

Double Trouble - The Overlap Syndrome: When OSA and COPD Meet

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Abstract

Although they may have similar pathophysiological mechanisms, because OSA and COPD are common, even by chance alone, a substantial number of patients are afflicted by both OSA and COPD-the overlap syndrome. Nocturnal oxygen desaturation is the most important pathophysiological effect of overlap syndrome. The morbidity and mortality of overlap syndrome is greater than that of either disease alone. During evaluation of patients with either OSA or COPD, a high index of suspicion is crucial to detect the overlap syndrome. The presence of daytime hypercapnia and pulmonary hypertension, in patients having either disease, especially when mild in severity, should prompt assessment for the other disorder. Currently, CPAP with or without oxygen therapy is the treatment of choice for overlap syndrome.

Keywords: Obstructive sleep apnea (OSA), chronic obstructive pulmonary disease(COPD), overlap syndrome, nocturnal oxygen desaturation, hypercapnic COPD, diagnosis, treatment.

Introduction

The Overlap syndrome, in simple terms implies the co-occurrence of two diseases in a patient - Obstructive sleep apnea (OSA) and Chronic obstructive pulmonary disease (COPD). Both these conditions are common ailments. The possibility that multiple respiratory diseases can overlap in the same individual had been considered by pulmonologists, but David Flenley in 1985 had first reserved the term “overlap syndrome” for the coexistence of OSA and COPD in the same individual¹. This is because he believed that the syndrome was a clinically distinct entity from either disease in isolation and that the prognosis, course, and urgency of treatment were equally unique.

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Definition

Overlap syndrome is a term used to describe the coexistence of obstructive sleep apnea (OSA) and COPD (Figure 1). However, this is not an ideal definition. Both these diseases occur on a spectrum of severity and it is undecided at what level of severity the combined diseases have synergistic clinical implications. It is not known whether patients with severe COPD and mild OSA are similar to those with mild COPD and severe OSA².

Some authors, after recognizing the “overlap” between COPD and Asthma have suggested that the two may be clubbed together as Obstructive lung disease (OLD) and the term overlap syndrome may be used to define the co-existence of OLD and OSA (“The OLD-OSA overlap”)³. However, in this review, we have restricted the term overlap syndrome to the “COPD-OSA overlap”.

Epidemiology

There is paucity of data regarding the exact prevalence of overlap syndrome and most estimates are imperfect. This is partially due to the absence of a standardized

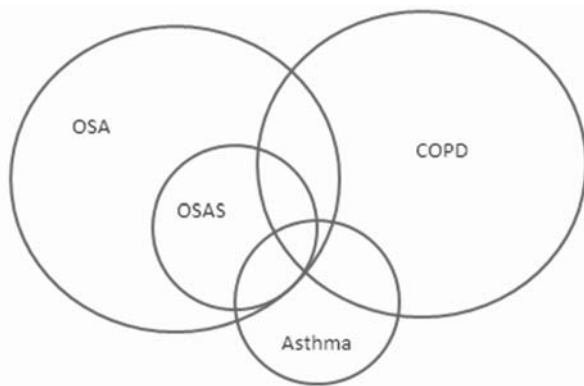


Figure 1: Non-Proportional Venn Diagram for the Overlap Syndrome

definition, and a lack of a unique diagnostic code. This is further compounded by the multiple revisions in the diagnostic tests and criteria of OSA and COPD in the last few decades.

The early studies had reported highly variable prevalence figures depending on the severity of COPD/OSA, the diagnostic techniques employed, and the associated risk factors in the patients being studied⁴⁻⁵. These studies were not truly cross-sectional; and the prevalence seemed excessively high.

However, a later large prospective cohort study reported that COPD in subjects with OSAS was as frequent as in the general population⁶. Furthermore, the presence of airway obstruction did not seem to affect the respiratory disturbance index. A European study also did not find any increased risk relationship between the two disorders⁷. However, the major limitation of these two studies is that most subjects had very mild airway obstruction on spirometry. When patients with moderate to severe COPD were assessed, Soler et al. in a recent study reported 66% prevalence of OSA⁸.

It is important to realize that because of the rising prevalence of these diseases, a patient with one of the disorders will often have the other disease. The BOLD study, a multinational, population based study has estimated the global prevalence of stage II or higher COPD as 10.1%; and the prevalence is expected to increase in the coming years⁹. The Wisconsin Sleep Cohort Study, a population-based study determining epidemiologic features of OSA reported a prevalence of OSA (AHI ≥ 5) in middle-aged adults between 30 and 60 years of age to be 9% for women and 24% for men¹⁰. The OSA syndrome, characterized by both an

AHI ≥ 5 along with daytime sleepiness (assessed by 3 subjective questions), was present in 2% of women and 4% of men¹⁰.

Even by chance alone, a patient with one of the disorders has a greater than 10% chance of also having the other disease. Thus, when seeing a patient with either disease, it is reasonable to screen for the other.

COPD-OSA interactions

Impact of COPD on OSA

Multiple mechanisms have been postulated to explain how one disorder might cause or aggravate the other. COPD may adversely affect the upper airway dilator muscles; either directly (COPD has been linked with sarcopenia) or indirectly (the use of inhaled steroids may have an impact); but the relevance of any such abnormality has been questioned¹¹. COPD (and asthma) are frequently associated with chronic mucosal inflammation which may contribute to the airway resistance and the airway collapsibility. Studies have shown that therapies targeted at reducing inflammation (eg. Nasal corticosteroids in pediatric patients) may help in alleviating OSA¹². The air-trapping and the parenchymal destruction in COPD may also decrease the tethering of airways, reducing the tracheal traction and producing a more collapsible airway. Also, patients of COPD frequently have right-heart failure, wherein the redistribution and rostral shift of edema fluid during supine sleep may cause an increase in the neck circumference and reduce the cross-sectional area of the upper airway; contributing to OSA¹³⁻¹⁴.

Impact of OSA on COPD

In an animal model, repetitive chronic intermittent hypoxia (CIH)-a hallmark feature of OSA has been shown to be associated with structural lung parenchymal changes; physiological deficits and other overlap syndrome related comorbidities¹⁵. In human studies, an increased levels of neutrophils, TNF- α and IL-8 in the bronchoalveolar lavage of adults with COPD and OSA as compared with adults with COPD only has been shown; this suggests that OSA may be causing an exacerbation in the airway inflammation in COPD patients¹⁶.

Pathophysiology of Overlap Syndrome - the Nocturnal Oxygen Desaturation

The most significant abnormality associated with overlap syndrome is the nocturnal oxygen desaturation. Patients with isolated COPD¹⁷ and OSA¹⁸ have nocturnal oxygen desaturation, and when the diseases overlap, the risk of prolonged and severe oxygen desaturation at night is greater than that with either disease alone⁶. This more prolonged hypoxemia, appears to increase morbidity and mortality considerably¹⁹.

Various mechanisms are believed to contribute to nocturnal oxygen desaturation: these include alveolar hypoventilation, ventilation-perfusion mismatching, and resetting of the minute ventilation set point. Alveolar hypoventilation is the predominant mechanism for most of the oxygen desaturation. Every episode of apnea during OSA leads to alveolar hypoventilation. Even in isolated COPD patients, minute ventilation is found to be decreased especially during REM sleep²⁰. The ventilation perfusion mismatch may also contribute to the hypoxia when the patient is lying recumbent. An alternative explanation has been that the respiratory drive changes suggesting that the minute ventilation set-point has changed in such patients²¹⁻²².

Consequences of Nocturnal Oxygen Desaturation

The nocturnal oxygen desaturation promotes oxidative stress by increased production of reactive oxygen species and angiogenesis, increased sympathetic activation with surges in both systemic and pulmonary blood pressure, and systemic and vascular inflammation with endothelial dysfunction that contributes to diverse multiorgan chronic morbidity and mortality affecting cardiovascular disease, metabolic dysfunction, cognitive decline, and progression of cancer²³. The short-term and long-term effects of repeated oxygen desaturation are believed to be causative for the multiorgan comorbidity and mortality seen in overlap syndrome.

Clinical Consequences of Overlap Syndrome

The recent GOLD guidelines for COPD, acknowledge the burden of pulmonary and systemic (extra-pulmonary) manifestations commonly seen in COPD²⁴. Similarly,

OSA has been shown to lead to neuro-cognitive dysfunction, increased risk of poor cardiovascular outcomes (developing hypertension, arrhythmias, coronary disease and stroke), and an adverse metabolic profile (particularly glucose and lipid homeostasis)²⁵.

The patients with overlap syndrome show a combination of these above mentioned effects. In addition to the obvious pulmonary morbidity, a common system involved in overlap syndrome is the cardiovascular system. The occurrence of pulmonary hypertension²⁶, right ventricular remodeling²⁷, and new onset atrial fibrillation²⁸ has been seen to be higher in OS patients than patients with either disease alone.

Patients with COPD²⁹ and OSA³⁰ often show neurocognitive impairments. Effects are more apparent in severe cases, whereas in moderate and mild cases the effects are equivocal. In overlap syndrome, the common risk factors of aging and the poor quality of sleep, hypoventilation, hypoxemia, and hypercapnia act in an intermingling and synergistic way in causing cognitive dysfunction³¹. This is an aspect which requires further investigation.

Consequent to the increased morbidity, the overlap syndrome patients have greater medical utilizations with greater mean overall annual costs compared to the COPD only group³². Studies have also shown that patients with overlap syndrome have a significantly worse quality of life, when compared to COPD-only controls³³⁻³⁴.

When the mortality was assessed in patients with OSA, it was seen that the diagnosis of concomitant COPD and markers of COPD are associated with increased mortality in OSA patients³⁵. Conversely, co-morbid OSA has been reported to increase mortality in COPD. Marin et al in a prospective cohort study with a median follow-up of over 9 years, found that patients with overlap syndrome not treated with CPAP had a higher mortality compared to the COPD-only group³⁶. Even when adjusted for COPD severity, comorbid OSA remained a risk factor for death. In a recent prospective study, assessing 227 patients with overlap syndrome treated with CPAP, it was seen that the less hours of CPAP use (that is, inadequate management of overlap syndrome), predicted a high risk of mortality³⁷.

The exact mechanisms that account for the increased morbidity and mortality risk are not completely understood. The role of repeated prolonged and severe nocturnal oxygen desaturation and hypercapnia has been

hypothesized. The systemic effects of the two diseases may also be synergistic or at least additive; both cause inflammation via various mediators (tumor necrosis factor alpha, interleukin-6, and interleukin-8), in addition to the oxidative stress they create; systemic inflammation may contribute to the pathogenesis of the common comorbid conditions and the cell/molecular pathways involved are similar to those identified in COPD and sleep apnea³⁸.

Diagnosis

The disorder is frequently diagnosed when a patient with either disease is screened for the other disease by the specialist. The other disease may be mild and may not necessarily produce overt clinical symptoms. It may be important to screen all patients in order to completely identify all the cases; however this is not always feasible.

Looking for OSA in COPD patients:

Sleep disturbance is a common complaint in patients with chronic obstructive lung disease (COPD)³⁹. However, the absence of symptoms does not necessarily rule out the possibility of overlap syndrome. It has been seen that a high BMI and smoking history are predictors of the overlap syndrome in a cohort of COPD patients, and these patients may be more often affected by hypertension and diabetes⁴⁰. It has been seen that in patients with overlap syndrome, pulmonary hypertension changes develop in patients with milder airway obstruction and less severe OSA than would be expected⁴¹⁻⁴². Hence it is recommended that patients with relatively mild COPD and evidence of pulmonary hypertension should be evaluated for coexisting OSA.

COPD patients with nocturnal oxygen desaturation who developed morning headaches when treated with nocturnal supplemental oxygen are another group of patients who are likely to be having overlap syndrome^{1,43}.

During evaluation for OSA, nocturnal oximetry is not routinely advisable as nocturnal oxygen desaturation could reflect only COPD. Polysomnography with transcutaneous CO₂ monitoring is currently the best tool to evaluate sleep disordered breathing for COPD patients. It is noteworthy that even patients who are minimally symptomatic for OSA have been shown to have significant cardiovascular morbidity⁴⁴. Because of expenditure/ logistic reasons, testing of all COPD

patients is not feasible. A reasonable approach may be to directly do polysomnography in the above mentioned groups of patients; in the remaining patients, a questionnaire based screening may be done and those who are deemed to be at high risk for OSA may undergo a polysomnographic evaluation.

Looking for COPD in OSA patients

It is advised that in patients with OSA, a detailed history (including history of smoking and occupational exposures), a review of respiratory symptoms and an evaluation for daytime hypoxemia or hypercapnia should be performed; and these could prompt pulmonary function testing. Performing a PFT is relatively simple and hence, if feasible, then should be routinely recommended in all patients of OSA.

Implications for Diagnosing Overlap Syndrome:

- The identification of the disorder allows better understanding of the underlying pathophysiology and permits the early initiation of appropriate aggressive management.
- The assessment of the severity of the component diseases and its synergistic effect permits better prognostication of the patient.
- The sleep- specialist will titrate the CPAP pressures to the airflow rather than oxygen desaturation.
- The diagnosis alerts the clinician to screen for diseases like pulmonary hypertension and other associated comorbidities.

Treatment

Treatment of the overlap syndrome requires the treatment of the constituent diseases. The goal of treatment is to alleviate the symptoms, mitigate the possible long-term ill effects, maintain adequate oxygenation at all times and to prevent OSA related hypoventilation.

Weight Loss

Sedentary lifestyles pose major challenges to the prevention of obesity and chronic respiratory diseases such as chronic obstructive pulmonary disease (COPD), obstructive sleep apnea and obesity hypoventilation syndrome. Obesity has emerged as an important risk factor for these respiratory diseases, and in many

instances weight loss is associated with important symptomatic improvement⁴⁵. Life-style modifications are an integral part of management of OS patients. Even in patients with severe COPD patients who may be cachexic, pulmonary rehabilitation is an essential component in the management of these patients. There is a dearth of studies which have evaluated weight loss as a therapeutic option in those with the overlap syndrome. It seems reasonable that obese patients with overlap syndrome would benefit from a calorie restricted diet and exercise program.

Long-term Oxygen Therapy (LTOT)

LTOT is the mainstay of treatment for COPD patients with daytime and nocturnal hypoxemia^{24,46}. However its role in isolated nocturnal hypoxia is not as straightforward. It has been seen that though COPD patients with normal oxygen saturation during day but nocturnal oxygen desaturation (especially during REM sleep) are at increased risk of mortality¹⁹; however, in a randomized controlled trial, correction of nocturnal hypoxemia alone, failed to significantly improve pulmonary hemodynamics or mortality⁴⁷.

The use of nocturnal oxygen therapy alone in OSA patients has also not been shown to significantly impact the sleep architecture, arousals, and subjective sleepiness; though the desaturations had reduced⁴⁸.

A study by Alford et al had investigated the role of oxygen administration in the overlap syndrome⁴⁹. Twenty obese men with sleep apnea and COPD were studied polysomnographically on two nights receiving air on one or oxygen at 4 L/min on the other. With oxygen therapy, though nocturnal oxygenation improved, the duration of obstructive events increased, along with an increase in the end-apneic $p\text{CO}_2$, with consequent decreases in pH. Thus, oxygen alone is not recommended for the treatment of the overlap syndrome. Its use is recommended in conjunction with CPAP/ NIV therapy⁵⁰.

Bronchodilators

Randomized controlled trials have shown that bronchodilator therapy in patients with moderate to severe COPD improved the nocturnal oxygen saturation⁵¹⁻⁵³ & subjective sleep quality⁵¹, and there was an increase in total REM time⁵¹. Oral steroid therapy in

stable COPD improves nocturnal oxygen desaturation and increases total sleep time⁵⁴. Optimal broncho dilatation can prevent nocturnal oxygen desaturation, and may decrease the need for supplemental oxygen in addition to CPAP.

Continuous Positive Airway Pressure (CPAP)

CPAP therapy has been evaluated for improvement in lung function in stable COPD patients. In theory, CPAP will ameliorate the repetitive airway collapse, reduce the upper airway resistance and counteract the intrinsic PEEP, with the consequent decline in respiratory muscle load might lead to an improvement in the lung function⁵⁵.

CPAP is the standard of care in the treatment for OSA, and currently is the accepted standard for overlap syndrome. CPAP therapy has been shown to improve daytime PaO_2 values both in OSAS and in overlap syndrome⁵⁶. CPAP treatment has been shown to improve the strength of respiratory and skeletal muscles and improved exercise tolerance in patients with overlap syndrome⁵⁷⁻⁵⁸ along with improvements in gas exchange, airflow obstruction and hospitalization rates⁵⁹. In the prospective trial by Marin et al, treatment with CPAP in patients with overlap syndrome was shown to reduce the hospitalizations due to exacerbation of COPD and mortality in these patients³⁶. Machado et al studied the effect of CPAP on the survival of hypoxaemic COPD patients on LTOT⁶⁰. The authors observed that after adjusting for several confounders, patients treated with CPAP showed a significantly lower risk of death and have recommended CPAP in the management of overlap syndrome.

Noninvasive Positive Pressure Ventilation (NIPPV)

The role of NIPPV in stable hypercapnic COPD has been an area of active research, with multiple studies and inconsistent results over the years⁶¹. McEvoy et al in a randomized control trial of NIPPV in patients with stable hypercapnic COPD, showed a significant improvement in adjusted mortality though associated with a worse quality of life⁶². Windisch et al had used "high-intensity NIPPV," with very high driving pressure (average inspiratory pressure 28 cm H₂O, average expiratory pressure 5 cm H₂O) and a high respiratory

rate; they reported improvements in spirometry and blood gas abnormalities and mortality⁶³.

In OSA patients, CPAP is the treatment of choice and NIPPV is rarely used. Whether long-term NIPPV would be better than CPAP in preventing complications and in improving outcomes in the overlap syndrome, is still an unanswered question. It seems logical that in cases where OSA predominates, CPAP may be most appropriate, whereas in cases where there is evidence of significant nocturnal hypoventilation with associated periods of sustained hypoxaemia, bilevel positive airway pressure may be more appropriate. Newer modalities of pressure support, such as adaptive servo ventilation, may be particularly suited to patients with the overlap syndrome.

Conclusions

Overlap syndrome is a common entity with a rising prevalence due to increase in the prevalence of COPD and OSA. Both the component diseases have a wide spectrum and it's difficult to predict the impact of severity of either disease on the overall impact that overlap syndrome has on the patient. It is believed that the presence of either of disorder aggravates the other; and the adverse impacts may be additive and possibly even synergistic.

The most significant abnormality associated with overlap syndrome is the nocturnal oxygen desaturation. Oxidative stress due to nocturnal desaturation leads to pulmonary and systemic hypertension and chronic inflammation leading to changes in multiple organs. Studies have documented that patients with overlap syndrome have a significantly impaired quality of life and increased morbidity and mortality as compare to either of disease alone. Thus, it is imperative for physicians to look for OSA in COPD patients and COPD in OSA patients. During evaluation of patients with either OSA or COPD, a high index of suspicion is crucial to detect the overlap syndrome. The presence of daytime hypercapnia and pulmonary hypertension, in patients having either disease, especially when mild in severity, should prompt assessment for the other disorder.

CPAP (and occasionally NIV) is the standard of care in the management of overlap syndrome. Oxygen therapy may be given along with CPAP/NIV (but never in isolation) to prevent desaturation in these patients. Weight loss, pulmonary rehabilitation and optimal

bronchodilators are important adjuncts in the management of this disorder.

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