

Obstructive Sleep Apnea in Patients with Chronic Obstructive Pulmonary Disease

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ABSTRACT

Obstructive sleep apnea (OSA) and chronic obstructive pulmonary disease (COPD) are common disorders in clinical practice and are associated with significant cardiovascular morbidity. The simultaneous occurrence of OSA and COPD happens frequently and is referred to as an overlap syndrome. These patients often have very poor quality sleep and more nocturnal hypoxemia. This combination may increase the severity of metabolic complications and cardiovascular disease, and these patients have increased mortality when compared to patients with either COPD or OSA alone. The treatment of overlap syndrome should focus on both coexisting diseases and includes continuous positive airway pressure, oxygen supplementation, and medications for chronic lung disease.

Key words: COPD, obstructive sleep apnea, hypoxemia, overlap syndrome

INTRODUCTION

Obstructive sleep apnea (OSA) is characterized by recurrent upper airway closure during sleep and affects 5–20% of the adult population in the United States¹. These patients have frequent cessation or reduction in airflow during sleep with consequent blood oxygen desaturation and sleep fragmentation. OSA is a potential risk factor for multiple diseases, including ischemic heart disease, stroke, hypertension, metabolic syndrome, and diabetes.

Chronic obstructive pulmonary disease (COPD) is also a common clinical disorder and occurs in 4–6% of the adult population in the United States². COPD is characterized by chronic airflow obstruction secondary to chronic bronchitis and/or emphysema and is associated with significant morbidity and mortality³. Patients with COPD often have poor sleep quality, nocturnal oxygen desaturation, especially during REM sleep, and comorbid sleep-related breathing disorders⁴.

The simultaneous occurrence of OSA and COPD is common, is called an overlap syndrome, and increases the likelihood of heart failure, pulmonary hypertension, and systemic hypertension⁵. This overlap syndrome occurs in approximately 1% of adults⁶ and 10–20 % of patients with OSA⁷. However, it is un-

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clear whether the coexistence of these two disorders has additive or synergistic adverse effects and what level of abnormality in either disorder is consequential when combined with the other disorder.

CONSEQUENCE OF OVERLAP SYNDROME

Sleep in the overlap syndrome

A cross-sectional study in five European countries found 78.1% of patients with COPD reported some degree of nocturnal symptoms⁸. COPD patients report difficulty falling asleep, difficulty maintaining sleep, and increased daytime sleepiness, and frequently have nocturnal hypoxemia. The mechanisms for nocturnal oxygen desaturation in patients with COPD include alveolar hypoventilation, reduction in the functional residual capacity, increased ventilation perfusion mismatch, and increased upper airway resistance. During REM sleep the PaO₂ can decrease to levels as low as 20 mmHg⁹. Patients with OSA have cyclical desaturation associated with apneas and hypopneas and sleep fragmentation. The degree of desaturation depends on the body habitus (BMI) and any coexisting alteration in lung function. Therefore, nocturnal hypoxemia is a frequent and important pathophysiological event in patients with the overlap syndrome and is associated with sleep arousals, fragmentation, decreased rapid eye movement (REM) sleep stage, and fluctuations in pulmonary artery and systemic pressures¹⁰. The Sleep Heart Health Study is a prospective multicenter cohort study designed to determine whether OSA is a risk factor for hypertension and cardiovascular events. This study did not find an association between mild COPD disease and OSA but demonstrated that subjects with both OSA and obstructive airway disease defined by spirometry were more likely to have low oxygen saturations at night¹¹.

Systemic inflammation in overlap syndrome

OSA and COPD are both associated with systemic inflammation, and activation of inflammatory cells and associated cascades lead to endothelial dysfunction and atherosclerosis¹². The combination of hypoxemia and hypercapnia may increase the en-

dothelial response to inflammatory cytokines, such as interleukin-1, interleukin-6, and tumor necrosis factor alpha, that cause chronic systemic inflammation and increase the risk of cardiovascular disease^{13, 14}.

Cardiovascular disease in overlap syndrome

Patients with OSA develop intermittent hypoxemia, sleep fragmentation, increased sympathetic activity, and changes in the hypothalamic pituitary axis that lead to systemic inflammation^{15, 16}. Repetitive hypoxemia and oxidative stress also occur and cause insulin resistance and promote cardiovascular disease. COPD causes chronic inflammation in lung tissue; the extent of this inflammatory process correlates with the severity of the disease. Chronic inflammation in the lung parenchyma leads to systemic inflammation, oxidative stress, and endothelial dysfunction. These mechanisms promote the cardiovascular diseases¹⁷. Since both OSA and COPD cause systemic inflammation, patients with the overlap syndrome might have more systemic inflammation with more adverse metabolic and vascular consequences than patients with either diagnosis alone. However, most studies do not have an adequate design or size to address these outcomes and more prospective studies are needed to prove this possibility.

Quality of life in the overlap syndrome

Both COPD and OSA have well defined effects on health-related quality of life^{18, 19}. When these two conditions coexist, there is potentially more desaturation during sleep and more sleep disruption, which could lead to a worse quality of life. Mermigkis compared quality of life in patients with overlap syndrome and with COPD alone and found a markedly impaired quality of life in the overlap syndrome group²⁰.

Mortality in the overlap syndrome

Marin et al reported that patients with untreated overlap syndrome have an increased risk of death from any cause, cardiovascular deaths, and hospitalization because of COPD exacerbations. They found that death from any cause occurred in 213 patients (32.7%) over a median follow-up of 9.4 years²¹. An-

other study also reported that patients with the overlap syndrome have a lower five year survival rate than patients with OSA alone²². The causes of death include COPD exacerbations, pulmonary hypertension with right heart disease, cardiac arrhythmias, coronary syndromes, and other diagnoses associated with cigarette smoking.

DIAGNOSIS AND SCREENING

Patients with COPD with clinical risk factors for OSA, such as snoring, obesity, daytime sleepiness, or significant weight gain, need additional evaluation for a sleep-related breathing disorder²³. The measurement of oxygen saturation by pulse oximetry overnight is an excellent screening tool for sleep-related breathing disorders²⁴, but polysomnography is the standard diagnostic test for OSA in all patients. Patients with OSA and daytime hypoxemia and/or hypercapnea should have pulmonary evaluation with pulmonary function testing. Patients with either COPD or OSA with unexpectedly high pulmonary artery pressures should be evaluated for the overlap syndrome.

TREATMENT

Alterations in nocturnal gas exchange, particularly oxygen desaturation, are important clinical problems in patients with overlap syndrome. The treatment of the overlap syndrome requires the treatment of OSA and COPD to maintain adequate ventilation and oxygenation at night.

Positive airway pressure

CPAP is the standard treatment for OSA and is the appropriate treatment for overlap syndrome. Treatment of OSA with continuous positive airway pressure (CPAP) significantly reduces non-fatal and fatal cardiovascular events²⁵. CPAP treatment has never been proven beneficial in patients with COPD alone but does improve outcomes in patients with OSA and COPD²¹. Recent studies on the long term use of CPAP in overlap syndrome have suggested mortality benefits in these patients²⁶. Michael and colleagues did a post hoc analysis of a 2007-2010 outpatient database of 10,272 patients. Of these, 227

patients had overlap syndrome, and 17 of them died (7.4%). Longer treatment times with CPAP were associated with reduced mortality (HR 0.71, $p < 0.001$)²⁷. Another recent cohort study demonstrated that CPAP mitigates the excess risk of mortality in hypercapnic patients but not in normocapnic patients with the overlap syndrome²⁸. Noninvasive ventilation has been considered a good treatment option in the overlap syndrome, but multiple small studies have had inconsistent results with this treatment.

Oxygen

Oxygen is the standard long treatment of COPD with hypoxemia. Patients with overlap syndrome have worse hypoxemia during the night⁹. Therefore, careful assessment of oxygen saturation after CPAP titration is essential as some of these patients also require supplemental O₂. In addition, supplemental oxygen for at least 15 hours per day during the day to correct any daytime hypoxemia is recommended. This therapy reduces mortality, reduces pulmonary artery pressures, and improves neurological outcomes²⁹.

Medication

Treatment of underlying COPD with bronchodilators and inhaled corticosteroids improves nocturnal oxygen saturations in patients with COPD. Studies with tiotropium and long-acting beta-agonists have shown that both drugs improved nocturnal oxygen saturations^{30, 31}. In the overlap syndrome hypoxemia is significantly worse during sleep. Therefore, intensive treatment of both COPD and OSA should improve oxygenation, improve cardiovascular outcomes, and reduce mortality in this syndrome.

KEY POINTS

1. Patients with OSA frequently have COPD, and patients with COPD frequently have OSA.
2. These patients with an overlap syndrome can have significant nocturnal hypoxemia and increased cardiovascular morbidity and mortality.
3. They need evaluation for both disorders and treat-

ment with CPAP if the OSA meets the usual criteria for treatment. They may require supplemental oxygen even if CPAP titration is successful.

KEY WORDS: COPD, obstructive sleep apnea, hypoxemia, overlap syndrome

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