Review Article

Sleep disordered breathing and chronic obstructive pulmonary disease: a narrative review on classification, pathophysiology and clinical outcomes

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Abstract: Chronic obstructive pulmonary disease (COPD) causes load-capacity-drive imbalance in both wakefulness and sleep, principally driven by expiratory flow limitation and hyperinflation. Sleep imposes additional burdens to the respiratory muscle pump, driven by changes in respiratory muscle tone, neural respiratory drive and consequences of the supine position. COPD patients are therefore at higher risk of decompensation during sleep, which may manifest as altered sleep architecture, isolated nocturnal desaturation, sleep hypoventilation and restless legs. Each form of sleep disordered breathing in COPD is associated with adverse clinical and patient-reported outcomes, including increased risk of exacerbations, hospitalisation, cardiovascular events, reduced survival and poorer quality of life. COPD-obstructive sleep apnoea (OSA) overlap syndrome represents a distinct clinical diagnosis, in which clinical outcomes are significantly worse than in either disease alone, including increased mortality, risk of cardiovascular events, hospitalisation and exacerbation frequency. Sleep disordered breathing is under-recognised by COPD patients and their clinicians, however early diagnosis and management is crucial to reduce the risk of adverse clinical outcomes. In this narrative review, we describe the pathophysiology of COPD and physiological changes that occur during sleep, manifestations and diagnosis of sleep disordered breathing in COPD and associated clinical outcomes.

Keywords: Chronic obstructive pulmonary disease (COPD); sleep; sleep disordered breathing; COPD-obstructive sleep apnoea (OSA) overlap; respiratory physiology; pulmonary mechanics

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Introduction

Optimal sleep duration and quality is fundamental to the maintenance of physical and psychological wellbeing but is associated with physiological changes that impose burdens onto the respiratory muscle pump. Such burdens are of limited significance in healthy subjects however may be amplified in respiratory diseases in which there is load-capacity-drive imbalance during wakefulness. Chronic obstructive pulmonary disease (COPD) is one of the most prevalent respiratory diseases worldwide. Pathological inflammatory responses to inhaled noxious particles lead to alveolar destruction, mucus hypersecretion and hyperinflation which impose elastic, resistive and threshold loads onto the respiratory system. In addition to the characteristic symptoms of breathlessness, cough and sputum production, COPD patients frequently report poor

sleep and nocturnal respiratory symptoms. There appears to be a bidirectional relationship between sleep quality and clinical outcomes in this population, with sleep disturbance promoting systemic inflammation, impaired immune function, physical inactivity and altered cognition, which potentially impacts on medication adherence, leading to adverse clinical outcomes, and nocturnal COPD symptoms, reduced physical activity, culprit medications and anxiety and depression are all associated with altered sleep architecture (*Figure 1*). In this review, we provide overviews of COPD and normal sleep physiology, delineate the classification of sleep disordered breathing in COPD and review the impact of sleep disordered breathing on clinical outcomes in COPD.

We present the following article/case in accordance with the Narrative review checklist (available at http://dx.doi.org/10.21037/jtd-cus-2020-006).

Pathophysiology of COPD

COPD is estimated to affect around 400 million people worldwide and has a prevalence of approximately 10%, although many millions are thought to be undiagnosed (1). The burden of COPD is projected to rise, with deaths attributable to the disease rising from 3 to 7 million between 2016 and 2060 (2). COPD develops as a consequence of inhalation of noxious particles, typically cigarette smoking, in suspectable individuals. Exposure to such stimuli lead to accumulation of inflammatory cells in the airways, predominantly CD8 T-lymphocytes, macrophages and neutrophils. These cells promote fibroblast activity, leading to abnormal airway remodelling and increased airway resistance, and protease-antiprotease imbalance, causing elastin breakdown and reduced elastic recoil of lung parenchyma. Oxidants released from airway inflammatory cells and directly from cigarette smoke also promote mucus hypersecretion, which is an additional resistive load (3). This abnormal inflammatory response ultimately causes expiratory flow limitation, which is the pathophysiological hallmark of COPD. Expiratory flow limitation results in gas trapping, or hyperinflation (4). This imposes elastic and threshold loads and causes respiratory muscle shortening and abnormal chest wall geometry, thus impairing the force generating capacity of the respiratory muscle pump and reducing the efficiency with which inspiratory muscle contraction in translated to inspiratory airflow (5). This leads to increased neural respiratory drive to maintain ventilation, which is perceived as breathlessness (*Figure 2*). Exacerbations of COPD are acute deteriorations in breathlessness, cough and/or sputum production that result in additional therapy (6). During exacerbations, there is an acute rise in airway resistance due to increased airway inflammation, smooth muscle constriction and excessive production of tenacious sputum, which further increases the end-expiratory volume. COPD exacerbations are associated with poor clinical outcomes, including accelerated lung function decline, reduced health-related quality of life and increased risk of hospitalisation and death (6).

Normal sleep

Sleep may be categorised into rapid eye movement (REM) and non-REM stages. Sleep architecture in healthy subjects typically progresses through increasingly deep stages of non-REM sleep, with stages 1–2 considered light and N3 as deep, interrupted by periods of REM sleep. The

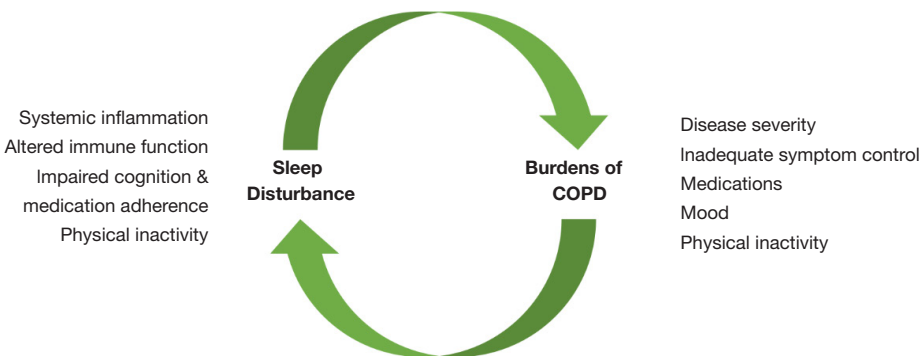

Figure 1 Illustration of the bidirectional relationship between sequelae of sleep-disturbance and adverse clinical outcomes in chronic obstructive pulmonary disease (COPD).

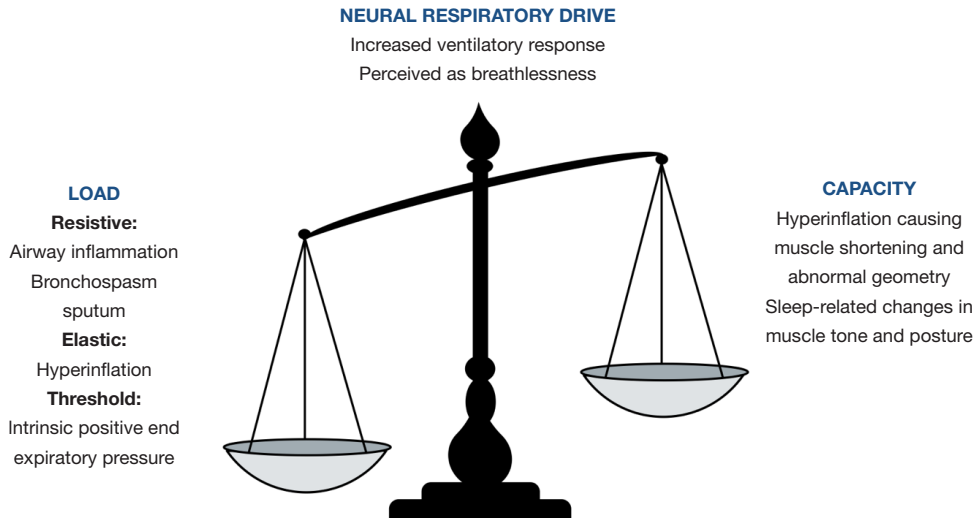

Figure 2 Schematic representation of load-capacity-drive imbalance of the respiratory muscle pump during exacerbations of chronic obstructive pulmonary disease (COPD).

normal physiology of sleep imposes burdens onto the load-capacity-drive relationship of the respiratory muscle pump. Generalised postural muscle hypotonia occurs throughout sleep and is most profound during REM. During this stage, there is almost complete loss of tone of intercostal muscles with relative preservation of diaphragm activity and thus increased reliance on the diaphragm to maintain ventilation (7,8). A rapid shallow breathing pattern is adopted in sleep which, in combination with reduced inspiratory muscle activity, results in reduced tidal volumes particularly during REM compared to wakefulness (9). Reduced tidal volumes may be accompanied by compensatory increases in respiratory rate during sleep, causing minute ventilation to remain unchanged or only slightly reduced compared to wakefulness (8,10). In healthy subjects with habitual snoring, upper airway resistance is increased throughout all stages of sleep. This is associated with increased end-tidal carbon dioxide (CO_2), which falls with externally applied positive airway pressure suggesting that this resistive load is an important contributor to sleep-related hypoventilation (11). The supine position adopted during sleep cranially displaces the diaphragm, which imposes additional load and reduces the capacity of respiratory muscles. This leads to reduced end-expiratory lung volume and reduced functional residual capacity (FRC) (12). Normal sleep is also associated with blunted ventilatory responses to both hypoxaemia and hypercapnia and significant reductions in oxygen saturation and increased arterial partial pressure of CO_2 ($PaCO_2$) of up to 6 mmHg (0.8 kPa) may occur in healthy subjects (13,14).

Sleep disordered breathing and COPD

The physiological burdens imposed onto the respiratory system during sleep are of little consequence in healthy subjects but are magnified in patients with load-capacity-drive imbalance during wakefulness, such as in COPD. These patients are at risk of decompensating during sleep which can largely be attributed to (I) sleep-related inspiratory muscle tone and (II) the supine position.

Inspiratory muscle tone

Sleep-related inspiratory muscle hypotonia leads to reliance on the diaphragm to maintain ventilation. In COPD, the diaphragm is mechanically inefficient due to hyperinflation. Measurement of diaphragm electromyography with multipair oesophageal electrode catheters demonstrates that COPD patients have significantly higher diaphragm activity during wakefulness than healthy subjects to achieve comparable rates of minute ventilation. During sleep, in contrast to healthy subjects, diaphragm activity in COPD falls precipitously, to 31% and 49% of awake values during NREM and REM sleep, respectively (*Figure 3*). This is accompanied by large falls in minute ventilation, principally mediated by reduced tidal volumes (8). Furthermore, accessory muscle activity, present during wakefulness and

NREM sleep in COPD, falls precipitously and may be entirely absent during REM (7). This, in combination with normal REM-related intercostal muscle hypotonia, leads to greater reliance on the functionally impaired diaphragm to maintain ventilation.

Supine posture

The supine posture is mechanically disadvantageous to pulmonary mechanics in healthy subjects and has additional implications in COPD. Increased airway resistance from smooth muscle hypertrophy, mucus hypersecretion, and alveolar damage leading to destruction of the alveolar attachments to small airways results in increased closing capacity (CC), meaning that airways collapse earlier, at higher lung volumes. The supine position decreases FRC. Once FRC-CC is less than zero, small airway closure occurs during tidal breathing, therefore their attached alveoli do not participate fully in gas exchange. This leads to or exacerbates pre-existing ventilation-perfusion mismatch, which causes hypoxaemia. Inspiratory muscle strength is also affected by posture, with falls in maximal inspiratory pressure observed in COPD patients in the supine position compared to the seated position (15). It is thus unsurprising that COPD patients preferentially adopt a lateral position during sleep, with only 10% preferring to sleep supine (16).

Physiological and postural changes that occur during sleep thus expose COPD patients to greater risk of developing sleep disordered breathing. This may manifest as (I) altered sleep architecture, (II) isolated nocturnal desaturation, (III) sleep hypoventilation and (IV) restless legs. COPD may co-exist with obstructive sleep apnoea (OSA), termed "overlap syndrome", which represents a distinct clinical entity and will be reviewed separately. A summary of sleep disordered breathing in COPD is provided in *Table 1*.

Altered sleep architecture

Sleep fragmentation is common in COPD. Up to 78% of patients report some form of nocturnal sleep disturbance and the prevalence rises with increasing severity of airflow limitation (24). Polysomnographic evaluation of COPD patients reveals prolonged sleep latency, frequent arousals (occurring on average 15 times per hour), reduced sleep efficiency, total sleep time and N3 and REM sleep and increased wakefulness after sleep onset compared to age, gender, BMI and smoking status matched controls (*Table 1*) (25-27). These changes in sleep architecture may be partially attributable to COPD-related symptoms, with evening or night-time cough and wheeze reported by up to a quarter of patients and higher levels of sleep disturbance reported in patients who produce frequent sputum compared to non-productive patients (16,28). Anxiety and depression are common co-morbidities in COPD, and patients are more likely to report trouble falling asleep, racing thoughts at bedtime and being unable to sleep for days compared to matched controls, which likely contribute to sleep fragmentation (27). COPD medications may also impact upon sleep. Theophylline improves nocturnal ventilation however is associated with worse polysomnographic indices of sleep quality whilst regular inhaled ipratropium bromide improves nocturnal oxygenation and objective sleep quality (29,30). Sleep analysis of smokers and non-smokers reveals differences in electroencephalogram indices in early sleep and smokers are more likely to report poor quality sleep, which may be attributed to nicotine withdrawal during sleep (31).

Associations between objectively measured alterations in sleep architecture and clinical outcomes in COPD have not been established. Subjective sleep quality and self-reported disturbance is associated higher risk of exacerbations and emergency healthcare utilisation, more severe daytime breathlessness and cough compared to those without night-time symptoms (17,24,32).

Isolated nocturnal desaturation

Nocturnal desaturation occurs in young healthy subjects, in whom saturations under 90% for up to 10% of total sleep time may be considered normal, and it is also considered to be part of the normal aging process (33,34). COPD patients are at greater risk of clinically significant nocturnal desaturation, which is considered to be present when more than 30% of total sleeping time is spent with oxygen saturations under 90% or mean overnight oxygen is under 90% (35) (*Table 1*, *Figure 4*). Its prevalence amongst non-smoking COPD patients is estimated to be low, at approximately 5% (36). Daytime oxygenation is an independent predictor of nocturnal desaturation and in patients with mild to moderate daytime hypoxaemia (PaO_2 7.4–9.2 kPa), this prevalence rises to 49–70% (36-38). Altered sleep architecture in COPD frequently co-exists with nocturnal oxygen desaturation. However, studies evaluating the effects of nocturnal oxygen therapy on sleep fragmentation are conflicting and beneficial effects on arousals, total sleep time and sleep stage distribution (reduced light sleep and increased REM) may only be

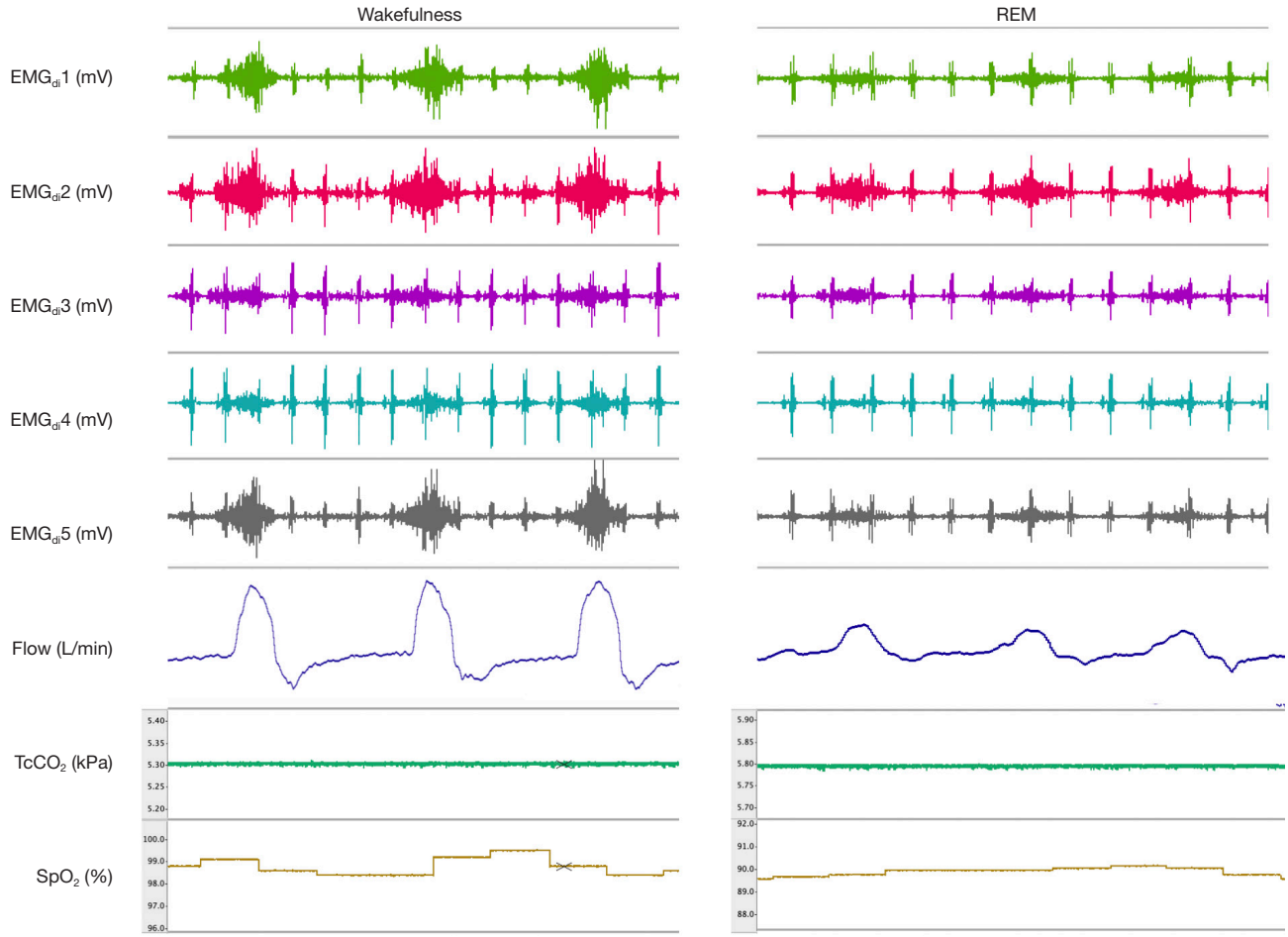

Figure 3 Physiological changes during wakefulness and rapid eye movement (REM) sleep including diaphragm electromyography (EMG_{di} pairs 1–5) from a multipair oesophageal electrode catheter, air flow at the mouth from a pneumotachograph, transcutaneous carbon dioxide ($TcCO_2$) and peripheral oxygen saturation (SpO_2). Data obtained from a patient with chronic obstructive pulmonary disease.

evident amongst patients with more profound daytime hypoxaemia (25,39). Furthermore, whilst nocturnal oxygen administration and regular long-acting bronchodilation improves nocturnal oxygenation without inducing hypercapnia, neither improve subjective sleep quality (40-42).

The clinical significance of isolated nocturnal desaturation in COPD has yet to be established, however patients with mild daytime hypoxaemia and nocturnal desaturation have worse survival than those without nocturnal desaturation (43). Cardiovascular disease commonly co-exists with COPD, with comorbid patients experiencing higher mortality and morbidity, including increased risks of exacerbations, cardiovascular events and hospitalisation, poorer health status and increased symptom burden than patients with either disease alone (44). The pathophysiological mechanisms underlying these poor clinical outcomes is incompletely understood however chronic intermittent hypoxaemia is likely a key component. Healthy subjects exposed to chronic intermittent hypoxaemia (SaO_2 84%) develop raised mean arterial blood pressure due to increased carotid body chemoreceptiveness, leading to increased sympathetic activation and peripheral vascular resistance (45). In COPD, nocturnal hypoxaemia is associated with electrocardiographic changes, with tachycardia, atrial and ventricular ectopics, prolonged QT_c interval, ST depression and right bundle branch block all observed and abolished with oxygen application (46). Chronic intermittent hypoxia may also be associated with increased pulmonary and systemic inflammation.

Table 1 Classification of sleep disordered breathing in chronic obstructive pulmonary disease (COPD), diagnostic criteria and associated clinical outcomes (data collated from references 7,8,17-23)

Manifestation of sleep disordered breathing	Diagnostics	Clinical outcomes
Altered sleep architecture	Polysomnography to evaluate: • Sleep latency • Arousal frequency • Sleep efficiency • Total sleep time • Time spent in each sleep stage	Subjective sleep disturbance is associated with: • Increased frequency of COPD exacerbation and healthcare utilisation • Increased daytime breathlessness and cough
Isolated nocturnal desaturation	>30% of total sleep time with oxygen saturation under 90% or mean overnight oxygen saturation under 90% on pulse oximetry	Chronic intermittent hypoxia may be linked with adverse cardiovascular outcomes including: • Cardiac arrythmias • Hypertension • Cardiovascular and cerebrovascular events Reduced survival
Sleep hypoventilation	Increased carbon dioxide (arterial, transcutaneous or end-tidal) either: • To a value >55 mmHg for ≥10 minutes or • By ≥10 mmHg compared to during wakefulness to a value >50 mmHg for 10 minutes	• Increased risk of hospitalisation • Increased symptom burden • Reduce health-related quality of life
Restless legs	Patient reported	Correlated with: • Daytime symptoms • Subjective sleep quality
COPD-OSA overlap syndrome	(I). Spirometric confirmation of expiratory flow limitation and (II). Confirmation of obstructive sleep apnoea using polysomnography or respiratory polygraphy	• Reduced survival from excess cardiovascular events • Increased risk of hospitalisation • Increased risk of COPD exacerbation • Reduced quality of life

Airway walls of smokers and COPD patients are typically infiltrated with macrophages and T-lymphocytes with the presence of neutrophils in the airway lumen and stable COPD patients with comorbid cardiovascular disease have raised serum levels of fibrinogen, IL-6 and IL-8 than in COPD patients without cardiovascular disease (47,48). These processes likely lead to the development of increased arterial stiffness which is observed in COPD patients and is an independent predictor of cardiovascular events (18). The effects of nocturnal oxygen therapy in COPD patients with isolated nocturnal desaturation (with or without daytime hypoxaemia) on cardiovascular risk is currently unknown. Pulmonary haemodynamics have also been investigated in patients with daytime hypoxaemia and nocturnal desaturation, with no correlation found between pulmonary artery pressure and severity and duration of nocturnal hypoxaemia (38).

Isolated nocturnal desaturation does not appear to have a

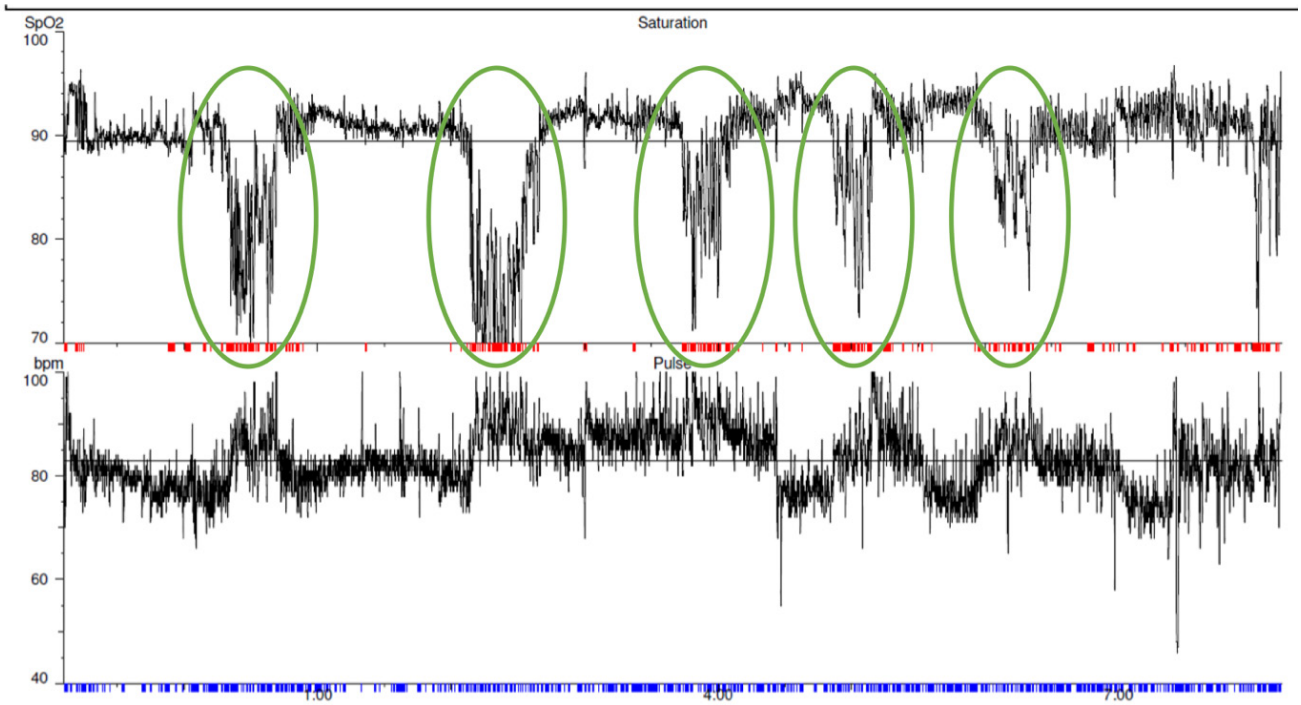

Figure 4 Example of overnight oximetry in a patient with nocturnal hypoxia. Episodes of nocturnal desaturation that are likely related to rapid eye movement (REM) stage sleep are highlighted in green.

detrimental impact on patient-reported outcomes, with no differences in subjective sleep quality, daytime somnolence or health-related quality of life observed between COPD patients with and without nocturnal desaturation (36). However, minimum and mean overnight oxygen saturation may be independent predictors of psychiatric-related sleep disturbance, which is more common in COPD compared to matched controls (27).

Sleep hypoventilation

Episodes of sleep hypoventilation are defined as increased in carbon dioxide [$PaCO_2$, transcutaneous ($TcCO_2$) or end-tidal ($ETCO_2$)] either (I) to a value >55 mmHg for ≥10 minutes or (II) by ≥10 mmHg compared to during wakefulness to a value >50 mmHg for 10 minutes (*Table 1*) (49). Sleep hypoventilation is observed in up to 43% of COPD patients with chronic respiratory failure (daytime $PaCO_2$ 46 mmHg/6 kPa) and is more prevalent with increasing severity of airflow limitation (50). There is a less well-defined cohort of eucapnic COPD patients with isolated nocturnal hypoventilation who may be at increased risk of frequent exacerbations and pulmonary artery hypertension, however the prevalence and clinical relevance of this phenomenon has not been prospectively evaluated (51,52). Benzodiazepine, opiate and hypnotic medications improve sleep efficiency and are effective in palliating chronic breathlessness. However, they are associated with reduced tidal volumes, minute ventilation and neural respiratory drive during sleep and so should be used judiciously, particularly in hypercapnic patients (53,54).

Sleep hypoventilation in COPD manifests both as transient and sustained increases in $PaCO_2$, with REM-related rises throughout the night and elevated morning $PaCO_2$ compared with $PaCO_2$ from the preceding evening (50). Nocturnal hypercapnia in COPD reflects reduced minute ventilation, which falls by up to 19% during non-REM sleep and 36% during REM compared to wakefulness (55). Sleep-related hypoventilation is likely a consequence of (I) excess load imposed by increased upper airways resistance and impaired dilatory upper airways response to hypercapnia, (II) impaired capacity due to functional diaphragm impairment and (III) blunted neural respiratory drive, as measured with airway occlusion pressure ($P_{0.1}$) and diaphragm electromyography, which occur during all stages of sleep compared to wakefulness, and particularly during REM (8,55-57) (*Figure 5*). Nocturnal hypercapnia does not impact upon objective sleep quality, with total sleep time, distribution of sleep

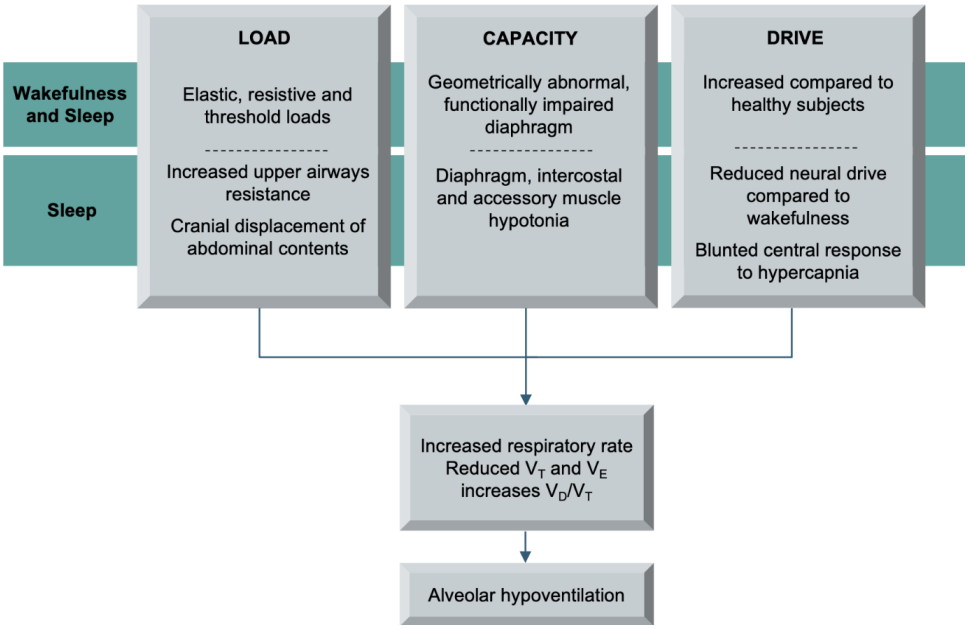

Figure 5 Excess load-capacity-drive imbalance during rapid eye movement (REM)-sleep in COPD leading to nocturnal hypoventilation. Abbreviations: VT, tidal volume; VE, minute ventilation; VD, dead space volume.

stages and arousal, hypopnoea and apnoea frequency comparable between COPD patients with and without daytime hypercapnia (51).

Untreated chronic respiratory failure in COPD is associated with poor clinical outcomes, including higher risk of hospitalisation, increased symptom burden and impaired health related quality of life (6). Median survival is 2.5 years, which is significantly lower than in respiratory failure from other causes (19,58). Nocturnal non-invasive bilevel positive pressure ventilation (NIV) improves physiological and clinical outcomes in COPD in both stable hypercapnic patients and those with persistent hypercapnia following hypercapnic exacerbation requiring acute NIV (59,60). In stable non-obese COPD patients, nocturnal NIV is associated with small increases in duration of REM sleep, reduced nocturnal rises in CO_2 and fewer apnoeic/hypopnoeic events during inpatient setup (61). In the long-term, when targeted to reduce daytime hypercapnia, nocturnal NIV improves survival, functional exercise capacity and health-related quality of life 12 months after initiation (59). Applying a high intensity approach (high inspiratory pressure and high back up rate) does not produce any difference in overnight oxygen saturation, $TcCO_2$, or sleep efficiency (as measured with actigraphy) compared to a high pressure strategy (high inspiratory pressure, low backup rate) and may adversely affect health related quality of life (62). Volume targeted NIV may enable delivery of lower pressures and, when titrated with polysomnography, is associated with improved patient-ventilator asynchrony, subjective comfort, morning breathlessness and nocturnal $TcCO_2$ (63). NIV devices with auto-titrating algorithms deliver a predefined tidal volume by adjusting delivered pressures and backup rate, so-called average or intelligent volume assured pressure support (AVAPS or iVAPS). These appear to improve nocturnal ventilation without adversely affecting subjective and objective indices of sleep quality (64,65). Following exacerbations requiring acute NIV, patients with persistent hypercapnia have improved daytime oxygenation and nocturnal hypoventilation when treated with nocturnal NIV and home oxygen compared to home oxygen alone, in addition to prolonged time to readmission or death, lower all-cause mortality and reduced exacerbation frequency (60). To date, there have been no studies evaluating physiological or clinical outcomes following application of positive airway pressure in isolated nocturnal hypoventilation.

Restless legs syndrome

Restless legs syndrome is characterised by a subjective compelling urge to move the limbs, typically worse at night

and relieved by activity (66). It is more common in COPD, affecting approximately one third of patients, with a female preponderance (20,21). Severity of restless legs is correlated with both daytime breathlessness and subjective sleep quality, with patients commonly reporting non-refreshing sleep, daytime somnolence and low mood (20,21).

COPD-obstructive sleep apnoea (OSA) overlap

OSA causes repetitive upper airway obstruction with transient hypoxaemia during sleep with daytime somnolence. It is more prevalent amongst men and those with hypertension or higher body mass index (BMI), affecting 10-17% of the middle-aged adult population (67,68). OSA is associated with increased mortality and morbidity from cardiovascular disease, including coronary artery disease, heart failure, arrythmias and stroke. The underlying pathophysiological mechanisms behind these poor clinical outcomes remain unclear, however strong associations have been identified between OSA and endothelial dysfunction, oxidative stress, systemic inflammation, coagulopathy and altered sympathetic drive which improve with overnight continuous positive airway pressure therapy (69). Given the high prevalence of COPD and OSA worldwide, the development of both diseases in an individual (the so-called "overlap syndrome") by chance alone is not unlikely. The prevalence of COPD-OSA overlap has been estimated at 1–3.6% of the general population, and studies evaluating patients with established diagnoses of either COPD or OSA indicate the prevalence of the overlap syndrome is up to 66% and 56%, respectively (70,71). These estimates must however be interpreted with caution since they are obtained from non-randomised trials (therefore subject to selection bias) with variable diagnostic criteria for each disease (spirometric values, definitions of hypopnoea, apnoea-hypopnoea index (AHI) cut-off values). Furthermore, the common occurrence of isolated nocturnal desaturation even in mild COPD may overestimate OSA prevalence in this cohort (67).

To date, there have been no studies demonstrating causal relationships between pre-existing COPD or OSA and development of the overlap syndrome. It has been speculated that COPD patients are at increased risk of upper airway obstruction during sleep as a consequence of rostral fluid shifts, which may be more significant with right heart failure, and generalised muscle atrophy, which is common in COPD and may predispose to pharyngeal muscle weakness (72,73). Corticosteroids, which are commonly used in COPD, could theoretically increase risk of sleep-related upper airway obstruction due to the common side effects of myopathy, central obesity and fluid retention (74). During NREM, minute ventilation falls significantly compared to wakefulness in patients with COPD, OSA and those with overlap. During NREM, neural respiratory drive falls in COPD, increases in OSA and remains stable in COPD-OSA overlap and upper airway resistance, which remains stable during sleep in COPD, increases in OSA and COPD-OSA overlap during NREM. Thus in COPD-OSA overlap, sleep hypoventilation is more likely a consequence of increased upper airway resistance than reduced neural drive in these patients (75). Furthermore, worsening airflow limitation and gas trapping in patients with OSA is associated with reduced upper airway dilation responsiveness to increased neural drive and increased instability of ventilatory control (76).

Conversely, data from clinical trials suggest that hyperinflation caused by expiratory airflow limitation may be protective against the development of OSA. Inverse relationships have been reported between AHI and forced expiratory volume in 1 second or radiological emphysema in patients with COPD-OSA overlap (68,77). These findings are consistent with observations that increased end-expiratory lung volume is associated with reduced upper airway collapsibility during NREM sleep (78,79). Whilst the mechanism underlying the negative correlation between airflow limitation and AHI have not been defined in patients with COPD-OSA overlap, it has been demonstrated that COPD patients effectively adapt their respiratory cycle in response to inspiratory airflow limitation compared to BMI- and AHI-matched smokers without COPD, as demonstrated by prolonged inspiratory duty cycle (T_i/T_{tot}) with a corresponding reduction in upper airway collapsibility (80). Reduced upper airway collapsibility observed during sleep in COPD may also be a consequence of increased end expiratory lung volume, which caused mediastinal caudal traction and transthoracic pressure changes (81,82).

Whilst a clear understanding of any pathophysiological links between the two diseases remains elusive, clinical outcomes in COPD-OSA overlap are uniformly worse than in either disease in isolation, suggesting a synergistic relationship between COPD and OSA. 10-year survival in untreated COPD-OSA is significantly poorer than in COPD or OSA alone, with cardiovascular events being the most common cause of death in this cohort (22,83). Causal mechanisms for increased cardiovascular risk in

this population have not been confirmed in prospective trials however it is likely that the more severe daytime and nocturnal hypoxaemia observed in COPD-OSA overlap compared to COPD or OSA alone (22,84) have three important consequences that may contribute to this risk:

Chronic inflammation

Chronic intermittent hypoxia is associated with systemic and pulmonary inflammation (85). Serum (CRP, IL-6) and airway (neutrophils, TNFα, IL-8) inflammatory biomarkers are higher in COPD-OSA overlap than COPD, which is associated with reduced physical activity and levels correlate with duration of nocturnal hypoxia (86,87). Chronic inflammation is associated with oxidative stress in both OSA and COPD which are likely linked to predispositions to vascular endothelial dysfunction and atherosclerosis observed in both conditions (88,89).

Pulmonary vasoconstriction

Chronic intermittent hypoxia promotes pulmonary vasoconstriction to minimise ventilation perfusion mismatch. This increased right ventricular load leads to remodelling, resulting in higher right ventricular mass which increases in relation to severity of nocturnal desaturation (90) and may lead to myocardial fibrosis in COPD (91). These pathological changes may account for the higher prevalence of pulmonary hypertension in COPD-OSA overlap compared to OSA alone (42% and 13%, respectively) (84) and the odds ratios of developing pulmonary hypertension in COPD-OSA overlap compared to COPD or OSA alone have been reported as 2.96 and 5.93, respectively (92). Right-heart failure is also a common consequence of hypoxaemia that occurs in both COPD and OSA and is associated with adverse clinical outcomes (44,93,94).

Fasting hyperglycaemia

Nocturnal desaturation is associated with impaired glucose metabolism which manifests as fasting hyperglycaemia, with higher risk of raised fasting glucose with increasing severity of hypoxaemic events (95). Whilst impaired glucose control has established associations with adverse metabolic and cardiovascular outcomes, glucose metabolism has not been explored in the COPD-OSA population therefore any causal relation to cardiovascular outcomes remains speculative.

Whilst there have been no randomised trials evaluating the impact of continuous positive airways pressure (CPAP) therapy in COPD-OSA overlap, observational data from large cohorts indicate that 10-year mortality is significantly higher in untreated COPD-OSA overlap compared to COPD alone, and CPAP use in COPD-OSA overlap is associated with a lower mortality risk that comparable to that for COPD alone (22,96). Treatment adherence is also relevant, with poorer survival observed in those using CPAP for less than two hours a night (97). There is a propensity to develop nocturnal hypoventilation with or without daytime hypercapnia in both COPD and OSA due to load-capacity drive imbalance, which is associated with poorer clinical outcomes as previously described. Positive airways pressure interventions (NIV and CPAP) have demonstrable benefits in COPD and OSA as single disease entities. NIV improves admission-free survival in stable hypercapnic COPD patients and those with persistent post-exacerbation hypercapnia (59,60) compared to usual medical care or home oxygen. In obese patients with severe OSA and daytime hypercapnia (obesity hypoventilation syndrome), NIV improves daytime and nocturnal gas exchange and sleep quality compared to lifestyle modification alone, and there are no significant differences in risks of hospitalisation of death between OHS patients treated with CPAP or NIV (98). Given the established evidence base that positive airways pressure improves clinical outcomes in hypercapnic COPD and hypercapnic OSA, it is conceivable that it may confer such benefits in the overlap syndrome, however no randomised trials have been conducted to date. Amongst such patients previously established on home NIV, auto-titrating and fixed-level NIV are associated with comparable control of daytime gas exchange, nocturnal hypoventilation and objective sleep quality, with auto-titrating devices associated with improved subjective sleep comfort and ventilator adherence (99).

Observational data demonstrate that patients with untreated COPD-OSA overlap are at increased risk of both community-treated exacerbations and those requiring hospitalisation (22,100) compared to those treated with CPAP. Indeed, admission-free survival amongst overlap patients treated with CPAP is comparable to that for patients with COPD in isolation (22). In undiagnosed (and therefore untreated) OSA in COPD patients hospitalised with an exacerbation is associated with significantly higher risks of 1-, 3- and 6-month readmission compared to those without OSA. In these patients, increasing OSA severity is also associated with shorter time to readmission of death (101).

Health-related quality of life is poorer amongst COPD

patients with co-existent OSA (23). This may be related to nocturnal hypoventilation and daytime sleepiness, and in theory should be alleviated by CPAP which improves sleep quality however prospective randomised trials evaluating patient-reported outcomes in this cohort are currently lacking.

Conclusions

COPD causes load-capacity-drive imbalance in both wakefulness and sleep, principally driven by expiratory flow limitation and hyperinflation. Sleep imposes additional burdens to the respiratory muscle pump, driven by changes in respiratory muscle tone, neural respiratory drive and consequences of the supine position. COPD patients are therefore at higher risk of decompensation during sleep and sleep disordered breathing which may manifest as altered sleep architecture, isolated nocturnal desaturation, sleep hypoventilation and restless legs. Each is associated with adverse clinical and patient-reported outcomes, including increased risk of exacerbations, hospitalisation, cardiovascular events, reduced survival and poorer quality of life. COPD-OSA overlap syndrome represents a distinct clinical diagnosis, in which clinical outcomes are significantly worse than in either disease alone, including increased mortality, risk of cardiovascular events, hospitalisation and exacerbation frequency. Sleep disordered breathing is under recognised by COPD patients and their clinicians, however early diagnosis and management, which may include non-invasive ventilation or continuous positive airway pressure, is crucial to improve patient-reported and clinical outcomes.

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Footnote

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