Respiratory disturbance during sleep in chronic obstructive pulmonary disease*

Perturbação respiratória durante o sono em doença pulmonar obstrutiva crônica

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Chronic obstructive pulmonary disease is a prevalent condition and is currently the forth leading cause of mortality in the US. The prevalence of respiratory disturbance during sleep, or overlap syndrome as it was commonly known in the past, is still undetermined as conflicting reports have been published. Because of the adverse effects of sleep-related respiratory impairment in patients with underlying pulmonary disease, this condition deserves further investigation. In this report, we will briefly discuss the mechanisms involved in generating respiratory disturbance during sleep in Chronic Obstructive Pulmonary Disease and will guide the reader into distinguishing those patients who would benefit from a more detailed sleep evaluation, discussing management issues and treatment options.

A doença pulmonar obstrutiva crônica é uma condição frequente e é hoje a quarta principal causa de mortes nos Estados Unidos. A prevalência de perturbação respiratória durante o sono, ou síndrome de superposição, como anteriormente denominada, ainda não foi determinada devido à publicação de relatos conflitantes. Esta condição deve continuar sendo investigada devido aos efeitos adversos causados por transtornos respiratórios relacionados ao sono em pacientes com doença pulmonar de base. Neste relato, discutiremos brevemente os mecanismos envolvidos na origem da perturbação respiratória durante o sono em doença pulmonar obstrutiva crônica e auxiliaremos o leitor a distinguir aqueles pacientes que se beneficiariam de uma avaliação do padrão do sono mais detalhada, com a discussão de tópicos de gerenciamento e opções de tratamento.

Key words: COPD. Sleep disorder breathing. Sleep apnea. Hypoxemia. Hypoventilation


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INTRODUCTION

Respiratory physiology during sleep is considerably different than during wakefulness. Respiratory control, neuromuscular functioning and airways resistance are altered during sleep. These physiological modifications do not bring significant consequences to healthy patients but may impair respiratory function in patients with underlying pulmonary disease.

Sleep-related respiratory abnormalities in Chronic Obstructive Pulmonary Disease (COPD) patients have been described for many years. Increases in arterial carbonic dioxide pressure (PaCO\textsubscript{2}) have been reported in the literature since the late 1950s\textsuperscript{(1-2)}. In 1962, decreases in oxygen saturation during sleep were described\textsuperscript{(3)}. Those findings were later confirmed by nocturnal arterial blood gas measurements\textsuperscript{(4)}. By using electroencephalographic measurements to monitor sleep, additional studies have demonstrated that the nocturnal hypercapnic and hypoxicemic episodes were closely related to rapid eye movement (REM) sleep periods\textsuperscript{(5-7)}. Connaughton et al evaluated overnight oximetry in 97 COPD patients and found a significant relationship between mean oxyhemoglobin saturation measured while awake and mean and lowest oxygen saturation during sleep (p< 0.001)\textsuperscript{(8)}. This was corroborated by Mulloy and Fletcher\textsuperscript{(9,10)}. The lowest levels of nocturnal oxygen saturation were found in the patients having the most severe daytime hypoxemia and the longest REM sleep duration\textsuperscript{(8)}. Additionally, the decrease in arterial oxygen tension during sleep was found to be more pronounced than during maximal exercise, and awake arterial oxygen pressure (PaO\textsubscript{2}) correlated better with nocturnal desaturation than did exercise oximetry\textsuperscript{(9)}. Owing to the usual duration of sleep, the hypoxic stress related to sleep was suggested as affecting patients’ prognosis more significantly than the limited periods of daily life physical activity. It should be pointed out that this was never prospectively tested. Furthermore, studies in which nocturnal oxygen supplementation was given to COPD patients with nocturnal desaturation despite awake PaO\textsubscript{2} levels above 60 mmHg, do not suggest benefit in terms of quality of sleep and long term mortality\textsuperscript{(11-14)}. In 19 patients studied by Mulloy, there was disproportional oxygen desaturation in a subgroup or patients, implying other mechanisms, possibly ventilation-perfusion mismatches and a lower position in the hemoglobin dissociation curve, to contribute to nocturnal oxygen desaturation in COPD\textsuperscript{(9)}.

Patients with awake hyperapnia are more likely to have nocturnal oxygen desaturation\textsuperscript{(9,10,15,16)}. However, whether awake PaCO\textsubscript{2} is an independent predictor of desaturation remains controversial\textsuperscript{(8,9,12,17)}. The relationship between daytime PaCO\textsubscript{2} and rise in sleep End-tidal CO\textsubscript{2} (PetCO\textsubscript{2}) has been found to be weak and with no significant correlation after multiple regression analysis\textsuperscript{(9)}. This suggests that the reduction in ventilation during sleep is critical in all patients, regardless of PaCO\textsubscript{2}, and is probably secondary to the withdrawal of the wakefulness drive to breath interacting with the baseline levels of ventilation.

PATHOPHYSIOLOGY

Several mechanisms have been postulated to cause nocturnal blood gas changes in COPD. However, only a few have been demonstrated directly. It appears that nocturnal hypoventilation is the major cause of hypoxemia during REM sleep in COPD. Contribution from the reduction in functional residual capacity (FRC) and impaired ventilation/perfusion matching has also been envisaged, both of which may be exacerbated by supine positioning and REM sleep. Some other conditions such as Obstructive Sleep Apnea (OSA) may also be found in a small percentage of COPD patients and contribute to sleep-related respiratory abnormalities. However, it does not represent the primary anomaly in these patients.

a. Changes in ventilatory control: Ventilatory control is physiologically altered during sleep, mainly during the REM stage, resulting in a diminished responsiveness to chemical, mechanical and cortical inputs\textsuperscript{(18,19)}. The relationship between metabolic CO\textsubscript{2} production ("metabolic control") and ventilation is decreased. The physiological reduction in basal metabolic rate during sleep is concomitant to a decrease in minute ventilation\textsuperscript{(20)}. The decrease in ventilation occurs during all stages of sleep and worsens during REM, particularly during phasic REM, as compared to wakefulness\textsuperscript{(21-23)}. In normal individuals, as a result of the fall in ventilation, PaCO\textsubscript{2} rises by 2-8 mm Hg, PaO\textsubscript{2} decreases by 3-10 mm Hg and oxygen saturation drops by less than 29\%\textsuperscript{(24-26)}. These occur despite reduced oxygen consumption and CO\textsubscript{2} production during sleep\textsuperscript{(24). Both the "classical" respiratory muscles responsible for the bellows function breathing and the upper airway respiratory muscles responsible for maintaining airway patency, exhibit a diminished response to ventilatory stimuli during sleep\textsuperscript{(18)}. As a result of the latter, upper
airway resistance is increased. It is important to remember that upper airway (UA) muscles are both responsible for maintaining UA tone during sleep (tonic activity) (21-23) and for preventing the pharynx from collapsing due to the increased negative pressure in the lumen generated by contraction of the diaphragm (phasic activity). During REM, there is also a dramatic reduction in intercostal muscles tonic and phasic activity. This is associated with both a slight reduction in tonic activity of the diaphragm and more critically a persistent phasic activity (18,19). This is why the function of the diaphragm is so critical in REM sleep, as no other respiratory muscle is spontaneously able to contribute to maintaining alveolar ventilation during this period. The decrease in muscular activity seems to be a particularly important factor in patients with obstructive lung disease, where the lung is hyperinflated and the already flattened diaphragm cannot contribute as efficiently to ventilation. As the diaphragm is the unique active respiratory muscle during REM sleep (20), alveolar ventilation in these patients will be highly affected during this period of sleep. Breathing irregularity with rapid shallow breathing during REM sleep (23) also increases the physiologic dead space in COPD patients and thus impairs gas exchange (28-31). Another important contributing factor relates to the ventilatory responses to hypoxia and hypercarbia that are decreased during sleep even in normal individuals, with a further decrease during REM sleep (24-31). The mechanisms are still unclear but both increased airway resistance and decreased activity of the medullary respiratory neurons during sleep have been suggested (21,22,23). However, the reduction in ventilatory drive associated with the loss of the wakefulness stimulus appears to be a major factor (20).

In summary, as already mentioned, tonic activity of the intercostal muscles is abolished during REM sleep but diaphragmatic phasic activity is preserved or even increased, which prevents the occurrence of alveolar hypoventilation during REM sleep in normal subjects. In COPD, as the diaphragm has to work in an unfavorable mechanical situation, alveolar hypoventilation is expected in the absence of intercostal activity. Other additional factors which may further aggravate this change in ventilation will be discussed next.

b. Change in Functional Residual Capacity (FRC): In normal subjects, FRC decreases in the supine position and has been reported to further decrease during stages of REM sleep, probably secondary to atonia of the intercostal muscles (20,29). In COPD, the available data from inductive plethysmography measurements is contradictory (29, 40), and its validity is questioned as plethysmography, does not provide accurate measurement of lung volumes during sleep (41). Data from non-REM sleep in adults patients with cystic fibrosis, by using a horizontal body plethysmography demonstrated no significant decreases in FRC as compared to wakefulness (42). A reduction in neuromuscular output was also confirmed by a progressive reduction in tidal volume and minute ventilation from wakefulness to slow wave sleep in those patients. Occlusion pressure at 100 ms (P0-1) was also significantly reduced during non-REM sleep (40).

c. Change in Ventilation/Perfusion ratio: Ventilation-perfusion mismatches have been postulated to explain the blood gas disturbances that occur during sleep in COPD (43,44). Several studies have demonstrated that mean nocturnal SaO2 correlates well with daytime PaO2 (8,16,17). This suggests that nocturnal desaturation is related to the position of hypoxic patients on the steeper portion of the oxyhemoglobin dissociation curve. However, in some COPD patients with more significant nocturnal desaturation, larger falls in PaO2 have been observed than it would be predicted from their position on the oxyhemoglobin dissociation curve (46). In the same study, the authors challenge the concept that desaturation was entirely due to a fall in overall ventilation, and they point to the similar increase in Pet CO2 which occurred in both minor and major desaturators, and invoke gas exchange abnormalities, such as changes in the ventilation-perfusion ratio occurring during sleep as a cause of excess desaturation (49).

d. Associated sleep-disordered breathing: Obstructive sleep apnea is a common condition in the general population (45,46). Thus its association with another frequent disease such as COPD is expected. In a large series of patients diagnosed with OSA in a sleep center the average frequency of concomitant obstructive lung disease determined by pulmonary function testing was 11% (47). In these patients, the pattern of nocturnal desaturation was different than that expected solely with COPD. The desaturation was widespread during the night, with further drops
during REM sleep. However, during REM sleep periods, obstructive apnea was uncommon and sustained hypoventilation was considered the most important contributing factor. This association of COPD with OSA resulting in such a nocturnal desaturation pattern has been named Overlap Syndrome. This does not imply, however, that the prevalence of sleep apnea in COPD is higher than in the general population. It is unclear to which point the increased airway resistance seen in COPD would increase the risk of developing OSA.

CLINICAL EVALUATION

OVERNIGHT SLEEP STUDIES

The importance of sleep studies in a selected group of COPD patients cannot be overstated, as therapy exists for several of the disorders which may be found. While routine polysomnography is unlikely to be performed in all COPD patients, there is a need to identify those patients who may benefit from sleep studies. There is still much debate over which diagnostic sleep procedure should be done, ranging from full polysomnograph (including staging of sleep) to studies using simplified techniques (e.g. oximetry, and respiratory monitoring by detecting chest and abdominal motion). Most authors agree that we are not able to distinguish the patients who will develop nocturnal desaturation from clinical features, daytime lung function measurements, or single measures of daytime PaO$_2$ or SaO$_2$. Fletcher et al demonstrated a relationship between mean oxygen saturation during wakefulness and the lowest oxygen saturation during sleep, but this correlation was not sufficient to be predictive for individual patients. Furthermore, the major indications for nocturnal polysomnography in COPD patients is for whom there is a suspicion of nocturnal hypoxemia, including those with unexpected cor pulmonale and polycythemia despite reasonable levels of daytime oxygen tension (e.g. PaO$_2$ above 60 mmHg) and those suspected of having both COPD and OSA, being prone to develop pulmonary hypertension and CO$_2$ retention at higher rates than patients with either disease alone. Overnight sleep monitoring for therapeutic purpose, such as titration of nocturnal oxygen, continuous positive airway pressure (CPAP) and non-invasive positive pressure ventilation (NPPV) is also an important consideration. Besides that, it may be an adjunct tool to overnight oximetry, providing more information regarding nocturnal changes in ventilation.

a. Evaluating nocturnal hypoxemia: The definition of significant nocturnal desaturation is not yet well established. However, the most commonly used definitions in the literature are: 1) greater than 30% of total time in bed spent below 90% of oxygen saturation, or 2) a drop in oxygen saturation below a baseline of 90% for longer than 5 minutes, reaching a nadir of 85% or lower. In a study by Connaughton, ninety-seven patients with COPD were followed after sleep studies. He was able to demonstrate a significantly higher mortality in those patients with the lowest levels of oxygen saturation during sleep. Despite that, similar predictions could be made by analyzing daytime oxygen levels and vital capacity, which were associated with a reduced survival after a mean follow-up of seventy months, independently of nocturnal SaO$_2$. Based on further analysis, the data from nocturnal polysomnography or oximetry did not influence more the prognosis than both wakefulness SaO$_2$ and daytime pulmonary function. Whether nocturnal hypoxemia per se carries a higher mortality risk for COPD patients without daytime hypoxemia has been much debated. Several authors have been evaluating nocturnal desaturation as a potential negative prognostic factor for survival in these patients. However, recent data issued from an European multicentre trial coordinated by Weitzenblum, demonstrated that in patients with daytime PaO$_2$ over 60 mm Hg and nocturnal desaturation much more severe than usually considered (> 30% of recording time at a SaO$_2$ less than 90%), there was no significant change in pulmonary haemodynamic during a two-year follow-up and no difference in terms of haemodynamic changes and survival rate for the same observation period, when comparing the patients with or without oxygen supplementation. In patients with cor pulmonale and polycythemia despite adequate daytime oxygen tension, sleep studies may, uncover nocturnal hypoventilation that may contribute for a worse outcome.

b. Evaluating associated obstructive sleep apnea: It appears that obstructive sleep apnea can be easily
suspected from clinical evaluation of patients, by investigating history of snoring, excessive daytime somnolence and witnessed apneas. The complaint of excessive daytime somnolence (EDS) is the most prominent symptom of patients with OSA and may be the best indicator of a need for sleep studies in patients with COPD. However, many of the questionnaires and clinical instruments used to assess EDS and other symptoms of OSA may be less specific in these patients, because cough and nocturnal exacerbations of lower airway obstruction can also disrupt sleep and contribute to daytime sleepiness and fatigue. Furthermore, daytime fatigue may also result from their inability to exercise due to airflow obstruction and cardiopulmonary limitations. It should also be kept in mind that EDS is common during acute exacerbation of Chronic Respiratory Failure owing to acute CO2 retention and acidosis. In stable condition, however, EDS may be present secondary to sleep fragmentation. Quality of sleep has been shown to be decreased in chronic obstructive respiratory failure patients, characterized by a reduced total sleep time, a decrease in stages 3 and 4 of non-REM and REM sleep, and sleep fragmentation\textsuperscript{14,51-53}. At this point, there is no proof that sleep studies in subjects denying EDS would yield unsuspected cases of OSA\textsuperscript{49}. Orr et al demonstrated no evidence of EDS in COPD patients as measured by Multiple Sleep Latency Test, unless concomitant OSA was present\textsuperscript{54}. The physicians should ask COPD patients about OSA symptoms, and when symptoms are elicited, polysomnography or simplified recording should be performed.

c. Evaluating therapeutic interventions: Nocturnal oxygen therapy has been used to treat COPD patients with daytime hypoxemia, but it is unclear how much oxygen is needed to overcome the overnight desaturations. The current recommendations by the American Thoracic Society are to prescribe oxygen based on the daytime requirements, with an increase by 1 l/min during sleep and exercise in those patients who fulfill the requirements for supplemental oxygen\textsuperscript{69}. However, the adequacy of this has not been tested\textsuperscript{12,17}. As previously discussed, it is difficult to predict nocturnal hypoxemia based solely on wakefulness arterial blood gas. Ideally, nocturnal oxygen prescription should be titrated based on the severity of oxygen desaturation, and this will be difficult to achieve without overnight measurements. In a study by Pływaczewski et al, a daytime PaO\textsubscript{2} below 65 mmHg combined to a PaCO\textsubscript{2} above 45 mmHg were the best predictors of nocturnal desaturation\textsuperscript{55}. Other therapeutic interventions which need a sleep study are related to the initiation or follow of continuous positive airway pressure treatment and non-invasive positive pressure ventilation. COPD patients in need of these devices should be monitored on the basis of an optimal recording of nocturnal oximetry, air flow and mask pressure. Sleep staging recording per se is not systematically required. The overnight monitoring will also document an adequate level of nocturnal ventilation with a limited amount of side effects (i.e. mouth or mask leaks). These leaks are associated with ineffective ventilation and induced sleep fragmentation\textsuperscript{56}. When both are suppressed, there is an improvement in both alveolar ventilation and daytime function, with decreased morbidity\textsuperscript{67}. Because of the cost limitations for performing a full night polysomnogram in every case, less complex studies evaluating airflow and oxygen saturation could be performed, given that no other indication for a full study and no additional risk for the patient are present.

TREATMENT ALTERNATIVES

The most important consideration when dealing with COPD patients is to optimize the management of the underlying condition. Additional therapeutic interventions targeted towards sleep-related abnormalities are discussed below.

a. Oxygen: With the use of supplemental oxygen, nocturnal oxygen saturation improves in patients with COPD\textsuperscript{15,58,59}. Despite that, some milder dips in saturation, mainly during REM sleep, may persist. In one study, there was a non significant trend for nocturnal oxygen to reduce the frequency of ectopic heart beats in COPD patients\textsuperscript{60}. As long-term use of oxygen is the only measure shown to date to decrease mortality in this population\textsuperscript{61,62}, one would assume that the decrease in hypoxemia during sleep is, at least, one adjuvant factor in the improved survival. The concentration of oxygen prescribed in these studies was based on wakefulness arterial oxygen tensions. Another studies demonstrated improvement in pulmonary arterial pressure without survival difference between two groups of COPD patients without daytime hypoxemia or hypercarbia when randomized to receive nocturnal oxygen\textsuperscript{12,63}. More recent data, however, failed to demonstrated such beneficial effect\textsuperscript{50}. In this last study, the authors
reached the conclusion that nocturnal oxygen therapy did not alter the evolution of pulmonary haemodynamics during a two-year follow-up and did not delay the need for long-term oxygen therapy (LOT - oxygen use > 15 hours/day). Furthermore, there was no effect of nocturnal oxygen therapy on survival, although the limited number of deaths precluded any firm conclusion. Consequently, the authors suggest that the prescription of nocturnal oxygen therapy in isolation is probably not justified in COPD, and the current international guidelines should be reconsidered\(^{(50)}\). From this perspective, another recent paper issued from the national French network Antadir has shown that, in a very large series of 7,700 COPD patients, about 18% exhibited a stable \(\text{PaO}_2\) over 60 mm Hg. Also, there was no difference in survival when comparing patients having a stable \(\text{PaO}_2\) above or below this threshold \(^{(64)}\). These last results do not support the use of 24hr or nocturnal oxygen therapy in moderate hypoxemia. The physician should be careful when using oxygen in patients with associated OSA, as it has been demonstrated that periods of apnea-hypopneas may be prolonged and occur with increased frequency during acute application of oxygen in those patients\(^{(64)}\). Furthermore, increases in \(\text{PaCO}_2\) monitored by transcutaneous \(\text{CO}_2\) during supplemental oxygen has been found mild when compared to wakefulness, and not progressive through the night\(^{(59)}\). Nevertheless, when prescribing oxygen to COPD patients, the physician must carefully clinically monitor the patients (i.e. new complaints such as morning headaches, insomnia, sudden EDS) in order to prevent any further \(\text{CO}_2\) retention. Thus, there is a need for careful oxygen titration and adequate follow-up of COPD patients, using arterial blood gas sampling during wakefulness when carbon dioxide retention is clinically suspected. It should emphasized however that it is rarely an issue. The device used for nocturnal oxygen delivery does not seem to really matter, but when a demand-delivery device is prescribed it would be judicious to evaluate its efficacy by continuous overnight oximetry to ensure the efficacy of oxygen delivery. Oxygen has also been shown by some investigators to improve sleep quality\(^{(69,66)}\). However, others have failed to demonstrate any improvement when looking at arousal frequency\(^{(67)}\).

**b. Medications:** The role of medical treatment specifically dedicated to the nocturnal hypoxemia of COPD has not been well defined. There are some medications known to improving oxyhemoglobin levels during sleep but carrying undesirable side-effects. The most recommended management is to be aggressive when treating underlying airway obstruction with safe medications in an attempt to decrease the deleterious effects that sleep, mainly REM sleep, has on ventilation and gas exchange in COPD patients.

1. **Acetazolamide:** Skatrud & Dempsey compared the use of acetazolamide and medroxyprogesterone acetate in COPD patients. Acetazolamide improved arterial oxygenation both during wake and sleep\(^{(68)}\). Its side-effect profile however limits its chronic use by causing potential acidosis, paresthesias and nephrolithiasis.

2. **Almitrine Bismesylate:** It is a peripheral chemoreceptor agonist that improves \(\text{PaO}_2\) during wakefulness. Its stimulant effects are only present at high doses and probably mediated by calcium-dependent potassium channels inhibition mechanism. Almitrine increases minute ventilation. The drug improves ventilation-perfusion matching even at lower doses and was shown to improve both wake and nocturnal oxygenation in COPD patients with a less pronounced effect on \(\text{PaCO}_2\)\(^{(69,70)}\). This agent is known to cause peripheral neuropathy and there is controversy regarding causing coincident pulmonary hypertension. At this point, its dosage for a safe use has not been yet defined\(^{(71)}\).

3. **Bronchodilators:** In a recent randomized, double blind placebo-controlled study by Martin et al, ipratropium bromide was associated with improvement in oxygenation and sleep quality in COPD patients without daytime \(\text{CO}_2\) retention or superimposed OSA\(^{(72)}\). There was also an improvement in subjective sleep quality and breathlessness. This reminds the reader about the importance of adequate treatment of the underlying obstructive lung disease in order to improve nocturnal gas exchange. Regarding beta2 agonists, there is not enough data to reach any firm conclusion against its effect on sleep-related abnormalities.
4. Medroxyprogesterone: Reduction in arterial CO$_2$ tension and improvement in oxygen levels during wakefulness and non-REM sleep were demonstrated in patients with hypercapnia and COPD using medroxyprogesterone$^{74}$. Another study in COPD patients demonstrated a limited improvement in nocturnal oxygen saturation when compared to almitrine$^{74}$. It seems that despite some improvement described, the role of this agent is limited, particularly owing to its side-effect profile.

5. Protriptyline: Studies have demonstrated improvement in daytime and nocturnal oxygenation in COPD patients$^{75}$. The improvement in nocturnal saturation is considered to rely on REM sleep suppression. It is unclear whether other mechanisms are involved. More data regarding its safety with long-term utilization, morbidity and mortality charts are required. It is known that side-effects limit its use. The risks of prolonged REM suppression are also a theoretical concern, and REM rebound when the drug has to be withdrawn may be associated with profound hypoxemia and hypercapnia, with potentially serious risk for the patients.

6. Theophylline: Berry et al demonstrated improvement in overnight oxygen saturation and transcutaneous CO$_2$ after oral ingestion of theophylline during non-REM sleep in non-hypercapnic patients with COPD$^{76}$. The effects were not carried on during REM sleep. Mulloy & McNicholas described similar findings regarding nocturnal oxygenation$^{77}$. However, significant impairment in sleep quality has been described after oral ingestion of theophylline$^{77,78}$. Ebden & Vathenen studied patients with COPD on 3 consecutive nights with intravenous theophylline infusion, and was not able to demonstrate any significant improvement in their overnight oxygenation$^{78}$. Based on the current data, its use to improve nocturnal oxygenation in COPD patients remains uncertain.

The use of other medications, such as hypnotic and sedative agents in patients with COPD must be very cautious, as benzodiazepinic agents may cause worsening of ventilatory responses during sleep, precipitating nocturnal hypoxemia and possibly, acute respiratory failure. Newer hypnotic agents like zolpidem did not demonstrate deleterious effects in nocturnal oxygenation or early morning arterial blood gases when taken for 7 consecutive nights by a series of stable hypercapnic COPD patients$^{79}$.

c. Inspiratory Muscle training: May be helpful in improving ventilatory reserve during sleep. More data is needed before further recommendation.

d. Negative pressure ventilation: Despite positive effects on arterial gases in patients with COPD$^{80,81}$, Levy et al has demonstrated deleterious effects on the upper airway during sleep, causing collapse and airway obstruction with sleep impairments$^{82}$. Its routine use has been discouraged.

e. Continuous Positive Airway Pressure (CPAP): Mezzanotte et al found improved inspiratory muscle strength and endurance and better functional ability in COPD patients treated with nocturnal CPAP$^{83}$. Mansfield & Naughton also demonstrated that CPAP was very effective in treating patients with combined COPD and OSA, with improvements in arterial blood gases and reduced hospitalization rates if adequate levels of CPAP was delivered and tolerated$^{84}$. Lately, we have found that the use of non-invasive positive pressure ventilation (NPPV) may be more beneficial to this population, at least for short term usage (unpublished data). Nevertheless, the use of CPAP may be a good option for patients with COPD presenting with obstructive sleep apnea. In such cases, oxygen should be added as needed when titrating CPAP in order to maintain adequate levels of saturation.

f. Non-invasive Positive Pressure Ventilation (NPPV): NPPV can be offered to COPD patients when the optimization of their disease and the adjunctive use of oxygen are not providing adequate resolution of the nocturnal desaturation. Studies have demonstrated an increase in total sleep time without significant changes in percentage of REM and non-REM sleep in COPD patients treated with NPPV$^{85,86}$. There did not seem to be a marked improvement in daytime respiratory function in those patients, but the number of hospitalizations during their first year on NPPV was significantly lower$^{87}$. Meecham Jones et al were able to demonstrate improved daytime PaCO$_2$ and PaO$_2$ after a 3-month period of NPPV with additional nocturnal oxygen, when compared to oxygen therapy alone in patients with daytime hypercapnia. There was no difference between treatment arms in regards to nocturnal oxygen saturation. There were however clear indicators of improved sleep efficiency and quality of life associated with the combined treatment$^{88}$. Although
there are some controversies regarding the optimal device for patients with COPD, a few studies found no major differences in the correction of hypoventilation when using a pressure- or volume-preset devices \(^{(89,90)}\). In clinical practice, pressure devices are often favored in COPD patients. Some of the reasons relate to improved comfort and leak compensation by increases in flow. The disadvantages are mostly secondary to variability in tidal volume and FIO\(_2\) delivered. In most patients, inspiratory pressures lower than 20 cm H\(_2\)O are sufficient to improve tidal volume and deliver effective ventilatory assistance. Pressures above those limits are rarely needed and anyway poorly tolerated. A back-up preset respiratory rate may be needed in some cases to assure a minimum ventilation. This can be done by using the assist (pressure or flow triggered) or control mode. If patients are unable to trigger the ventilator a back up rate similar to their respiratory rates during sleep should be preset on the device. Lower respiratory rates are also well tolerated and carry a lower risk of hyperinflation.

To help synchronization between patient and ventilator, there is an option to discontinue the inspiration when airflow approximates zero. The availability of PEEP is also convenient to patients with COPD, because they frequently have intrinsic PEEP with consequent higher effort requirement for triggering the ventilator. PEEP is also important in such devices because there is no separate expiratory port and, maintaining PEEP will reduce or avoid CO\(_2\) rebreathing. It will also maintain airway patency during sleep, an important consideration in patients with obstructive sleep apnea. On the other side, increases in PEEP may cause increased mask leak.

Every time a ventilation device is used, it is important to assess patient comfort. Daytime sessions using the device for adaptation prior to the sleep study is recommended. NIPPV can worsen hyperinflation and subjective patient evaluation during those sessions is important. It will also improve patient’s compliance. After proper adjustment of the equipment, a full nocturnal polysomnography is indicated\(^{(56,57)}\). When not available, nocturnal oximetry with daytime arterial blood gas sampling while breathing spontaneously may help assessing the efficacy of nocturnal ventilation. A reduction in previously elevated PCO\(_2\) levels should be expected after the initial nights on the device. Close follow-up by the specialist is recommended when treating such patients.

Issues regarding indication of this treatment technique because of reimbursement concerns, was recently addressed by a consensus conference report\(^{(91)}\). It was found that there is enough data demonstrating favorable effects of NPPV in COPD, determined by either arterial blood gas analysis or sleep quality data. Although significant long-term data with survival advantage when compared to long-term oxygen therapy is still lacking, the use of NPPV in hypercapnic COPD patients was considered likely beneficial.

**FINAL REMARKS**

It is probably established that the severity of nocturnal oxygen desaturation does not correlate with excess mortality in patients with COPD, and other factors associated with hypoxemia in COPD patients should be considered during their evaluation and management. Cardiovascular issues should be addressed, as there is increased number of ectopic beats during sleep in these patients despite no current evidence of clinical relevance\(^{(92)}\). We have for instance shown in a very limited subset of patients that REM-related desaturations have an impact on left ventricular ejection fraction that is comparable to maximal exercise\(^{(93)}\). Actually, very little tissular impacts of nocturnal hypoxemia have been established in patients with COPD. It has been demonstrated increased levels of erythropoietin in the morning in patients with COPD\(^{(94,95)}\). Nocturnal levels of erythropoietin may also rise in this patient population when nocturnal oxygen saturation falls below 60%\(^{(96)}\). In another study red cell mass increased in patients with nocturnal oxygen desaturation\(^{(97)}\). Those patients also had lower daytime oxygen saturation, which may have accounted for the difference. Fitzpatrick \textit{et al} reported rises in nocturnal erythropoietin only in patients which daytime PaO\(_2\) was lower than 45 mmHg\(^{(96)}\).

**CONCLUSIONS**

Chronic obstructive pulmonary disease is a very prevalent disease associated with several sleep-related abnormalities in gas exchange and respiratory physiology. The long-term survival for these patients is poor, as they progress to respiratory failure. Treating oxygen desaturation is an accepted and important part
of the acute care of COPD. Long term chronic oxygen clearly benefits the patients with the most severe airway obstruction and daytime hypoxemia, but the relevance of nocturnal hypoxemia is less well proven. Nocturnal polysomnography should be considered in these patients when obstructive sleep apnea is suspected or when assisted ventilation is being considered. Long-term domiciliary use of oxygen is the treatment of choice for nocturnal hypoxemia in COPD patients and it has been associated with an improved survival. However, the exact contribution of nocturnal desaturation is still largely unknown. For patients with associated obstructive sleep apnea, other treatment alternatives as the combined use of CPAP with supplemental oxygen should be considered. Non-invasive positive pressure seems to be a better alternative for patients with nocturnal desaturations despite long-term oxygen treatment that present with daytime hypocapnia. No single medication has been indicated to treat these specific cases, but adequate treatment of the underlying pulmonary disease is mandatory and associated with improvement in sleep quality. The importance of adequate treatment for nocturnal desaturation is under current investigation and further outcome studies are necessary to establish the best treatment strategy.

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