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Sleep and Obstructive Lung Diseases

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Abstract

Asthma and chronic obstructive pulmonary disease (COPD) are common obstructive lung diseases affecting millions of people in the United States. As sleep disorders are also common, it is not surprising that many people with obstructive lung disease also suffer from sleep disorders. However, people with COPD and those with asthma have worse sleep quality and more sleep-related problems when compared to people with other chronic health problems. In addition, a pathologic relationship may exist between obstructive sleep apnea (OSA) and obstructive lung diseases. This review focuses on the epidemiology, pathogenesis, and clinical implications of sleep disturbances in asthma and COPD.

Keywords

Sleep; Asthma; Chronic obstructive pulmonary disease; nocturnal hypoxemia

Introduction

Obstructive lung diseases are characterized by a limitation of airflow when measured by spirometry. Asthma and chronic obstructive pulmonary disease (COPD) are the two most common forms of obstructive lung diseases. Asthma is defined by reversible airway obstruction caused by inflammation of the lung's airways, often as a response to various triggers. Asthma affects over 14 million adults and 6 million children in the United States. [1] COPD is characterized by airway obstruction that is not fully reversible.[2] It is estimated that 16 million people in the United States have COPD.[3]

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Asthma symptoms including cough, wheezing, chest tightness, and dyspnea often worsen at night. Nocturnal asthma is a variable exacerbation of the asthmatic condition occurring at night. Nocturnal asthma is associated with increases in symptoms, worsening of lung function, and increased morbidity. COPD patients often also have increased symptoms at night. It is unclear why asthma and COPD worsen at night, but this may be due to circadian variations in pulmonary function, inflammation, secretion of hormones, and influences from other concomitant health problems such as gastroesophageal reflux disease. Strikingly, both asthmatic patients and COPD patients are more likely to die at night when compared to the general population.[4,5]

It appears that there is also a correlation between sleep quality and the obstructive lung diseases. People with COPD and those with asthma have been shown to have worse sleep quality and more sleep-related problems when compared to people with other chronic health problems. Sleep fragmentation and resultant sleep deprivation can lead to excessive daytime sleepiness and contribute to poor daytime cognitive function leading to social and mental problems. It has also been suggested that there may be a pathologic relationship between obstructive sleep apnea (OSA) and obstructive lung diseases.

This review will focus on the epidemiology, pathogenesis, and clinical implications of sleep disturbances in asthma and COPD, and briefly discuss the diagnostic evaluation and available therapies.

Epidemiology of Asthma and Sleep Disorders

Approximately 14–20 million people in the United States have asthma. In addition, a significant and clinically relevant interaction between sleep and asthma has been demonstrated.[6–8] The interaction is reciprocal, as asthma can affect sleep quality and impact obstructive sleep apnea, but sleep-related physiological changes can also affect the clinical presentation of asthma.

The vast majority of asthmatics experience nocturnal symptoms at least once in their lifetimes and many suffer from them routinely. Turner-Warwick surveyed 7729 patients with asthma and found that 74% of respondents experience nocturnal cough and wheeze at least once a week, 64% complained of nocturnal awakenings with asthma symptoms at least three times per week, and 40% awaken nightly.[8] Another study demonstrated asthmatics were twice as likely to complain of difficulty initiating sleep or early morning awakenings, and were 50% more likely to have symptoms of excessive daytime sleepiness.[7]

In addition to increased symptoms at night and impaired sleep quality, there appears to be a significant relationship between obstructive sleep apnea and nocturnal asthma. There is a positive association between OSA, snoring, a history of asthma, and common symptoms of asthma such as wheezing.[6,8] In addition, there is a positive correlation between gastroesophageal reflux disease and OSA, and the presence of both disorders may exert a synergistic negative effect on nocturnal asthma.[9,10]

Pathogenesis of Sleep Disorders in Asthma

Many physiologic changes that occur normally in sleep may have important consequences related to asthma and may promote nocturnal worsening of asthma (Box 1). Several hypotheses have been proposed to explain why asthma symptoms often worsen at night and will be discussed below.

Circadian variations in lung function

There is a circadian variation in objective measurements of lung function (Figure 1). Both asthmatics and healthy people experience their lowest peak expiratory flow rates (PEFR) in the early morning hours, usually between 3:00 AM and 6:00 AM; however, asthmatics typically have much lower PEFR values indicating more severe bronchospasm.[11] The fluctuations in amplitude from highest to lowest PEFR (PEFR variability) in one study were only 5 to 8 percent in normal controls compared to 50 percent or more in asthmatics.[11]

The mechanism responsible for the circadian variability in PEFR and airway resistance remains unknown. Several possible mechanisms have been proposed. One theory suggests that as the body cools normally during sleep, the cooling contributes to nocturnal bronchospasm. Breathing warm, humidified air can reduce the nocturnal worsening of lung function, even if the core body temperature is kept artificially lower, suggesting a direct effect of relatively cold air on the airway.[12] Alternatively, nocturnal symptoms may increase due to prolonged exposure to antigens such as dust mites that live in pillows and mattresses. However, a meta-analysis of studies that used physical barriers or chemical strategies to eliminate dust mites concluded such interventions had no significant effect on morning PEFR or symptom scores. This suggests there may be other antigens in addition to dust mites that must be accounted for and that may play a role in nocturnal symptoms of asthma.[13]

In addition to variations in PEFR, there is a decrease in functional residual capacity (FRC) that occurs during sleep in both normal patients and in patients with asthma. FRC is significantly reduced while supine and sleeping when compared to supine and awake which suggests that sleep itself is important in the observed reduction in lung volumes.[14] Decreases in FRC may have a significant influence on the increased lower airway resistance that occurs in patients with nocturnal asthma. In addition to decreases in FRC, inspiratory muscle activity is reduced in sleep which could further contribute to the reduction in lung volumes and increases in lower airway resistance.

Inflammatory Changes at Night

Airway inflammation in nocturnal asthma appears to differ in comparison to non-nocturnal asthma. Bronchoalveolar lavage (BAL) fluid obtained between 4 PM and 4 AM from asthmatics with nocturnal symptoms has an increase in total leukocyte count, neutrophils, and eosinophils.[15] These and other similar data suggest that the nocturnal worsening of asthma has an associated cellular inflammatory response that is not seen in patients without overnight decrements in lung function.

Inflammation in asthma is typically treated with corticosteroids. Glucocorticoid receptor binding affinity and steroid responsiveness also have circadian variation in subjects with nocturnal asthma.[16] It has been suggested that this may contribute to nocturnal airway inflammation by inhibiting the anti-inflammatory effects of glucocorticoids.

Variation in the Parasympathetic Nervous System

The parasympathetic nervous system has also been implicated in nocturnal asthma. Increased vagal tone during sleep could promote increased bronchoconstriction. There is a diurnal variation in vagal activity that has been demonstrated in asthmatic patients, with higher vagal activity occurring at night. Administration of intravenous atropine to patients in one study with nocturnal asthma produced improvement in the peak expiratory flow rate (PEFR) at 4 AM compared to 4 PM.[17] That study also demonstrated a significant correlation between heart rate and PEFR which further suggests increased vagal tone at night.

Neurohormonal changes

In addition to variations in pulmonary function and parasympathetic nervous system tone, there are similar circadian variations in the levels of various neurotransmitters and hormones. Histamine, a potent bronchoconstrictor, has been shown to be significantly higher in asthmatics during sleep when compared to normals.[18] Enhanced nighttime airway inflammation in nocturnal asthma might provide a stimulus for increased endogenous anti-inflammatory activity in the form of increased serum cortisol levels. However, a blunted adrenal response to corticotrophin, which may play a permissive role in the nocturnal worsening of asthma, has been demonstrated.[19] In addition, melatonin, an endogenous sleep-inducing hormone with pro-inflammatory properties, is higher in asthmatics with nocturnal symptoms as compared to normals.[20] These studies suggest that circadian variation of hormones may play a role in nocturnal worsening of asthma.

Gastroesophageal Reflux (GERD)

There is a significant association between gastroesophageal reflux disease and asthma.[21–23] Several mechanisms have been proposed to explain the effects of GERD on asthma. GERD is pro-inflammatory which can affect the inflammatory environment that is the backdrop of chronic asthma.[21] In addition to promoting inflammation, GERD may exacerbate asthma as a result of direct contact of the esophagus with acid which has been shown in animal models to be associated with increased respiratory resistance.[24] Furthermore, microaspiration of gastric contents into the airway can lead to vagally-mediated bronchospasm.[22] Many patients have worse symptoms of GERD at night, due to supine body positioning which facilitates the entry of stomach contents into the esophagus and airway. This may subsequently exacerbate nocturnal asthma symptoms.

Relationship Between Asthma and Obstructive Sleep Apnea (OSA)

There is evidence supporting a positive association between OSA and occasional wheezing, persistent wheezing, snoring, and a history of asthma.[25–27] There are several possible explanations for how asthma may worsen OSA and, conversely, how OSA may complicate asthma which will be discussed.

Sleep Fragmentation

Asthmatics have disrupted sleep architecture as a result of frequent arousals from sleep.[8] Polysomnography in asthmatics has demonstrated increases in spontaneous arousals, decreases in sleep efficiency, and variable effects on sleep stage distribution when compared to healthy controls.[28] Furthermore, evidence also suggests that disrupted sleep architecture may lay the foundation or predispose asthmatics for the subsequent development of OSA. There is a significant association between fragmented sleep and increased airway collapsibility and upper airway resistance indicating that fragmented sleep may lead to early upper airway closure.[29] Thus, one can postulate that frequent arousals secondary to nocturnal asthma may unmask or exacerbate coexisting OSA by increasing the magnitude of airway collapse.

Corticosteroid Therapy

Inhaled corticosteroids are the recommended initial controller therapy for patients with persistent asthma symptoms, including nocturnal symptoms.[1] Severe, uncontrolled asthma may require oral corticosteroids. However, oral steroid therapy may predispose patients to OSA. An unexpectedly high prevalence of OSA has been demonstrated among patients with unstable asthma receiving long-term chronic or frequent burst of oral corticosteroid therapy.[30] Whether similar effects are seen in chronic, long-term use of inhaled corticosteroids is less well described. It is possible that prolonged and especially continuous oral steroid

therapy in asthma may increase upper airway collapsibility possibly via effects on upper airway muscle function and this may play a role in the development of OSA.

GERD

There is a positive correlation between GERD and OSA,[31] and the presence of both disorders may exert a synergistic negative effect on nocturnal asthma. The increased negative inspiratory pressure generated to overcome upper airway obstruction during apneic events may precipitate gastric reflux, which can subsequently exacerbate nocturnal asthma.

Sinus Disease

Sinus and tonsillar inflammation and obstruction, a very common problem in asthmatics, may also play a role in the development of OSA. Nasal congestion from allergies or sinus disease has been suggested to be an independent predictor of snoring in some patients.[32]

Increased airway hyperreactivity

Patients with OSA are frequently hypoxic while sleeping. Hypoxia can lead to reflex bronchoconstriction through stimulation of the carotid bodies and subsequent increased vagal tone. In addition, snoring causes repetitive stimulation of the pharynx and glottic inlet which can also increase parasympathetic tone. Increased vagal tone can lead to nocturnal bronchospasm.[17]

Impaired arousal responses

The increased frequency of bronchoconstriction at night can become dangerous as patients with asthma often have poor perception of the symptoms of bronchoconstriction. The response to bronchoconstriction can be further impaired by sleep deprivation, because patients with sleep-disordered breathing have significantly impaired arousal responses to alterations in blood gases.[33,34] Specifically, OSA patients with hypercapnia and/or hypoxemia have reduced ventilatory responses to hypercapnic and hypoxic stimulation. In patients with both OSA and asthma, the impaired responses to hypoxia and increased prevalence and decreased perception of bronchoconstriction may lead to a vicious cycle of worsening asthma and sleep deprivation and potentially increased morbidity and mortality.

Inflammation

Inflammation is an essential component of asthma and recent data demonstrate that OSA is also characterized by an inflammatory response. Many of the cytokines that are elevated in OSA have also been implicated in the inflammatory pattern demonstrated in asthma.[35] Histologic changes including increased interstitial edema, mucous gland hypertrophy, and infiltration of the uvula lamina propria with T-cells in the pharyngeal epithelium in patients with OSA are similar to changes in the bronchi of asthmatics.

Relationship between Nocturnal Asthma and Sleep Quality

Sleep quality is impaired in asthmatics. Specifically, patients with nocturnal asthma have disrupted sleep architecture, more frequent arousals and report overall worse sleep quality. Positive associations between physician-diagnosed asthma and difficulty initiating sleep, daytime sleepiness, snoring, and self-reported apneas have been reported.[26] Asthmatics are also significantly more likely to report that their sleep is unrefreshing.[25] The presence of impaired sleep quality is clinically significant, because it has been correlated with impaired quality of life and impaired cognitive performance.[36]

Diagnostic Approach

The evaluation of the patient with asthma should include a targeted sleep history in addition to investigation of control of nocturnal symptoms. Frequent wheezing, cough, and bronchodilator use at night are indicators that the patient may need more effective asthma control. In addition, presence and control of syndromes that can worsen nocturnal symptoms of asthma such as poor sleep hygiene, OSA, snoring, gastroesophageal reflux disease, and allergic rhinitis should be addressed.

Accumulated data suggest that routine evaluation of the patient with nocturnal asthma should also include a comprehensive sleep history given the poor sleep quality in asthmatics and overlap of OSA and nocturnal asthma. Current guidelines for management of asthma recommend asking about nocturnal asthma symptoms, but do not advise that clinicians take a global sleep history from their asthma patients. If screening questions suggest the possibility of a concomitant sleep disorder, then objective evaluation including instruments such as the Epworth Sleepiness Scale or the Pittsburgh Sleep Quality Index should be considered. If clinical suspicion of a sleep disorder such as OSA remains significant, then polysomnography may be required.

Clinical Management

Medical treatment of nocturnal asthma includes control of contributing factors that can worsen asthma including specific environmental control measures such as plastic covers on pillows and mattresses, adequate ventilation, and optimal humidity in the sleeping environment with minimization of dust. Other factors that are also important in the management of nocturnal asthma include diagnosis and treatment of coexistent medical problems such as poor sleep hygiene, OSA, gastroesophageal reflux, rhinitis, and sinusitis.

Direct pharmacologic interventions in the treatment of nocturnal asthma include medications that are routinely used in the management of asthma in general. However, consideration of optimal dosing levels and timing of administration may be important in the management of nocturnal symptoms.

Epidemiology of Sleep Disorders in COPD

The incidence of COPD has been increasing over several decades and it is projected to be the third leading cause of death in the United States by 2020. Cigarette smoking is the greatest risk factor for the development of COPD and cigarette smoking has also been associated with a high prevalence of sleep-related complaints.[37] Cigarette smoking is associated with a longer sleep latency at onset and a shift toward more stage 1 sleep and less slow wave sleep.[38] Although the exact mechanisms for these changes are not defined, withdrawal from nicotine in cigarettes during sleep may be one of the causes of sleep disturbance in smokers without evidence of COPD.[39]

Patients with COPD have abnormal nocturnal alterations in ventilation and gas exchange. [40] COPD patients with significant daytime hypoxemia ($\text{PaO}_2 < 55 \text{ mmHg}$) and hypercapnia, often experience a profound drop in nocturnal oxygen saturation, particularly during rapid eye movement (REM) sleep. These oxygen desaturations can exceed 15 minutes and reach nadirs of 60% or lower. Nocturnal desaturations may also occur in non-REM sleep in COPD, but are generally less severe. Nocturnal oxygen desaturations in COPD patients with mild daytime hypoxemia (PaO_2 between 60 to 70 mmHg) are also common, but the fall in oxygen saturations is mild, with nadir of approximately 88%. [41–44]

Several potential clinical predictors of nocturnal oxygen desaturation in COPD patients have been evaluated. Daytime oxygen saturation, the minimum oxygen saturation with exercise, carbon dioxide retention, forced expiratory volume in one second (FEV1), and elevated body mass index (BMI) have all been investigated as predictors of nocturnal desaturation. [44–47] Of these, daytime oxygen saturation appears to be the most consistent predictor, with a positive correlation between a resting daytime oxygen saturation less than 93% and nocturnal desaturation.[45,47,48] Both moderate desaturation during exercise [40] and resting PaCO₂ > 50 mm Hg have some predictive value, while FEV1 and BMI fail to accurately predict nocturnal desaturations.

A significant number of patients with COPD experience nocturnal symptoms and these symptoms can fragment their sleep. Klink et al surveyed patients with COPD and found that 39% of patients with nocturnal cough or wheezing reported difficulty initiating or maintaining sleep. If cough and wheezing were both present, 53% reported difficulty initiating or maintaining sleep and 23% reported excessive daytime sleepiness.[49] In addition to increased symptoms at night and impaired sleep quality, there are a number of patients with COPD who also have OSA. This has been labeled the “overlap syndrome” and will be discussed later.

Pathogenesis of Nocturnal Hypoxemia in COPD

There is a combination of factors that can contribute to hypoxemia during sleep in people with COPD. Physiologic hypoventilation during sleep is accentuated in COPD and can contribute to nocturnal oxygen desaturation. People who are hypoxemic during wakefulness have resting oxygen levels on the steep portion of the oxy-hemoglobin dissociation curve and have a greater fall in oxygen saturation during sleep (Figure 2). In addition to hypoventilation and the role of the oxy-hemoglobin dissociation curve, ventilation-perfusion mismatching and a reduced function residual capacity (FRC) may also play a role in nocturnal hypoxemia in COPD (Box 2).

Hypoventilation

During all sleep stages, ventilation is decreased compared with wakefulness in healthy people and people with COPD.[50,51] In healthy individuals during REM sleep, ventilation may be 40% lower than during wakefulness. This is predominantly due to a reduction in tidal volume. A similar breathing pattern is present during sleep in people with COPD.[52] However, in people with COPD, the physiologic hypoventilation normally present during sleep can result in significant oxygen desaturation.[51] In people with severe COPD, oxygen saturation may decrease by 20% during non-REM sleep and may be 40% lower during REM sleep.[53] This is likely a result of the increased physiologic dead space in COPD that leads to an even greater decrease in alveolar ventilation with lower tidal volumes than in normal subjects. This decrease in alveolar ventilation may also lead to a profound decrease in oxygen saturation in COPD patients because of the lower starting point on the oxy-hemoglobin dissociation curve.

Hypoventilation during sleep is the result of several factors. There is mild bronchoconstriction during sleep from the normal circadian change in airway caliber which results in an increase in airway resistance.[11] In non-REM sleep, the basal metabolic rate[54] and ventilatory drive are decreased.[55] These effects may result in a decreased central respiratory drive in non-REM sleep. In REM sleep, the respiratory center has a diminished response to chemical and mechanical inputs. Additionally, there is hypotonia of skeletal muscles, which includes the accessory muscles of respiration, during REM sleep. People with COPD often are dependent upon the accessory muscles of respiration for adequate ventilation, and therefore REM-related muscle paralysis may result in poor

ventilation during sleep. The diaphragm is not paralyzed during REM, however, one of pathologic consequences of COPD is stretching of the diaphragm so that it does not function properly. Thus, people with severe COPD may be totally dependent upon a poorly functioning diaphragm for nocturnal ventilation.

Changes in Nocturnal Pulmonary Function During Sleep in COPD Patients

The loss of accessory muscle function during REM sleep and the increase in airway resistance during sleep can result in a decrease in functional residual capacity (FRC).[56] In addition, supine posture is associated with a 10% decrease in FRC in normal subjects.[56] These physiologic changes in pulmonary function, when imposed upon people with COPD, may adversely affect the ventilation/perfusion matching and contribute to nocturnal hypercapnia and hypoxemia. In addition, in one study of COPD patients, a decrease in nocturnal ventilation was determined to be the result of a decrease in tidal volume with no change in FRC.[50] Normally during sleep these changes in lung function and ventilatory drive result in only a small increase in PaCO₂ and usually no hypoxemia.[55] In people with COPD however nocturnal changes in ventilation, airway resistance, lung function, and ventilation/perfusion matching may result in significant hypercapnia and hypoxemia.

Effects of Nocturnal Desaturations in COPD

There may be marked decreases in oxygen saturation during sleep in COPD that may in fact be more profound than during maximal exercise.[40] The clinical implication of isolated nocturnal desaturations in COPD patients is unclear; however some physiologic consequences have been documented. While COPD patients with isolated nocturnal desaturations do not appear to develop pulmonary hypertension [41], COPD patients with nocturnal desaturations plus mild daytime hypoxemia have demonstrated higher daytime pulmonary artery pressures with possible pulmonary hypertension than in a similar group of patients who did not desaturate at night.[43] The clinical implications though of a minor increase in pulmonary artery pressure are unclear.

In addition to elevated pulmonary artery pressures, there is an increase in premature ventricular contractions (PVC) during sleep in COPD patients with nocturnal desaturations. [57] The increase in PVC's is related to the severity of desaturation as patients with COPD who have nocturnal desaturations to less than 80 percent show an increase in premature ventricular complex frequency.[58] These PVC's tend to decrease in frequency with supplemental oxygen, but the clinical significance of PVCs in this case is not established. [57]

It is well documented that among COPD patients with severe daytime hypoxemia, death is more common at night than during the day.[5] It is not clear however, if there is increased mortality risk associated with nocturnal hypoxemia in COPD patients with mild daytime hypoxemia as studies have been conflicted.[59,60]

Relationship between COPD and OSA

COPD and OSA are both common diseases and thus, both conditions could be expected to occur in the same individual by chance. When this occurs, it has been termed "the overlap syndrome". There have been several studies that have examined the association between COPD and obstructive sleep apnea.[61–64] A study of 265 patients referred to a sleep laboratory for various reasons found 11% to have obstructive lung disease by spirometry. [63] At the time, this was a higher prevalence than would be expected in the general population and thus suggested there may be a pathologic link between the two diseases. However, in the Sleep Heart Health study, participants with obstructive airways disease as

defined purely by spirometry ($FEV_1/FVC < 70\%$) had a prevalence of sleep apnea ($RDI > 10$) of 22.3% versus 28.9% in participants with normal spirometry.[65] Moreover, there was minimal alteration in sleep quality in those with obstruction.[65] These authors thus proposed that when obstructive airways disease and OSA occur in the same individual it is by chance and there is no pathophysiologic link between the two disorders. This study was limited by a low percentage of subjects with severe obstructive airways disease and by reliance solely on a single spirometry for the diagnosis of chronic obstructive lung disease. Although a pathologic link between the two diseases may or may not exist, it is clear that when they coexist patients may display more profound nocturnal desaturations and worsened sleep quality. In addition, patients with the overlap syndrome may be more prone to the development of pulmonary hypertension, especially if they have daytime hypoxemia. [66] In general, people with COPD do not develop pulmonary hypertension unless they have severe obstruction with significant hypoxemia. However, people with the overlap syndrome can develop pulmonary hypertension with only mild to moderate obstruction. This may result from the combined effects of both diseases contributing to hypoxemia and effects on pulmonary hemodynamics.

COPD and Sleep Quality

There have been several studies demonstrating that people with COPD have worse sleep quality compared with healthy individuals.[67–69] There is a higher prevalence of insomnia, use of hypnotic medications, and an increase in daytime sleepiness in people with COPD than the general population.[69,70] The exact mechanisms of these sleep disturbances in COPD are not clear, but there have been several studies evaluating sleep architecture in COPD patients.

Studies utilizing polysomnography have documented sleep fragmentation with frequent arousals, less total sleep time, and less slow wave and REM sleep in people with COPD compared to healthy controls.[71,72] In the Sleep Heart Health Study however, people with mild obstructive airways disease without OSA were not sleepier by the Epworth Sleepiness Scale than those without obstructive airways disease. Furthermore, people with obstructive airways disease had no significant differences in sleep architecture compared to those without obstructive airways disease and OSA.[65] However, participants with the overlap syndrome had higher Epworth sleepiness scores, lower total sleep time, lower sleep efficiency, and a higher arousal index compared to those with obstructive airways disease alone, but there was only a small difference between those with OSA alone and those with the overlap syndrome.[65] Thus, it appears that in patients with mild obstructive airways disease there is little effect on sleep quality. However, as obstructive lung disease becomes more severe there are increased sleep complaints. In addition, when OSA is superimposed upon obstructive lung disease there are more sleep complaints and possibly more deleterious physiologic effects.

Diagnostic Approach

Patients with COPD should be questioned about global sleep issues with particular emphasis on symptoms of sleep apnea including daytime hypersomnolence, morning headaches, snoring, and witnessed apneas. If symptoms are found, these patients should undergo polysomnography (PSG) testing. In addition, the Global Initiative for Obstructive Lung Disease (GOLD) guidelines recommend evaluation by PSG when hypoxemia or right heart failure develops in COPD in the presence of relatively mild airflow limitation.[73] As previously described, the overlap syndrome may contribute to pulmonary artery pressure elevations in these patients. If there is concern for nocturnal desaturations alone based on oxygen saturations less than 93% during the day, this may be evaluated by a simple

nocturnal oximetry. Nocturnal oximetry may also be used to evaluate the effectiveness of oxygen therapy in improving oxygen saturations.

Clinical Management

The best practices for management of COPD may also improve nocturnal hypoxemia. Anticholinergics have been shown to improve nocturnal oxygenation as well as sleep quality in COPD.[74,75] Theophylline, on the other hand, may improve gas exchange but studies conflict regarding the effect on the quality of sleep in COPD.[76–78] Other medications that have been studied in COPD for nocturnal hypoxemia including medroxyprogesterone acetate, acetazolamide, almitrine, and protriptyline have all been limited by side effects and lack strong supportive data. COPD patients with either severe COPD and/or hypercapnia should avoid hypnotics and alcohol which may decrease respiratory drive with resultant hypercapnic respiratory failure. There is evidence that zolpidem does not decrease respiratory drive or minute ventilation in patients with COPD and therefore might be a useful sleep aid.[79,80]

The clinical question of what level of nocturnal hypoxemia in COPD that warrants treatment is controversial and lacks firm evidence based recommendation. The Nocturnal Oxygen Therapy Trial and the Medical Research Council Working Party both showed improved survival with long-term oxygen therapy that included use during sleep, however they did not target people with isolated nocturnal desaturations.[61,81] Currently, the GOLD guidelines recommend that nocturnal oxygen therapy should be provided to patients whose oxygen saturations fall below 88% or have a PaO₂ less than 55mmHg during wakefulness. This is based on B level evidence (limited body of data from randomized controlled trials).[73] The primary goal of oxygen administration is to increase the baseline PaO₂ to 60 mmHg or an SpO₂ of 90% during the day.[73] Caution is needed when instituting oxygen therapy in those with daytime hypercapnia. Daytime arterial blood gas determinations should be considered soon after instituting oxygen to evaluate for worsening hypercapnia. There are no current recommendations from the GOLD committee on nocturnal oxygen management as there are ongoing trials in this area. Noninvasive positive pressure ventilation in combination with oxygen therapy may be of benefit to a subset of patients with daytime hypercapnia, but more studies are needed before this can be recommended for routine clinical practice.[73] Lung volume reduction surgery also results in improved sleep quality and nocturnal oxygenation in severe COPD and further long term outcomes are awaited from current trials.[82]

Conclusion

Obstructive lung diseases and sleep disorders are both common conditions with a complex intertwined relationship. The factors that contribute to worsened symptoms and oxygenation at night in asthma and COPD are not completely understood. In addition, asthma and COPD as well as OSA result in disrupted sleep architecture and decreased sleep quality. It is important as a clinician to recognize that management of the patient with obstructive lung disease should include a comprehensive sleep history including sleep hygiene, symptoms of GERD, sinus disease, and OSA. Recognition of sleep-related disturbances in patients with obstructive lung disease will assist clinicians in the management of their patients and allow for improved respiratory and sleep-related quality of life.

Box 1. Physiologic variables that may influence nocturnal asthma

Many factors have been hypothesized to contribute to the worsening of asthma symptoms at night.

Physiologic variables that may influence nocturnal asthma

- Airway cooling
- Glucocorticoid receptor changes
- Decreased inspiratory muscle activity
- Decreased peak expiratory flow
- Increased inflammation
- Beta-2 receptor down regulation
- Neurohormonal changes
- Decreased FRC
- Increased parasympathetic nervous system activity

Box 2. Physiologic changes that may result in nocturnal hypoxemia in COPD

A combination of factors may contribute to nocturnal hypoxemia in COPD.

Physiologic changes that may contribute to nocturnal hypoxemia in COPD

- Hypoventilation
- Oxyhemoglobin dissociation curve
- Increased airway resistance
- Ventilation-perfusion mismatching
- Decreased FRC
- Hypotonia of the skeletal muscles

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Figure 1. Diurnal variation in peak expiratory flow rates

Peak flow rates can vary widely in asthmatic patients and often reach their nadir at night during sleep.

Figure 2. Oxyhemoglobin dissociation curve in nocturnal hypoxemia

In COPD with hypoxemia (**A**), there is a greater change in oxygen saturation with a 15 mmHg drop in PaO₂ due to the steep portion of the curve. A small change occurs in oxygen saturation with a drop in PaO₂ of 15 mmHg in a normal person (**B**) since this occurs on the flat portion of the curve.