

Chronic obstructive pulmonary disease and obstructive sleep apnoea – the overlap syndrome

Walter T. McNicholas

Department of Respiratory and Sleep Medicine, St. Vincent's University Hospital, Conway Institute of Biomolecular and Biomedical Research, University College Dublin, Dublin, Ireland

Correspondence to: Prof. Walter T. McNicholas, MD. Pulmonary and Sleep Disorders Unit, St. Vincent's University Hospital, Elm Park, Dublin 4, Ireland. Email: walter.mcnicholas@ucd.ie.

Abstract: Chronic obstructive pulmonary disease (COPD) and obstructive sleep apnoea (OSA) are highly prevalent disorders and the co-existence of both disorders, termed the overlap syndrome, affects at least 1% of the adult population. Patients with the overlap syndrome typically experience more pronounced nocturnal oxygen desaturation and there is a high prevalence of pulmonary hypertension in such patients. Recent evidence suggests that the prevalence of each disorder together is higher than might be predicted by simple prevalence statistics, although the evidence is not clear-cut in this regard. Sleep itself can have several negative effects in patients with COPD. Sleep quality is diminished with reduced amounts of slow wave and rapid-eye-movement (REM) sleep, which may contribute to daytime symptoms such as fatigue and lethargy. Furthermore, normal physiological adaptations during sleep that result in mild hypoventilation in normal subjects are more pronounced in COPD, which can result in clinically important nocturnal oxygen desaturation. Management of sleep disorders in patients with COPD should address both sleep quality and disordered gas exchange. Non-invasive pressure support is beneficial in selected cases, particularly during acute exacerbations associated with respiratory failure, and is particularly helpful in patients with the overlap syndrome. There is limited evidence of benefit from pressure support in the chronic setting in COPD patients without OSA.

Keywords: Chronic obstructive pulmonary disease (COPD); obstructive sleep apnoea (OSA); overlap syndrome; epidemiology; co-morbidity

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Introduction

Chronic obstructive pulmonary disease (COPD) and obstructive sleep apnoea syndrome (OSAS) are highly prevalent disorders (1-3), so the possibility of both occurring together in the same patient is relatively high by chance alone. Current estimates for the prevalence of COPD are in the region of 10% (1,4) and the prevalence of OSAS is at least 10% (3,5). The co-existence of both disorders, termed the overlap syndrome, carries additional prognostic implications relating to worsening respiratory failure, cardiovascular and other co-morbidities, and ultimately survival (6). The present review addresses epidemiology, pathophysiology, clinical assessment, management, and

implications for co-morbidities of the overlap syndrome.

Epidemiology

The most prevalent chronic respiratory disorders are COPD, asthma and OSA. COPD prevalence is related to the prevalence of tobacco smoking but reports indicate that 10% of the general population around the world have moderate to severe COPD [forced expiratory volume in 1 second (FEV₁)/forced vital capacity (FVC) <0.7 plus FEV₁ <80% of predicted] (4). The prevalence of OSA is equally high with over 25% of adult males having an apnoea hypnoea index (AHI) >5 and up to 15% having AHI >5 with associated excessive daytime sleepiness (EDS) (3,7,8).

Table 1 Factors in COPD that influence the potential for obstructive sleep apnoea

Direct sleep effects of COPD
Diminished sleep quality
Oxygen desaturation
Promoting factors for obstructive apnoea
Rostral fluid shift when supine
Cigarette smoking
Medication—e.g., corticosteroids
Protective factors against obstructive apnoea
Low BMI
Diminished REM sleep
Medication—e.g., theophylline

COPD, chronic obstructive pulmonary disease; BMI, body mass index; REM, rapid-eye-movement.

Prevalence figures for both disorders are influenced by definitions such as the presence of symptoms in addition to objective abnormalities. Furthermore, the prevalence of OSA has been increasing over recent decades, most likely as a consequence of the rising prevalence of obesity (3). Both disorders have a high global prevalence and affect all socio-economic groups.

Based on prevalence figures for each disorder alone, it can be estimated that at least one percent of the general population will have at least some degree of both conditions together, but several studies have explored the possibility of a higher prevalence than would be expected from simple coincidence. A report based on data from the Sleep Heart Health Study (9) found a relatively low rate of OSA in patients with lower airway obstruction, but this was a consequence of lower body mass index (BMI), as AHI was similar when values were stratified for BMI. Similar findings were reported by the MONICA (Multinational Monitoring of Trends and Determinants in Cardiovascular Disease) II project, sponsored by the World Health Organisation (10). In this study, AHI >5 with sleepiness was found in 11.3% of subjects and 10.7% had FEV₁/FVC ratio <70%, but lower airway obstruction did not predispose to OSAS, or vice versa.

More recent studies suggest that the prevalence of each disorder together may be higher than that predicted by chance occurrence alone. An Israeli study reported that COPD was more prevalent in patients with OSA with a reported odds ratio (OR) for COPD in males of 1.8 and in females of 4.3 compared to matched controls (11).

Furthermore, the recent report of Soler and co-authors (12) found a high prevalence of OSA in patients with severe COPD, particularly when overweight. Thus, this question remains uncertain and warrants further study.

Pathophysiology

Sleep has a number of adverse effects on breathing that include negative effects on respiratory control, respiratory muscle function, and lung mechanics (13). These effects produce negligible adverse consequences in normal subjects but may result in profound disturbances of gas exchange in patients with COPD. These adverse effects of sleep on gas exchange have been recognised for many years and patients with COPD may experience profound oxygen desaturation, particularly during rapid-eye-movement (REM) sleep, in addition to carbon dioxide retention, and the oxygen desaturation encountered during sleep may exceed that during maximum exercise (14). This hypoxaemia predisposes to arrhythmias (15), pulmonary hypertension (16) and nocturnal death, particularly during acute exacerbations (17). Furthermore, patients with COPD experience poor sleep quality with diminished amounts of slow-wave and REM sleep (18,19).

An important factor that contributes to disordered breathing during sleep in patients with COPD is the diminution of skeletal muscle function, especially during REM sleep, which particularly affects the accessory muscles of respiration such as the intercostal muscles (20). These effects are not peculiar to patients with OSA, and a number of additional factors can be considered that may influence the relationship between COPD and OSA, which are summarised in *Table 1*. Factors that may promote the development of OSA include rostral fluid shift during sleep when supine (21), which is particularly relevant to patients with cor pulmonale where peripheral oedema is a common finding. Additional factors include cigarette smoking, which contributes to upper airway inflammation and oedema, and certain medications such as corticosteroids which contribute to central fat deposition (6). On the other hand, several factors relevant to COPD may protect against the development of OSA, including low BMI, diminished REM sleep, and certain medications used in patients with COPD such as theophylline (22). A recent report identified BMI and pack years smoking as major predictors of OSA among patients with COPD (23), and awake hypoxaemia, hypercapnia, and pulmonary hypertension are more common in patients with the overlap syndrome than in

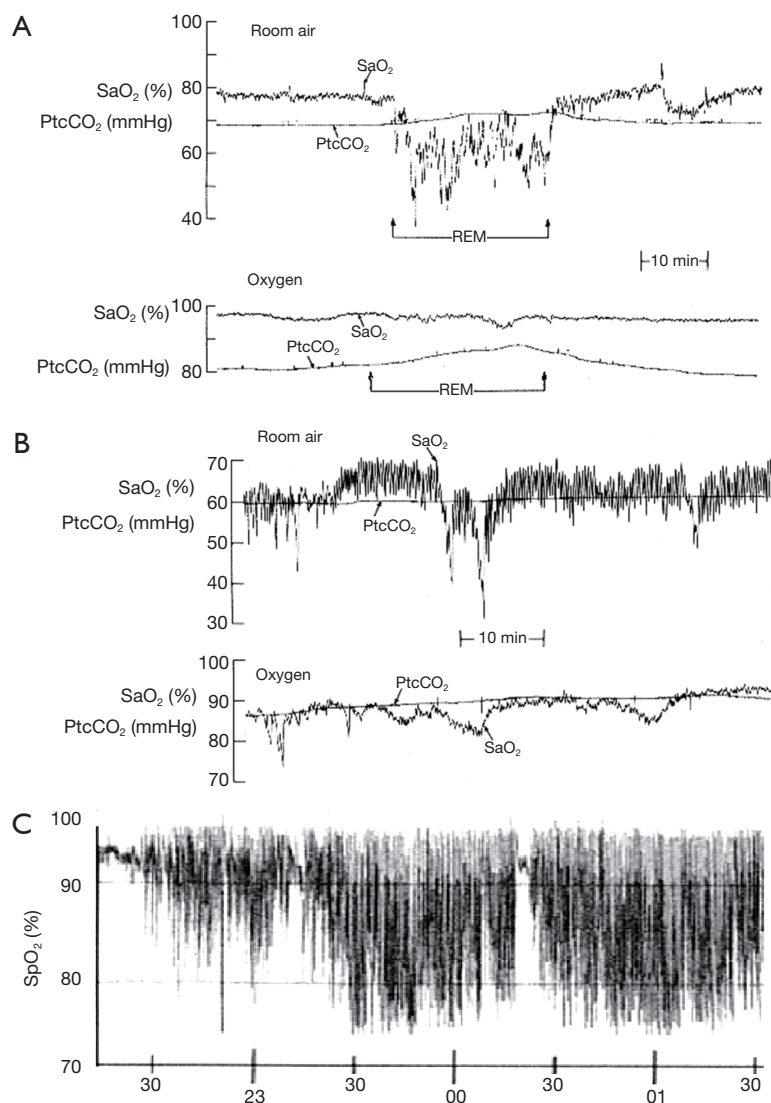


Figure 1 Different patterns of oxygen desaturation during sleep in patients with COPD (A), overlap syndrome (B) and OSA (C). SaO₂/SpO₂, oxygen saturation; PtcCO₂, transcutaneous carbon dioxide tension; REM, rapid-eye-movement; COPD, chronic obstructive pulmonary disease; OSA, obstructive sleep apnoea.

those with either condition alone (24).

Clinical assessment

While the gold standard investigation for sleep disordered breathing is overnight polysomnography (25), this investigation is not practical for the large numbers of patients susceptible to the overlap syndrome. Since nocturnal oxygen desaturation is more pronounced in patients with the overlap syndrome, overnight oximetry represents a simple screening tool for these patients. The desaturation characteristics

may also provide insight into the pathophysiology of sleep-disordered breathing, as patients OSA typically demonstrate a profile of intermittent desaturation whereas patients with hypoventilation demonstrate a more sustained pattern of oxygen desaturation during sleep. An example of nocturnal saturation profiles in the different disorders is presented in *Figure 1*. Sleep apnoea per se is better demonstrated by ambulatory cardiorespiratory polygraphy (26), which represents a suitable specific investigation for this possibility.

Patients with COPD typically report poor sleep quality and daytime fatigue, whereas patients with OSA typically

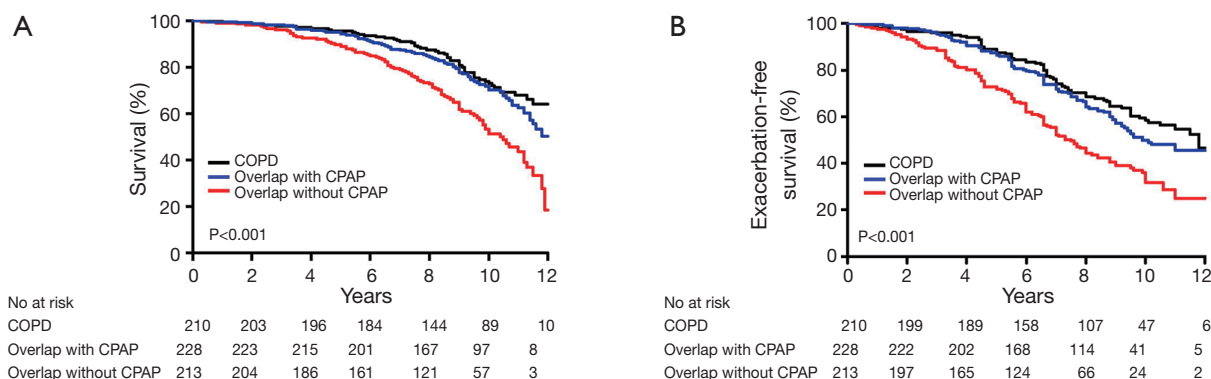


Figure 2 Kaplan-Meier survival curves for outcomes among COPD patients without obstructive sleep apnoea (OSA) (COPD group), patients with COPD and coexisting OSA (overlap group), and patients with overlap syndrome treated with CPAP since enrolment (overlap with CPAP group). Percentage survival (A), percentage of severe COPD exacerbation-free survival curves among the three study groups (B). The differences between COPD only and COPD with OSA treated with CPAP are statistically significant from patients with COPD and untreated OSA ($P < 0.001$). COPD, chronic obstructive pulmonary disease; CPAP, continuous positive airway pressure. Reprinted with permission of the American Thoracic Society (37).

report snoring, broken and unrefreshing sleep, in addition to EDS. Thus, there is clear overlap in symptom profile between the two disorders which reinforces the importance of considering the possibility of overlap when patients present for assessment.

Management

Oxygen therapy remains the principal management of COPD patients with associated hypoxaemia. There are documented survival advantages (27) and the risk of carbon dioxide retention with controlled oxygen therapy is relatively low (28,29). Optimising lung function will also benefit oxygenation, and most available bronchodilators have demonstrated efficacy in this regard (30-32).

The role of non-invasive pressure support ventilation (NIV) in the management of COPD patients with nocturnal sleep disordered breathing is not clear-cut. While NIV has established efficacy in the management of respiratory failure during acute exacerbations of COPD (33), the role of nocturnal NIV in stable hypercapnic COPD patients remains uncertain. A Cochrane review on the subject, published in 2013, concluded that there was no evidence for a consistent clinical or statistically significant beneficial effect on gas exchange, exercise tolerance, health-related quality of life (HRQoL), lung function, respiratory muscle strength or sleep efficiency; and furthermore, a meta-analysis of two long-term studies did not show significant improvements in blood gases, HRQoL or lung function after 12 months of

NIV (34). Another more recent meta-analysis from 2014 (35) agreed with the Cochrane findings but reported that higher inspiratory positive airway pressure (IPAP) levels, better compliance and higher baseline arterial carbon dioxide tensions (PaCO_2) appeared to improve PaCO_2 .

Building on this recent meta-analysis, the recent report of Köhnelein and co-authors indicated that NIV targeted to markedly reduce hypercapnia ($>20\%$) compared to best usual care in patients with advanced stable hypercapnic COPD resulted in lower 1-year all-cause mortality and improved quality of life scores (36).

There are few studies that have specifically addressed the role of NIV in patients with the overlap syndrome. Marin and co-workers have provided probably the best data on this topic in a long-term study comparing the outcomes in three groups with over 200 patients each: overlap patients treated with NIV, overlap patients not treated with NIV, and compared with COPD patients without OSA (37). Over a 12-year follow-up period, the survival was significantly better among overlap patients treated with NIV, and not significantly different than patients with COPD alone (Figure 2).

Co-morbidities

COPD (38) and OSA (39) have separately been identified as independently associated with several co-morbidities, most notably cardiovascular. Thus, one could anticipate that co-morbidities would be more prevalent in patients with the overlap syndrome than with either disease alone. However,

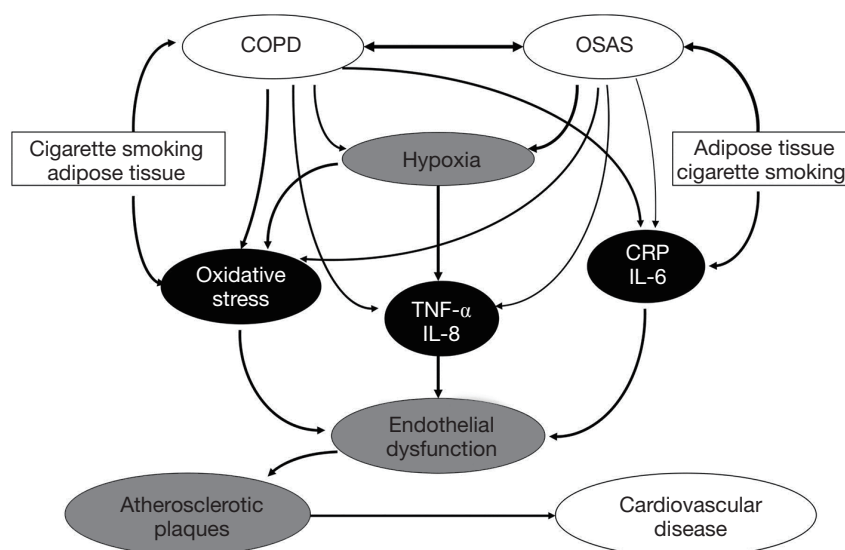


Figure 3 Interactions of COPD and OSAS in inflammatory mechanisms that predispose to cardiovascular disease. Both COPD and OSAS are associated with elevated levels of C-reactive protein (CRP) and interleukin-6 (IL-6), in addition to tumour necrosis factor-alpha (TNF- α) and interleukin-8 (IL-8), and are also associated with oxidative stress. However, cigarette smoking and obesity are confounding variables in these associations. Hypoxia is a key factor in elevated TNF- α production in OSAS, which is particularly relevant to the overlap syndrome. Each inflammatory pathway has been associated with atherogenesis and subsequent cardiovascular disease. COPD, chronic obstructive pulmonary disease; OSAS, obstructive sleep apnoea syndrome. Reprinted with permission of the American Thoracic Society (6).

there is little published evidence on the relative prevalence of cardiovascular or other co-morbidities in patients with the overlap syndrome compared to patients with COPD or OSA alone.

A variety of molecular pathways have been identified as potential contributors to co-morbidity, including systemic inflammation mediated by C-reactive protein (CRP) and by the downstream products of nuclear transcription factor-kappa B (NF- κ B) activation such as tumour necrosis factor-alpha (TNF- α) and interleukin-8 (IL-8) (6). These inflammatory mechanisms have been identified as important mechanisms in cardiovascular disease, and each has been associated with both COPD (40) and OSA (41-43). Whether the overlap of each disorder amplifies these responses is unclear, but the additional burden of hypoxia in the overlap syndrome could be an important mechanism in this regard, particularly in the context of TNF- α (44). Additional shared mechanisms that likely play a role in the development of cardiovascular co-morbidity include oxidative stress (45,46) and increased neutrophil productions and/or dysfunction (40,47). This topic represents an important area for future research and it cannot be assumed that inflammatory processes will necessarily be amplified, as the mechanisms involved may not be synergistic. For example, TNF- α elevation in COPD is associated with

muscle wasting (48), likely relating to TNF- α accumulation in muscle tissue, which could be less relevant in patients with the overlap syndrome. However, these aspects remain unexplored. A potential mechanistic interaction between COPD and OSA in the development of cardiovascular co-morbidity is given in *Figure 3*.

Conclusions

COPD and OSA are both highly prevalent disorders but whether each disorder predisposes to a higher incidence of the other is unclear. While sleep can produce clinically significant detrimental effects on sleep quality and gas exchange in patients with COPD, many clinicians ignore this aspect, despite the fact that appropriate management may produce considerable benefits to gas exchange and quality of life. The role of NIV is well established in acute exacerbations of COPD but less so in the chronic setting. However, patients with the overlap syndrome clearly benefit from continuous positive airway pressure (CPAP), particularly in long-term survival. Overlapping co-morbidities are prevalent in each disorder, but whether this association is amplified in patients with the overlap syndrome remains unclear. Thus, there remains a major

opportunity for further research in this area, which appears particularly important given the relatively high prevalence of the overlap syndrome in the general population.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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