Sleep Problems in Chronic Obstructive Pulmonary Disease

Kronik Obstrüktif Akciğer Hastalığında Uyku Problemleri

Kannan Ramar
Division of Pulmonary, Sleep and Critical Care Medicine Mayo Clinic Rochester, USA

ABSTRACT

Effects of chronic obstructive pulmonary disease (COPD) during sleep is stil being investigated. Sleep problems affect as many as 50% of people with COPD. Patients with COPD have an increased risk while asleep that leads to gas exchange abnormalities resulting in significant hypoxemia and related clinical consequences like pulmonary hypertension, arrhythmias and possibly death, This review will discuss the physiology of breathing in normal subjects while asleep, followed by sleep related issues specific to COPD patients, and current diagnostic and treatment options.
(Tur Toraks Der 2008;9:117-23)

Key words: Chronic obstructive pulmonary disease (COPD), Sleep Problems

Received: 19.08.2008 *Accepted: 01.09.2008*

ÖZET

Kronik obstruktif akciğer hastalığının uykuya etkisini araştıran çalışmalar devam etmektedir. KOAH lı hastaların %50 sinde uyku problemleri görülmektedir.
KOAH lılar uykuda sağlıklı kişilerden daha fazla risk altındadır.
Uykuda gelişen gaz değişimi bozuklukları belirgin hipoksemi,ve bununla ilgili olarak pulmoner hipertansiyon,aritmi hatta ölüme neden olabilir. Bu derlemede önce sağlıklı kişilerde uyku fizyolojisi sonra da KOAH'lılarda uyku sorunları ve tanı ve tedavisi gözden geçirilmiştir.
(Tur Toraks Der 2008;9:117-23)

Anahtar sözcükler: Kronik Obstrüktif Akciğer Hastalığı (KOAH), uyku problemleri

Geliş Tarihi: 19.08.2008 *Kabul Tarihi: 01.09.2008*

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is the fourth leading cause of mortality in the United States with the prevalence of this disease continuing to increase [1]. While the debilitating effects of COPD on daytime functioning are well known, its effect during sleep is still being investigated. Sleep problems affect as many as 50% of people with COPD [2]. The physiology of normal breathing during sleep leads to mild clinically non significant hypoventilation. Patients with COPD have a heightened physiological disturbance and risk while asleep that leads to gas exchange abnormalities resulting in significant hypoxemia and related clinical consequences like pulmonary hypertension, arrhythmias and possibly death, [3] though these are not conclusively proven. This review will discuss the physiology of breathing in normal subjects while asleep, followed by sleep related issues specific to COPD patients, and current diagnostic and treatment options.

NORMAL BREATHING PHYSOLOGY DURING SLEEP

The physiological effects of sleep on breathing are similar to the wake state except that the magnitude of response and feedback network is reduced. There is a drop in metabolic rate during sleep that is accompanied by diminished responsiveness to various chemical, mechanical and cortical inputs [4]. The normal ventilatory response to changes in partial pressure of carbon dioxide ($PaCO_2$) and partial pressure of oxygen in arterial blood (PaO_2) are blunted compared to wakefulness, most impressively seen during rapid eye movement (REM) sleep [4, 5]. A reduction in lung volumes is also observed due to decreased respiratory muscle tone and cephalad displacement of the diaphragm [6]. The resultant consequence of all these physiological responses is a decrease in minute ventilation and hypoventilation. Mild hypoxemia with a drop in PaO_2 of around 2-8 mm Hg and hypercapnia with an increase in $PaCO_2$ of around 3-10 mm Hg is observed due to this sleep related hypoventilation [4, 7, 9, 10]. This

Address for Correspondence / Yazışma Adresi: Kannan Ramar, Assistant Professor of Medicine Division of Pulmonary, Sleep and Critical Care Medicine Center for Sleep Medicine 200 First Street SW Mayo Clinic Rochester, MN 55901 USA
Phone: 507 284 2447 Fax: 507 266 7772 E-mail: ramar.kannan@mayo.edu

is clinically non significant and does not lead to adverse consequences in normal subjects. These physiological effects vary with different sleep stages and are most pronounced during REM sleep [7-10]. The physiological effects during sleep in normal subjects can prove deleterious in COPD patients as it may interfere with gas exchange and cause significant hypoventilation resulting in clinically significant hypoxemia and hypercapnia, especially during REM sleep.

EFFECTS OF SLEEP ON COPD AND ITS CLINICAL SIGNIFICANCE

Lower baseline oxygenation and abnormal respiratory mechanics in patients with COPD become clinically important when combined with the physiologic alterations in ventilatory control and respiratory muscle function during sleep as discussed above. This leads to nocturnal oxygen desaturation (NOD) and poor sleep quality that may lead to polycythemia, cor pulmonale, arrhythmias, and possibly increased mortality, though these relationships are not conclusively proven by current evidence.

NOCTURNAL OXYGEN DESATURATION

Prevalence

The prevalence of NOD in patients with COPD has not been clearly established and appears to vary based on various factors like the presence or absence of daytime hypoxemia, severity of underlying obstruction in COPD based on forced expiratory volume in one second (FEV_1), associated co-morbid disorders, and the definition of NOD.

Definition of NOD

The definition of NOD varies depending on the study. At least three different definitions have been used in various studies and this has to be borne in mind when reading and interpreting them. The various definitions are as follows:

1. Mean nocturnal oxygen saturation (SaO2) of less than 90%
2. More than 30% of recording time (total time in bed(TIB) spent under 90% SaO2
3. More than 5 minutes of recording time spent under 90% of SaO2 with a nadir of at least 85%.

Most studies either use definition #2 or #3. Similarly, the definition for the amount of desaturation dip is not universal. Wynee and colleagues [11] proposed to define a desaturation dip by a fall in SaO2 by more than 4% from baseline during quiet breathing just before the episode of hypoxemia. Flenley's group [12, 13] proposed to define a dip by more than a 10% drop in SaO2.

Predictors of NOD

Despite the lack of a uniform definition and measurement of NOD, many investigators have attempted to determine daytime physiological parameters that might help to predict NOD.

COPD patients can develop NOD despite adequate oxygenation during wakefulness, but it is more pronounced in COPD patients with daytime hypoxemia [11, 14]. Those with the 'blue bloater' rather than the 'pink puffer' phenotype [15] are more likely to have NOD. 'Blue bloater' phenotype is characterized by a total lung capacity (TLC) less than 120 percent predicted, PaO_2 of less than 65 mm Hg, a $PaCO_2$ greater than 45 mm Hg, body weight greater than 110 percent predicted, a recent history of peripheral edema, and a chronic cough lasting for at least three months per year for two years. The 'pink puffers' were characterized by a TLC greater than 120 percent predicted, diffusing capacity (DLco) less than 50 percent predicted, a $PaCO_2$ of less than 45 mm Hg, and normal or lower than normal body weight. Using these phenotype characteristics, various studies found that the blue bloaters had lower baseline oxygen saturations, more episodes of nocturnal oxygen desaturation, larger falls in nocturnal oxygen saturation, and spent more time at low levels of oxygen saturation while asleep, than the pink puffers [11-13]. Also, other studies have noted a significant relationship between waking values of low PaO_2 and high $PaCO_2$ with NOD [16-18]. In addition to the relationship between NOD and daytime gas exchange problems mentioned above, Heijdra and coworkers [19] demonstrated a correlation between FEV_1 and maximal inspiratory muscle strength. The desaturation during sleep may be greater than during exercise in COPD patients [14]. Though there was a good correlation between mean sleep and exercise SaO2, and minimum sleep and exercise SaO2, awake PaO_2 appeared to be a better predictor for NOD than exercise desaturation [14].

Mechanisms

Several mechanisms have been proposed to explain NOD and will be discussed below.

1. Hypoventilation

Alveolar hypoventilation plays a significant role, especially during REM sleep. The exact mechanism resulting in alveolar hypoventilation in COPD patients is not uniformly accepted and this could be due to the type of measurements used, the stage of sleep (REM vs NREM), and whether the studies were performed in normocapnic or hypercapnic COPD patients. A drop in minute ventilation of 16% and 32% during non-REM and REM sleep respectively was observed by Becker and coworkers [20], predominantly due to a decrease in tidal volume as measured by a pneumotachograph. Though, Ballard and coworkers [21] also showed a decrease in minute ventilation in COPD patients, it was due to an increase in upper airway resistance and a decrease in neuromuscular output to the respiratory muscles, and not due to a decrease in lung volumes. O'Donoghue and coworkers [22] noted a decline in minute ventilation in NREM sleep in hypercapnic COPD patients due to a decrease in tidal volume and an increase in upper airway resistance. Whatever the mechanism might be, the overall result is alveolar hypoventilation during sleep and probably plays a significant part in NOD in COPD patients.

2. Ventilation-perfusion (V/Q) mismatch

V/Q mismatch has not been directly measured during sleep. However, for a mild and similar increase in $PaCO_2$ (and thereby alveolar hypoventilation), some COPD patients had more significant decreases in nocturnal PaO_2 than others, suggesting a role for V/Q mismatch as a mechanism for NOD 14. The altered V/Q mismatch can be a result of reduction in lung volumes (Functional residual capacity) due to a reduction in respiratory muscle tone, particularly during REM sleep, 23 leading to atelectasis at the lung bases.

3. Impact of oxyhemoglobin dissociation curve

Hypoxemic patients at baseline (as measured by PaO_2) are more likely to drop their SaO2 with hypoventilation during sleep, compared to normoxic patients at baseline due to the effect of the oxyhemoglobin dissociation curve 23. Someone with a PaO_2 of 55 mm Hg (though the SaO2 may be around 88-92%) is more likely to desaturate during sleep since this patient is already on the edge of the downward slope of the oxyhemoglobin dissociation curve, c ompared to someone with a PaO_2 of 65 mm Hg, who still may be on the top plateau portion of the curve. Obviously, this is not the sole mechanism, but plays a part when combined with the other factors discussed so far.

4. Coexisting obstructive sleep apnea (Overlap syndrome)

Patients with coexisting obstructive sleep apnea may be hypoxemic at the commencement of the apnea (due to underlying COPD), and hence more likely to desaturate compared to patients with only OSA who may be able to resaturate to normal SaO2 after the apneic episode. Studies to address this mechanism have not been done so far. We will discuss Overlap syndrome in more detail below.

Consequences of NOD

Potential consequences of NOD are many and will be discussed below.

1. Pulmonary hypertension

An acute progressive increase in pulmonary artery pressure was noted in 12 patients with COPD across all sleep stages, more significantly during REM sleep. The increase in pulmonary artery pressure was more strongly associated with a decrease in PaO_2 compared to a rise in $PaCO_2$ 24. Is this acute increase sufficient to lead to chronic pulmonary hypertension? Pulmonary hemodynamic studies thus far in severe COPD patients, with daytime hypoxemia and marked nocturnal hypoxemia, and daytime pulmonary hypertension (pulmonary artery pressure (PAP) > 20 mm Hg), have shown significant PAP elevation during sleep, especially in REM sleep [25-27]. Nocturnal elevation of PAP appears to correlate with NOD in this patient population [27]. What about patients with less severe COPD, and less diurnal hypoxemia? Unfortunately, studies are not conclusive and it probably depends to the type of definition and the amount of drop in PaO_2 (as discussed above in the definition section of NOD) used for NOD. Fletcher and coworkers [28] studied 36 COPD patients who had daytime PaO_2 > 60 mm Hg and NOD during REM sleep (defined as a drop in SaO2 < 90% for 5 minutes or more coinciding with REM sleep and a nadir of 85% or less). They demonstrated an increase in systolic and mean pulmonary artery pressures, as well as pulmonary vascular resistance. A study by Levi-Valensi and coworkers 29 in forty COPD patients with a daytime PaO_2 between 60-70 mm Hg and who had NOD defined as > 30% of total time in bed (TIB) with an SaO2 < 90%, had higher mean pulmonary artery pressure than controls (without NOD). A subsequent study by Chaouat and coworkers [30] looked at a larger group of COPD patients (sixty six patients) with a daytime PaO_2 of more than 60 mm Hg and NOD defined by the same criteria used by Levi-Valensi and coworkers, found no difference in the mean pulmonary artery pressure as measured by right heart catheterization.

2. Mortality

The effect of NOD without significant daytime hypoxemia on survival is not well established. Fletcher and coworkers performed a retrospective study in 169 COPD patients with NOD (using two different definitions) to examine survival. The first definition was a drop in SaO2 below 90% for 5 or more minutes, reaching a nadir of 85% and the second definition was > 30% of TIB spent below 90% SaO2. Though patients with NOD had improved survival compared to the non-NOD group, correcting NOD has not shown improved survival (see section on treatment with oxygen). Connaughton and coworkers [31] found no survival advantage when they studied ninety-seven COPD patients and followed them for a median of 70 months following nocturnal SaO2 measurement.

3. Cardiac arrhythmias

Though some studies have shown increased frequency of premature supraventricular and ventricular contractions (PVC) during sleep in COPD patients, overall there appears to be no correlation between PVC and nocturnal SaO2 [32, 33]. Clinical importance of these PVCs in COPD patients is not well established.

4. Polycythemia

Daytime hypoxemia in COPD patients is a well known cause of polycythemia. However, NOD without daytime hypoxemia has not been clearly documented to induce polycythemia [18, 29]. Also, Erythropoietin production does not appear to increase in COPD patients with primary NOD [34].

5. Sleep quality

NOD can also affect sleep quality and this will be discussed in the section below.

SLEEP QUALITY

Characteristics of sleep disturbances

Sleep disturbances are common in patients with COPD. The most commonly reported sleep disturbances are insomnia (both sleep initiation and sleep maintenance), early morning awakenings and headaches, daytime sleepiness, and these are seen in around 30-70% of patients with COPD [2, 17, 35]. Subjective complaints of sleep disturbances appear to be associated with the presence of respiratory symptoms of

cough, dyspnea, wheezing or sputum production. Many COPD patients report use of hypnotics (28% compared to controls- 10%)17 to combat these sleep disturbances.

Objective evidence for disturbed sleep quality has also been found in patients with COPD (predominantly in small cohorts of patients with severe COPD) as documented by overnight polysomnograms (PSGs). These findings from various studies include increased sleep latency, decreased total sleep time, decreased sleep efficiency, increased nocturnal arousals, decreased slow-wave sleep and decreased REM sleep [11, 12, 17, 36]. Also, Cormick and colleagues found significant agreement between subjective complaints of initiating and maintaining sleep and objective findings of poor sleep quality as shown by a decreased total sleep time of 208 minutes and increased arousal index [17]. Sleep disturbances in most of these studies were in patients with severe COPD.

What about patients with mild COPD? The sleep heart health study (SHHS) did not show altered sleep quality in mild COPD patients (FEV_1/FVC 63.81 ± 6.56%, mean ± SD) [37].

Mechanisms

There are various reasons for sleep disturbances in COPD patients. The most common include cough, dyspnea, nocturnal oxygen desaturation (NOD), hypercapnia, and degree of airway obstruction as measured by FEV_1, and medication side effects [11, 12, 17, 36, 38]. There is no clear established relationship between sleep quality measures and degree of airway obstruction [35], though the SHHS may suggest a lesser degree of affect on sleep quality in patients with milder degree of COPD.

Consequences

The poor sleep quality in COPD patients may lead to decreased daytime functioning due to excessive daytime sleepiness, altered neurocognition and psychomotor vigilance. There are no studies to date that address whether neurocognition or psychomotor vigilance are affected in COPD patients. As mentioned above, COPD patients do complain of daytime sleepiness but interestingly, Orr and colleagues [39] did not find objective evidence for daytime sleepiness based on the multiple sleep latency test (mean sleep latency 11 + 4 minutes) in 14 severe COPD patients though they had poor sleep quality as evidenced by decreased total sleep time and increased arousal index.

Obstructive Sleep Apnea and COPD (Overlap Syndrome)

Overlap syndrome, a term coined by Flenley [40], is used to describe the simultaneous presence of OSA and COPD. Since the prevalence of both COPD and OSA is high in the general population, it is very common to see both disorders together.

Is the prevalence of COPD higher in patients with OSA? Initial reports suggested that the prevalence of COPD in patients with OSA was higher than in the general population (11 to 14%) [41, 42]. However, at the time when these studies were done, the prevalence data for COPD in the general population were unreliable. Now, we know that the prevalence of COPD is over 10% in adults over 40 years of age (based on the FEV_1/FVC ratio of less than 70%) [43, 44] suggesting that the prevalence of COPD may not be higher in patients with OSA compared to the general population.

On the contrary, is the prevalence of OSA higher in patients with COPD?

The recent Sleep Heart Health Study (SHHS) by Sanders and coworkers showed that the prevalence of OSA is not higher in patients with COPD (mild COPD based on a mean FEV_1/FVC of 64) than in the general population. It is more likely that the two disorders occur together by chance rather than to have a common pathophysiological link.

Why is it important to know about the coexistence of OSA with COPD (overlap syndrome)? I will discuss this very briefly.

1. Quality of sleep

We have already discussed sleep disturbances in patients with severe COPD, however mild COPD does not affect sleep quality based on the SHHS data [37]. In the same data set, Sanders and coworkers found higher Epworth sleepiness scores, lower total sleep time, lower sleep efficiency and higher arousal index, in the overlap patients than in patients with mild COPD alone [37]. On the other hand, comparing overlap with OSA alone, there were only small differences in the measures of sleep quality [37], indicating the importance of OSA presence than COPD in affecting sleep quality.

2. NOD

Chaouat and coworkers [42] noted significant NOD, higher risk of developing respiratory failure and pulmonary hypertension in the overlap patients (COPD with FEV_1/FVC ratio of less than 60% - the severity of COPD being worse than in the SHHS) compared to OSA patients alone, though the severity of OSA measured by AHI was similar in both groups. Similarly, the SHHS clearly showed greater NOD (defined as > 5% of total sleep time spent SaO2 of < 90%) in overlap than either disorder alone [37]. Also, for the same degree of bronchial obstruction in COPD, patients with overlap have more important sleep-related oxygen desaturation.

TOOLS TO ASSESS FOR SLEEP DISORDERED BREATHING IN COPD

Overnight polysomnogram

PSGs do not need to be performed routinely in COPD patients to assess for sleep disordered breathing. The recent American Thoracic Society (ATS) and European Respiratory Society (ERS) task force [45] recommended PSG in COPD patients if there was a clinical suspicion of OSA (based on clinical history and physical findings), or complications of hypoxemia that were unexplained by

the awake PaO_2 like the presence of polycythemia with a daytime PaO_2 > 60-65 mm Hg, or the presence of pulmonary hypertension that is out of proportion to degree of airflow obstruction [46].

Overnight oximetry

Overnight oximetry is generally sufficient to assess for the presence of nocturnal oxygen desaturation and to check and monitor the adequacy of therapy with oxygen during sleep.

TREATMENT

1. Oxygen

Sleep Quality

Few studies have examined the effect of oxygen therapy on sleep quality. A decrease in sleep latency, increase in the continuity of sleep, and increase in REM sleep were noted by Calverley and coworkers [12], with the addition of oxygen. At the same time, another study by Fleetham and coworkers [38] noted no improvement in total sleep time (TST), sleep stage distribution, or frequency of arousals, with the addition of oxygen.

NOD

The role of continuous oxygen therapy to improve survival in COPD patients with severe daytime hypoxemia (49-52 mm Hg) has been clearly established by both the British Medical Research Council (MRC) Long-Term Domiciliary Oxygen Therapy Trial [47] and the Nocturnal Oxygen Therapy Trial (NOTT) [48]. The survivals in both studies were seen in the continuous oxygen therapy group with the average continuous use being 15 hours/day and 18 hours/day in the MRC and NOTT respectively.

What about patients with moderate hypoxemia? When COPD patients with moderate hypoxemia (defined as PaO_2 between 56 and 69 mm Hg) were assessed for survival at 3 years, no difference was noted between the supplemental oxygen therapy group (average use of 14 hours/day) and the control group [49]. Another study by Fletcher and coworkers [50] noted no survival benefit in COPD patients with NOD and an awake PaO_2 > 60 mm Hg, when they were randomized to 3 L/minute of oxygen or sham control for 36 months. Pulmonary hemodynamics improved in the oxygen therapy group. Similarly, Chaouat and coworkers [51] noted no survival advantage in COPD patients with mild to moderate hypoxemia (PaO_2 56-69 mm Hg), who were randomized to oxygen therapy versus controls for up to 60 months. The same authors found no difference in developing a need for conventional long-term oxygen therapy or in the improvement of pulmonary hemodynamics [51].

Overall, survival benefit is attained with long term oxygen therapy in COPD patients with severe daytime hypoxemia, but the use of oxygen is unproven in moderate hypoxemia or in NOD patients. Similarly, oxygen to improve pulmonary hemodynamics and sleep quality is not proven.

2. Medication

Sleep quality

Ipratropium bromide has shown improvement in sleep quality [52] in patients with moderate to severe COPD, while tiotropium did not affect sleep quality [53] at least in patients with severe COPD. The effects of theophylline on sleep quality have been variable, with some studies showing sleep quality disturbances [54], and others showing no changes [55-57].

As mentioned above, 28% of COPD patients use hypnotics to help with insomnia and other sleep disorders. Use of benzodiazepines should be avoided in COPD patients because of their effects in worsening frequency, duration and severity of nocturnal hypoxemia [58]. Nonbenzodiazepine imidazopyridine compounds like Zolpidem may be safer to use in COPD patients [59].

NOD

Though, the bronchodilators have variable effects on sleep quality, their effects to improve NOD have been significant. Theophylline [54, 56], ipratropium [52] and tiotropium inhalers [53] have shown improvements in NOD.

3. Non invasive positive pressure ventilation (NIPPV)

The role of NIPPV has been clearly established in COPD patients with an acute exacerbation. What about the role of NIPPV in stable COPD patients?

The studies to date have mixed results and tend to vary depending on design of these trials. A recent systematic review of NIPPV in severe stable COPD patients was conducted by Kolodziej and coworkers [60]. They reviewed six randomized controlled trials (RCTs) and nine non-RCTs and found no improvement in gas exchange with NIPPV among the RCTs. Among the non-RCTs, improvement in gas exchange and reduction in lung hyperinflation and diaphragmatic work of breathing were noted [60]. Although NIPPV may have favorable effects (at least among the non-RCTs), its therapeutic role has not been firmly established in stable COPD patients. Despite this, use of NIPPV in United States medical centers has been increasing. Guidelines from the American College of Chest Physicians (ACCP) were published to help us [61] to guide therapy with NIPPV in stable COPD patients. According to these guidelines, NIPPV can be considered in stable COPD when: Symptoms (fatigue, morning headache, daytime hypersomnolence) and one of the following: 1. $PaCO_2$ > 55 mm Hg; (OR) 2. $PaCO_2$ of 50 to 54 mm Hg and nocturnal desaturation (overnight oximetry demonstrating SaO2 < 88% for 5 minutes while receiving oxygen therapy > 2 L/minute; (OR) 3. $PaCO_2$ of 50 to 54 mm Hg and hospitalization related to recurrent episodes (two or more in a 12-month period) of hypercapnic respiratory failure61.

CONCLUSIONS

Sleep disturbances are common in COPD patients. Patients with severe COPD have both subjective and objective complaints of poor sleep quality. NOD is common in COPD patients, though the role of treating with nocturnal oxygen therapy in patients without

daytime hypoxemia is still uncertain, especially in terms of its effects on sleep quality and pulmonary hemodynamics. There are still a number of unanswered questions regarding NOD in COPD patients and future well controlled trials will hopefully help answer these questions.

REFERENCES

1. Mannino DM, Homa DM, Akinbami LJ, et al. Chronic obstructive pulmonary disease surveillance--United States, 1971-2000. MMWR Surveill Summ 2002;51:1-16.
2. Klink M, Quan SF. Prevalence of reported sleep disturbances in a general adult population and their relationship to obstructive airways diseases. Chest 1987;91:540-6.
3. Fleetham JA. Is chronic obstructive pulmonary disease related to sleep apnea-hypopnea syndrome? Am J Respir Crit Care Med Jan 2003;167:3-4.
4. Berthon-Jones M, Sullivan CE. Ventilatory and arousal responses to hypoxia in sleeping humans. Am Rev Respir Dis 1982;125:632-9.
5. Douglas NJ, White DP, Weil JV, et al. Hypercapnic ventilatory response in sleeping adults. Am Rev Respir Dis 1982;126:758-62.
6. Hudgel DW, Devadatta P. Decrease in functional residual capacity during sleep in normal humans. J Appl Physiol 1984;57:1319-22.
7. Douglas NJ. Sleep in patients with chronic obstructive pulmonary disease. Clin Chest Med 1998;19:115-25.
8. Douglas NJ, White DP, Pickett CK, et al. Respiration during sleep in normal man. Thorax 1982;37:840-4.
9. Gay PC. Chronic obstructive pulmonary disease and sleep. Respir Care 2004;49:39-51; discussion 51-32.
10. McNicholas WT. Impact of sleep in COPD. Chest 2000;117:48S-53S.
11. Wynne JW, Block AJ, Hemenway J, et al. Disordered breathing and oxygen desaturation during sleep in patients with chronic obstructive lung disease (COLD). Am J Med 1979;66:573-9.
12. Calverley PM, Brezinova V, Douglas NJ, et al. The effect of oxygenation on sleep quality in chronic bronchitis and emphysema. Am Rev Respir Dis 1982;126:206-10.
13. Catterall JR, Douglas NJ, Calverley PM, et al. Transient hypoxemia during sleep in chronic obstructive pulmonary disease is not a sleep apnea syndrome. Am Rev Respir Dis 1983;128:24-9.
14. Mulloy E, McNicholas WT. Ventilation and gas exchange during sleep and exercise in severe COPD. Chest 1996;109:387-94.
15. DeMarco FJ Jr., Wynne JW, Block AJ, et al. Oxygen desaturation during sleep as a determinant of the "Blue and Bloated" syndrome. Chest 1981;79:621-5.
16. Bradley TD, Mateika J, Li D, et al. Daytime hypercapnia in the development of nocturnal hypoxemia in COPD. Chest 1990;97:308-12.
17. Cormick W, Olson LG, Hensley MJ, Saunders NA. Nocturnal hypoxaemia and quality of sleep in patients with chronic obstructive lung disease. Thorax 1986;41:846-54.
18. Fletcher EC, Miller J, Divine GW, et al. Nocturnal oxyhemoglobin desaturation in COPD patients with arterial oxygen tensions above 60 mm Hg. Chest 1987;92:604-8.
19. Heijdra YF, Dekhuijzen PN, van Herwaarden CL, Folgering HT. Nocturnal saturation and respiratory muscle function in patients with chronic obstructive pulmonary disease. Thorax 1995;50:610-2.
20. Becker HF, Piper AJ, Flynn WE, et al. Breathing during sleep in patients with nocturnal desaturation. Am J Respir Crit Care Med 1999;159:112-8.
21. Ballard RD, Clover CW, Suh BY. Influence of sleep on respiratory function in emphysema. Am J Respir Crit Care Med 1995;151:945-51.
22. O'Donoghue FJ, Catcheside PG, Eckert DJ, McEvoy RD. Changes in respiration in NREM sleep in hypercapnic chronic obstructive pulmonary disease. J Physiol 2004;559:663-73.
23. Catterall JR, Calverley PM, MacNee W, et al. Mechanism of transient nocturnal hypoxemia in hypoxic chronic bronchitis and emphysema. J Appl Physiol 1985;59:1698-703.
24. Coccagna G, Lugaresi E. Arterial blood gases and pulmonary and systemic arterial pressure during sleep in chronic obstructive pulmonary disease. Sleep 1978;1:117-24.
25. Boysen PG, Block AJ, Wynne JW, et al. Nocturnal pulmonary hypertension in patients with chronic obstructive pulmonary disease. Chest 1979;76:536-42.
26. Fletcher EC, Levin DC. Cardiopulmonary hemodynamics during sleep in subjects with chronic obstructive pulmonary disease. The effect of short- and long-term oxygen. Chest 1984;85:6-14.
27. Weitzenblum E, Muzet A, Ehrhart M, et al. [Nocturnal changes in blood gases and pulmonary arterial pressure in chronic bronchitis patients with respiratory insufficiency (author's transl)]. Nouv Presse Med 1982;11:1119-22.
28. Fletcher EC, Luckett RA, Miller T, et al. Pulmonary vascular hemodynamics in chronic lung disease patients with and without oxyhemoglobin desaturation during sleep. Chest 1989;95:757-64.
29. Levi-Valensi P, Weitzenblum E, Rida Z, et al. Sleep-related oxygen desaturation and daytime pulmonary haemodynamics in COPD patients. Eur Respir J 1992;5:301-7.
30. Chaouat A, Weitzenblum E, Kessler R, et al. Sleep-related O2 desaturation and daytime pulmonary haemodynamics in COPD patients with mild hypoxaemia. Eur Respir J 1997;10:1730-5.
31. Connaughton JJ, Catterall JR, Elton RA, et al. Do sleep studies contribute to the management of patients with severe chronic obstructive pulmonary disease? Am Rev Respir Dis 1988;138:341-4.
32. Flick MR, Block AJ. Nocturnal vs diurnal cardiac arrhythmias in patients with chronic obstructive pulmonary disease. Chest 1979;75:8-11.
33. Shepard JW Jr., Schweitzer PK, Keller CA, et al. Myocardial stress. Exercise versus sleep in patients with COPD. Chest 1984;86:366-74.
34. Fitzpatrick MF, Mackay T, Whyte KF, et al. Nocturnal desaturation and serum erythropoietin: a study in patients with chronic obstructive pulmonary disease and in normal subjects. Clin Sci (Lond) 1993;84:319-24.
35. Bellia V, Catalano F, Scichilone N, et al. Sleep disorders in the elderly with and without chronic airflow obstruction: the SARA study. Sleep 2003;26:318-23.
36. Krachman SL, Chatila W, Martin UJ, et al. Effects of lung volume reduction surgery on sleep quality and nocturnal gas exchange in patients with severe emphysema. Chest 2005;128:3221-8.
37. Sanders MH, Newman AB, Haggerty CL, et al. Sleep and sleep-disordered breathing in adults with predominantly mild obstructive airway disease. Am J Respir Crit Care Med 2003;167:7-14.
38. Fleetham J, West P, Mezon B, et al. Sleep, arousals, and oxygen desaturation in chronic obstructive pulmonary disease. The effect of oxygen therapy. Am Rev Respir Dis 1982;126:429-33.
39. Orr WC, Shamma-Othman Z, Levin D, et al. Persistent hypoxemia and excessive daytime sleepiness in chronic obstructive pulmonary disease (COPD). Chest 1990;97:583-5.
40. Flenley DC. Sleep in chronic obstructive lung disease. Clin Chest Med 1985;6:651-61.

41. Bradley TD, Rutherford R, Lue F, et al. Role of diffuse airway obstruction in the hypercapnia of obstructive sleep apnea. Am Rev Respir Dis 1986;134:920-4.
42. Chaouat A, Weitzenblum E, Krieger J, et al. Association of chronic obstructive pulmonary disease and sleep apnea syndrome. Am J Respir Crit Care Med 1995;151:82-6.
43. Chapman KR, Mannino DM, Soriano JB, et al. Epidemiology and costs of chronic obstructive pulmonary disease. Eur Respir J 2006;27:188-207.
44. Lopez AD, Shibuya K, Rao C, et al. Chronic obstructive pulmonary disease: current burden and future projections. Eur Respir J 2006;27:397-412.
45. Celli BR, MacNee W. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. Eur Respir J 2004;23:932-46.
46. Douglas NJ, Flenley DC. Breathing during sleep in patients with obstructive lung disease. Am Rev Respir Dis 1990;141:1055-70.
47. Long term domiciliary oxygen therapy in chronic hypoxic cor pulmonale complicating chronic bronchitis and emphysema. Report of the Medical Research Council Working Party. Lancet 1981;1:681-6.
48. Continuous or nocturnal oxygen therapy in hypoxemic chronic obstructive lung disease: a clinical trial. Nocturnal Oxygen Therapy Trial Group. Ann Intern Med 1980;93:391-8.
49. Gorecka D, Gorzelak K, Sliwinski P, et al. Effect of long-term oxygen therapy on survival in patients with chronic obstructive pulmonary disease with moderate hypoxaemia. Thorax 1997;52:674-9.
50. Fletcher EC, Luckett RA, Goodnight-White S, et al. A double-blind trial of nocturnal supplemental oxygen for sleep desaturation in patients with chronic obstructive pulmonary disease and a daytime PaO_2 above 60 mm Hg. Am Rev Respir Dis 1992;145:1070-6.
51. Chaouat A, Weitzenblum E, Kessler R, et al. A randomized trial of nocturnal oxygen therapy in chronic obstructive pulmonary disease patients. Eur Respir J 1999;14:1002-8.
52. Martin RJ, Bartelson BL, Smith P, et al. Effect of ipratropium bromide treatment on oxygen saturation and sleep quality in COPD. Chest 1999;115:1338-45.
53. McNicholas WT, Calverley PM, Lee A, Edwards JC. Long-acting inhaled anticholinergic therapy improves sleeping oxygen saturation in COPD. Eur Respir J 2004;23:825-31.
54. Mulloy E, McNicholas WT. Theophylline improves gas exchange during rest, exercise, and sleep in severe chronic obstructive pulmonary disease. Am Rev Respir Dis 1993;148:1030-6.
55. Berry RB, Desa MM, Branum JP, Light RW. Effect of theophylline on sleep and sleep-disordered breathing in patients with chronic obstructive pulmonary disease. Am Rev Respir Dis 1991;143:245-50.
56. Man GC, Champman KR, Ali SH, Darke AC. Sleep quality and nocturnal respiratory function with once-daily theophylline (Uniphyl) and inhaled salbutamol in patients with COPD. Chest 1996;110:648-53.
57. Martin RJ, Pak J. Overnight theophylline concentrations and effects on sleep and lung function in chronic obstructive pulmonary disease. Am Rev Respir Dis 1992;145:540-4.
58. Block AJ, Dolly FR, Slayton PC. Does flurazepam ingestion affect breathing and oxygenation during sleep in patients with chronic obstructive lung disease? Am Rev Respir Dis 1984;129:230-3.
59. Girault C, Muir JF, Mihaltan F, et al. Effects of repeated administration of zolpidem on sleep, diurnal and nocturnal respiratory function, vigilance, and physical performance in patients with COPD. Chest 1996;110:1203-11.
60. Kolodziej MA, Jensen L, Rowe B, Sin D. Systematic review of noninvasive positive pressure ventilation in severe stable COPD. Eur Respir J 2007;30:293-306.
61. Clinical indications for noninvasive positive pressure ventilation in chronic respiratory failure due to restrictive lung disease, COPD, and nocturnal hypoventilation–a consensus conference report. Chest 1999;116:521-34.