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11 Sleep and COPD: The Overlap Syndrome

Key Points
1. Sleep disturbances occur in 34–78% of patients with COPD due to nocturnal respiratory symptoms, intrinsic sleep disordered breathing, or a combination of both processes.
2. The overlap syndrome is the concurrence of COPD and obstructive sleep apnea (OSA).
3. Although the prevalence of OSA among those with COPD was initially thought to be increased, more recent studies suggest that the prevalence of the overlap syndrome is about 1% of the general population which is the predicted prevalence if COPD and OSA are independent processes.
4. The recognition and identification of sleep disordered breathing among patients with COPD requires a strong index of suspicion and a sleep-directed history and physical examination.
5. Overlap syndrome is characterized by more profound nocturnal hypoxemia and deranged sleep architecture than either COPD or OSA alone.
6. The physiologic derangements of COPD accentuate normal sleep-related respiratory changes to cause hypoventilation and ventilation-perfusion mismatching during sleep increasing PaCO₂ and decreasing PaO₂.
7. Management of the overlap syndrome includes optimal treatment of COPD and use of noninvasive positive pressure ventilation for the OSA.

11.1 Introduction

Sleep quality is worse in individuals with COPD compared with those without COPD (Fleetham, 1982; Calverley, 1982; Brezinova, 1982). Between 34 and 78% of individuals with COPD report difficulty initiating or maintaining sleep, nocturnal awakenings, or nonrestorative sleep (Agusti, 2011; Tashkin, 2008; Price, 2013, Weizenblum 2004; Marrone, 2006; Klink, 1994; Rennard, 2002). Sleep efficiency is only 50–70% in patients with COPD and the proportion of sleep time is increased in light sleep and decreased in REM sleep, shifts between sleep stages occur more frequently, and micro-arousals disrupt sleep (McNicholas, 2013). At least half of all patients with COPD experience nocturnal respiratory symptoms (Miravitlles, 2014). Some studies suggest that this proportion increases as lung function worsens whereas other investigations show no relationship between nocturnal respiratory symptoms and COPD severity (Kessler, 2011; Lange, 2014; Miravitlles, 2014).

Nocturnal symptoms are associated with worse sleep quality, greater daytime breathlessness, more frequent COPD exacerbations, and greater number of respira-
atory medications (Price, 2011; Miravitlles, 2014). In addition, patients with nocturnal respiratory symptoms have greater dyspnea, anxiety, and depression and worse health status (Miravitlles, 2014). Nocturnal breathlessness is associated with daytime respiratory symptoms including dyspnea, phlegm production, and wheezing (Lange, 2014; Miravitlles, 2014; Kessler 2011).

Approximately one third of patients with OSA have chronic cough (Chan, 2010). Those with cough have similar sleep and respiratory symptoms but are more likely to be female and have more rhinitis and nocturnal gastrointestinal reflux symptoms than those without cough. In a group of 75 patients with chronic cough, 44% had OSA and 93% of them had improvement in their cough with optimized CPAP treatment (Sundar, 2010). Thus, OSA may contribute to chronic cough in patients with COPD and the cough may be improved with CPAP.

Physicians greatly underestimate the prevalence of nocturnal symptoms and their effects in patients with COPD (Price, 2011). Conversely, only 11.8% of patients with COPD discuss sleep concerns with their provider (Ohayon, 2014). The Nighttime Symptoms of COPD Instrument is a recently developed and validated patient-reported outcome instrument to document nocturnal symptoms in patients with COPD which may help in the recognition of night-time manifestations of COPD (Hareendran, 2013).

In addition to OSA, other sleep disorders that occur in individuals with COPD can include insomnia, periodic limb movement syndrome, and psychiatric sleep disorders (Ohayon, 2014; Valipour, 2012). Approximately half of all patients with COPD have insomnia symptoms, which is twice the prevalence as in those who do not have COPD (Ohayon, 2014). Concurrent depression or anxiety increases the prevalence of insomnia to 84.4% and 59.7%, respectively (Ohayon, 2014). Insomnia symptoms appear to correlate positively with COPD severity measured by the BODE index, current smoking, and greater sadness/anxiety and negatively with supplemental oxygen use (Hynninen, 2013; Budhiraha, 2012). Periodic limb movement and psychiatric sleep disorder scale scores derived from the Sleep Disorders Questionnaire are greater in patients with mild to moderate COPD compared with those who do not have obstructive lung disease (Valipour, 2012).

### 11.2 Smoking, Sleep, and COPD

Inhalation of tobacco smoke is the major cause of COPD (See Chapter 9, Natural History, Phenotypes, and Gender Differences in COPD and Chapter 6, Pathogenesis of COPD). Many patients with COPD continue to smoke and tobacco smoke inhalation is associated with sleep disturbances including reduced sleep efficiency, increased sleep latency, nonrestorative sleep, and alterations in sleep stages with less REM sleep and more time in lighter sleep (Lan, 2012; Wetter, 1994A; Wetter, 1994B; Zhang, 2006; Zhang, 2008; Jaehne, 2009). Some smokers may experience nocturnal partial nicotine withdrawal which can disrupt sleep by inducing frequent and prolonged awakenings.
Prevalence of Overlap Syndrome

In 1985, David Flenley coined the term overlap syndrome to refer to the co-existence of OSA and any chronic respiratory disorder and, over the past three decades, overlap syndrome has been most commonly used to denote the concurrence of COPD and OSA (Flenley, 1985; Weitzenblum, 2008). Earlier studies suggested that the prevalence of OSA was increased among individuals with COPD. However, these studies sampled populations from sleep or respiratory clinics and their conclusions may be affected by selection bias. The prevalence of the overlap syndrome among men is estimated to be approximately 1% (Chaouat, 1995; Ioachimescu, 2013; Sanders, 2003; Bednarek, 2005; McNicholas, 2009; Owens 2010). If one estimates a prevalence of 10% for both COPD and OSA, the expected prevalence of the overlap syndrome is 1%. However, since both COPD and OSA are under-recognized and under-diagnosed,
the actual prevalence of the overlap syndrome is most likely greater than reported or estimated.

The largest epidemiologic study of the overlap syndrome analyzed the 5,954 participants in the Sleep Health Heart Study who underwent unattended home polysomnography testing and spirometry (Sanders, 2003). This study was designed to address the relationship between sleep disordered breathing and hypertension and cardiovascular disease in adults and oversampled individuals younger than 65 years old who snored. The proportion of participants with OSA with or without airflow limitation was similar, 22.32% versus 28.86%, or 13.97% versus 18.63%, using apnea-hypopnea index (AHI) thresholds of either >10 or >15 events/hour to define OSA, respectively (Sanders, 2003). The AHI was positively correlated with the FEV1/FVC ratio, suggesting that among individuals with mild airflow limitation, more severe obstruction was associated with a lower AHI. Participants with both airflow limitation and OSA had greater sleep disturbances and greater nocturnal desaturations than those with either disorder alone. The OR for nocturnal desaturation (defined as SpO2 <90% for more than 5% of total sleep time) was 3.36 (95% CI, 1.98, 5.70) in those with an FEV1/FVC ratio less than 60% and as the FEV1/FVC ratio declined the proportion of participants with nocturnal desaturation increased (Sanders, 2003). Participants with overlap syndrome had higher Epworth Sleepiness Scale scores (a measure of sleepiness), and greater proportions of total sleep time in stage 2 and less time in REM and stage 3/4 sleep than those with either disorder alone (Sanders, 2003). Thus, the Sleep Health Heart Study showed that the prevalence of OSA is not increased among individuals with mild COPD but those with the overlap syndrome do have more deranged sleep architecture and greater nocturnal oxygen desaturation than those with either disorder alone.

The results of the SHHS were corroborated by the Monica II study that showed that the prevalence of airflow limitation in participants with OSA was the same as in the general population, approximately 10–11% (Bednarek, 2005). Those with the overlap syndrome had a lower mean SpO2 and spent more time with a SpO2 <90%.

### 11.4 Predictors of Overlap Syndrome

Among individuals with COPD, the risk of sleep disordered breathing increases with body mass index (BMI), age, smoking status, presence of peripheral edema, and use of systemic steroids (Chaouat, 2005; McNicholas, 2013). A small study of 177 subjects with COPD, 33 of whom had OSA, suggested that BMI and smoking history measured in pack years were associated with the AHI (Steveling, 2014). A recent study of patients with overlap syndrome did not find that they were more obese or had more excessive daytime sleepiness than those who did not have OSA and suggested that a high index of suspicion is needed to recognize and diagnose overlap syndrome (Venkateswaran, 2014).
The GOLD Guidelines recommend screening patients with COPD for OSA if they are experiencing sleep related symptoms or excessive nocturnal awakenings (GOLD). Because of the high association of pulmonary hypertension with the overlap syndrome, screening sleep studies may be indicated in individuals with COPD and elevated pulmonary artery pressures (See Chapter 12, COPD and Pulmonary Vasculature) (Celli, 2004). A small retrospective study found an association between the severity of airflow and the presence of OSA and suggested that sleep studies should be considered in patients with severe COPD (Lopez-Acevedo, 2009). However, another study did not find an association between OSA and severity of airflow limitation among patients with COPD (Sharma, 2011). In patients with the overlap syndrome, lung hyperinflation measured by the inspiratory capacity divided by the total lung capacity (IC/TLC) correlates with worse sleep efficiency independent of the AHI or severity of hypoxemia; therefore, the presence of hyperinflation might be another screening pulmonary physiologic variable to consider in determining which patients to evaluate for overlap syndrome (Kwon, 2009).

11.5 Screening and Diagnosis

The recognition and diagnosis of COPD is discussed in Chapter 3, COPD Recognition and Diagnosis. A high level of vigilance and attentiveness are required for the recognition and diagnosis of OSA in patients with COPD.

A comprehensive sleep history is an important first step in the evaluation of patients with COPD and sleep related symptoms. The discrimination of sleep disordered breathing due to intrinsic sleep disorders from disrupted sleep due to nocturnal respiratory symptoms can be difficult. The sleep history and examination may increase the suspicion of obstructive sleep apnea or other sleep disturbance, but polysomnography is required to establish the diagnosis and initiate treatment.

In general, patients who are obese, have highly associated comorbidities such as congestive heart failure, atrial fibrillation, hypertension that is difficult to control, pulmonary hypertension, and who work in potentially high risk occupations (pilot, school bus driver) should be evaluated further (Epstein, 2009). Another key historical feature is previous motor vehicle accidents especially if they are related to sleepiness. Key elements of the sleep history include sleep initiation including insomnia, total sleep time, quality of sleep (restorative versus nonrestorative), presence or absence of recalled dreams, snoring, observed apneas or episodes of choking, gasping, or sputtering, excessive daytime sleepiness, nocturnal awakenings including nocturia, morning headache, excessive daytime sleepiness, reduced memory, and emotional lability (Epstein, 2009). A review of the accuracy of the clinical history in the diagnosis of OSA showed that a history of choking or gasping at night was the most predictive historical finding, summary likelihood ratio (LR), 3.3; (95% CI, 2.1–4.6) when an AHI ≥10/h was used to diagnose OSA (Myers, 2013). Although patients with OSA fre-
sequently reported snoring, it was not useful in discriminating OSA (summary LR, 1.1; 95% CI, 1.0–1.1) (Myers, 2013). Thus, in individuals with COPD, these discriminating characteristics may not be as reliable and the clinician should consider a careful sleep history while maintaining a high index of suspicion for sleep disturbances. Finally, it may be difficult to differentiate sleep dysfunction related to respiratory symptoms due to COPD such as cough and sleep symptoms related to OSA.

Several validated surveys are available to assist clinicians in the identification of individuals at risk for sleep disordered breathing. The Epworth sleepiness scale is a measure of sleep propensity and correlates with sleep latency, the apnea hypopnea index, and minimal nocturnal SpO\textsubscript{2} in individuals with OSA (Johns, 1991). The Berlin questionnaire is a screening survey for OSA in the general population that has a sensitivity and specificity of 86% and 77%, respectively, in primary care patients (Netzner, 1999). The Nighttime Symptoms of COPD Instrument assists in the identification of nocturnal respiratory symptoms (Hareendran, 2013). The use of these instruments in the overlap syndrome is less well studied.

Elements of the physical examination may also suggest the presence of OSA. Hypertension, especially when it is refractory to treatment, and elevated body mass index are abnormal vital signs that may be associated with OSA. An increased neck circumference, reduced posterior pharyngeal diameter, enlarged tonsils, and retrognathia may also increase the risk of OSA.

There are no elements of the history or physical examination that can conclusively diagnose OSA and further evaluation with a form of sleep diagnostic testing, formal full polysomnographic study in a sleep laboratory or home study, is usually indicated. Overnight pulse oximetry has limited utility in the diagnosis of OSA in patients with COPD and is not reliable for the diagnosis of the overlap syndrome due to the indiscriminant frequency, pattern, and severity of oxygen desaturation events in both disorders (Scott, 2014).

11.5.1 Normal Sleep Physiology

Physiologic regulation of respiration during wakefulness is an integrally connected tripartite system of sensors, central control, and effectors. Aortic and carotid body sensors monitor changes in oxygen and carbon dioxide, vagal afferent neurons sense lung parenchymal alterations, and other systems respond to external stimuli and volitional control (Newton, 2014). Within the medullary ventilator center, neurons generate an automated respiratory rhythm that is modulated by these sensory and volitional inputs. The signals from the respiratory center stimulate the diaphragm and other respiratory muscles to generate inspiratory and expiratory airflow and maintain upper airway muscle tone and patency modulating both respiratory frequency and tidal volume. This system is highly regulated to maintain usual PaO\textsubscript{2} and PaCO\textsubscript{2} levels within narrow ranges.
Respiratory physiology is markedly altered during sleep and the ventilatory changes vary during different stages of sleep. With sleep onset, external stimuli and volitional signals are no longer processed or produced and internal biochemical and biomechanical sensory inputs predominant. The usual change from primarily upright to horizontal posture alters thoracic musculoskeletal and diaphragmatic mechanics and may also affect posterior pharyngeal architecture by reducing the airway lumen. During sleep, respiratory center responses to biochemical stimuli, PaO₂ and PaCO₂, are blunted. Combined with a lower metabolic rate, the diminished chemosensitivity to oxygen and carbon dioxide levels causes a reduction in minute ventilation mainly through a decrease in tidal volume. Consequently, PaCO₂ rises and PaO₂ may decline slightly. During REM sleep, skeletal muscle atonia occurs and the diaphragm is the only functioning respiratory muscle which reduces tidal volume and minute ventilation and further accentuates hypoxemic and hypercarbic changes.

11.5.2 Sleep Physiology and OSA

OSA is diagnosed by the presence of either cessation (apnea) or reduction (hypopnea) of airflow caused by recurrent upper airway occlusion or blockage during sleep despite maintained central respiratory drive. These events are measured by the apnea-hypopnea index (AHI), the number of apneas and hypopneas per hour, and OSA is usually defined as an AHI greater than 5 events per hour. Central sleep apnea is caused by the absence of central respiratory drive stimuli. Initiation and maintenance of airflow during sleep requires central signaling, activation of respiratory muscles including not only the diaphragm and accessory muscles, but also those controlling the posterior pharyngeal lumen to maintain upper airway patency and counteract the inward negative pressure of inspiration. If the airway aperture is not maintained, airflow is reduced (hypopnea) or stopped (apnea). Depending upon the duration and severity of reduced airflow, PaCO₂ levels may rise and PaO₂ levels decrease. Apneic or hypopneic events are usually terminated by an arousal followed by augmented minute ventilation to normalize oxygen and carbon dioxide levels. Reduced biochemical sensitivity may derange normal feedback loops causing over or under compensation and wide variation in respiratory patterns. These arousals lead to sleep fragmentation and reduced REM sleep time. Factors that may contribute to the development of OSA include individual anthropomorphic features, upper airway architecture which is determined by anatomic, mechanical, and neuromuscular processes, medications including alcohol, and respiratory center function (Deegan, 1995).
11.5.3 Sleep Physiology and COPD

COPD-related respiratory derangements may adversely affect normal sleep physiology. Supine positioning during sleep may reduce the posterior pharyngeal aperture increasing airway resistance. Resistance to airflow is greatest in the posterior pharynx in the region circumscribed by the base of the tongue and the soft palate. The airway in this zone is flexible and potentially collapsible. The base of the tongue may move posteriorly and approach the posterior pharyngeal wall reducing the anterior-posterior aperture and the lateral walls may also encroach upon the lumen due to excessive soft tissue, mucosal edema and inflammation, negative intraluminal pressure during inspiration, and relaxed pharyngeal dilator muscle tone (Mieczkowski, 2014). This increase in upper airway resistance necessitates generation of a greater inspiratory force by the respiratory muscles which may be handicapped due to intrinsic muscle weakness related to COPD and mechanical disadvantages.

Intrinsic muscle dysfunction associated with COPD may affect the upper airway musculature as well as the diaphragm and accessory muscles of respiration diminishing their function. In individuals with hyperinflation and air trapping, the diaphragm may be mechanically disadvantaged due to elongation and distension of diaphragmatic muscle fibers. Hyperinflation is associated with worse sleep efficiency in patients with overlap syndrome (Kwon, 2009). Additionally, the pressure of abdominal contents in the supine positioning further disadvantages the diaphragm by increasing its load due to the additional caudad force required for movement during inspiration. Individuals with COPD and hyperinflation may be more reliant upon accessory muscles of respiration to maintain minute ventilation; the hypotonia of REM sleep may further reduce minute ventilation by eliminating the contribution of accessory muscles to ventilation. These physiologic changes may cause more profound hypoxemia, up to 40% declines in oxygen saturation during REM sleep and 20% reductions during non-REM sleep, in patients with severe COPD (Becker, 1999).

11.5.4 Sleep Physiology and Overlap Syndrome

COPD-related respiratory derangements may augment and accentuate many of the physiologic consequences of OSA. Patients with the overlap syndrome generally have more profound sleep-related hypoxemia and hypercarbia than individuals with either disorder alone (McNicholas, 2013). Factors that may contribute to hypoxemia severity in the overlap syndrome include lower baseline oxygen level, ventilation/perfusion mismatching, and blunted oxygen sensing. Worsened ventilation perfusion mismatching due to reductions in functional residual capacity, supine posture, intrinsic parenchymal lung disease, retained secretions occluding or blocking airways, may contribute to nocturnal desaturations in individuals with COPD (McNicholas, 2013).
Although isocapnic hypoxemia is not a usual stimulus for arousal during sleep and desaturations to 70% may not trigger awakenings, individuals with COPD may have resting low normal oxygenation levels that place them on the shoulder of the oxygen-hemoglobin desaturation curve. Thus, even slight declines in oxygenation may precipitate severe desaturation. An increase of approximately 15 mmHg in end tidal carbon dioxide level is the threshold for usual hypercapnic-induced arousals but patients with COPD and hypercarbia may have severely blunted responses to further increases in carbon dioxide levels (Ayas, 2000).

Both COPD and OSA are characterized by systemic inflammation. The pathophysiology and consequences of inflammation in COPD are discussed in Chapter 6, Pathogenesis of COPD and Chapter 10, COPD is a Multi-Organ Disorder: Systemic Manifestations. OSA is categorized by enhanced production of inflammatory cytokines, sympathetic nervous system activation, and abnormal vascular and coagulant function. Recurrent hypoxic stress and sleep disruption are believed to be primary etiologic factors. The relationship between etiologic processes underlying systemic inflammation in the overlap syndrome and its component disorders, COPD and OSA, is an active area of research.

As discussed below in Comorbidities, the prevalence of comorbidities including COPD exacerbations and cardiovascular events related to inflammation and excessive mortality in the overlap syndrome appears to be greater than can be accounted for by either OSA or COPD alone suggesting a synergistic interaction.

11.6 Ventilation and Ventilation Perfusion Matching

During sleep, the cough reflex is diminished and the normal clearance of respiratory secretions (the production of which is increased in chronic bronchitis and bronchiectasis) is reduced (Power, 1984). These secretions may accumulate within the airways causing partial or total occlusion increasing airway resistance and altering ventilation patterns. These perturbations may disrupt ventilation-perfusion matching precipitating lower oxygenation and desaturation.

11.7 Polysomnography

Polysomnography (PSG) is the usual diagnostic study to evaluate sleep disordered breathing. PSG tests are multimodality studies that usually include electroencephalographic (EEG), electrooculographic (EOG), electrocardiographic (ECG), and electromyographic (EMG) measurements as well as monitoring pulse oximetry, thoracic and abdominal respiratory efforts, and audiovisual recording. Based upon EEG and EOG tracings, sleep is categorized into wakefulness, N1, N2, N3, and REM sleep (Silber, 2007). Most individuals progress through the nonREM stages to REM several times
during the night with more time in deep, N3 sleep during the early cycles and an increasing proportion of time in REM during the later cycles prior to awakening. Normally deep N3 sleep and REM sleep each account for approximately one quarter of sleep time and the remaining half of sleep time is transitional N1 and N2 sleep.

11.7.1 Consequences of Overlap Syndrome

In a group of 177 patients with COPD who underwent home sleep studies, 20% had apnea hypopnea indices greater than 10 events/hour, and this group had a higher BMI and greater smoking history and more arterial hypertension and diabetes than the group who did not have OSA (Steveling, 2014). Measures of arterial stiffness are greater in individuals with overlap syndrome compared with those with OSA alone and this increase is independent of nocturnal hypoxemia and systemic inflammatory markers (Shiina, 2012). The elevated arterial stiffness may contribute to increased cardiovascular comorbidities in the overlap syndrome.

Patients with overlap syndrome have higher PaCO₂ (44.59 mmHg) compared with those with either OSA (39.22 mmHg) or COPD (39.63 mmHg) which could only be partially explained by weight and airflow limitation (Resta, 2002). Patients with the overlap syndrome and daytime hypercapnia have more profound nocturnal desaturations and greater derangements in sleep quality including more apneas and hypopneas than those with normocapnia (Lopez-Acevedo, 2006).

11.7.2 Pulmonary Hypertension

The prevalence of pulmonary hypertension is greater among individuals with overlap syndrome compared with those with either COPD or OSA only (Rizzi, 1997; Bady, 2000; Laks, 1995; Sanner, 1997; Chaouat, 1996; Hawrylkiewicz, 2004). The diagnosis and treatment of pulmonary hypertension are discussed in Chapter 12, COPD and Pulmonary Vasculature.

11.7.3 Atrial fibrillation

A retrospective two year study revealed the incidence of new onset atrial fibrillation was 21% in those with the overlap syndrome compared with 10% among patients with COPD, 6% among those with OSA, and 4.9% for those with neither disorder (Ganga, 2013). Even after adjusting for comorbidities, overlap syndrome was associated with new onset atrial fibrillation, OR 3.66, 95% CI 1.056, 6.860. Another study showed that incident AF is associated with OSA and smoking but did not assess airflow (Gami, 2007).
11.7.4 Cognitive Dysfunction

Both COPD and OSA are associated with neurocognitive dysfunction including impaired attention, memory and learning, language and higher executive functions, and deranged visuospatial and constructional capacity (Andreou, 2014). Normally, cerebral blood flow (CBF) increases during episodes of arterial hypoxemia to protect the brain from neuronal injury but this compensatory mechanism is lost during non-rapid eye movement sleep (Alexancre, 2014). Thus, this loss of compensatory CBF during sleep may contribute to enhanced hypoxemia-induced neuronal injury and increased cognitive dysfunction in the overlap syndrome. Cognitive function in the overlap syndrome has not been well studied but, since hypoxemia is believed to be the major factor contributing to poor performance, these impairments may be more pronounced in individuals with overlap syndrome.

11.8 Mortality and COPD Exacerbations

The leading cause of death among patients with the overlap syndrome is cardiovascular disease (Marin, 2010; McNicholas, 2009). Among patients with OSA, mortality is associated with concurrent COPD, OR, 7.07, 95% CI 2.75–18.16 (Lavie, 2007). Conversely, mortality is increased in individuals with COPD and untreated OSA compared with those with the same severity of COPD and no OSA (Marin, 2010). Patients with overlap syndrome not treated with CPAP have a higher mortality, relative risk (RR) 1.79, 95% CI 1.16, 2.77, and greater risk of a COPD exacerbation requiring hospitalization, RR 1.70, 95% CI 1.21–2.38 compared with patients with COPD after adjusting for age, sex, body mass index, tobacco and alcohol use, comorbidities, COPD severity, AHI, and daytime sleepiness (Marin, 2010).

11.8.1 Treatment

In general, there is no specific treatment for the overlap syndrome and management is directed toward the two underlying disorders, COPD and OSA, and associated comorbidities.

11.8.2 Respiratory Medications

Therapy for COPD is discussed in Chapter 14, Management of Stable COPD. Both short and long acting anticholinergics improve nocturnal oxygenation and sleep quality in patents with COPD (Martin, 1999; McNicholas, 2004). In patients with OSA alone, the mean $\text{SpO}_2$ and duration of time with $\text{SpO}_2 \leq 90\%$ are reduced after treatment with sal-
meterol but total sleep time, quality of sleep, and AHI were unchanged (Rasche, 1998; Rasche, 1999). The proportion of respiratory symptom free nights increase in patients with COPD treated with high dose but not low dose combined LABA/ICS and with LABA alone (Tashkin, 2012). The proportion of patients with stable COPD who have insomnia is less in those treated with a beta agonist, either albuterol or formoterol, or with a long acting inhaler, either tiotropium or formoterol (Budhiraja, 2012).

Some treatments for COPD may reduce sleep quality. Systemic corticosteroids are associated with an increased risk of insomnia in individuals with COPD (Wood-Baker, 2005; Aaron, 2003). In addition, prolonged or recurrent, intermittent use of steroids may cause weight gain, a risk factor for OSA, and steroid myopathy which might reduce respiratory muscle strength further worsening hypoventilation during sleep (Mieczkowski, 2014).

Despite its benefits on physical conditioning, quality of life, anxiety, and depression, the effect of pulmonary rehabilitation on sleep quality in patients with COPD is not clear with some studies demonstrating improvement and others showing no effect (Lan, 2014; McDonnell, 2014).

### 11.8.3 Oxygen

Oxygen improves survival in individuals with COPD and resting hypoxemia despite optimized medical management (reviewed in Chapter 14, Management of Stable COPD). The effect of supplemental oxygen for patients with COPD with resting low normal oxygenation and transient desaturations during exercise or sleep is not known. Similarly, the effect of nocturnal supplemental oxygen in individuals with OSA remains unclear. Earlier studies with small numbers of patients studied for short periods suggested that nocturnal supplemental oxygen improved sleep parameters and nocturnal oxygenation (Martin, 1982; Smith, 1984; Gold, 1986) but a more recent double blind, randomized trial showed that supplemental oxygen did not improve sleep parameters and only increased nocturnal oxygen levels (Loredo, 2006).

A large prospective trial comparing CPAP and oxygen treatment in individuals with OSA and cardiovascular disease or risk factors showed that CPAP but not supplemental oxygen reduced 24 hour mean arterial blood pressure; sleep parameters were not assessed but C reactive protein, a measure of systemic inflammation was only reduced with CPAP (Gottlieb, 2014).

In patients with profound nocturnal hypoxemia that is refractory to CPAP and supplemental oxygen, use of transtracheal oxygen may maintain oxygen levels during sleep (Biscardi, 2014).
11.8.4 Lung Volume Reduction Surgery (LVRS)

In patients with emphysema amenable to surgical treatment, LVRS improves sleep quality (increased total sleep time and sleep efficiency and reduced arousal index) and nocturnal oxygenation (Krachman, 2005). These benefits appear to be more related to improvements in lung mechanics, reduced air trapping and hyperinflation, than oxygenation (Krachman, 2008).

11.8.5 Noninvasive Positive Pressure Ventilation

For patients with OSA, noninvasive ventilation with positive pressure, usually continuous positive airway pressure (CPAP), is the main treatment (Epstein, 2009). In patients with the overlap syndrome, CPAP improves quality of sleep, reduces complications and mortality, and decreases COPD exacerbations (Stanchina, 2013; Marin, 2010). A retrospective review of 227 patients with overlap syndrome revealed that 17 (7.4%) died over a 3 year period; adherence with CPAP was greater in surviving patients, 65.9±1.8% of nights with > 4 hours use and mean use 5.4±0.1 hr/night, than in patients who died, 21.2±8.1% of nights with >4 hours of use and 1.7±0.2 hr/night (Stanchina, 2013). Patients with overlap syndrome not treated with CPAP have a higher mortality, RR 1.79, 95% CI 1.16, 2.77, and greater risk of a COPD exacerbation requiring hospitalization, RR 1.70, 95% CI 1.21–2.38, compared with patients with COPD after adjusting for age, sex, body mass index, tobacco and alcohol use, comorbidities, COPD severity, AHI, and daytime sleepiness (Marin, 2010). Patients with overlap syndrome treated with CPAP had the same risk of death and hospitalization for COPD exacerbations as those with COPD alone (Marin, 2010). In a study of 271 patients with overlap syndrome treated with CPAP, those with hypercapnia had less mortality than those with normocapnia, hazard ratio (HR) 0.47 (95% CI 0.23–0.89) versus 0.72 (95% CI 0.32–1.63), respectively (Jaoude, 2014). This study suggested that CPAP’s mortality benefit in the overlap syndrome occurred only in patients with hypercapnia.

In patients with obesity hypoventilation or overlap syndrome, nocturnal NIV may reduce daytime PACO$_2$ levels and this decrease is associated with less daytime somnolence and EEG activation suggesting that hypercarbia may be a contributing factor to daytime sleepiness (Wang, 2014).

A prospective randomized controlled study comparing standard therapy with or without nocturnal noninvasive ventilation in patients with stable, hypercapneic COPD for 1 year showed that, when NIV was targeted to achieved a 20% reduction in baseline PaCO$_2$ or to achieve a PaCO$_2$ less than 48.1 mmHg, mortality decreased from 33% (NIV+standard therapy) to 12% (standard therapy alone), HR 0.24 (95% CI, 0.11–0.49) (Köhnlein, 2014). A meta-analysis of NIV in patients with stable COPD showed that non-targeted routine use of NIV did not affect sleep efficiency (Struik, 2014). Thus, it appears that CPAP treatment using pressure levels determined by the
measured effect on PaCO₂ optimizes CPAP’s benefits but these studies need to be verified in a population of patients with overlap syndrome. In general, these titration studies are best performed in a monitored setting such as a sleep laboratory, measuring oxygen saturation and end tidal CO₂ levels. Bilevel noninvasive ventilation is most frequently used to augment minute ventilation and reduce PaCO₂ levels by increasing the difference between the inspiratory and expiratory pressures.

Nocturnal intelligent volume-assured pressure support noninvasive ventilation improves sleep quality and reduces PACO₂ more than high-intensity noninvasive positive pressure ventilation in patients with COPD and resting hypercapnea (Ekkemkamp, 2014). These ventilator modes have not yet been evaluated for the overlap syndrome.

Nocturnal noninvasive ventilation may improve exercise capacity in individuals with the overlap syndrome. Walking capacity measured by the incremental shuttle walking test improves after CPAP treatment (Wang, 2013). A small study suggested that exercise tolerance measured by maximal work load during cardiopulmonary exercise testing increased in patients with overlap syndrome treated with CPAP (Nowinski, 2007).

CPAP reduces paroxysmal atrial fibrillation, sinus bradycardia, and sinus pauses among patients with OSA but its effect on these dysrhythmias in the overlap syndrome is not known (Abe, 2010).

11.9 Conclusion

Sleep disturbances may occur in up to 75% of individuals with COPD and may be due to nocturnal respiratory symptoms especially cough, sleep disordered breathing mainly OSA, or combinations of these processes. The concurrence of COPD and OSA is known as the overlap syndrome and, although its prevalence is not greater than would be predicted from the prevalence of either disorder alone, the overlap syndrome is associated with significant nocturnal hypoxemia and impaired sleep quality. This profound desaturation is due to the combined effects of COPD’s detrimental consequences on ventilation and ventilation-perfusion matching and usual hypoventilation and REM-related skeletal muscle atony. The overlap syndrome is associated with pulmonary hypertension. Treatment of the overlap syndrome includes minimizing nocturnal respiratory symptoms through optimal management of COPD, supplemental oxygen, and noninvasive positive pressure ventilation. CPAP improves sleep quality, and reduces COPD exacerbations, nocturnal desaturation, and mortality. More recent studies suggest that CPAP is mostly, and potentially only, beneficial in individuals with hypercapnia, and that use of noninvasive ventilation targeted to achieve a reduction in hypercarbia is more advantageous than non-targeted therapy.
11.10 Summary Points

1. Sleep disturbances due to nocturnal respiratory symptoms, sleep disordered breathing, or both processes occur commonly in patients with COPD.
2. Approximately 10% of individuals with COPD have OSA and the concurrence of COPD and OSA, the overlap syndrome, occurs in approximately 1% of the general population.
3. To identify sleep issues in patients with COPD, a careful and complete sleep history and sleep directed examination should be obtained.
4. Factors associated with the overlap syndrome include pulmonary hypertension, obesity, and possibly worse airflow limitation.
5. The overlap syndrome is characterized by profound nocturnal desaturation due to the combined effects of COPD and sleep on nocturnal ventilation.
6. Treatment of the overlap syndrome includes respiratory medications, supplemental oxygen, and noninvasive positive pressure ventilation.
7. Use of continuous positive airway pressure (CPAP) improves sleep symptoms, decreases COPD exacerbations, and increases survival.
8. CPAP is most beneficial in patients with overlap syndrome and hypercarbia.

References


References


