

Sleep Overlap Syndrome: A Narrative Review

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ABSTRACT

Overlap syndrome, which is known as the coexistence of chronic obstructive pulmonary disease (COPD) and obstructive sleep apnea (OSA), was first defined by Flenley. Although it can refer to concomitant occurrence of any of the pulmonary diseases and OSA, overlap syndrome is commonly considered as the coexistence of OSA and COPD. This disease has unique adverse health consequences distinct from either condition alone. Given the high prevalence of each solitary disease, overlap syndrome is also likely to be common and clinically relevant. Despite the fact that overlap syndrome has been described in the literature for nearly 30 years, paucity of evaluations and studies limited the discussion on diagnosis, prevalence, pathophysiology, treatment, and outcomes of this disease. This review article addresses these issues by reviewing several recent studies conducted in Iran or other countries. This review suggests that overlap syndrome has worse outcomes than either disease alone. Our findings accentuated the urgent need for further studies on overlap syndrome and all overlaps between OSA and chronic pulmonary disease to provide a deeper insight into diagnosis and non-invasive treatments of this disease.

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Introduction

Obstructive sleep apnea (OSA) and chronic obstructive pulmonary disease (COPD) are the two common pulmonary diseases in the worldwide (1-3), which have common pathophysiological mechanisms. A multitude of patients sustain both diseases concomitantly, which is known as overlap syndrome (4-6). Overlap syndrome is clinically distinct from either disease alone, and the course of disease, prognosis, and urgency of treatment are exclusive for each one (4). In this review, we confirm that overlap syndrome is a common and clinically important disease that may have a higher prevalence rate than OSA or COPD alone.

Sleep overlap syndrome

Concomitant OSA and COPD was termed overlap

syndrome by David Flenley (1). OSA is characterized by intermittent collapse of the upper airway, which results in repetitive hypoxemia and arousal (7). In this situation, an increase in upper airway resistance reduces airflow and arterial oxygen pressure (8). OSA severity was evaluated by apnea-hypopnea index (AHI), which is the the number of respiratory events per hour (9, 10). OSA reduces quality of life and health. Daytime sleepiness, fatigue, and headache are the cardinal manifestations of OSA (11, 12). The main risk factors for OSA are advanced age and obesity (13, 14).

Chronic Obstructive Pulmonary Disease (COPD)

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COPD is a common preventable disease identified by persistent airflow limitation that is not fully reversible (15). COPD is a leading cause of mortality and morbidity across the world (15-20). COPD is recognized as the fourth leading cause of mortality in the United States (16, 17). Progressive airflow restriction is correlated with systemic inflammation in the airways. (18, 19). Spirometry is a simple method for pulmonary function evaluation, which measures the volume of air that the patient can exhale from the lungs after a maximal inspiration. COPD is confirmed when forced expiratory volume in 1 second (FEV1)/forced vital capacity (FVC) ratio of less than 70% is observed in patients not exhibiting any other chronic respiratory diseases (20, 21).

The incidence of COPD has been on a growing trend in the recent decades. Chronic cough, dyspnea, and sputum production are the main clinical manifestations in patients with history of cigarette smoking. Several studies indicated that sleep quality is lower in COPD patients compared to healthy individuals. Increased nocturnal symptoms, poor sleep quality, and effects on pulmonary gas exchange were reported in COPD patients (22).

Incidence, Impact and Diagnosis

The incidence of overlap syndrome is 1% in the adult population. OSA has an incidence rate of 2% in females and 4% in males, and the rate of its concomitant incidence with COPD is 5-10% (23-25). Former studies exhibited that the frequency of hypoxemia, hypercapnia, and pulmonary hypertension as well as the mean age in overlap syndrome patients were higher than in patients with OSA alone (26-34).

O'Brien and Whitman found that overlap patients had higher mean age and lower mean weight compared to patient with OSA alone (34). Resta et al. demonstrated that overlap patients had higher PaCO₂ and AHI compared to OSA patients alone (35). One of the pathological consequences of COPD is stretching of the diaphragm due to pulmonary hyperinflation, which may diminish efficiency of diaphragmatic contraction and thus necessitating higher accessory muscle contribution to breathing (36-43). Supine situation affects Diaphragmatic functions, (42, 43). The diaphragm is virtually the only respiratory muscle that is active during rapid eye movement (REM) sleep, paradoxical breathing and further hypoventilation occur during sleep.

The loosening of accessory muscle function during REM sleep and the increase in airway resistance during sleep can lower functional residual capacity (FRC) (44). In addition, supine position is associated with 10% decrease in FRC in healthy individuals (44-50). These physiological changes in COPD patients may adversely affect the

ventilation and perfusion matching and contribute to nocturnal hypercapnia and hypoxemia (21). However, physiologic hypoventilation is more deteriorate in COPD patients leads in hypercapnea and hypoxemia.

So, nocturnal desaturation occurred more commonly in overlap syndrome patients than patients with either OSA or COPD alone (21, 22). Furthermore, Lacedonia suggested that daytime hypoxemia in overlap patients is highly associated with overweight and severity of nocturnal hypoxia (51). Lacedonia showed that AHI is not associated with daytime PaO₂, while it was significantly related to nocturnal desaturation, which more commonly occurs in patients with overlap syndrome than in those with only OSA. Advanced age and high body mass index (BMI) are significantly associated with OSA. Several factors can affect the relationship between COPD and OSA, one of which is BMI (51).

Muscle atrophy and low BMI (less than 21 kg/m²) correlate with reduced functional state, quality of life, and rate of survival in patients with COPD (27-28). Obesity is a major contributing factor to OSA, while low BMI is common in COPD patients, especially in those with advanced disease (22, 51, 52). Nonetheless, former studies revealed that there is no significant relationship between AHI and BMI in COPD patients (52). Considering the multifactorial nature of overlap syndrome, anatomic defects should be considered besides weight (52-60). In COPD patients, OSA might occur in those with higher BMI (60). However, there is conflicting evidence regarding the association between BMI and OSA.

Another COPD-related factor that may predispose patients to OSA include rostral shift of peripheral edema in supine position, resulting in fluid accumulation in the neck, which in turn, contributes to pharyngeal narrowing (61-96). Wang et al. showed that bone mass density (BMD) of femur in overlap syndrome patients was significantly lower than that of COPD patients, and low total lung capacity was significantly associated with high oxygen desaturation index (ODI) and low BMD (96), indicating that low BMD might cause severe OSA due to decreased total lung capacity. Therefore, OSA may be a contributory factor to BMD in patients with COPD (93).

Patients with OSA experience repetitive episodes of hypoxia/re-oxygenation during apnea and hypopnea, and while asleep, they sustain arterial stiffness, hypertension, and sympathetic activity (64, 65). In patients with severe COPD, sleep disorders are often present. However, in those with milder respiratory diseases, COPD did not significantly affect sleep quality and architecture.

Therefore, sleep complaints or classic symptoms of OSA in these patients should be addressed and evaluated with polysomnography, although this

approach may underestimate the number of affected patients as OSA can be minimally symptomatic (but still clinically relevant) (66). Nocturnal polysomnography is recommended in COPD patients whose symptoms suggest coexistent OSA, which includes COPD patients who have daytime hypercapnia with only moderately reduced FEV1, obese snorers, or those who develop headache after nocturnal oxygen therapy (4, 56).

Daytime sleepiness and the occurrence of apnea during asleep are highly suggestive of OSA (38-45). However, the presence of concomitant OSA is often difficult to predict from daytime symptoms in COPD patients. The majority of OSA patients do not have daytime hypercapnia or headache and some of them are not obese or have daytime sleepiness (3, 34). High rates of cardiovascular morbidity and mortality associated with untreated OSA, reversible with CPAP treatment, strongly supports a more aggressive approach to diagnosis of coexistent OSA among COPD patients (24, 56, 67).

Untreated OSA increases the risk of hypertension, cardiac arrest, cerebrovascular accident, and increased rate of mortality (68-70). Incidence of fatal and nonfatal cardiovascular events is more prevalent in patients with untreated severe OSA than in those treated with CPAP after adjustment for pre-existing cardiovascular risk factors (73-83). In OSA patients, history of smoking and review of respiratory symptoms should be considered, which could prompt pulmonary function testing. OSA patients with daytime hypoxemia or hypercapnia should also be screened for COPD, since it provides useful prognostic information and may be helpful in determining the aggressiveness of treatment for either underlying disease.

Providing registered sleep technicians with more information on the diagnosis of COPD may facilitate CPAP titration based on oronasal airflow rather than oxygen desaturation (84). Finally, for the diagnosis of overlap syndrome, clinicians should focus their attention on the assessment of pulmonary hypertension or other diagnostic workups such as echocardiography or right-heart catheterization (80, 81).

Numerous studies indicated that OSA patients have a lower level of diurnal PaO₂ compared to healthy individuals, but the causes of daytime hypoxemia are not clear yet. The presence of pulmonary hypertension with pulmonary vasoconstriction was identified as the main contributing factor to low oxygen level in arterial blood. Variation in pulmonary volume, and in particular, reduction of functional reserve capacity (FRC) associated with elevated body oxygen requirement (74) could be the main reason for deeper nocturnal desaturation in obese patients than in lean ones (75).

Lacedonia et al. showed that high AHI due to nocturnal desaturation is common in patients with overlap syndrome (51). However, in patients with overlap syndrome, daytime hypoxemia is secondary to a slightly different mechanism. Indeed, in overlap syndrome patients diurnal PaO₂ level is lower than that of OSA patients. While BMI is not correlated with diurnal PaO₂, nocturnal hypoventilation is strongly correlated with low level of PaO₂, which can be considered as a diagnostic factor for overlap syndrome (82-85). Lacedonia also found that in overlap syndrome, deeper and longer desaturation with SaO₂ less than 90% presented while asleep (83).

It is known that overlap syndrome results in greater sleep disturbance and oxygen desaturation than OSA alone (32, 33). C-reactive protein level was elevated in patients with sleep overlap syndrome compare than healthy individuals. (87). Untreated OSA is associated with systemic inflammation, as well (77). The presence of undiagnosed OSA may potentiate systemic inflammation and accelerate progression of coronary atherosclerosis leading to high cardiovascular morbidity and mortality rates in COPD patients. Furthermore, untreated OSA causes excessive daytime sleepiness that leads to increased risk of accidents at work and while operating a motor vehicle (78-100).

Previous studies reported that patients with overlap syndrome have high percentages of neutrophils in induced sputum, which is similar to patients affected by COPD or OSA alone. However, the level of serum C-reactive protein, a marker of inflammation, was similar in the two groups (72-92). American Thoracic Society/European Respiratory Society guidelines also suggest that those with relatively mild COPD and manifestations of pulmonary hypertension should be screen for Obstructive sleep apnea. In addition, Chaouat (39), Resta (35), and Kessler (89) stated that overlap syndrome patients with pulmonary hypertension often have relatively mild abnormalities, as measured by spirometry or oxygenation, especially when compared to COPD-only patients with pulmonary hypertension. Flenley advocated polysomnography for COPD patients with nocturnal oxygen desaturation who develop morning headaches when treated with nocturnal supplemental oxygen (1, 11). The previous studies showed that brachial-ankle pulse wave velocity (baPWV) was significantly higher in patients with overlap syndrome than in those with OSA alone (29). Arterial stiffness is thought to be a cardiovascular risk factor in these patients since it causes increased cardiac afterload, impaired coronary blood supply, and high shear stress on the microvascular endothelium damage (80-82); thus, the rate of cardiovascular events is higher in overlap

syndrome.

Pulmonary hypertension is observed in 75% of overlap patients and in only 12–20% of undetected OSA patients (71). Overlap syndrome patients are 2.53 times more likely to experience tachyarrhythmias during sleep than patients with OSA alone (83). Diagnosis and treatment of coexistent OSA may attenuate the rates of cardiovascular morbidity and mortality in patients with COPD (67). Theerakittikul et al. found that hyperinflation, as assessed by the diaphragm position on the lateral view, was associated with reduced nocturnal adherence to positive airway pressure (PAP) therapy (94). Wang et al. proposed that hypercapnia, but not hypoxia, was significantly correlated with daytime sleepiness and electroencephalogram activation in patients with hypercapnic sleep disordered breathing (e.g., overlap syndrome patients) (99).

Sharma et al. revealed that overlap syndrome had higher association with increased right ventricular mass and right ventricular remodeling compared to COPD alone. In addition, they indicated that the extent of adverse right ventricular remodeling was correlated with nocturnal oxygen desaturation (97). Former studies exhibited that an explicit approach for the interpretation of pulse oximetry tracing could be a reliable strategy for diagnosis or selection of patients who would most benefit from further polysomnographic assessment for sleep-related breathing disturbances (98,100).

Management

The goal of management in the overlap syndrome is to maintain sufficient oxygenation at all times and prevent sleep-disordered breathing events (101–118).

Positive airway pressure (PAP)

Non invasive mechanical ventilation was suggested for sleep overlap syndrome, which has important beneficial effects on secondary cardiovascular events including systemic hypertension, pulmonary arterial pressure, and recurrent atrial fibrillation after ablation (119–122).

Conclusion

Overlap syndrome is a common disease since COPD and OSA are both prevalent. Based on this review, the complications and mortality rate of this syndrome is higher than those of COPD or OSA alone and clinicians should not miss these patients. COPD or OSA patients should be screened for diagnosis of overlap syndrome. Although pulse oximetry and other tools are now available, the most efficient diagnostic tool for detecting overlap syndrome is polysomnography in combination with spirometry. The treatment of choice for overlap syndrome is CPAP plus oxygen therapy. Performing

further meta-analyses on diagnostic approaches for overlap syndrome is recommended.

Conflict of Interest

The authors declare no conflict of interest.

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