Sleep-induced hypoxaemia in patients with chronic obstructive pulmonary disease

Patients with moderate or severe chronic obstructive pulmonary disease run a high risk of developing sleep-induced hypoxaemia, because of alveolar hypoventilation and ventilation–perfusion mismatch. This article looks at the prevalence, significance and treatment of sleep-induced hypoxaemia in chronic obstructive pulmonary disease.

Chronic obstructive pulmonary disease is characterized by persistent airflow limitation that is usually progressive and is a leading cause of morbidity and mortality worldwide (Vestbo et al, 2013). When pulmonary function deteriorates, and when the disease progresses, the risk of alveolar hypoxia and consequent hypoxaemia in the patient with chronic obstructive pulmonary disease increases. Hypoxia plays an important role in the progression of chronic obstructive pulmonary disease and extrapulmonary comorbidities.

Previous studies found significant nocturnal desaturation in patients with chronic obstructive pulmonary disease with mild awake hypoxaemia who did not qualify for home oxygen therapy. The phenomenon of nocturnal hypoxaemia complicating chronic obstructive pulmonary disease has been recognized for at least 50 years (Kardos and Keenan, 2006). Increased sleep latency, decreased total sleep time, decreased slow-wave sleep, decreased rapid eye movement sleep and, most importantly, sleep-induced hypoxaemia have been noted in many polysomnographic studies of patients with chronic obstructive pulmonary disease (Krachman et al, 2005). Sleep-induced hypoxaemia may predispose to pulmonary hypertension, cardiac arrhythmias during sleep and nocturnal death during exacerbations in patients with chronic obstructive pulmonary disease (Tirlapur and Mir, 1982; McNicholas and Fitzgerald, 1984; Fletcher et al, 1989). However, its importance and significance is not fully established.

Definition of sleep-induced hypoxaemia

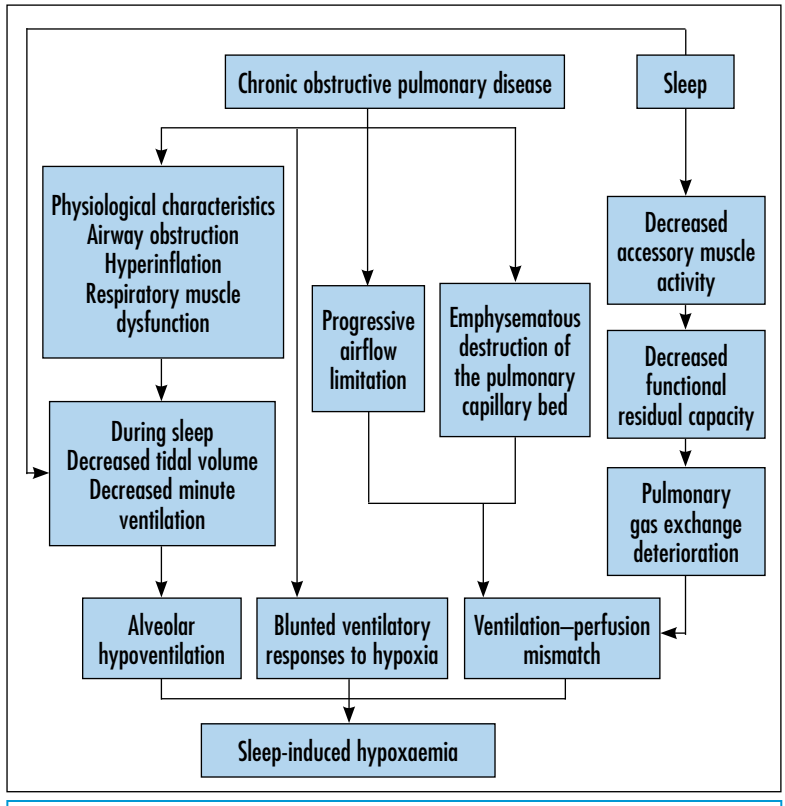
The *International Classification of Sleep Disorders: Diagnostic and Coding Manual* defines sleep-induced hypoxaemia as 'an oxyhemoglobin saturation (SpO_2) during sleep of <90% for more than five minutes with a nadir of at least 85%' or '>30% of total sleep time with an SpO_2 of <90%' in a subject with a baseline awake SpO_2 of ≥90% (American Academy of Sleep Medicine, 2005; Casey et al, 2007).

Reasons for sleep-induced hypoxaemia in chronic obstructive pulmonary disease

Patients with chronic obstructive pulmonary disease run a high risk of developing nocturnal hypoxaemia (Brijker et al, 2001; O'Donoghue et al, 2004). The possible mechanisms associated with chronic obstructive pulmonary disease contributing to sleep-induced hypoxaemia are outlined in *Figure 1*.

First, sleep-induced hypoxaemia occurs in patients with chronic obstructive pulmonary disease, independent of any changes in upper airway mechanics, as a result of a number of factors, including airway obstruction, hyperinflation, respiratory muscle dysfunction, blunted ventilatory responses to hypoxia and ventilation–per-

Figure 1. Mechanisms associated with chronic obstructive pulmonary disease contributing to sleep-induced hypoxaemia.



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fusion mismatch. Alveolar hypoventilation, a normal feature during sleep, has a disproportionate effect on hypoxaemic patients because of their position on the oxyhaemoglobin dissociation curve, leading to significant nocturnal desaturation, even in patients with mild awake hypoxaemia (Catterall et al, 1985). Alveolar hypoventilation appears to play a major role, especially during rapid eye movement sleep. This was demonstrated by Becker et al (1999) in a study of nine patients with underlying chronic obstructive pulmonary disease. Compared with wakefulness, minute ventilation decreased 16% during non-rapid eye movement sleep and 32% during rapid eye movement sleep, predominantly because of a decrease in tidal volume, measured with a pneumotachograph.

Second, arterial hypoxaemia alone may be the product of worsening ventilation–perfusion mismatch with greater effective shunt (Nikolaou et al, 2003; Orem et al, 2005; Casey et al, 2007). In addition, loss of accessory muscle activity during sleep, especially rapid eye movement sleep, results in a decreased functional residual capacity and a deterioration in pulmonary gas exchange, which leads to worsening ventilation–perfusion relationships and also aggravates nocturnal hypoxaemia.

Alveolar hypoventilation occurs predominantly during rapid eye movement sleep. Ventilation–perfusion mismatch can occur during non-rapid eye movement sleep episodes as well (Brijker et al, 2001). Overall, tidal volume and minute ventilation are decreased during rapid eye movement, but the breathing pattern during rapid eye movement sleep is irregular, with sudden changes in respiratory amplitude and frequency (Krieger, 2005).

Prevalence and clinical characteristics of sleep-induced hypoxaemia in chronic obstructive pulmonary disease

The prevalence of sleep-induced hypoxaemia among patients with chronic obstructive pulmonary disease is unknown, but the lower the baseline SpO_2 in the population studied the higher the prevalence of sleep-induced hypoxaemia is likely to be. There is limited information regarding the extent to which patients with chronic obstructive pulmonary disease with mild to moderate daytime hypoxaemia not qualifying for long-term oxygen therapy experience transient nocturnal desaturation. Several reports have assessed the epidemiological relationships between chronic obstructive pulmonary disease and sleep-induced hypoxaemia (Fletcher et al, 1987; Thomas et al, 2002; Zanchet and Viegas, 2006; Krachman et al, 2008; Lewis et al, 2009; Lacasse et al, 2011; Scott et al, 2011), as shown in *Table 1*.

Fletcher et al (1987) showed that 27% of 135 patients with chronic obstructive pulmonary disease and awake arterial partial pressure of oxygen (PaO_2) exceeding

Table 1. Prevalence of sleep-induced hypoxaemia in chronic obstructive pulmonary disease

Reference	Study details	Findings
Fletcher et al (1987)	152 patients with chronic obstructive pulmonary disease and a daytime arterial partial pressure of oxygen ≥60 mmHg underwent formal polysomnography to detect the presence of nocturnal, non-apnoeic, oxyhaemoglobin desaturation (17 subjects were disqualified)	27% desaturated below a baseline sleep saturation of 90% for 5 minutes or more, reaching a nadir saturation of at least 85%
Zanchet and Viegas (2006)	25 patients with chronic obstructive pulmonary disease having no sleep apnoea and presenting with mild daytime hypoxaemia were divided into two groups: those with nocturnal desaturation and those without	Of the nocturnal desaturation group 13 patients (52%) had sleep-induced hypoxaemia; this group presented with lower daytime oxyhaemoglobin saturation and nocturnal oxyhaemoglobin saturation
Thomas et al (2002)	30 consecutive patients with chronic obstructive pulmonary disease were divided into two groups, desaturators and non-desaturators	47% experienced nocturnal oxygen desaturation; desaturators had lower awake oxyhaemoglobin saturation, arterial partial pressure of oxygen, forced vital capacity, forced expiratory volume in 1 second and peak expiratory flow rate
Lewis et al (2009)	1104 consecutive patients with chronic obstructive pulmonary disease attending outpatient services at the study centre between 2002 and 2005	49% of the 59 subjects with a daytime oxyhaemoglobin saturation <95% agreed to undergo overnight oximetry and had significant nocturnal desaturation
Lacasse et al (2011)	128 patients with chronic obstructive pulmonary disease and mild-to-moderate daytime hypoxaemia (arterial partial pressure of oxygen 56–69 mmHg) in five-site cross-sectional study	38% were classified as nocturnal desaturators without evidence of sleep apnoea
Scott et al (2011)	A total of 103 patients with chronic obstructive pulmonary disease were recruited into the exploratory cohort. Subsequently 200 patients with chronic obstructive pulmonary disease, about one third of them desaturating to or below 88% during a 6-minute walk test, were recruited into the validation study which was performed for predicting nocturnal hypoxaemia with daytime oxygen desaturation during a 6-minute walk test	In the exploratory cohort 19% (20/103 patients) had significant nocturnal oxyhaemoglobin desaturation; in the validation cohort 35% (69/200 patients) had significant nocturnal oxyhaemoglobin desaturation

60 mmHg had sleep-induced hypoxaemia. Although patients with rapid eye movement-associated sleep-induced hypoxaemia had a lower awake PaO_2 and higher awake arterial partial pressure of carbon dioxide ($PaCO_2$), these parameters did not predict which patients suffered sleep-induced hypoxaemia.

Subsequently, several small studies of patients with chronic obstructive pulmonary disease reported the prevalence of significant nocturnal desaturation to be approximately 50% in patients who had some degree of daytime hypoxaemia (Thomas et al, 2002; Zanchet and Viegas, 2006). Similarly, after screening more than 800 patients with chronic obstructive pulmonary disease, Lewis et al (2009) found nocturnal desaturation in 29 of 59 (49%) patients with a daytime SpO_2 <95%. In another study, up to 25% of patients with chronic obstructive pulmonary disease exhibited sleep-induced hypoxaemia, despite having a daytime PaO_2 above 60 mmHg (Krachman et al, 2008).

Two large studies of patients with chronic obstructive pulmonary disease were undertaken to assess the prevalence of nocturnal desaturation in 2011. Lacasse et al (2011) found that a significant proportion (38%) of patients with moderate-to-severe chronic obstructive pulmonary disease who did not qualify for home oxygen therapy based on their daytime PaO_2 had nocturnal oxygen desaturation without evidence of sleep apnoea. This study found that nocturnal desaturation without sleep apnoea could not be predicted by any patient characteristic or physiological measure and home oximetry was an effective practical method for screening this population. Another study included a wide range of unselected individuals with chronic obstructive pulmonary disease and reported that 20 of 103 (19.4%) patients had significant nocturnal desaturation (Scott et al, 2011). Results from this study suggested that monitoring oxygen saturation changes during a 6-minute walk test was useful in helping to identify patients with chronic obstructive pulmonary disease who would experience significant nocturnal desaturation.

Koo et al (1975) found a mean decrease in PaO_2 of 13.5 mmHg and a mean increase of $PaCO_2$ of 8.3 mmHg during rapid eye movement sleep. In a study of 16 patients with chronic obstructive pulmonary disease (Krachman et al, 2005), the mean arterial oxyhaemoglobin saturation (SaO_2) was 90±6% and the lowest SaO_2 during the night was 83±8%. The percentage total sleep time with a SaO_2 <90% was 37±45%. In another study, $PaCO_2$ increased 3–10 mmHg, and PaO_2 decreased 2–8 mmHg during the period of rapid eye movement sleep (Krieger, 2005).

Compared to non-hypoxaemic patients, hypoxaemic patients with chronic obstructive pulmonary disease have greater degrees of pulmonary hypertension and cor pulmonale, require more frequent hospitalization and have higher mortality rates.

Pulmonary hypertension has been associated with sleep-induced hypoxaemia (Minai et al, 2007). The increase in pulmonary artery pressure was associated with the decrease in PaO_2 and less so with the increase in $PaCO_2$. Profound hypoxaemia and hypercapnia can occur in rapid eye movement sleep and contribute to the development of cor pulmonale (McKenzie et al, 2009). Pulmonary vascular remodelling in chronic obstructive pulmonary disease is the main cause of increase in pulmonary artery pressure and is thought to result from the combined effects of hypoxia, inflammation and loss of capillaries in severe chronic obstructive pulmonary disease (Chaouat et al, 2008).

Sergi et al (2002) found that sleep-induced hypoxaemia in patients with chronic obstructive pulmonary disease may represent an independent risk factor for the development of chronic respiratory failure in patients with chronic obstructive pulmonary disease with daytime PaO_2 >60 mmHg. Survival may also be affected by the presence of sleep-induced hypoxaemia in chronic obstructive pulmonary disease. In a retrospective study of 169 patients with chronic obstructive pulmonary disease, Fletcher et al (1992a) noted significantly decreased survival among patients with sleep-induced hypoxaemia compared with those without. Multiple regression analysis showed that quality of sleep was the best predictor of life quality in subjects with chronic obstructive pulmonary disease. Increased efforts to diagnose and treat sleep problems, including measures to improve factors that adversely affect sleep, should receive more attention in the daily management of these patients (Nunes et al, 2009), but isolated nocturnal desaturation was not associated with impairment of sleep quality or daytime function (Lewis et al, 2009).

Systemic inflammation is positively activated by sleep-induced hypoxaemia. Although nocturnal hypoxaemia does not reduce exercise capacity or hand-grip strength in patients with mild or moderate chronic obstructive pulmonary disease, its effect on maximal exercise diastolic blood pressure seems to depend on the degree of hypoxaemia. In addition, there is a positive relationship between maximal inspiratory pressure and mean peripheral oxygen saturation during sleep, as well as evidence of pronounced inflammatory activation in patients with nocturnal hypoxaemia (Mueller et al, 2008).

Patients with chronic obstructive pulmonary disease demonstrated significantly worse results in terms of accident frequency in the simulated driving situation because of sleep-induced hypoxaemia (Orth et al, 2008) and had a high prevalence of restless legs syndrome related to sleep-induced hypoxaemia (Lo Coco et al, 2009).

Treatment of isolated sleep-induced hypoxaemia in chronic obstructive pulmonary disease: is it necessary?

Physical treatments

The necessity of treatment of isolated sleep-induced hypoxaemia in chronic obstructive pulmonary disease has been debated for many years (O'Reilly and Bailey, 2007).

The specific effect of worsening hypoxaemia during sleep is difficult to assess. Whatever the specific role of sleep-related oxygen desaturation in severely hypoxaemic patients with chronic obstructive pulmonary disease, such individuals are usually treated with long-term oxygen therapy according to usual criteria (American Thoracic Society, 1995; Chaouat et al, 2001). Fletcher et al (1992b) found no improvement in mortality but did demonstrate a haemodynamic benefit when patients with normal daytime oxygenation but nighttime hypoxaemia received oxygen during sleep. Oxygen therapy during sleep did not lead to either an improvement in survival despite a reduction in pulmonary artery pressures or a delay in the time to prescription of continuous oxygen therapy (Fletcher et al, 1992a,b). Other randomized controlled trials of nocturnal oxygen treatment failed to demonstrate any improvement in pulmonary haemodynamics (Chaouat et al, 1999).

When long-term oxygen therapy is started, the oxygen flow is individually adjusted to increase PaO_2 to >60 mmHg (American Thoracic Society, 1995; Siafakas et al, 1995). Such flow may be insufficient during sleep. American Thoracic Society guidelines (American Thoracic Society, 1995; Plywaczewski et al, 2000) for diagnosis and treatment of chronic obstructive pulmonary disease recommended increasing oxygen flow by 1 litre/min during sleep in patients undergoing long-term oxygen therapy to prevent nocturnal oxygen desaturation. However, those recommendations were not supported by any formal study demonstrating frequency of nocturnal desaturation in patients with chronic obstructive pulmonary disease breathing oxygen (Plywaczewski et al, 2000; O'Donoghue et al, 2004; Kim et al, 2008). Because most patients did not exhibit overnight desaturation despite not increasing their long-term oxygen therapy prescription overnight, these results challenge the recommendation of routinely increasing overnight oxygen flow in patients receiving long-term oxygen therapy (Croxton and Bailey, 2006; Nisbet et al, 2006). If sleep-related hypoxaemia has no effect on the outcome of the disease, prescription of oxygen during sleep would be a waste of medical resources.

The recommendation to use nocturnal non-invasive positive pressure ventilation to treat severe, stable chronic obstructive pulmonary disease remains controversial, although a subgroup of patients with hypercapnoea and sleep-disordered breathing seems most likely to respond favourably (Ozsancak et al, 2008). Rehabilitation with nocturnal non-invasive positive pressure ventilation resulted in improvements in the 6-minute walk test and the longest non-stop walk distance. Further significant improvements were found for forced expiratory volume in 1 second (FEV_1), lung hyperinflation and blood gases in those treated with nocturnal non-invasive positive pressure ventilation, but not in the control subjects in advanced stage chronic obstructive pulmonary disease (Köhnlein et al, 2009). However, a meta-analysis of clinical trials did not support treatment with nocturnal non-invasive positive pressure ventilation for isolated sleep-induced hypoxaemia in chronic obstructive pulmonary disease (Wijkstra et al, 2003). Another study did not furnish compelling evidence to change this point of view (Clini et al, 2002). McEvoy et al (2009) found that, compared with long-term oxygen therapy alone, nocturnal non-invasive positive pressure ventilation resulted in a small improvement in survival. FEV_1 and $PaCO_2$ measured at 6 and 12 months were not different between groups. Patients assigned to nocturnal non-invasive positive pressure ventilation and long-term oxygen therapy had reduced general and mental health (McEvoy et al, 2009).

Pharmacological treatments

Pharmacological therapies which ameliorate some of the factors contributing to hypoxaemia during sleep might be an alternative approach. Previous studies support an improvement in lung function as an important mechanism of improving SaO_2 during sleep (Postma et al, 1985; Mulloy and McNicholas, 1993; Ryan et al, 2010).

Bronchodilators are commonly used drugs in patients with chronic obstructive pulmonary disease. Oral theophylline therapy may reduce the degree of air trapping in the lungs with consequent improvements in sleep SaO_2 (Mulloy and McNicholas, 1993). Postma et al (1985) found that the nocturnal fall in SaO_2 occurring in patients with chronic obstructive pulmonary disease was abolished by the β-agonist terbutaline in a slow-release oral form, which was also associated with an improvement in FEV_1, but β-agonists are now rarely used in this form.

Long-acting β-agonists are a recommended part of care in patients with moderate or severe chronic obstructive pulmonary disease (Vestbo et al, 2013). Ryan et al (2010) assessed the effect of inhaled salmeterol (a long-acting β-agonist) on nocturnal arterial oxygen saturation and sleep quality and indicated that the addition of inhaled salmeterol to conventional therapy improved SaO_2 during sleep in patients with advanced chronic obstructive pulmonary disease. Having considered the pulmonary function testing results the authors proposed a reduction in hyperinflation as one likely underlying mechanism in this improvement. However, another double-blind randomized study evaluated the short-term effect of a single evening dose of formoterol or tiotropium on isolated nocturnal hypoxaemia in a group of patients with moderate to severe stable chronic obstructive pulmonary disease and diurnal PaO_2 >60 mmHg. They reported that formoterol did not seem to influence the nocturnal hypoxaemia in stable patients with chronic obstructive pulmonary disease, probably as a result of the worsening ventilation–perfusion ratio, but tiotropium seemed to improve the nocturnal desaturations, probably as a result of reduction in the nocturnal bronchial cholinergic tone (Sposato and Franco, 2008).

Another choice of therapy for sleep-induced hypoxaemia in chronic obstructive pulmonary disease may be inhaled long-acting anticholinergics. A multicentre study assessed the effect of the long-acting anticholinergic agent tiotropium and reported a significant improvement in SaO_2 during sleep, which was accompanied by an improvement in spirometry (McNicholas et al, 2004).

Surgical treatments

More recently, as part of the National Emphysema Treatment Trial, lung volume reduction surgery has been shown to improve both sleep quality and nocturnal oxygenation in chronic obstructive pulmonary disease and improvements in nocturnal oxygenation correlated with improvements in airflow obstruction and a decrease in hyperinflation and air trapping (Krachman et al, 2005).

Although indications for performing an overnight polysomnogram in patients with chronic obstructive pulmonary disease have been debated, recommendations (Celli et al, 2004) have been presented. The literature recommended that sleep studies be performed only under special circumstances, including when there is clinical suspicion of obstructive sleep apnoea, if there are complications from hypoxaemia that are unexplained on the basis of the awake arterial oxygen level, or if there is pulmonary hypertension that is out of proportion to the degree of airflow obstruction (Celli et al, 2004). Future studies investigating disease mechanism and response to therapy in patients with sleep abnormalities and severe chronic obstructive pulmonary disease are warranted (Krachman et al, 2008).

Combined effects of inflammation, endothelial cell dysfunction and angiogenesis appear to contribute to the development of pulmonary hypertension associated with chronic obstructive pulmonary disease. Systemic vasodilators have not been found to be effective therapy. Selective pulmonary vasodilators including inhaled nitric oxide and phosphodiesterase inhibitors are promising treatments for patients with chronic obstructive pulmonary disease-associated pulmonary hypertension but further evaluation of these medications is needed before their routine use (Elwing and Panos, 2008).

Conclusions

Sleep-induced hypoxaemia has a high prevalence in patients with chronic obstructive pulmonary disease. Determination of sleep-induced hypoxaemia is important because it may impact on sleep quality, extrapulmonary comorbidities and quality of life in chronic obstructive pulmonary disease. Perhaps most clinically relevant, nocturnal oxygen desaturation is a marker of increased mortality in chronic obstructive pulmonary disease. However, the relevance of evaluating nocturnal hypoxaemia in patients with chronic obstructive pulmonary disease is still under debate. A large multicentre research study is necessary to evaluate the adverse consequences of sleep-induced hypoxaemia and the benefit of correcting isolated sleep-induced hypoxaemia on long-term mortality rates in patients with chronic obstructive pulmonary disease. **BJHM**

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KEY POINTS

- Sleep-induced hypoxaemia is defined as an oxyhaemoglobin saturation during sleep of <90% for more than 5 minutes with a nadir of at least 85% or >30% of total sleep time with an oxyhaemoglobin saturation of <90% in a subject with a baseline awake oxyhaemoglobin saturation of ≥90%.
- Sleep-induced hypoxaemia has a high prevalence in patients with chronic obstructive pulmonary disease.
- Sleep-induced hypoxaemia may predispose to pulmonary hypertension, cardiac arrhythmias during sleep and nocturnal death during exacerbations in patients with chronic obstructive pulmonary disease. However, its mechanisms and significance are not fully established.
- To improve prognosis, treatment of isolated sleep-induced hypoxaemia in chronic obstructive pulmonary disease through a variety of methods may be necessary.

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