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Chronic Obstructive Pulmonary Disease (COPD) Nocturnal Desaturator patients associated with Obesity and Lung Microbiota Dynamics

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Abstract

COPD is often accompanied by other chronic diseases that are also associated with systemic inflammation, such as obesity, diabetes, and arteriosclerosis. Recent data indicate that nocturnal oxygen desaturation and coexisting metabolic syndrome are related to systemic inflammation in patients with COPD. Alveolar hypoxia and consequent hypoxemia increase in prevalence as COPD severity increases. Chronic hypoxemia contributes to the development of adverse sequelae of COPD, such as pulmonary hypertension, atherosclerosis, lung microbiome diversity and systemic inflammation. COPD is a heterogeneous disease with airway inflammation driven by bacterial infections, few studies to date they examined microbiology or infection. The introduction of culture-independent techniques for the microbiological analysis of respiratory samples confirmed that respiratory system hosts a large number of microorganisms, which include a wide range of bacteria. Regular exposure to tobacco smoke, lifestyle and food pattern can change the microbiome in healthy smokers and at-risk COPD patients, increasing the presence of a limited number of genres that reach a high relative abundance, a pattern, which can be considered as a dysbiosis. We assume that in patients with COPD and concurrent obesity and lung dysbiosis at least three factors play a role in the systemic inflammatory syndrome. Recent data showed that changes in the lung microbiome are associated with numerous exacerbations of COPD and are involved in mediating inflammatory responses of the host in some patients. Further research should elucidate the complex relationship between obstructive lung disease, obesity and lung microbiome diversity systemic inflammation accompanying these different conditions, and the causative role of systemic inflammation in obese COPD with nocturnal oxygen desaturation.

Keywords: COPD, BPCO, microbiome.

Introduction

Chronic obstructive pulmonary disease (COPD) is a disease associated with chronic inflammation of the airways and lung parenchyma. (Faner and Agustí 2017) Yet, COPD is a complex, multi-component, heterogeneous disease, whose clinical, functional presentation greatly varies from patient to patient despite similar degree of airflow limitation. (Faner and Agustí 2017; Burgel et al. 2017) The current classification of airways disorders is imprecise with an overlap of phenotypes (e.g. asthma, chronic bronchitis and emphysema), resulting in difficulties of differentiating the disorders from one another.

The prevalence, distribution and interrelationships of the main clinical and functional manifestations of the disease in a large, well-characterised and controlled population of patients are lacking. 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 part of the commonly prevalent non-pulmonary sequelae of the disease. (Barnes and

Celli 2009, 1165–85; Chatila et al. 2008, 549–55) Sleep-disordered breathing and COPD are among the most common pulmonary diseases. Nevertheless, the pathological mechanisms and clinical manifestations of COPD are not restricted only to pulmonary inflammation and airway remodelling. In contrast, over the last decade, the recognition of COPD as a systemic disease has developed. (Barnes and Celli 2009, 1165–85)

Low-grade systemic inflammation can be defined as a two- to fourfold elevation in circulating levels of proinflammatory and anti-inflammatory cytokines, naturally occurring cytokine antagonists, acute phase proteins, as well as minor increases in counts of neutrophil and natural killer cells. (Brüünsgaard and Pedersen 2003, 15–39) 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, cachexia and muscle dysfunction, osteoporosis, anaemia, clinical depression and anxiety in COPD (Sin and Man 2003, 1514–19)

The human microbiota consists of 10-100 billion symbiotic microbial cells hosted by each person, mainly bacteria in the lung; the human microbiome is made up of the genes that these cells host (Turnbaugh et al. 2007, 804–10). These cells are likely to influence genetic influences outcomes of pulmonary disease and microbiota composition through the modulation of the host's defense mechanisms.

There are few studies on genetic modifiers of exacerbation risk in COPD (Erb-Downward et al. 2011, e16384).

We assume that in patients with obese COPD and diabetes mellitus type II both genes and lifestyle are influenced. All this is known, but the genes in the human microbiome also may play an important 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. The gut bacteria synthesize vitamins and proteins and help degrade toxins. Many genes in the human microbiome produces hormones, neurotransmitters, cytokines and molecules of inflammation, which are released into the systemic circulation and affect health.

Recent evidence demonstrated that the microbiome might affect in the COPD patients including patients with obesity and diabetes type II (Eduard Monsó 2017, 251). Exposure to tobacco smoke modifies the lung microbiome in healthy smokers, first in the oropharynx, increasing the presence of a limited number of bacteria that reach a high concentration in the lower respiratory tract, a pattern that can be considered pathological as a dysbiosis pulmonary. In the COPD, the microbiome analyzes of the sputum samples have shown an important change in bacterial diversity, with a variation in a restricted flora with an over-representation of the Proteobacteria strand, which includes most of the bacteria considered to be pathogenic microorganisms, together with a decrease of the relative abundance of microorganisms' part of the phylum Firmicute-s. Severity of COPD also influences degree of oxygen desaturation and obesity and lifestyle. Several data suggest that the pulmonary microbiome plays a fundamental role during the exacerbations of COPD and its role in the aetiology of the disease remains poorly understood.

This brief review focuses on COPD and nocturnal hypoxaemia with obesity and lung microbiome and dysbiosis that can be the cause of systemic inflammation and vascular atherosclerosis.

Systemic and airway inflammation

Several studies have found markers of systemic inflammation, such as high-sensitivity C-reactive protein (hs-CRP), to be higher in blood of patients with COPD when compared with the blood values of subjects without COPD. (Pinto-Plata et al. 2006, 23–28; Leonardo M Fabbri and Rabe 2007, 797–99). A question arises whether systemic inflammation is the result of a local inflammation spill-over to the systemic compartments or a systemic component of COPD not necessarily related to the local inflammatory processes in the lung. (L M Fabbri et al. 2008, 204–12; Broekhuizen et al. 2006, 17–22)

As a point of interest, it should be noted that systemic inflammation has failed, so far, to show substantial correlations with airway obstruction, (de Torres et al. 2006, 902–7; Watz et al. 2009, 1039–46) whereas a connection has been reported between local inflammatory pro-

cesses and airway obstruction. (Peleman et al. 1999, 839–43; Turato et al. 2002, 105–10; Baraldo et al. 2004, 308–12) Markers of systemic inflammation have been shown to be elevated in blood of patients with COPD when compared with control subjects without COPD. COPD is often accompanied by other chronic diseases that are also associated with systemic inflammation, such as chronic heart failure, diabetes, and arteriosclerosis. (Roy et al. 2009, 41) Alternatively, increased levels of inflammatory mediators in the blood of COPD patients may stem from extra pulmonary cells (circulating leukocytes, endothelium or muscle cells). A particular problem in COPD patients with marked alveolar wall destruction is intermittent and continuous hypoxia. Significant inverse correlation between arterial oxygen tension (PaO_2) and circulating tumor necrosis factor alpha (TNF-a) and soluble tumor necrosis factor receptor (sTNF-R) levels in patients with COPD has been reported. (Takabatake et al. 2000, 1179–84) Similarly, a significant relationship between reduced oxygen delivery and TNF-levels in the peripheral circulation, highlighting the role of nocturnal hypoxia of the tissue was found (Yu et al. 1998, L818-26)

It has been suggested that systemic inflammation may explain part of the heterogeneity of COPD phenotypes, such as loss of lean body mass and the higher prevalence of co morbid disorders such as coronary heart disease (CHD), depression and hypertension. Finally, this study reinforces the view that systemic inflammation is an important phenotypic feature of COPD (Eagan et al. 2010, 540–48). Future prospective studies should investigate whether these markers will give important prognostic information in relation to disease progression and severity in COPD.

Sleep disturbance in COPD

COPD alone can cause subjective and objective changes during sleep. When patients with either chronic bronchitis or emphysema were surveyed across a broad range of symptoms, "sleep difficulties" were endorsed as occurring "almost always" or "always" in 43% of subjects (third most common, after dyspnoea and fatigue). (Kinsman et al. 1983, 755–61) More than just the diagnosis of COPD, the presence of COPD symptoms such as cough or sputum production or wheezing strongly correlated with difficulty in falling or staying asleep.(Klink, Dodge and Quan 1994, 151–54) Other investigations have objectively confirmed poor sleep quality, with decreased total sleep-time and decreased sleep efficiency. (Douglas et al. 1982, 840–44). A brief review of the normal changes in respiration that occur with sleep onset and the various sleep stages is useful to understand the changes occurring during sleep in patients with COPD. In healthy subjects, minute ventilation drops from wakefulness to non-rapid-eye-movement (non-REM) sleep, and drops further during REM sleep (about 15%,compared to the awake value) (Douglas et al. 1982, 286–89). Most of the drop in minute ventilation is due to a decrease in tidal volume not fully compensated by a concomitant increase in respiratory rate. There is a blunted ventilatory response to hypoxia and hypercapnia, again with the greatest changes during REM sleep. (Douglas et al. 1982, 758–62) Sleep-related hypoventilation has been demonstrated in COPD, particularly during REM sleep, with associated oxygen desaturation. (Hudgel et al. 1983, 669–77).

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 PaO_2 levels in the mildly hypoxaemic range can also develop clinically significant nocturnal oxygen desaturation, which may predispose to pulmonary hypertension. (Fletcher et al. 1987, 604–8)

Finally, possible mechanisms responsible for this reduction include respiratory muscle hypotonia, cephalic displacement of the diaphragm and a decrease in lung compliance. (Johnson and Remmers 1984, 1011–17).

Sleep-related breathing disturbances: nocturnal oxygen desaturation and alveolar hypoventilation.

Sleep-related hypoventilation has been demonstrated in COPD, particularly during REM, with associated oxygen desaturation (Hudgel et al. 1983, 669–77) There is a close relationship between the awake arterial oxygen tension PaO_2 and nocturnal oxygen saturation $SatO_2$ levels, (Connaughton et al. 1988, 341–44) although hypercapnia is associated with a more pronounced nocturnal oxygen desaturation than

normocapnia for any given level of waking $SatO_2$.(Bradley et al. 1990, 308–12)

Nocturnal hypoxemia has been defined as a $SatO_2$ of ≤ 90% for at least 5 min with a Nadir $SatO_2$ of ≤ 85%. Time in bed has been defined as the time from the start to the end of the recording. The percentage of total recording time (TRT) has been defined as the time spent in bed -- sleep latency + intrasleep wakefulness. The TRT spent in bed with a $SatO_2$≤ of 90% has been defined as the T_{90}%. The minimal TRT required for a satisfactory analysis of nocturnal recordings was/has been 2 hours. COPD patients with a T_{90} ≥ of 30% and a Nadir $SatO_2$ of 85% have been defined as Desaturators (D) and the others as Non-Desaturators (ND). (Toraldo et al. 2005, 3828–37) In this study the authors, as revealed by cluster analysis, have shown that clinical parameter predictors when awake from nocturnal desaturation were different. COPD D patients may be identified by a clinical pattern of variables T_{90}, Mean Pressury Artery Pulmonary (MPAP), 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 that many clinical variables describe not only as respiratory when awake. Alveolar hypoventilation probably accounts for most of the oxygen desaturation. Becker and colleagues (Becker et al. 1999, 112–18) 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 (O'Donoghue et al. 2004, 663–73) who have found an even greater drop in minute ventilation during non-REM sleep in hypercapnic COPD patients.

Clinical impact of nocturnal oxygen desaturation

The exact prevalence of Pulmonary Hypertension (PH) in patients with COPD is unclear. (Naeije 2005, 20–22) 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. (RHF) The diagnosis of PH in COPD patients is difficult. The published studies differ not only in their definition but also for conditions under which PH has been reported (rest, exercise, and exacerbation). According the European Society Cardiology and European Respiratory Society (Galie et al. 2009, 1219–63) PH has been defined as an increase in mean pulmonary arterial pressure PAP ≥ 25 mmHg at rest as assessed by right heart catheterisation. (RCH) The definition of PH on exercise as a Pulmonary Artery Pressure (PAP) ≥ 30 mmHg as 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. (Kessler et al. 2001, 219–24) The authors have performed a longitudinal study on 131 patients with COPD by performing serial RHC at baseline and then at follow-up (mean follow-up was 6.8 ± 2.9 years). All subjects have had normal mean PAP at rest (≤ 20 mm Hg). They have been divided into two groups based on presence or absence of elevated mean PAP with exercise (≥30 mm Hg) 25% of patients developed PH on follow up and was mild by hemodynamic criteria (mean PAP 26.8 ± 6.6 mm Hg). Subjects who showed elevated PH with exercise were more likely to exhibit resting mean PAP elevation upon follow up. The rate of progression was +0.4 mm Hg per year.

Nocturnal oxygen desaturation seems to contribute to the development of PH; even in the absence of significant awake hypoxemias. (Fletcher et al. 1989, 757–64) REM-associated falls in $SatO_2$ are associated with increases in pulmonary artery pressure during sleep that can be reversed by supplemental oxygen, although most COPD patients with sustained pulmonary hypertension are also hypoxaemic during the daytime. Various arrhythmias are also reported

during episodes of nocturnal desaturation. (Douglas et al. 1982, 758–62) These consequences might help to explain why nocturnal oxygen desaturation is a marker of increased mortality, and why COPD patients are reported to die more frequently at night than expected (W T McNicholas and Fitzgerald 1984, 878)

Tissue hypoxia is another mechanism that can contribute to systemic inflammation in COPD. In a clinical study (Yu et al. 1998, L818-26) it has been shown that TNF-a and receptor levels were significantly higher in patients with COPD, but significantly correlated with the severity of arterial hypoxaemia. These results suggest that arterial hypoxaemia in COPD is associated with activation of the TNF-a system in vivo.

The systemic effects of inflammation may significantly contribute not only to respiratory abnormalities, 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 disease (Mal 2007, 114–19) The nocturnal desaturation–reoxygenation sequence is a typical pattern coupled with the majority of respiratory events. This sequence, defining intermittent hypoxia (IH), leads to oxidative stress, with production of reactive oxygen species. (ROS) (Lavie 2003, 35–51) Hypoxia induced pulmonary vasoconstriction is a protective response to keep ventilation-perfusion ratio optimum by shunting blood away from the hypoxemic areas. The traditional hypoxic model of PH is based on the hypothesis that chronic hypoxia initiates vascular remodelling leading to permanent changes in pulmonary vasculature. Studies performed in vitro elucidated the mechanisms underlying hypoxia driven vascular changes. Barbera et al., (Barberà et al. 1994, 423–29) have evaluated COPD patients undergoing lung resection and demonstrated that vascular changes contribute to vascular remodelling and reputedly may have an effect on vascular dynamics leading to PH. Nocturnal hypoxia may induce endothelial cells to release proliferate cytokine leading to cellular hypertrophy in the vessel wall and increase in extra cellular matrix. In conclusion, the nocturnal hypoxic insult occurring during sleep-disordered breathing may also contribute to chronic vascular remodelling; these mechanisms generate vascular endothelial damage and dysfunction increasing the risk of pulmonary hypertension in COPD. (Jyothula and Safdar 2009, 351–63)

The review by Mc Nicholas shows how disease act through similar pathways to cause cardiovascular disease. (Walter T McNicholas 2009, 692–700) 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 (Donaldson et al. 2002, 847–52; Soler-Cataluña et al. 2005, 925–31).

Interaction of COPD and Obesity in Systemic Inflammation

Recently, the concept of systemic inflammation as a consequence of spill over of inflammatory mediators from the lungs to the systemic compartment in COPD has been broadly discussed. (Chung and Adcock 2008, 1334–56; van Eeden and Sin 2008, 224–38; Kim, Rogers and Criner 2008, 478–85) Several factors likely play a role in the genesis of systemic inflammation of COPD. These include tobacco use, airway inflammation, airflow obstruction, and hyperinflation. However, an independent role for tissue hypoxia seems likely. (Agusti 2005, 367–70)

The transcription factor nuclear factor κB (NFκB) is the master regulator of cellular inflammatory responses, controlling expression of key inflammatory cytokines, such as tumor necrosis factor alpha (TNFα) and interleukin-8. (Garvey, Taylor and McNicholas 2009, 1195–1205) Evidence of a role for hypoxia in the induction of an NFκB response comes from in vitro, in vivo, and clinical studies. Intermittent hypoxia is classically seen in patients with obstructive sleep apnea syndrome, but may arise in COPD, particularly during sleep or exertion. In sustained hypoxia, NFκB appears to interact with HIF-1α to promote the expression of inflammatory genes, such as cyclo-oygenase II. (Fitzpatrick et al. 2011, 1091–96)

Similarly, in a rodent model, 24 hours of sustained hypoxia has been shown to up regulate NFκB activity in pulmonary and cardiac tissue. (Fitzpatrick et al. 2011, 1091–96) Meanwhile, clinical studies in COPD patients have found that circulating levels of TNFα and soluble TNF receptors increase as arterial oxygen ten-

sion decreases. (Takabatake et al. 2000, 1179–84).

A number of studies have suggested it may result from "overspill" of inflammatory mediators from the lungs and pulmonary circulation, while others have failed to find any correlation between measurable pulmonary and circulating inflammatory mediators. (Sinden and Stockley 2010, 930–36) One potentially important source of inflammation in
obese patients with COPD with nocturnal hypoxaemia is white adipose tissue. In patients with COPD, obesity is characterized by an absolute abundance of fat mass (FM), similar to other diseases associated with excessive adiposity. The prevalence of obesity is the highest among patients with milder forms of the disease (GOLD Stages 1 and 2), and the lowest in patients with the most severe lung function impairment in Stage 4. (Sin and Man 2003, 1514–19; M Poulain et al. 2008, 35–41) Marquis et al. (Marquis et al., 226-32-4) demonstrated the presence of one or more components of the metabolic syndrome in almost 50% of COPD patients. High adiposity and fat tissue accumulation impair pulmonary functions and exercise performance. (Magali Poulain et al. 2006, 1293–99) Obesity and the presence of metabolic syndrome are related to increased insulin resistance in overweight and obese COPD patients (Bolton et al. 2007, 121–26)

The study by Bolton et al. (Bolton et al. 2007, 121–26) suggests that insulin resistance is aggravated by both, high BMI and increases in circulatory inflammatory mediators such as IL-6 in these patients. Indeed, inflammatory mediators TNF-α, IL-6, and leptin were significantly higher while plasma adiponectin levels were reduced in the presence of excess weight in COPD patients. Chronic low-grade adipose tissue inflammation in obesity may represent a specific response to relative hypoxia of adiposities. (Trayhurn and Wood 2004, 347–55) Several factors may contribute to cell hypoxia within adipose tissue in association with high adiposity: (a) blood flow per unit 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 studies in
vitro and animal models. Studies in vitro have shown that hypoxia results in enhanced TNF-α production, increased expression of PAI-1, and reduced adiponectin and peroxisome proliferators-activated receptor gamma (PPARγ) expression (Chen et al. 2006, 549–56; Hosogai et al. 2007, 901–11)

On the other hand, however, obesity-related hypoxia evokes local inflammatory response within adipose tissue per se, and systemic hypoxia likely contributes to the adipose tissue inflammation. If so, elevated circulating levels of inflammation-related proteins may reflect also spill over from the adipose tissue to the systemic circulation in patients with COPD and concurrent obesity.

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 hypoxemia. Risk of sleep-disordered breathing and consequent nocturnal hypoxemia correlates with the degree of obesity, (Young et al. 1993, 1230–35) 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 hypoxemia in COPD patients (Kessler et al. 2001, 369–76)

The lung microbiome diversity plays an important role in COPD exacerbations: microbiota study.

The introduction of bacterial culture techniques for the microbiological analysis of respiratory samples confirmed that the respiratory system hosts many microorganisms (microbiome), including bacteria, viruses and broad-spectrum fungi**.** Studies using culture-independent techniques such as PCR amplification and sequencing the ribosomal RNA 16 (R) 16S gene have investigated a distinct bacterial community in the airways of COPD patients compared to healthy subjects and suggest that changes in the microbiota pulmonary disease could be associated with inflammation and airway exacerbations and disease progression. However, most

studies on pulmonary microbiome involved small groups of subjects with limited longitudinal sampling and modest clinical information. (Huang et al. 2014, 2813–23; Zakharkina et al. 2013, e68302) Acute exacerbations of COPD are a rapid worsening of symptoms in which the role of bacteria is one of the major etiological factors (E Monsó et al. 1995, 1316–20; Soler et al. 1998, 1498–1505) Then, the dynamics of bacterial prevalence during exacerbations and its role in the pathogenesis of the disease remain poorly known.

Most of the studies on COPD lung microbiota have used sputum as a representative sample of the respiratory system, thanks to its easy recovery and standardized processing procedure. In the respiratory microbiome analysis, it should be considered that the sputum comes mainly from the proximal airways, which possess a flora that showed clear differences with the microbial pattern found in the distal bronchi and in the alveolar space (Cabrera-Rubio et al. 2012, 3562–68; Pragman et al. 2012, e47305) which is studied on the contrary through bronchial biopsies, and / or bronchoalveolar lavage, while in COPD the microbial diversity model has been shown to be different between the microbiological examination of the sputum (upper airways) and the microbiological examination coming from the distal samples (lower airways), a finding that confirms the differences between proximal and distal bronchial flora. Microbial cultures have correlated respiratory symptoms in COPD exacerbations to the detection of new strains in bronchial flora (Sethi and Murphy 2008, 2355–65) but this change in bacterial flora does not occur in all disease exacerbations. The microbiome analyzes show a high relative abundance of specific bacterial genera, which can be considered etiological, for most exacerbations, while the remaining bacterial flora does not change significantly (Millares et al. 2014, 1101–11; Dy and Sethi 2016, 196–202) Furthermore, exacerbations are not only related to the prevalence of isolated bacterial genes, but are also associated with changes in the composition of the microbiome as a whole, but not always identifiable through the measurement of the relative infectious microbial load (Molyneaux et al. 2013, 1224–31).

An increase in the relative abundance of a specific bacterial genus can be considered causal in a COPD, but often subsequently, it is not confirmed by culture results. Several studies have showed that bacteria prevalent in the analysis of bronchial secretions may not be confirmed by the examination of the culture, while the microorganisms of the culture grow easily from the sample analysed, although their relative abundance has not changed compared to the previous stability (Sethi et al. 2006, 991–98; Millares et al. 2014, 1101–11) The microbiome analyses demonstrated a different pattern in infectious and eosinophilic exacerbations, with a clear prevalence of the Firmicutes genus in eosinophilic exacerbation, in the face of the predominance of Proteobacteria in exacerbations that show positive cultures for bacteria (Wang et al. 2016, 1082–92) This finding supports the clinical characterization of exacerbations in these two categories (bacterial and eosinophilic), considering that their microbial pattern is completely different and will require different therapeutic approaches. The interaction between different bacterial microorganisms can be addressed through analysis of microbiomes and in a clinical model; an important role of viral infection on the composition of the microbiome in patients with COPD has been demonstrated. Induced rhinovirus infection showed no effect on the microbiome of bronchial secretions in healthy subjects, but was associated with an increase in the prevalence of Proteobacteria in patients with COPD (Molyneaux et al. 2013, 1224–31). This observation confirms the role of rhinovirus infection as an inducer of changes in respiratory bacterial flora with prevalence of Proteobacteria and justifies the virus-virus detection of coinfections in one quarter of COPD exacerbations (Papi et al. 2006, 1114–21) The presence of bacterial diversity, often related to a relative increase in the bacterium Proteobacteria, is associated with greater severity in COPD and may be one of the determinants influencing the progression of exacerbations and pulmonary disease, as previously demonstrated in idiopathic pulmonary fibrosis (Molyneaux and Maher 2013, 376–81).

Conclusion

The hypoxic insult occurring during sleep-disordered breathing to COPD varies from one condition to another. However, there are com-

mon cardiovascular and metabolic morbidities in these various conditions

There are major differences with continuous hypoxia, suggesting specific pathways originating from the occurrence of oxidative stress and inflammatory cascade activation. Nocturnal hypoxaemia during sleep and diurnal hypoxaemia seems to be the major factor in morbidity. Also, the hypothesis that adipose tissue may contribute to the overall systemic inflammatory phenotype in patients with early stages COPD with obesity or relative abundant fat mass is novel (Millares et al. 2014, 1101–11). The recent role played by the lung microbiota in systemic inflammation is been presented. The microbial composition of the lung bacterial flora in COPD has been studied through microbiome analysis, the involvement of respiratory flora in the pathogenesis of the disease, it is practically unknow. In conclusion, recent data showed that lung microbiota is dynamic in which rapid changes appeared to be associated with exacerbations and disease progression events indicative of specific exacerbation phenotypes.

Disclosure

The authors declare that do not have a conflict of interest and that do not have a financial relationship with any commercial entity that has an interest in the subject of this manuscript.

Contributors

All authors participated to review. All authors were involved in writing and revising the article prior to submission.

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