morbidity and mortality of overlap syndrome is greater than that of either COPD & SAHS alone. Many unanswered questions remain

pertaining to the mechanical interaction between COPD and SAHS, like levels of SAHS and COPD that are clinically relevant, the degree of suspicion to be maintained in regards to the other disease in the presence of one and finally needed is assessment of NIV in the patients of Overlap Syndrome.

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