COPD NOCTURNAL DESATURATOR PATIENTS WITH OBESITY AND PULMONARY HYPERTENSION: CROSS-TALK BETWEEN ADIPOCYTE TISSUE SYSTEMIC HYPOXIA AND LUNG-TO-BLOOD TRANSLOCATION OF INFLAMMATORY MEDIATORS

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ABSTRACT

Chronic obstructive pulmonary disease (COPD) is often accompanied by other chronic diseases associated with systemic inflammation, such as chronic heart failure, diabetes, and atherosclerosis. Nocturnal oxygen desaturation waxing and waning plays a central role in conditions leading to systemic inflammation in COPD obese patients. Obesity and metabolic syndrome (MetS) represent two different metabolic abnormalities that may be linked by the presence of underlying systemic inflammation. Alveolar hypoxia and consequent hypoxaemia increase in prevalence as the severity of COPD also increases. Chronic hypoxaemia contributes to the development of adverse sequelae of COPD such as pulmonary hypertension (PH), secondary and systemic inflammation. The innovation of COPD phenotyping is defined as COPD desaturators. These sleep-related changes predispose to nocturnal cardiac dysrhythmias, PH and potentially nocturnal death, particularly during acute exacerbations. In patients with COPD, systemic inflammatory phenotype likely reflects pulmonary inflammation, which results from lung-to-plasma spillover of inflammatory mediators. However, obesity-related hypoxia evokes local inflammatory response within adipose tissue per se, and systemic hypoxaemia likely contributes to the presence of adipose tissue inflammation. The nocturnal hypoxic insult occurring during sleep-disordered breathing may also contribute to chronic vascular remodelling. Consequently, these mechanisms may result in endothelial dysfunction and vascular damage, leading to increased risk of PH in COPD. In patients with COPD and concurrent obesity, we have proposed that three factors can play a role in the systemic inflammatory syndrome: the severity of pulmonary impairment, the degree of obesity-related adipose tissue hypoxia, and the severity of systemic hypoxia due to reduced pulmonary function.

Keywords: Chronic obstructive pulmonary disease (COPD), metabolic syndrome (MetS), oxygen desaturation waxing and waning, pulmonary hypertension (PH).

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a complex, multi-factorial, heterogeneous disease, whose clinical and functional presentation greatly varies from patient to patient, despite similar degree of airflow limitation.[1,2] Comorbidities such as chronic heart failure, cardiovascular disease, depression, diabetes, muscle wasting, weight loss, lung cancer, and osteoporosis can frequently be found in patients with COPD and are considered to be part of the commonly prevalent non-pulmonary sequelae of the disease.[3,4] Sleep-disordered breathing and COPD are among the most common pulmonary diseases. The severity of COPD also influences the degree of oxygen desaturation. The lower the FEV1/FVC ratio (≤70%), the more likely that significant desaturation occurs during sleep.[5,6] Systemic inflammation is considered a hallmark of COPD and one of the key mechanisms that may be responsible for the increased rate of comorbidities, including cardiovascular complications, obstructive sleep apnoea syndrome (OSAS), muscle dysfunction, osteoporosis, clinical depression, and anxiety.[7,8] The metabolic syndrome (MetS) was assessed according to International Diabetes Federation criteria (Table 1). Recently, the correlation between MetS and COPD has been confirmed, MetS being a risk factor for increased number of exacerbations in COPD patients due to the shared inflammatory cytokine burden.[9,10] A high prevalence (61%) of MetS was found in COPD patients participating in a respiratory study, while another study reported a lower prevalence (44%) in patients without COPD.[11,12]

This brief review focuses on COPD and nocturnal hypoxaemia with obesity and MetS that can be the cause of systemic inflammation. In patients with COPD and concurrent obesity and MetS, we propose (Figure 1) that at least three factors play a role in the systemic inflammatory syndrome: the severity of pulmonary impairment, the degree of obesity-related adipose tissue hypoxia, and the severity of systemic hypoxia due to reduced pulmonary functions.

Table 1. Different inflammatory mechanisms involved in COPD/disease process/obesity and comorbidities.

1	Epidemiological data suggest that nocturnal symptoms and nocturnal oxygen desaturation with symptomatic sleep disturbance is common, and may exceed 43% among patients with chronic obstructive pulmonary disease (COPD).
2	COPD patients with a T_{90} ≥30% with mean nocturnal SaO_2 ≤90% and a Nadir $SatO_2$ ≤85% are defined as desaturators (D); all others are defined as non-desaturators (ND).
3	Nocturnal oxygen desaturation waxing and waning in COPD patients is a major inflammatory stimulus: the desaturation–reoxygenation sequence is a typical pattern coupled with the majority of nocturnal respiratory events.
4	It has been shown that 50% of COPD patients have one or more MetS defining criteria.
5	Obesity is diagnosed when body mass index is ≥30 kg/M^2.
6	Metabolic syndrome (MetS) defining criteria are: central obesity (waist circumference: men ≥94 cm; women ≥80 cm); plus any two of the following four factors: triglyceride levels ≥150 mg/dL; high-density lipoprotein cholesterol levels of ≤40 mg/dL in men and ≤50 mg/dL in women; systolic BP ≥130 mm Hg or diastolic BP ≥85 mm Hg; fasting plasma glucose levels of ≥100 mg/dl or previously diagnosed type 2 diabetes.
7	The principal contributor to hypoxaemia in COPD patients is ventilation/perfusion (V/Q) mismatch resulting from progressive airflow limitation and emphysematous destruction of the pulmonary capillary bed.

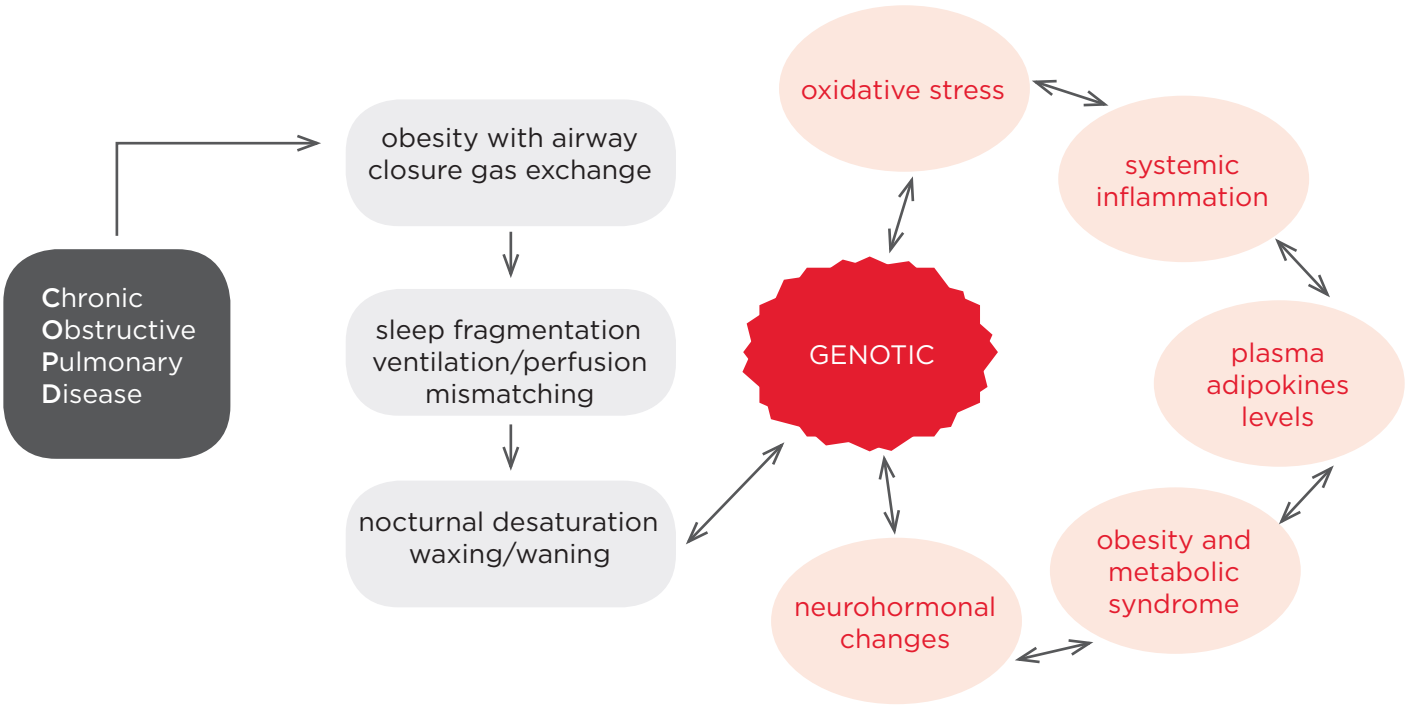

Figure. 1. Biological mechanisms for the development of various inflammatory processes in obese COPD patients with metabolic syndrome.
The diagram shows the pathophysiological effects of chronic nocturnal hypoxaemia and obesity in COPD patients.

SLEEP FREQUENTATION IN COPD

Nocturnal Oxygen Desaturation Waxing-Waning with Hypoxic Vascular Remodelling and Pulmonary Hypertension

Patients with COPD may experience changes in sleep and clinical symptoms. Evidence indicates that as many as 43% of patients with chronic bronchitis or emphysema have sleeping difficulties.[13] More than just the diagnosis of COPD, the presence of COPD symptoms, such as a cough or sputum production or wheezing, strongly correlated with difficulty in falling or staying asleep.[14] Other investigations have objectively confirmed poor sleep quality, with decreased total sleep-time and decreased sleep efficiency in patients with respiratory problems.[15,16]

Nocturnal oxygen desaturation in COPD is likely to be the consequence of the combined effects of physiological hypoventilation during sleep. However, there is evidence that some patients with awake arterial oxygen tension (PaO_2) levels in the mildly hypoxaemic range can also develop clinically significant nocturnal oxygen desaturation, which may predispose to pulmonary hypertension (PH).[17] Potential causative mechanisms for this reduction include respiratory muscle hypotonia, cephalic displacement of the diaphragm and a decrease in lung compliance.[18] Sleep-related hypoventilation has been demonstrated in COPD, particularly during rapid eye movement (REM), with associated oxygen desaturation.[19] There is a close relationship between the awake PaO_2 and nocturnal oxygen saturation ($SatO_2$) levels,[20] although hypercapnia is associated with a more pronounced nocturnal oxygen desaturation than normocapnia for any given level of waking $SatO_2$.[21]

Nocturnal hypoxaemia has been defined as a $SatO_2$ of ≤90% for at least 5 minutes with a Nadir $SatO_2$ of ≤85%. The percentage of total recording time (TRT) has been defined as the time spent in bed minus sleep latency plus intrasleep wakefulness. A TRT with a $SatO_2$ of ≤90% has been defined as T_{90}%. The minimal TRT required for a satisfactory analysis of nocturnal recordings was 2 hours. COPD patients with a T_{90} of ≥30% and a Nadir $SatO_2$ of 85% have been defined as desaturators (D) and all others as non-desaturators (ND).[22-24] In this study, as revealed by cluster analysis, authors

showed that clinical parameter predictors, when awake from nocturnal desaturation, were different. COPD D patients may be identified by a clinical pattern of variables such as T_{90}, mean pressure artery pulmonary and $PaCO_2$ values, rather than by T_{90} alone, with the latter two variables being predictors of nocturnal desaturation severity.

This study has revealed the complexity of the nocturnal desaturation. Alveolar hypoventilation probably accounts for most of the nocturnal oxygen desaturation and hypoxic vasoconstriction and vascular remodelling. Several authors[25,26] measured minute ventilation during wakefulness, non-REM sleep, and REM sleep in normal subjects and patients with COPD. The greater drop in minute ventilation in subjects with COPD may reflect increased dependence on accessory muscles that become hypotonic during sleep, particularly during REM sleep. An alternative explanation comes from the work by O'Donoghue and colleagues[27] who have found an even greater drop in minute ventilation during non-REM sleep in hypercapnic COPD patients.

The exact prevalence of PH in patients with COPD is unclear.[28] PH is a complication of advanced COPD observed in patients who show severe longstanding hypoxaemia. Even if PH is generally mild to moderate in most COPD patients, it may markedly worsen during acute exacerbations, sleep and exercise, and these acute increases in PH could facilitate the development of right heart failure. Diagnosis of PH in COPD patients is difficult: published studies differ not only in their definition but also for the conditions under which PH has been reported (rest, exercise, and exacerbation). According to the European Society of Cardiology and the European Respiratory Society,[29] PH has been defined as an increase in mean pulmonary arterial pressure (PAP) ≥25 mmHg at rest as assessed by right heart catheterisation (RHC). The definition of PH under exercise conditions as a PAP ≥30 mm Hg, assessed by RHC, is not supported by published data, and healthy individuals can reach much higher values.

The incidence of PH in COPD patients has been evaluated by Kessler and colleagues.[30] In this longitudinal study on 131 patients with COPD, serial RHCs were performed at baseline and at follow-up (mean follow-up was 6.8±2.9 years). All subjects had normal mean PAP at rest (≤20 mm Hg). They have been divided into two groups based on the presence or absence of elevated mean PAP under exercise (≥30 mm Hg). On follow-up, 25% of patients had mild PH according to haemodynamic criteria (mean PAP 26.8±6.6 mm Hg).

Nocturnal oxygen desaturation appears to contribute to the development of PH even in the absence of significant awake hypoxaemias.[31] REM-associated drops in $SatO_2$ are associated with increases in PAP during sleep that can be reversed by supplemental oxygen, although most COPD patients with sustained PH are also hypoxaemic during the daytime. Various arrhythmias are also reported during episodes of nocturnal desaturation.[32] These consequences might help explain why nocturnal oxygen desaturation is recognised as a marker of increased mortality, and why COPD patients are reported to die more frequently at night than expected.[33]

Tissue hypoxia is another mechanism that can contribute to systemic inflammation in COPD. It has previously been demonstrated that TNF-α and receptor levels have been shown to be significantly higher in patients with COPD, but significantly correlated with the severity of arterial hypoxaemia.[34] These results suggest that arterial hypoxaemia in COPD is associated with activation of the TNF-α system *in vivo*. The systemic effects of inflammation may significantly contribute not only to respiratory abnormalities, respiratory symptoms and functional impairment (e.g. exercise intolerance) associated with COPD, but also to its chronic marked changes of vasomotor and endothelial function as pulmonary vascular remodelling.[35]

The nocturnal desaturation–reoxygenation sequence, waxing and waning sequence, is a typical pattern coupled with the majority of respiratory events. This sequence (Figure 2) of waxing and waning desaturation, differently from nocturnal desaturation of OSAS, leads to oxidative stress and the production of reactive oxygen species.[36] Hypoxia-induced pulmonary vasoconstriction is a protective response to maintain an optimised ventilation-perfusion ratio by shunting blood away from the hypoxaemic areas. The traditional vascular hypoxic model of PH is based on the hypothesis that chronic hypoxia initiates vascular remodelling leading to permanent changes in pulmonary vasculature.

Barbera et al.,[37] evaluated COPD patients undergoing lung resection and demonstrated that vascular changes contribute to vascular remodelling and may have an effect on vascular dynamics leading to PH. Nocturnal hypoxia may induce endothelial cells to release proliferation-stimulating cytokines,

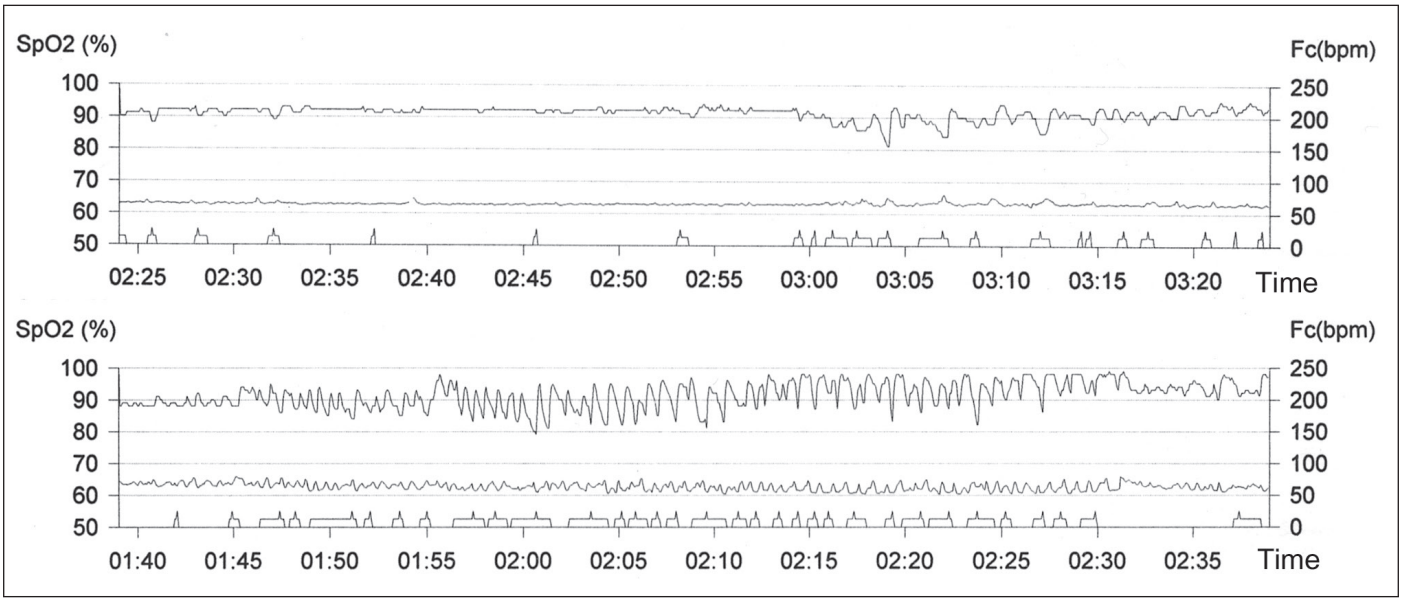

Figure 2. Simultaneous recording of nocturnal oximetry and heart rate in a patient with COPD desaturator (above) and in patient with OSAS (below).
Oxygen nocturnal desaturation with waxing/waning morphology in a COPD patient and the morphology of cyclical recurrence aspect with short, rapid intermittent nocturnal hypoxia in an OSAS patient, are shown.

leading to cellular hypertrophy in the vessel wall and an increase in extra-cellular matrix. Another intriguing possibility reported in that study is that nocturnal desaturation in COPD may contribute to an increased incidence of COPD exacerbations, which may accelerate lung-function decline and be associated with greater mortality.[38,39]

EXCESS BODY WEIGHT AND CHANGES IN METABOLISM

Obesity-Related Systemic Hypoxia

A potentially important source of inflammation in obese patients with COPD with nocturnal hypoxaemia is white adipose tissue. Obesity and MetS are increasingly prevalent in modern COPD, and may contribute to abnormalities in gas exchange. In patients with COPD, obesity is characterised by an absolute abundance of fat mass, similar to other diseases associated with excessive adiposity.[40] The prevalence of obesity is highest among patients with milder forms of the disease, and lowest in patients with the most severe lung function impairment.[41] It has been demonstrated that one or more components of MetS are present in almost 50% of COPD patients.[42] High adiposity and fat tissue accumulation impair pulmonary functions and exercise performance.[43]

The study by Trayhurn et al.[44] suggests that insulin resistance is aggravated by both high body mass index and increases in circulatory inflammatory mediators, such as IL-6, in this set of patients. Indeed, inflammatory mediators TNF-α, IL-6, and leptin were significantly higher while plasma adiponectin levels were reduced in overweight COPD patients. Chronic low-grade adipose tissue inflammation in obesity may represent a specific response to relative hypoxia of adiposities.[45]

Several factors may contribute to cell hypoxia within adipose tissue in association with high adiposity: (a) blood flow per unit of adipose tissue mass is reduced in obese humans resulting in decreased blood supply to the tissue; (b) large adipocytes are further from the vasculature than the normal diffusion distance for O_2. Adipocyte tissue hypoxia has detrimental effects on cell metabolism and function, as evidenced by *in vitro* studies and animal models. *In vitro* studies have shown that hypoxia results in enhanced TNF-α production, increased expression of PAI-1 and reduced adiponectin and peroxisome proliferators-activated receptor gamma, or PPARγ, expression.[46,47]

Even in the absence of COPD, obesity is associated with small airways dysfunction, decreased chest wall compliance, V/Q mismatch, and increased peripheral oxygen consumption, all potentially

leading to relative hypoxaemia. Risk of sleep-disordered breathing and consequent nocturnal hypoxaemia correlates with the degree of obesity[48] and, in extreme cases, morbid obesity can lead to profound alveolar hypoventilation with chronic hypercapnic respiratory failure. Dysregulated ventilatory control is another factor contributing to the occurrence and persistence of hypoxaemia in COPD patients.[49]

CONCLUSIONS

The hypoxic insult occurring during sleep-disordered breathing in COPD patients varies from one condition to another. However, there are cardiovascular and metabolic morbidities which are common among different conditions. Major differences are found in continuous hypoxia, suggesting specific pathways originating from the occurrence of oxidative stress and inflammatory cascade activation. In addition, the hypothesis that adipose tissue may contribute to the overall systemic inflammatory phenotype in patients with early stages of COPD and obesity or relative abundant fat mass is novel.[50] The potential links between night-time symptoms and long-term clinical outcomes will have to be explored in order to ensure that any interventions aimed at acutely improving night-time symptoms and/or sleep disturbance in COPD patients are also aimed at improving or stabilising the long-term health of COPD patients.

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