Review

Nocturnal hypoxaemia in patients with chronic obstructive pulmonary disease: who should be treated and how?


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1. Introduction

Chronic obstructive pulmonary disease (COPD) is characterised by progressive loss of lung function and oxygen uptake capacity. As a consequence, extensive morbidity and mortality do occur in these patients due to complications of hypoxaemia such as polycythaemia, pulmonary hypertension, cor pulmonale and cardiac arrhythmias. In the course of the disease, periods with arterial oxygen desaturations may first occur during REM sleep [1], due to hypoventilation [2]. Prospective studies estimate that this occurs in 25–100% of the patients with COPD who are normoxaemic during the day, depending on the definition of desaturation and the severity of the disease [1,3,4].

Treatment modalities to improve nocturnal saturation in these patients include supplemental oxygen, respiration-stimulating agents, assisted ventilation and training of the respiratory muscles. In this article we will discuss some aspects of the breathing disorders during sleep that may occur in patients with COPD and the different treatment modalities.

2. Diagnosis

2.1. Polysomnography

Nocturnal breathing disorders and their underlying mechanisms can be assessed by polysomnography. During the night arterial oxygen saturation, carbon dioxide tension measured in respiratory air, arterially or transcutaneously, thoraco-abdominal movements, oscillation in oesophageal pressure and sleep stages are recorded. Sleep stages are recorded to define the adequacy of sleep, i.e. is there enough sleep to be representative, and conformation of REM sleep to catch the presence of REM sleep-related phenomena [5]. When analysing polysomnography records, several irregular breathing patterns can be distinguished. Central apnoea is defined as the absence of PCO₂ oscillations or oro-nasal airflow for at least 10 s, in combination with absent chest wall
movements or oesophageal pressure swings. **Obstructive apnoea** is defined as the absence of PCO$_2$ oscillations or oro-nasal airflow for at least 10 s, in combination with a normal or decreased chest wall movement. **Hypopnoea** is defined as an episode of alveolar hypoventilation of at least 10 s detected by an increase in PCO$_2$. **Central hypopnoea** is caused by a decrease in central ventilatory drive, and ideally it should be deduced from a parameter that measures ventilatory drive more or less directly. Integrated respiratory muscle EMG or oesophageal pressure oscillations are such parameters. Indirect parameters of a decrease in ventilatory drive, such as movements of the thoracic wall, should be interpreted with extreme caution. The term **central hypoventilation** is often used to indicate hypoventilation of a non-obstructive origin, such as respiratory muscle failure, although the latter is no central problem in the strict sense.

**Obstructive hypopnoea** is associated with a normal or even increased central ventilatory drive and decreased ventilation. A combination of central and obstructive breathing disorders may also be present. These irregular breathing patterns occur most frequently during REM sleep.

Several studies have tried to find daytime parameters to predict nocturnal saturation in patients with COPD, because nocturnal hypoxaemia caused by central hypopnoea is often symptomless. Although, polycythemia, pulmonary hypertension, cor pulmonale, morning headache or generalised fatigue indicate the presence of severe disturbances. Daytime SaO$_2$ ($r = 0.87$), PaCO$_2$ ($r = -0.73$), FEV$_1$ ($r = 0.61$), the hypercapnic ventilatory response (HCVR) ($r = 0.41$) and maximal inspiratory mouth and transdiaphragmatic pressures ($r = 0.65$ and 0.53, respectively) are related to nocturnal saturation in groups of patients [4,6,7]. However, none of these variables is able to predict nocturnal saturation in the individual patient, precisely enough to replace polysomnography. Therefore, polysomnography or a screening oximetry is advised in patients with a daytime PaO$_2$ between 7.3–11.0 kPa combined with one of the following disorders: polycythemia, pulmonary hypertension, cor pulmonale, PaCO$_2$ > 45 mmHg, morning headache or generalised fatigue [8], an HCVR below 3.5 l·min$^{-1}$·kPa$^{-1}$ [4] or low maximal inspiratory pressures (females < 5.0 kPa, males < 7.5 kPa) [9].

**3. Mechanisms involved in the occurrence of nocturnal desaturations**

In many patients with COPD, transient decreases in nocturnal arterial oxygen saturation occur. This may be caused by a variety of factors. The importance of these factors will be outlined below.

**Hypoventilation ("central hypopnoea"):** During sleep, ventilation is reduced in normal subjects and in patients with COPD [3]. This hypoventilation is most severe during REM sleep. The cause of this phenomenon is not fully understood but may be related to a decrease in brainstem respiratory activity, diminished respiratory responses to hypoxia and hypercapnia during REM sleep, and a loss of inspiratory activity of intercostal muscles and accessory respiratory muscles. The latter is due to the REM-sleep-related supraspinal inhibition of the gamma motor neuron drive. Since the gamma motoneuron innervation of the diaphragm is sparse, this muscle is relatively spared. These changes occur in patients with COPD as well as in healthy subjects, but the consequences are worse in the first group. Firstly, patients with COPD often have somewhat lower arterial oxygen tensions awake. The starting position on the oxygen saturation curve is closer to the steep part, so a small drop in PaO$_2$ during the night causes a large fall in SaO$_2$. Secondly, the flattened diaphragm cannot compensate for the decreased activity of intercostal and accessory muscles during REM sleep. Thirdly, desaturating patients have a larger decrease in functional residual capacity during hypopnoea [2]. Finally, the ventilatory responses in some patients with COPD during wakefulness are already lowered, thus further contributing to the degree of nocturnal desaturations [4].

**Ventilation/perfusion inequality:** Previously, this was considered as the major cause of REM-sleep-related hypoxaemia in patients with COPD.
However, these studies were based on the assumption that there is a steady state of gas transfer, which does not exist during REM sleep. It is inevitable, though, that hypoventilation during REM sleep is accompanied by some alteration in ventilation/perfusion matching.

Abnormal hypercapnic and hypoxic responses: Ventilatory responses during wakefulness to hypercapnia and hypoxia seem to be lower in hypoxic patients [3].

Obstructive sleep apnoea / hypopnoea syndrome (OSAHS): OSAHS, defined as a sleeping disorder in which obstructive apnoea/hypopnoea events occur more than 10 times per sleeping hour, may affect 1–4% of the general population [3]. Thus, a similar percentage of patients with COPD may also suffer from OSAHS, but the prevalence is most probably not higher than in the general population.

4. Consequences of nocturnal hypoxaemia

When desaturations are severe and result in nocturnal hypoxaemia, side-effects may occur. Nocturnal hypoxaemia is associated with pulmonary hypertension [11–14], which causes cor pulmonale [15,16]. Furthermore, polycythaemia may exist [17]. Cardiac arrhythmia is an uncommon complication, but premature ventricular complexes, bradycardia and tachycardia have been described [18]. In the study of Levi-Valensi and colleagues [11] a correlation \( r = 0.33 \) was found between the total duration of saturation dips and pulmonary hypertension in 40 patients with COPD and a daytime \( \text{PaO}_2 \) between 8.0–9.3 kPa (60–70 mmHg). Pulmonary hypertension was only present in 6 out of 18 patients who desaturated. These findings are in line with the data published by Fletcher and co-workers [12]. These authors found that the systolic pulmonary arterial pressure was significantly higher in desaturating \( (n = 36) \) than in non-desaturating \( (n = 13) \) patients with COPD and with a daytime \( \text{PaO}_2 > 8 \) kPa (60 mmHg) (33 versus 26 mmHg, \( p < 0.01 \)). In the study of Boysen and colleagues [13] the effects of hypoxaemic episodes on the pulmonary artery pressure (Pap) during the night were studied in 4 patients with COPD. All nocturnal episodes of desaturations were accompanied by elevations in the Pap. Low flow oxygen abolished the drops in arterial oxygen saturation and no elevations in the Pap were observed. Weitzenblum and co-workers [14] investigated prospectively the changes in \( \text{PaO}_2 \) and Pap in 93 hypoxaemic patients with severe COPD for at least 5 years. In 27 patients an increase \( \geq 5 \) mmHg in the Pap was observed. Only in this patient group was a marked worsening of the \( \text{PaO}_2 \) seen, which was not observed in the remaining 66 patients. There was a significant correlation between the change in Pap and \( \text{PaO}_2 \) \( (r = -0.50, \ p < 0.001) \). All these studies suggest that nocturnal hypoxaemia is associated with the development and progression of pulmonary hypertension.

The relationship between daytime or nocturnal hypoxaemia and cor pulmonale was studied by Midgren and colleagues [16]. Seven of the 21 included patients with COPD had suffered from right ventricular failure at least once. They had lower \( \text{PaO}_2 \) and higher \( \text{PaCO}_2 \) levels than the patients without a history of right heart failure. They were more hypoxaemic during the night. In the group as a whole no correlations were found between daytime oxygenation and right ventricular hypertrophy. However, oxygen saturation during the night and right ventricular hypertrophy were inversely related \( (r = -0.56, \ p < 0.01) \). Therefore, in normoxic patients during the day but with signs of right heart failure a polysomnography is advised.

The effects of nocturnal hypoxaemia on survival are not clear yet. One study is available in which survival in desaturating and non-desaturating patients is compared [1]. One hundred and sixty-nine patients with COPD and a \( \text{FEV}_1 \) of 35% predicted, who were all normoxaemic (daytime \( \text{PaO}_2 > 8.0 \) kPa [60 mmHg]), were investigated. Desaturating patients had a worse survival than non-desaturating patients (mean survival 2.9 [1.7] and 3.7 [1.7] years, respectively). Also, 5-year survival was significantly better in the non-desaturating group (after stratification for oxygen supplementation). However, this was a retrospective multicentre study in which patients were included who were already being treated with oxygen.
5. Treatment of nocturnal hypoxaemia

5.1. Supplemental oxygen

Studies on the effects of oxygen have only been performed in patients who were also hypoxaemic during the day. In these studies an improvement of the quality of life [19], some reversal of ECG changes (less right axis deviation or the loss of the finding of “p-pulmonale” [19]) and a decrease in the pulmonary artery pressure combined with an increase in cardiac output [20] were observed. Supplemental oxygen during the night can be given safely because it improves nocturnal oxygenation with only a small rise in $\text{PaCO}_2$ [21]. Nocturnal oxygen supply should be titrated individually during a full night and should be controlled by oximetry. The mean nocturnal arterial oxygen saturation should be more than 90% [22].

5.2. Ventilatory stimulants

Stimulating agents may be considered if any reserve-capacity of the ventilatory pump is present. The progestogens medroxyprogesterone acetate and chlormadione acetate increased daytime $\text{PaO}_2$ and decreased $\text{PaCO}_2$, but the effects on nocturnal saturation were marginal or absent in the whole group of patients. Nevertheless, for the individual patient, chlormadione acetate may have a substantially positive effect on day- and nighttime blood gas values [23,24]. Acetazolamide, a carbonic anhydrase inhibitor, stimulates ventilation presumably by inducing metabolic acidosis. In a 1-week double-blind, placebo-controlled study it caused an improvement in the mean daytime $\text{PaO}_2$ of 1.9 kPa (14 mmHg) and in the mean nocturnal saturation of 4% [24]. However, acetazolamide may be ineffective in some patients. Daytime parameters, however, failed to select the non-responders. Recently, Mulloy et al. [25] showed in a 3-week double-blind, placebo-controlled study that theophylline improved gas exchange during sleep in 10 patients with severe COPD. The mean $\text{SaO}_2$ asleep improved by 2% while the mean transcutaneously measured $\text{PCO}_2$ asleep decreased by 0.5 kPa (4 mmHg). Loop diuretics have an adverse effect on nocturnal saturation since they can result in a metabolic alkalosis and blunt the respiratory drive [15].

5.3. Assisted ventilation

Continuous positive pressure ventilation during the night, administered through a nasal mask, can effectively reduce inspiratory muscle effort during sleep, but $\text{SaO}_2$ and transcutaneously measured $\text{PCO}_2$ were unaffected [26]. The effects of nasal intermittent positive pressure ventilation were described in an uncontrolled study by Carroll and co-workers [27]. They showed in 4 hypoxaemic patients with COPD and with a mean FEV₁ of 19% of the predicted value that daytime $\text{PaO}_2$ did not change significantly while daytime $\text{PaCO}_2$ decreased by 1.1 kPa (14.3 mmHg). Oxygenation during the night improved. This was shown by a decrease in the time spent below 90% $\text{SaO}_2$ from 100 to 40% of the total monitoring time. However, the patients slept less well, as shown by a decrease in REM sleep from 12 to 5% of the monitoring time.

5.4. Training of the respiratory muscles

Target-flow inspiratory muscle training (TF-IMT) is the most recently described form of therapy [28]. During 10 weeks, 10 patients with COPD underwent TF-IMT at 60% of their maximal inspiratory mouth pressure ($\text{PI}_{\text{max}}$) and 10 control patients with COPD received sham TF-IMT at 10% of $\text{PI}_{\text{max}}$. Two times a day patients trained on an incentive flow meter with an added resistance for 15 min. $\text{PI}_{\text{max}}$, maximal inspiratory transdiaphragmatic pressure (Pdi), and respiratory muscle endurance improved significantly in the 60% training group. No changes were found in the sham training group. The improved respiratory muscle function resulted in a mean increase in mean nocturnal saturation by 2% ($p = 0.01$); the most pronounced improvements (up to 7%) were found in patients with the lowest nocturnal saturations.

6. Clinical consequences and recommendations

Although positive effects of the different forms of therapy on nocturnal saturation have been described, no placebo-controlled studies have
Table 1
Treatment of nocturnal hypoxaemia

<table>
<thead>
<tr>
<th>Daytime oxygenation</th>
<th>Nocturnal oxygenation</th>
<th>Treatment modality</th>
</tr>
</thead>
<tbody>
<tr>
<td>PaO₂ 7.3–8.0 kPa (55–60 mmHg)</td>
<td>SaO₂ &lt; 90%</td>
<td>Continuous oxygen</td>
</tr>
<tr>
<td>combined with Ht &gt; 55% or pulmonary artery pressure &gt; 3 kPa or cor pulmonale</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PaO₂ ≥ 7.3 kPa (55 mmHg)</td>
<td>SaO₂ &lt; 85% (&gt; 2 h)</td>
<td>Oxygen during the night</td>
</tr>
<tr>
<td>PaO₂ ≥ 7.3 kPa (55 mmHg)</td>
<td>SaO₂ 85–90%</td>
<td>Acetazolamide, theophyllines, progestogens, IMT</td>
</tr>
</tbody>
</table>

Acetazolamide, progestogens, theophylline and respiratory muscle training may be considered to treat patients with mild hypoxaemia only during the night. Polysomnography should be used for diagnosing nocturnal hypoxaemia, its underlying mechanisms, and for establishing the presence of REM sleep in the diagnostic night. Oximetry can be used for screening purposes, and for titrating the required amount of supplemental nocturnal oxygen.

References


