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Chapter 6

COPD and Sleep Apnea Syndrome – Impact and Interaction of Coexisting Disease

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1. Introduction

Chronic obstructive pulmonary disease (COPD), a common preventable and treatable disease, is characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases (Global Strategy for the Diagnosis, 2013).

The chronic airflow limitation characteristic of COPD is caused by a mixture of small-airway disease (obstructive bronchiolitis) and parenchymal destruction (emphysema). The relative contributions of each vary from person to person. Chronic inflammation causes structural changes and narrowing of the small airways.

Symptoms of COPD include sputum production, cough and dyspnea. These respiratory symptoms are chronic and progressive over time. As a result, subjects increasingly experience deterioration in their health-related quality of life, in their capacity to work and reduced participation in social and physical activities (Rabe et al., 2007).

COPD includes heterogeneous lesions that variably affect the airways, lung parenchyma and systemic structures. COPD is caused by various pathogenic mechanisms and does not present a uniform histological substrate. Patients with this disease present with different clinical features: non-exacerbator with emphysema or chronic bronchitis; mixed COPD-asthma; exacerbator with emphysema and exacerbator with chronic bronchitis (Miravitlles et al., 2013). In addition to affecting the lungs, the disease presents significant systemic consequences including skeletal muscle dysfunction, nutritional disorders and weight loss (Andreassen &
Vestbo, 2003; Agusti, 2005). As a result COPD causes a progressive decrease in the ability to perform the essential activities of daily living.

COPD is a leading cause of morbidity and mortality worldwide and results in an economic and social burden that is both considerable and increasing. According to some studies, the prevalence of COPD in Spain is 10.6% (Sobradillo et al., 1999), and the mortality rate in 2011 was 51.2 deaths per 100,000 males and 14.6 deaths per 100,000 females (Instituto Nacional de Estadística, 2011).

Due to its high prevalence, morbidity and mortality, COPD generates significant economic costs to the health system and is considered a significant health problem.

Obstructive sleep apnea syndrome (OSAS) is a disorder characterized by recurrent upper airway collapse during sleep (Young et al., 1993). This results in a reduction or complete cessation of airflow despite ongoing inspiratory efforts and leads to arousals, sleep fragmentation, and oxyhemoglobin desaturation (Remmers et al., 1978).

OSAS is a common disease, affecting 3.4% in men and 3% in women of the adult population and appears to be associated with a number of forms of morbidity (Duran et al., 2001). At least 6.8% of subjects 50-70 years of age are affected (Zamarron et al., 1999).

The most common symptoms of OSAS patients include chronic loud snoring, excessive daytime sleepiness, personality changes and deterioration of quality of life. Though clinically recognized for more than three decades (Gastaut et al., 1965; Lugaresi et al., 1972; Guilleminault, 1985), general awareness of OSAS has been slow to develop.

Treatment with continuous positive airway pressure (CPAP) has been shown to decrease the frequency and severity of sleep disturbances and associated symptoms (Kiely et al., 1999). Other treatments include mandibular advancement prosthesis (Doff et al., 2013) or surgery (Tuncel et al., 2012).

OSAS may coexist with COPD and this combination has been the focus of extensive study. Fenley referred to it as “overlap syndrome” (Flenley, 1985). Recently, to encourage further research in this area, another terminology has been proposed to integrate OSAS in the setting of obstructive lung disease, which is called OLDOSA (obstructive lung disease and obstructive sleep apnea) (Ioachimescu & Teodorescu, 2013).

The aim of the present review is to analyse the association and interaction of obstructive sleep apnea syndrome and chronic obstructive lung disease.

2. Epidemiology

There have been a number of studies evaluating the presence of OSAS among COPD patients. Chaouat et al. found a 14% prevalence of OSAS among patients with mild COPD (Chaouat et al., 1995), and O’Brien found overlap syndrome in 11.9% of COPD patients (O’Brien & Whitman, 2005).
On the other hand, there have also been studies evaluating the presence of COPD among patients with OSAS. In a group of 265 OSAS patients, Chaouat found that 11% also had COPD (Chaouat et al., 1995). Sanders et al. found 11% of overlap syndrome among patients with OSAS (Sanders et al., 2003). Nevertheless, a very large study including 5,954 participants done in conjunction with the Sleep Heart Health Study found no significant difference in the prevalence of OSAS, defined as apnea hypopnea index greater than 10, among COPD subjects (14.0%) and those without COPD (18.6%) (Sanders et al., 2003). A study involving 356 males and 320 females with OSAS found a lower prevalence of overlap syndrome (9.2%) (Bednarek et al., 2005). Recently, in 524 male subjects with OSAS diagnosed by the prevalence rate of COPD was 12% (Shiina et al., 2012).

All of this suggests that the coexistence of COPD and OSAS is due more to chance than a pathophysiologic link between the two conditions.

Among the different phenotypes that constitute COPD, OSAS is preferably associated to chronic bronchitis. Study results COPDGene showed that patients with chronic bronchitis phenotype showed prevalence of OSAS 22.4% versus 14.4% in those who did not meet this criterion (Kim et al., 2011). These findings are consistent with the idea that the chronic bronchitis patient may present episodic nocturnal desaturations during REM sleep. Izquierdo et al. also found that the prevalence of OSAS is more prevalent in the phenotype chronic bronchitis and emphysema, compared to COPD and asthma (23.6, 4.9% and 12.5%, respectively (Izquierdo-Alonso et al., 2013).

3. Physiopathological consequences

Sleep has profound effects on ventilation (Douglas et al., 1982), partly because it is accompanied by a fall in metabolic rate (White et al., 1985). Sleep represents a challenge to the respiratory system, especially in patients debilitated by respiratory disease. As occurs in some respiratory diseases, patients affected by respiratory failure while awake, are even more seriously affected during sleep.

In overlap syndrome, ventilatory response may be disturbed by lung mechanics and gas exchange. Radwan et al. studied breathing pattern and CO$_2$ response in obese patients with overlap syndrome and obese patients with OSAS only. The OSAS group presented similar values to non-obese controls in ventilatory response to CO$_2$ and occlusion pressure responses. The overlap group had a higher breathing frequency and lower tidal volume than the OSAS-only group. This author concluded that overlap patients with hypercapnia had both blunted ventilatory and mouth occlusion pressure responses during CO$_2$. In patients with chronic hypercapnia, there is an increased blood bicarbonate concentration, which may inhibit CO$_2$ sensitivity and decreases mouth occlusion pressure response (Radwan et al., 1995).

In patients with overlap syndrome, sleep-related hypoventilation is associated to a reduction in respiratory drive, loss of accessory muscle activity and ventilation perfusion mismatch. Hypoventilation in such patients is due to an increased breathing effort, related to upper and
lower airway obstruction. Respiratory muscles may also fatigue which is related to the mechanical disadvantage of chest wall hyperinflation. Moreover, there is also a reduction in functional residual capacity which is related to supine posture and sleep state (McNicholas, 1997). Kwon et al. suggest that increased severity of hyperinflation is associated with worse sleep efficiency, independent of apnea and nocturnal hypoxemia. The mechanisms underlying this observation are uncertain. These authors speculate that therapies aimed at reducing lung hyperinflation may improve sleep quality in patients with overlap syndrome (Kwon et al., 2009).

Overlap patients present more nocturnal desaturation than patients with either OSAS or COPD alone (Chaouat et al., 1995; Sanders et al., 2003). Sanders examined the degree to which COPD and OSAS independently and jointly contribute to desaturation during sleep. After adjusting for age, sex, height, weight, race, smoking status, and awake oxygen saturation, the OR for nocturnal oxyhemoglobin desaturation was found to be considerably increased in OSAS patients (Sanders et al., 2003). Furthermore, Lacedonia suggest that day-time hypoxemia in overlap patients is largely determined by the increase of body weight and severity of nocturnal hypoxia (Lacedonia et al., 2013).

4. Pulmonary hypertension

Patients with overlap syndrome are more likely to develop daytime pulmonary hypertension (Weitzenblum et al., 1988) and right heart failure (Bradley & Phillipson, 1985) than patients with either condition alone. COPD patients are affected by pulmonary hypertension secondary to alveolar hypoxia (Bonsignore et al., 1994), which is associated to increased morbidity and mortality (Chaouat et al., 2005). In these patients, pulmonary hypertension is primarily observed in those with severe disease, when the FEV₁ is lower than 50% predicted and diurnal PaO₂ is less than 60 mm Hg (Ashutosh et al., 1983).

OSAS patients may also be affected by pulmonary hypertension (Bady et al., 2000). However, this impact is higher when associated with COPD. In fact, Hawrylkiewicz et al. found a prevalence of pulmonary hypertension among overlap patients of 80% compared to 16% among individuals with OSAS alone (Hawrylkiewicz et al., 2004).

Patients with simultaneous COPD and OSAS have a more serious sleep related oxygen desaturacian than patients with COPD alone and the same degree of bronchial obstruction. Chaouat et al. reported a PaO2 ≤ 65 mm Hg in 54 (23%) out of 235 non-OSAS COPD patients and compared to 17 (57%) out of 30 patients with overlap syndrome (Chaouat et al., 1995). In the same report, right-heart catheterization identified pulmonary hypertension in 7% of patients with COPD and 36% of those with overlap syndrome. In fact, hypoxemia, hypercapnia, and pulmonary hypertension were observed in the presence of even mild to moderate bronchial obstruction in overlap patients (Fletcher et al., 1987). When COPD reaches an advanced-stage, concomitant OSAS is likely to cause significant adverse clinical consequences (Hiestand & Phillips, 2008).
5. Sleep apnea syndrome and COPD association and vascular disease

COPD is a systemic disease with multiple effects on target-organs including cardiovascular system. Until recently, exacerbations of disease and progression of respiratory insufficiency have been the focus of mortality studies in COPD, however, a number of epidemiologic reports have shown that significant morbidity and mortality in COPD involves cardiovascular diseases.

In France, Fuhrman et al found that cardiovascular disease accounted for 32% of deaths in COPD patients (Fuhrman et al., 2006). Similar results were obtained in previous retrospective studies conducted in Canada (Huiart et al., 2005; Curkendall et al., 2006). In these reports, cardiovascular morbidity and mortality were higher in the COPD group than in the general population.

Moreover, some prospective reports have shown that FEV\textsubscript{1} is a factor that predicts mortality risk from all causes and specifically mortality from ischemic heart disease in both genders independently of the smoking habit (Schunemann et al., 2000). In Spain, De Lucas-Ramos et al. in a cross sectional multicentre study of 572 COPD patients found a prevalence of 16.4% of ischemic heart disease (De Lucas-Ramos et al., 2008). In a subsequent paper of 1200 COPD patients and 300 control subjects, these authors found that COPD was an independent risk factor for cardiovascular disease with an odds ratio of 2.23 (1.18 to 4.24) (De Lucas-Ramos et al., 2012). However, Izquierdo et al, in another case-control study found no association between ischemic heart disease and COPD and concluded that the higher prevalence of traditional cardiovascular risk factors in patients with COPD may explain the higher incidence of ischemic heart disease in these patients (Izquierdo et al., 2010).

A close relationship exists between COPD, systemic inflammation and cardiovascular disease, but the mechanisms by which COPD patients develop systemic inflammation remain unclear. Although the main abnormality favouring vascular disease associated with COPD is systemic inflammation, other factors include the activation of platelets related to hypoxia and oxidative stress (Takabatake et al., 2000; Mills et al., 2008). In COPD there is a systemic inflammatory component which manifests itself in the presence of several inflammatory mediators in peripheral blood (Gan et al., 2004).

An extensively-studied inflammatory mediator is C-reactive protein. Studies have shown that patients with COPD have higher values of C-reactive protein and that these are independent of smoking (Pinto-Plata et al., 2006; Karadag et al., 2008). C-reactive protein exerts diverse effects on endothelial biology by promoting proinflammatory and proatherogenic phenotype, currently considered to be a systemic marker of the inflammatory process associated with cardiovascular disease.

It has also been found that homocysteine in blood, another marker for cardiovascular disease, was elevated in severe stable COPD patients (Seemungal et al., 2007). In a three-year follow-up study of a cohort of 3247 subjects, Nunomiya et al. found that levels of homocysteine in blood were predictive of FEV\textsubscript{1} reduction (Nunomiya et al., 2013). In addition, elevated levels
of inflammatory markers such as TNF-alpha, IL-6, IL-8 have also been reported in patients with COPD (Pinto-Plata et al., 2012).

We should also point out that several studies have found a relation between endothelial dysfunction and COPD (Cella et al., 2001; Moro et al., 2008; Nakanishi et al., 2011; Minet et al., 2012).

The relation between OSAS and cardiovascular disease involves a number of mechanisms such as the followings.

OSAS-associated disturbances, especially chronic intermittent hypoxia and enhanced sympathetic activity, lead to up-regulation of the renin-angiotensin system and down-regulation of nitric oxide synthases (Fletcher et al., 1999; Prabhakar et al., 2001). When an obstructive apnea occurs, it is terminated by a sudden arousal, that is, lightening of sleep or awakening from sleep (Somers et al., 1995).

Furthermore, increased oxidative stress has been associated with development of cardiovascular diseases and can be promoted by the chronic intermittent hypoxia characteristic of OSAS (Park et al., 2007). In fact, a variety of studies suggest that oxidative stress is present in OSAS at levels relevant to tissues such as the arterial wall (Barcelo et al., 2006; Grebe et al., 2006). This process enhances lipid uptake into human macrophages and may contribute to atherosclerosis in OSAS patients (Lattimore et al., 2005).

Furthermore, OSAS decreases blood antioxidant status in high-BMI subjects and may change the relationship between oxidative stress markers (Wysocka et al., 2008).

Systemic inflammation is increasingly being recognized as a risk factor for a number of complications including atherosclerosis (Ross, 1999) and is a well-established factor in the pathogenesis of cardiovascular disease (Hansson, 2005). C-reactive protein is an important serum marker of inflammation with major implications for cardiovascular morbidity and atherogenesis (Rutter et al., 2004). C-reactive protein levels are increased in OSAS in accordance with disease severity (Shamsuzzaman et al., 2002; Kokturk et al., 2005; Punjabi & Beamer, 2007; Taheri et al., 2007).

A variety of findings support the existence of a relation between hypercoagulability, OSAS and cardiovascular disease. Patients with OSAS present higher plasma levels of several procoagulant factors such as fibrinogen (Reinhart et al., 2002; Tkacova et al., 2008), platelet activity (Akinnusi et al., 2009) and the fibrinolysis-inhibiting enzyme plasminogen activator inhibitor (PAI-1) (Von et al., 2006; Zamarron et al., 2008b).

Finally, a number of studies involving OSAS patients indicate an associated endothelial dysfunction (Niets et al., 2004; Kohler et al., 2008; De la Peña et al., 2008). Endothelial dysfunction is frequently present in OSAS (Kheirandish-Gozal et al., 2010) and may have a potential role in the pathogenesis of vascular diseases that is pertinent to OSAS (Berger & Lavie, 2011). Several studies have reported higher endothelin-1 levels in OSAS patients (Phillips et al., 1999; Saarelainen & Hasan, 2000)
As inflammatory diseases, both OSAS and COPD are associated to higher cardiovascular risk. The mechanisms that may be involved different factors and include vascular inflammation, endothelial dysfunction, and tonic elevation of sympathetic neural activity (Figure 1).

Evidence of systemic inflammation and oxidative stress in COPD and sleep apnea provides insight into potential interactions between both disorders that may predispose to cardiovascular disease (Lee & McNicholas, 2011). In sum, OSAS is one of the most frequent comorbidities and/or associations of COPD, and may bring on increased inflammation (Carratu & Resta, 2008; Macnee et al., 2008; Gilmartin et al., 2008; Shiina et al., 2012).

6. Clinical characteristics

The most common symptoms of OSAS patients include chronic loud snoring, excessive daytime sleepiness, personality changes, depression, impairment of thinking and deterioration of quality of life (Zamarron et al., 1998; Pichel et al., 2004). COPD patients, on the other hand, may present cough; sputum production; or dyspnea (Miravitlles et al., 2013).
Nevertheless, overlap patients present unique characteristics, which set them apart from either COPD-only or OSAS-only patients (Zamarron et al., 2008). After comparing overlap patients with OSAS-only patients, Radwan et al. found no significant differences in OSAS severity, mean arterial oxygen saturation during sleep, and BMI (Radwan et al., 1995). Chaouat et al. found that, compared to the OSAS-only group, the overlap population tended to be older, but similar BMI (Chaouat et al., 1995). O’Brien and Whitman found that overlap patients were older, and less obese than the OSAS-only group (O’Brien & Whitman, 2005). Resta et al. showed that overlap patients had higher PaCO$_2$ than OSAS-only group, but similar apnea hypopnea index. This author developed a model for predicting PaCO$_2$ in overlap patients based on PaO$_2$, FEV$_1$, and weight (Resta et al., 2002).

Cardiac arrhythmias and sudden death are common and important causes of mortality in patients with COPD (Yildiz et al. 2002). Several factors such as hypoxemia, hypercapnia, acid-base disturbances, autonomic dysfunction, and medication may contribute to the development of arrhythmias in these patients (Sarubbi et al., 1997; Yildiz et al., 2002). Patients with OSAS have a higher frequency of cardiac rhythm disturbances and ST-segment depression episodes than snoring and control subjects. Moreover, ST-segment changes are related to sympathetic tone and sleep fragmentation, whereas most of the rhythm disturbances in OSAS patients are associated to sleep fragmentation, nocturnal hypoxemia, and sympathetic tone (Alonso-Fernandez et al., 2005).

Sleep disturbance in patients with COPD is usually related to nocturnal cough, wheezing, and shortness of breath (Weitzenblum & Chaouat, 2004). It is common for moderate to severe COPD patients to complain about poor-quality sleep, particularly elderly patients in the form of morning tiredness and early awakenings (Bellia et al., 2003). Sleep studies in COPD have shown frequent arousals and awakening, and decreased total sleep time with increased number of arousals (Fleetham et al., 1982). Furthermore, Sandek made reference to the fact that reduced average nocturnal oxygenation is associated with increased superficial sleep (Sandek et al., 1999).

In contrast, Sanders et al. observed that COPD patients without OSAS had minimally perturbed sleep. Thus, it appears that COPD per se does not affect or only slightly affects the quality of sleep. Instead, it may be that hypoxemia is a determinant of poor-quality sleep in patients with advanced COPD. In these patients, oxygen therapy has been shown to improve the quality of sleep, daytime hypoxemia and severe sleep-related oxygen desaturation (Sanders et al., 2003).

Colt indicates that in OSAS patients, one of the most incapacitating symptoms is excessive daytime somnolence, which results from disrupted sleep or nighttime oxygen desaturation (Colt et al., 1991). In overlap patients, Sanders et al. observed that, compared to COPD-only subjects, they had higher Epworth sleepiness scores, lower total sleep time, lower sleep efficiency, and higher arousal index. Indeed, the quality of sleep in COPD seems to be influenced by the presence of OSAS but not by the severity of airway obstruction (Sanders et al., 2003).

Regarding hypercapnia, although overlap patients were expected to be at greater risk, Weitzenblum et al. found that diurnal pCO$_2$ levels were similar for COPD and overlap patients.
In fact, significant differences were only found with respect to healthy subjects (Weitzenblum et al., 2008).

In addition, some studies have shown that overlap syndrome has a major impact on quality of life. Mermigkis studied 30 subjects with overlap syndrome and 15 control subjects. Quality of life was determined by St George’s Respiratory Questionnaire. The control group included subjects with COPD and no evidence of OSAS by polysomnography. All subjects were habitual snorers with normal Epworth Sleepiness Scale scores. Significant differences were found in total score and in each of the three questionnaire components suggesting worse quality of life in overlap patients. It is fair to say that OSAS has a major impact on quality of life in patients with overlap syndrome and can exist in COPD patients with habitual snoring even in the absence of daytime sleepiness (Mermigkis et al., 2007).

7. Diagnostic procedures

The diagnosis of OSAS should be based on clinical findings and confirmed by polysomnography which has traditionally been regarded as the gold standard for diagnosis (Kushida et al., 2005). However, alternatives that are less expensive and time-consuming are increasingly becoming popular (Flemons et al., 2003).

Subjects with COPD normally have well-preserved sleep architecture; hence, when faced with sleep complaints, the possible existence of associated sleep disorders should be considered and polysomnography applied for further characterization. Not all COPD patients necessarily need to be tested for OSAS. Nocturnal polysomnographic monitoring in COPD is usually performed when OSAS is suspected (Table 1). Only COPD subjects who have the typical risk factors for OSAS, such as obesity, chronic snoring, enlarged neck, daytime sleepiness, and hypertension, should be considered for further testing (Marrone et al., 2006; Lopez-Acevedo et al., 2009). Other indications include the presence of nocturnal hypoxaemia complications that are not explained by awake arterial oxygen levels, pulmonary hypertension, or cor pulmonale out of proportion to the severity of pulmonary function derangement in COPD patients whose daytime PaO₂ is 60–65 mmHg (Douglas & Flenley, 1990).

Clinical suspicion of OSAS:

| Headache upon awakening, |
| Excessive daytime sleepiness. |
| Snoring and breathing pauses |
| Obesity |

Normal daytime blood oxygen with

| Cor pulmonale |
| Polycythemia and normal daytime oxygen. |

Table 1. Indications for nocturnal polysomnography in COPD
8. Treatment

Conventional oxygen therapy is prescribed to stable COPD patients who exhibit marked and persistent hypoxemia. This therapy is sufficient to correct even severe nocturnal desaturation and has favourable effects on the observed hypoxemia-related peaks in pulmonary hypertension (Boysen et al., 1979). Furthermore, some authors report that oxygen therapy improves the quality of sleep by shortening latency to sleep, increasing REM sleep as well as stages III and IV, and by decreasing number of arousals (Calverley et al., 1982).

All patients with OSAS should be counselled about the potential benefits of therapy and the risks of going without treatment as well as the value of avoiding factors that increase the severity of upper-airway obstruction, such as sleep deprivation; the use of alcohol, sedatives, and hypnotic agents; and excessive weight (Haynes, 2005). CPAP therapy is a well-established, widely used treatment (Giles et al., 2006), but, it is not suitable for all patients.

The coexistence of OSAS and COPD defines a high-risk group of patients because their awake and sleep related hypoxemia and hypoxemic cardiovascular consequences are more marked. Although the natural history of overlap syndrome is not well-known, a major aim of therapy should be to correct both upper airway obstructive episodes and sleep hypoxemia.

Treatment for overlap syndrome consists of CPAP or non-invasive positive pressure ventilation, with or without associated O₂, for correction of the upper airway obstructive episodes and hypoxemia during sleep (Pronzato, 2010; Nural et al., 2013).

Sampol studied a group of overlap patients over three consecutive nights. This study found that the application of CPAP corrected apneas and hypopneas, but not oxygen desaturation. With the addition of oxygen at a flow of 1.5 L.min⁻¹ at suboptimal CPAP levels, they observed an increase in apnea frequency, persistence of apneas at CPAP levels which eliminated them when no supplemental oxygen was administered, and longer duration of apneas and hypopneas. However, when the effective CPAP level was reached with supplemental oxygen, its efficacy in eliminating apneas and hypopneas was maintained and, furthermore, oxygen desaturation was corrected. The authors conclude that CPAP with supplemental oxygen constitutes a practical therapeutic alternative for hypoxic patients with overlap syndrome (Sampol et al., 1996).

De Miguel evaluated the effects of CPAP therapy on lung function in patients with overlap syndrome over two consecutive years. After six months of CPAP therapy, there were statistically significant increases in PaO₂, FEV₁, and FVC, accompanied by significant decreases in PaCO₂, serum bicarbonate levels, and alveolar-arterial oxygen difference. However, these patients also had significant weight loss during this time, which may explain the benefits observed. Also, the degree of obstruction, as reflected by the FEV₁/FVC ratio, did not change. Interestingly, there was no improvement from six to eighteen months, a period in which there were no changes in patient weight. Response of overlap syndrome patients to CPAP therapy was greater in the hypercapnic group, particularly in relation to improvement of arterial blood gases.¹³
Mansfield and Naughton studied fourteen patients, ten of whom were able to tolerate CPAP for at least three months. They found an improvement in gas exchange and FEV1 associated with a decrease in hospitalizations (Mansfield & Naughton, 1999). Similar results were reported by other studies (Peker et al., 1997; Marin et al., 2010).

CPAP treatment may have other potentially beneficial effects. Seeing as COPD is an inflammatory airways disorder and OSAS may act as an inflammatory stimulus, coexistent of both diseases in overlap may augment airway inflammation. Thus, the improvement in OSAS resulting from the application of CPAP may, in turn, lead to an improvement in the coexistent COPD. In some studies, the improvement in some markers of bronchial hyper responsiveness following the application of CPAP suggests the possibility that CPAP therapy may have a bronchodilator effect (Chan et al., 1988).

A decrease of serum C reactive protein in overlap patients following effective CPAP treatment shows that CPAP is an effective treatment method for systemic inflammation (Nural et al., 2013)

Nocturnal oxygen attenuates sleep desaturations among stable overlap patients and does not produce clinically significant increases in PaCO2. However, hypoxemia and hypercapnic may persist in the most severe overlap patients in spite of efficient application of nocturnal CPAP and oxygen therapy. For these patients, some authors recommend nocturnal treatment with positive pressure ventilators, and the monitoring of treatment effectiveness by sleep study (Marrone et al., 2006).

9. Prognosis

Regarding the complications that modify the natural history of COPD, it has previously been shown that, compared to COPD-only patients, overlap syndrome patients are at an increased risk for respiratory failure, pulmonary hypertension and cor pulmonale, independently of the degree of airway obstruction (Table 2).

<table>
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<th>Complication</th>
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<tr>
<td>Daytime pulmonary hypertension and right heart failure</td>
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<tr>
<td>High cardiovascular risk</td>
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<tr>
<td>Major impact on quality of life</td>
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<tr>
<td>Increased overall and cardiovascular mortality</td>
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<td>Higher medical utilization and cost</td>
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Table 2. Overlap syndrome: impact of coexisting disease

In order to evaluate the cost-effectiveness of early interventions and disease management programs, Shaya studied the economic impact of OSAS among Medicaid beneficiaries with COPD. The diagnosis of concomitant COPD was associated with substantially higher medical
utilization and cost than the diagnosis of either alone, and OSAS may add additional economic burden on beneficiaries who already have COPD or concomitant COPD (Shaya et al., 2009).

Machado carried out a prospective cohort study of 603 hypoxemic COPD patients receiving long-term oxygen therapy, 95 subjects were diagnosed with moderate-to-severe OSAS. After adjusting for several confounders, patients treated with CPAP had a significantly lower risk of death (Machado et al., 2009). This observational study indicated a positive effect of CPAP treatment on survival in moderate-to severe OSAS patients with hypoxemic COPD receiving long-term oxygen therapy. This study recommends an active search for OSAS in patients with hypoxemic COPD using a screening questionnaire and/or nocturnal oximetry.

Overlap syndrome exhibit both increased overall and cardiovascular mortality in patients with COPD. Marin et al. in a cohort of patients with SAS followed for nine years, patients with COPD and SAS had a relative risk of death of 1.79 (1.16 to 2.77), with cardiovascular and pulmonary causes the most common mortality even adjusted for the severity of COPD.

In conclusion, overlap syndrome constitutes a worsening of the complications inherent in either COPD or OSAS alone. Early identification and treatment of overlap syndrome is fundamental in order to avoid serious potential effects.

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