Sleep-Disordered Breathing and COPD: The Overlap Syndrome

Robert L Owens MD and Atul Malhotra MD

Sleep-disordered breathing (mainly obstructive sleep apnea [OSA]) and COPD are among the most common pulmonary diseases, so a great number of patients have both disorders; this "overlap syndrome" causes more severe nocturnal hypoxemia than either disease alone. This common combination of OSA and COPD has important implications for diagnosis, treatment, and outcome. Specifically, patients with COPD and OSA have a substantially greater risk of morbidity and mortality, compared to those with either COPD or OSA alone. Only now are the interactions between these 2 systemic diseases being determined and appreciated. Many questions remain, however, with regard to disease definition, prognosis, and optimal treatment. Treatment currently consists of continuous positive airway pressure, and oxygen as needed. Noninvasive ventilation may be helpful in overlap syndrome patients, but this has not yet been well studied. *Key words: obstructive sleep apnea; chronic obstructive pulmonary disease; COPD; overlap syndrome; nocturnal oxygen desaturation; hypercapnic COPD.* [Respir Care 2010;55(10):1333–1344.

Introduction

Sleep-disordered breathing (mainly obstructive sleep apnea [OSA]) and COPD are among the most common pulmonary diseases. Although they may have common pathophysiological mechanisms, even by chance alone, a substantial number of patients will have both OSA and COPD—what Flenley termed "the overlap syndrome."[1] He felt that the syndrome was clinically distinct from either disease in isolation and that the prognosis, course, and urgency of treatment were equally unique. As this review reaffirms, the overlap syndrome is a common and clini-

cally important disease that may be more than the sum of its parts. Many questions remain, however, with regard to disease definition, diagnosis, prognosis, and optimal treatment.

Definitions, Epidemiology, and Treatment of COPD and OSA

COPD

COPD is defined by the Global Initiative for Chronic Obstructive Lung disease (GOLD) as:

> A preventable and treatable disease with some significant extrapulmonary effects that may contribute to the severity in individual patients. Its pulmonary component is characterized by air-flow limitation that is not fully reversible. The air-flow limitation is usually progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases.[2]

Spirometric criteria (forced expiratory volume in 1 second [FEV_1] and the ratio of FEV_1 to forced vital capacity [FVC] after bronchodilation) are used to assess the severity of COPD. Approximately 10% of people around the world have moderate COPD ($FEV_1/FVC < 0.70$, and $50\% \leq FEV_1 < 80\%$ predicted) or more severe COPD.[3] COPD affects approximately 20 million people in the United States.[4]

This most recent definition of COPD emphasizes that COPD is a systemic disease with extrapulmonary manifestations such as skeletal-muscle myopathy, osteoporosis, anemia, and depression.[5-7] COPD is also linked to cardiovascular comorbidities and various malignancies.[8,9] Because of this, and its high prevalence, COPD is associated with major morbidity and mortality. In the United States, COPD is the fourth leading cause of death (behind heart disease, cancer, and stroke), accounting for more than 119,000 deaths per year; however, the number of deaths due to COPD is increasing while most others causes are declining.[10] Furthermore, the prevalence and mortality of COPD have been increasing faster over the last 2 decades in women than in men, so that mortality attributable to COPD is now equal among men and women. Thus, COPD is projected to overtake stroke as the third most common cause of death in the United States by 2020. The direct cost of COPD in the United States is estimated at more than 32 billion dollars per year.

Treatment of COPD is most often focused on relieving air-flow obstruction and inflammation, as well as smoking cessation. Smoking cessation delays disease progression, even after substantial smoking exposure, and reduces mortality.[11] Inhaled β-agonists (albuterol, salmeterol) and anti-cholinergics (ipratropium, tiotropium), both short and long-acting, are used as bronchodilators. Corticosteroids, both systemic and inhaled, are used for their anti-inflammatory effects. These medications improve symptoms and may modestly delay disease progression; however, mortality has not been observed to improve.[12] For those with daytime hypoxemia or borderline hypoxemia and evidence of right-heart dysfunction, supplemental oxygen therapy decreases mortality, and more hours of use per day have a greater benefit.[13,14]

Obstructive Sleep Apnea

OSA is defined by intermittent collapse of the upper airway, which results in repetitive hypoxemia and arousal. Severity is assessed by the apnea-hypopnea index (AHI), which is the number of respiratory events per hour. The prevalence of the OSA syndrome (the combination of an $AHI > 5$ events/h and hypersomnolence) has previously been estimated at 4% of American men and 2% of women.[15] These data suggest that almost 10 million people in the United States are affected, although that is probably an underestimate. Obesity, as measured by the body mass index, is a risk factor for the development of OSA. As obesity rates have risen over the last 15 years, the current prevalence of OSA is almost certainly much greater.

As a result of fragmented sleep, OSA leads to excessive daytime sleepiness, neurocognitive dysfunction, and increased risk of motor-vehicle accidents, and may be related to decreased productivity.[16] Individuals with OSA are also at increased risk of developing hypertension and, probably, coronary disease and stroke.[17,18] Thus, OSA carries major morbidity and mortality and a substantial economic burden.[19] Continuous positive airway pressure (CPAP) is the current accepted standard treatment, although surgical approaches and/or oral appliances may have efficacy in some patients.

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The Overlap Syndrome

While imperfect, there exist reasonable estimates of the prevalence of OSA and COPD. Furthermore, as the major risk factors for each disorder are known, the expected incidence and future prevalence can also be predicted. Unfortunately, such prevalence data are not available for the overlap syndrome. In part this deficiency reflects the lack of a standardized definition, and a lack of a unique diagnostic code. Additionally, both OSA and COPD have undergone revisions in diagnostic techniques and/or criteria in the last 25 years.

Flenley considered that multiple respiratory diseases (eg, COPD and idiopathic pulmonary fibrosis) could "overlap" in the same individual; however, he reserved the term "overlap syndrome" for the coexistence of OSA and COPD in the same individual. Unfortunately, this definition is not ideal in several ways. Because both COPD and OSA occur on a spectrum of severity, it is unclear at what level of severity the combined diseases begin to have additive or synergistic clinical relevance. It is also unknown if patients with severe COPD and mild OSA should be evaluated and treated similarly to those with mild COPD and severe OSA.

Regardless, given the high prevalence of both COPD and OSA, we would expect a large cohort of patients affected with both of these common diseases. Most early studies examined patients with one of these disorders to see how many were also affected with the other illness. Those initial studies were not true cross-sectional studies and tended to suggest that the prevalence of the overlap syndrome was very high. For example, patients with obstructive lung disease, referred mostly for evaluation of excessive daytime sleepiness, were determined to frequently (22 out of 26 patients) have OSA as well.[20] Conversely, patients with known OSA were evaluated with spirometry, and 11% were found to have an $FEV_1/FVC < 0.60$.[21] At that time (prior to the International Variation in the Prevalence of COPD [the BOLD study][3]), that value seemed higher than expected. Another study in a Veterans Administration population found the prevalence of the overlap syndrome to be 29%, although the data were gathered in a retrospective chart study of patients who had been referred for polysomnogram and who also had an interpretable pulmonary function test.[22] The seemingly very high prevalence prompted speculation that OSA and COPD were linked by a common mechanism or common pathophysiology.

Indeed, there are many possible mechanisms by which one disorder might cause or exacerbate the other. For example, COPD has been linked with skeletal-muscle myopathy,[6] and it may be that COPD (or cigarette smoking) affects the upper-airway dilator muscles or reflexes. Similarly, COPD treatment with inhaled corticosteroids may cause local pharyngeal muscle myopathy, although the relevance of any such abnormality could be questioned.[23,24] Increased end-expiratory lung volume within an individual improves upper-airway mechanics, probably via tracheal traction.[25] Although end-expiratory lung volume may be elevated in those with emphysematous COPD, this type of end-expiratory lung-volume elevation may not be protective of upper-airway mechanics because of loss of lung recoil. Indeed, one could speculate that the decreased tethering of airways by destruction of parenchyma may produce a more collapsible upper airway. In right-heart failure, redistribution of edema fluid during supine sleep might also contribute to OSA.[26] Conversely, one could imagine ways in which OSA might exacerbate COPD. In an animal model, repetitive upper-airway collapse increased lower-airway resistance.[27] Those with OSA might smoke more heavily or frequently than those without OSA, in order to lose or maintain weight, or to counteract excessive daytime sleepiness.

More recently, however, data were analyzed from the Sleep Heart Health Study, a prospective multicenter cohort study.[28] In this study of a cohort derived from cardiovascular studies, no increased association was found between (generally mild) obstructive airways disease and OSA. Furthermore, the presence of airway obstruction did not seem to affect the respiratory disturbance index. A similar, European study (the Multinational Monitoring of Trends and Determinants in Cardiovascular Disease [MONICA-II]) also found no increased risk between the 2 disorders.[29] The major limitation of these studies is that most subjects had very mild airway obstruction on spirometry. Whether any pathophysiological link exists between OSA and severe COPD is still unknown.

It is also still worth emphasizing that, although there may be no increased association between relatively mild COPD and OSA, because of the rising prevalence of these diseases, a patient with one of the disorders will often have the other disease. For example, in the Sleep Heart Health Study and the MONICA-II study, GOLD stage II COPD was found in 19% and 11% of the subjects, respectively. Sleep-disordered breathing was seen in 14% of subjects in the Sleep Heart Health Study (respiratory disturbance index > 15 events/h) and 11% of subjects (AHI > 5 events/h and excessive daytime sleepiness) in the MONICA-II cohort.[28,29] Even by chance alone, a patient with one of the disorders has a greater than 10% chance of also having the other disease. Thus, when seeing a patient with either OSA or COPD, it is reasonable to screen for the other, based on history and review of systems.

Sleep and COPD

Sleep in Patients With COPD

COPD alone can cause subjective and objective changes during sleep. When those with either chronic bronchitis or emphysema were surveyed across a broad range of symp-

toms, "sleep difficulties" were endorsed as occurring "almost always" or "always" in 43% of subjects (third most common, after dyspnea and fatigue).[30] Specifically, patients with COPD report more difficulty both initiating and maintaining sleep than controls, and also complain of excessive daytime sleepiness.[31] Sleep architecture in some of these same patients was notable for many arousals. More than just the diagnosis of COPD, the presence of COPD symptoms such as cough or sputum production or wheezing strongly correlated with difficulty falling or staying asleep.[32] Other investigations have objectively confirmed poor sleep quality, with decreased total sleep time and decreased sleep efficiency.[33]

Sleep and Breathing

A brief review of the normal changes in respiration that occur with sleep onset and the various sleep stages is helpful to understand the changes that occur during sleep in those with COPD. In normals, 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).[34] Most of the drop in minute ventilation is due to a decrease in tidal volume that is not fully compensated for 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.[35,36] REM is characterized by skeletal-muscle atonia, except for the diaphragm, and shallow, irregular breathing. Finally, even in normal subjects without OSA, upper-airway resistance increases during sleep.[37]

Nocturnal Oxygen Desaturation

The most significant sleep abnormality associated with COPD is nocturnal oxygen desaturation.[38,39] Even without any upper-airway contribution, various studies have reported that 27–70% of patients with COPD with awake oxygen saturation of 90–95% can experience substantial desaturation at night, particularly during REM sleep (Fig. 1).[40-42] Nocturnal oxygen desaturation can be defined or measured in terms of oxygen nadir or time below some oxygen-saturation limit, such as 88% or 90%. The desaturation nadir is more profound than during exercise, with oxygen saturation falling an average of 6 ± 4% during peak exercise and 13 ± 9% during sleep.[43] Awake oxygen saturation has the greatest predictive value, although it imperfectly predicts nocturnal desaturation.[44,45] Daytime P_{aCO_2} has also been found to be predictive. Perhaps most clinically relevant, nocturnal oxygen desaturation is a marker of increased mortality in COPD.[46]

Flenley identified 3 mechanisms that might contribute to nocturnal oxygen desaturation: alveolar hypoventilation, decreased ventilation-perfusion matching, and decreased end-expiratory lung volume. Subsequent research has largely confirmed Flenley's initial hypotheses. First, alveolar hypoventilation probably accounts for most of the oxygen desaturation. Becker and colleagues measured minute ventilation during wakefulness, non-REM sleep, and REM sleep in normal subjects and patients with COPD. In normal subjects, minute ventilation changes little, whereas minute ventilation in COPD patients falls approximately 16% from wakefulness to non-REM sleep, and almost 32% during REM sleep, compared to wakefulness, largely as a result of decreased tidal volume.[47] 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.

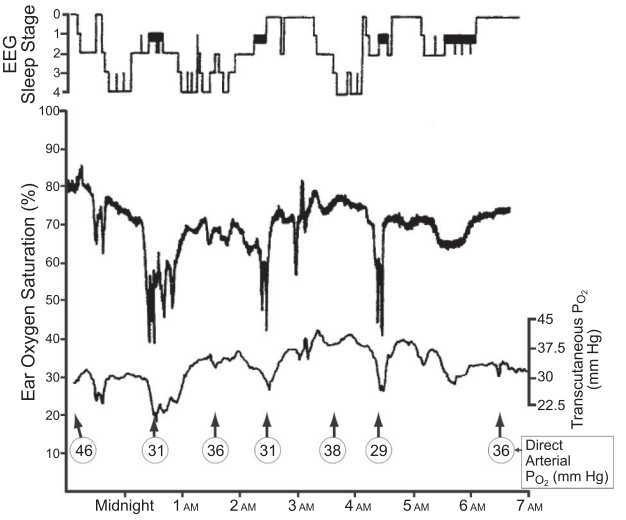

Fig. 1. Example of nocturnal oxygen desaturation. The top graph shows the electroencephalogram (EEG) sleep stages (rapid-eye-movement sleep [REM] in bold). The lower graph shows transcutaneous oxygen measurements during sleep in a subject with COPD. Hypoxemia worsens during sleep, most substantially during REM sleep. (Adapted from Reference 1, with permission.)

An alternative explanation comes from the work by O'Donoghue and colleagues, who found an even greater drop in minute ventilation during non-REM sleep in hypercapnic COPD patients.[48] When the inspired air was changed to a helium-oxygen mixture (heliox, which should relieve some of the flow limitation), minute ventilation remained the same, suggesting that the minute ventilation set-point has changed in COPD patients. Hypoventilation cannot explain all of the observed desaturation, since, while there appears to be a uniform rise in carbon dioxide, P_{O_2} falls a variable amount. Although never directly measured, this suggests that ventilation and perfusion matching is altered during sleep, perhaps due to changes in lung volume that occur with sleep onset and/or REM sleep. There

are conflicting reports on the magnitude of the potential lung-volume change.[48-50]

Consequences of Nocturnal Oxygen Desaturation

Acutely, nocturnal oxygen desaturation causes surges in both systemic and pulmonary blood pressure.[51] It now seems likely that repetitive, transient oxygen desaturation can cause pulmonary hypertension.[52] Various arrhythmias are also reported during episodes of nocturnal desaturation.[36] These consequences might help 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.[53]

Arousals may be related to episodes of desaturation,[31] and consistent with this observation some (but not all) studies have shown supplemental oxygen to improve sleep quality.[54]

Clinical Consequences of Overlap Syndrome

Patients with both COPD and OSA have 2 reasons to have nocturnal oxygen desaturation, and the Sleep Heart Health Study did find that those with both OSA and COPD are at greater risk of prolonged oxygen desaturation at night than those with OSA but without COPD; the degree of obstruction, as measured by FEV_1/FVC, correlates with the risk of prolonged hypoxemia.[28] This more prolonged hypoxemia, or the coexistence of COPD, appears to increase morbidity and mortality considerably, compared to OSA alone.

Just as the term "overlap syndrome" was being coined, Bradley studied 50 consecutive patients with OSA and found that about 10% had evidence of right-heart failure.[55] The risk factors for development of right-heart failure were daytime hypoxemia and a reduced FEV_1. Daytime hypercapnia in patients with OSA was also found to be correlated with a reduced FEV_1.[56] Later larger studies, some of which used right-heart catheterization, have also confirmed the presence of resting and exercise-induced pulmonary hypertension in those with obstructive lung disease and daytime hypoxemia and hypercapnia.[57-60] Even those with severe OSA alone tend not to develop marked pulmonary hypertension if they are free from other cardiopulmonary disease,[61] or the degree of pulmonary hypertension is mild and of uncertain clinical importance.[52,62,63]

For example, Hawrylkiewicz and colleagues observed that 16% of those with OSA had pulmonary hypertension, compared with 86% of those with overlap syndrome.[63] In regression analysis, traditional markers of OSA severity, such as the AHI or oxygen-saturation nadir, have generally not correlated with the presence of pulmonary hypertension. Even patients with COPD and daytime normoxia who have *only* nocturnal oxygen desaturation generally do not develop substantial pulmonary hypertension, which is supported by lack of efficacy of nocturnal supplemental oxygen in treatment trials in this patient population, as discussed below.[64]

Mortality data for patients with the overlap syndrome have not been well studied until recently. While some COPD patients die due to respiratory failure, they more frequently die from cardiovascular disease or malignancy.[65] As above, there is some evidence that these deaths occur predominantly at night. For example, McNicholas reported in 1984 that patients admitted to the hospital with chronic bronchitis or emphysema were more likely to die at night than other admitted hospital patients; deaths were particularly high among so-called "blue-bloaters," and we can speculate that some of these may have had the overlap syndrome.[53] Similarly, OSA patients have also been shown to die (usually of cardiovascular disease) disproportionately during the night, compared to control groups, who are at greatest risk during the morning hours.[66] Ominously for patients with the overlap syndrome, several pulmonary parameters have been shown to increase mortality in patients with OSA. Both the diagnosis of concomitant COPD and markers of COPD such as a reduced FEV_1 or smoking history are markers for increased mortality in OSA patients.[67-69] The largest analysis by Lavie showed that, in a univariate analysis, COPD conferred a 7-fold risk of death in OSA patients.[68]

Conversely, comorbid OSA was recently reported to increase mortality in patients with COPD. Marin and colleagues recently published outcomes data on patients with COPD and patients with the overlap syndrome, both with and without CPAP treatment.[70] Subjects were initially referred to a sleep clinic for suspicion of sleep-disordered breathing (usually snoring), and then underwent a diagnostic polysomnogram and spirometry. After a median follow-up of over 9 years, all-cause mortality was higher in the untreated (no CPAP) overlap group (42.2%) than in the COPD-only group (24.2%). Even when adjusted for COPD severity, comorbid OSA remained a risk factor for death.

Recent work by Mermigkis showed that, in addition to increased morbidity and mortality, patients with the overlap syndrome also have significantly worse quality of life (measured with the St George's Respiratory Questionnaire), when compared to COPD-only controls.[71] Of note, the overlap syndrome patients in their study were COPD patients with habitual snoring but without reported excessive daytime sleepiness or elevated Epworth sleepiness score, which highlights the difficulties with clinical diagnosis and screening. Of these snoring but non-sleepy COPD patients, two thirds had an AHI $>$ 5 events/h.

The exact mechanism(s) that account for this increased morbidity and mortality risk are not known exactly. Increased risk of death may be due to more prolonged hyp-

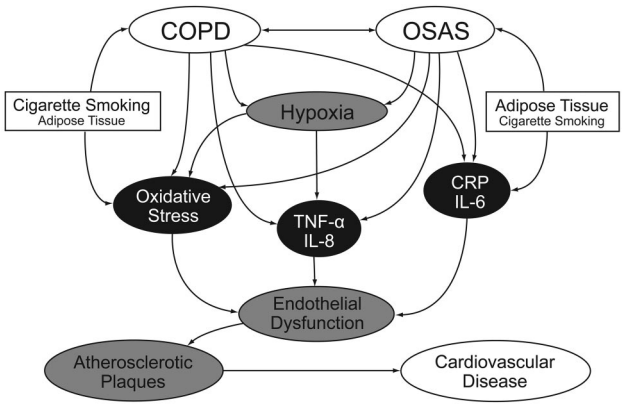

Fig. 2. COPD and obstructive sleep apnea (OSA) are systemic disorders that cause cardiovascular disease via various common pathways. Both inflammatory and oxidative stress pathways may be critical to the pathogenesis of OSA and COPD complications. Hypoxia is central to the pathogenesis of both OSA and COPD, although the continuous hypoxia of COPD may be somewhat different biologically from the intermittent hypoxia of OSA syndrome (OSAS). The study of these pathways is complicated by co-variates, especially smoking and obesity. TNF = tumor necrosis factor. CRP = C-reactive protein. (Adapted from Reference 72, with permission.)

oxia. However, the nighttime hypercapnia is probably also greater in overlap syndrome than in either OSA or COPD alone, and could also be important. There is also increasing evidence that both COPD and OSA have systemic consequences. Both cause inflammation via various mediators (tumor necrosis factor alpha, interleukin-6, and interleukin-8), in addition to the oxidative stress they create. The excellent recent review by McNicholas shows how both diseases act through similar pathways to cause cardiovascular disease (Fig. 2).[72] Whether these mechanisms are additive or synergistic is not known. In the observational study by Marin, death in the untreated overlap group was most commonly attributed to cardiovascular disease.[70] One other intriguing possibility reported in that study is that OSA may contribute to an increased incidence of COPD exacerbations, which may accelerate lung-function decline and are associated with greater mortality.[73,74]

Diagnosis

The most common clinical scenario is a patient known to have either OSA or COPD and subsequently evaluated by a primary care physician, pulmonologist, or sleep specialist. In patients with severe COPD, sleep symptoms are often present. However, in those with more mild respiratory disease (GOLD stage I or II COPD) in the Sleep Heart Health Study, there were only very minor effects of COPD on sleep quality and architecture. Thus, sleep complaints or classic symptoms of OSA in these patients should be evaluated with polysomnography, although this approach

Table 1. Physiologic Variables in Patients With COPD, Patients With OSA Only, and Patients With Both COPD and OSA*

	COPD Group (n = 32)	Overlap Group (n = 29)	Pure OSA Group (n = 152)
Age (y)	60.1 ± 10.4	57.2 ± 9.5	48.9 ± 12.9
Weight (kg)	87.6 ± 17.5	102.2 ± 20.6	106.8 ± 28.8
BMI (kg/m^2)	31 ± 7	36 ± 6	39 ± 10
FVC (% predicted)	60 ± 19	72 ± 17	87 ± 20
FEV_1 (% predicted)	47 ± 16	63 ± 16	89 ± 20
FEV_1/FVC (%)	59 ± 9	67 ± 5	87 ± 9
P_{aO_2} (mm Hg)	69 ± 10	70 ± 11	79 ± 12
P_{aCO_2} (mm Hg)	40 ± 5	45 ± 5	39 ± 4
AHI (events/h)	6 ± 5	40 ± 20	42 ± 23
% Time $S_{pO_2} < 90\%$	16 ± 28	48 ± 28	30 ± 28

* Values are mean ± SD.
OSA = obstructive sleep apnea
Overlap = both COPD and OSA
(Data from Reference 77.)

may underestimate the number of affected patients, since some OSA may be minimally symptomatic but still clinically relevant.[75]

American Thoracic Society/European Respiratory Society guidelines also suggest that those with relatively mild COPD and evidence of pulmonary hypertension should be referred for overnight testing.[76] This recommendation reflects data collected by Chaouat[57] and Resta[77] and emphasized by Kessler[78]: overlap-syndrome patients with pulmonary hypertension often have relatively mild abnormalities, as measured by spirometry or oxygenation, especially when compared to COPD-only patients with pulmonary hypertension (Table 1). For example, overlap patients with pulmonary hypertension have an average FEV_1 of 1.8 L, FEV_1/FVC of 0.64, and awake P_{aO_2} of 64 mm Hg. COPD-only patients with pulmonary hypertension have much more severe obstructive disease, with $FEV_1 < 1$ L, FEV_1/FVC < 0.50, and awake $P_{aO_2} < 55$ mm Hg. Finally, Flenley also advocated polysomnograms for COPD patients with nocturnal oxygen desaturation who developed morning headaches when treated with nocturnal supplemental oxygen.[1,79]

Why patients with overlap syndrome hypoventilate during the day is not known. When measured, their chemosensitivity has been reduced, compared to those with OSA alone, but it is unknown whether this is a cause or an effect of the overlap syndrome.[80] It is interesting to speculate that overlap syndrome patients have either a genetic predisposition to hypercapnia; a change in P_{CO_2} set-point as a result of inflammation, nocturnal CO_2 elevations, and/or obesity (for example, leptin has been implicated as a modulator of respiratory drive[81]); or that the higher P_{CO_2} reflects the increased muscle load in those with both increased upper and lower airway resistance.

Nocturnal oximetry alone is probably not helpful diagnostically in COPD patients, as nocturnal oxygen desaturation could reflect only COPD or some combination of COPD and OSA, and treatment will differ (see below). Definitions of nocturnal oxygen desaturation differ, and physician decision and management based on nocturnal oximetry results differ greatly.[82] Finally, there is little evidence that correction of nocturnal hypoxemia in COPD with only nocturnal desaturation improves outcomes.[64,83]

In patients with OSA, a detailed smoking history and review of respiratory symptoms should be performed, and this alone could prompt pulmonary function testing. OSA patients with daytime hypoxemia or hypercapnia should also undergo investigation for COPD.

Diagnosis of the overlap syndrome is helpful in a number of ways. First, it provides useful prognostic information, which may be helpful in determining the aggressiveness of treatment for either underlying disease. Alerting registered sleep technicians to the diagnosis of COPD may facilitate CPAP titration based on oronasal air flow rather than on oxygen desaturation.[84] Finally, the diagnosis of the overlap syndrome may focus clinicians on assessment for pulmonary hypertension or further diagnostic testing, such as echocardiography or right-heart catheterization.

Treatment

Treatment of the overlap syndrome largely does not differ from treatment of the constituent diseases. The goal of treatment is to maintain adequate oxygenation at all times and to prevent sleep-disordered breathing.

Weight Loss

Weight loss can clearly be of benefit for those with OSA and obesity.[85] However, in COPD, weight loss has generally been associated with increased mortality, since cachexia sets in with increasing disease severity. Thus, there are no data to recommend weight loss as a therapeutic option in those with the overlap syndrome; however, it seems reasonable that those with less severe COPD would benefit from a diet and exercise program.

Oxygen

Supplemental oxygen is the mainstay of treatment for those with daytime *and* nocturnal hypoxemia, and has been shown to improve overall mortality if used for more than 18 hours per day, including during sleep.[13,14] This improvement was seen in comparison to supplemental oxygen administered only at night. It may be that COPD patients with hypoxemia only during sleep are at increased risk of mortality, compared to those who do not, although this finding is based only on a single study of retrospective data.[46] Again, correction of nocturnal hypoxemia alone (in patients with daytime normoxia) does not seem to significantly improve pulmonary hemodynamics or mortality,[64,83] although it may improve sleep quality and is frequently prescribed.[54]

Similarly, data are lacking for improvement with supplemental oxygen therapy alone in OSA.[86] While the degree of nocturnal oxygen desaturation is improved, sleep architecture, arousals, and subjective sleepiness are not impacted,[87] and administration for 2 weeks does not improve blood pressure (which is improved after 2 weeks of CPAP therapy).[88]

Only one study has looked at oxygen administration in the overlap syndrome. Alford and colleagues administered 4 L/min supplemental oxygen to 20 men with both OSA and COPD. While nocturnal oxygenation improved, the duration of obstructive events increased from 25.7 seconds to 31.4 seconds, resulting in an end-apneic P_{CO_2} increase from 52.8 mm Hg to 62.3 mm Hg, with corresponding decreases in pH.[89] Thus, oxygen alone should not be used for the treatment of the overlap syndrome.

Bronchodilators and Corticosteroids

Treatment of the underlying obstructive lung disease is helpful in preventing or ameliorating nocturnal oxygen desaturation in those with COPD. Data exist for the cholinergic bronchodilators ipratropium and tiotropium. Martin and colleagues studied the effect of ipratropium inhaled 4 times a day in 36 patients with moderate to severe COPD ($FEV_1 < 65\%$ of predicted).[90] After 4 weeks, nocturnal oxygen saturation improved, subjective sleep quality was better, and there was an increase in total REM time. Tiotropium also improved nocturnal oxygen saturation, although sleep quality was not affected.[91] Long-acting β-agonists show similar benefits.[92] Oral steroid therapy in stable COPD improves nocturnal oxygen desaturation and increases total sleep time.[93] Although there are no data, we might expect a similar improvement with inhaled corticosteroids. Taken together, the data suggest that treatment of COPD in overlap syndrome will ameliorate nocturnal oxygen desaturation, and may decrease the need for supplemental oxygen in addition to CPAP. Whether treatment of COPD in the overlap syndrome also improves OSA is not known.

Continuous Positive Airway Pressure

CPAP remains the accepted standard treatment for OSA, and currently is the accepted standard for overlap syndrome. But CPAP alone may not fully correct hypoxemia, so supplemental oxygen may be required.[94] Controversy exists as to whether CPAP therapy improves daytime lung function in those with stable COPD. At least in an animal model, upper-airway irritation increased lower-airway re-

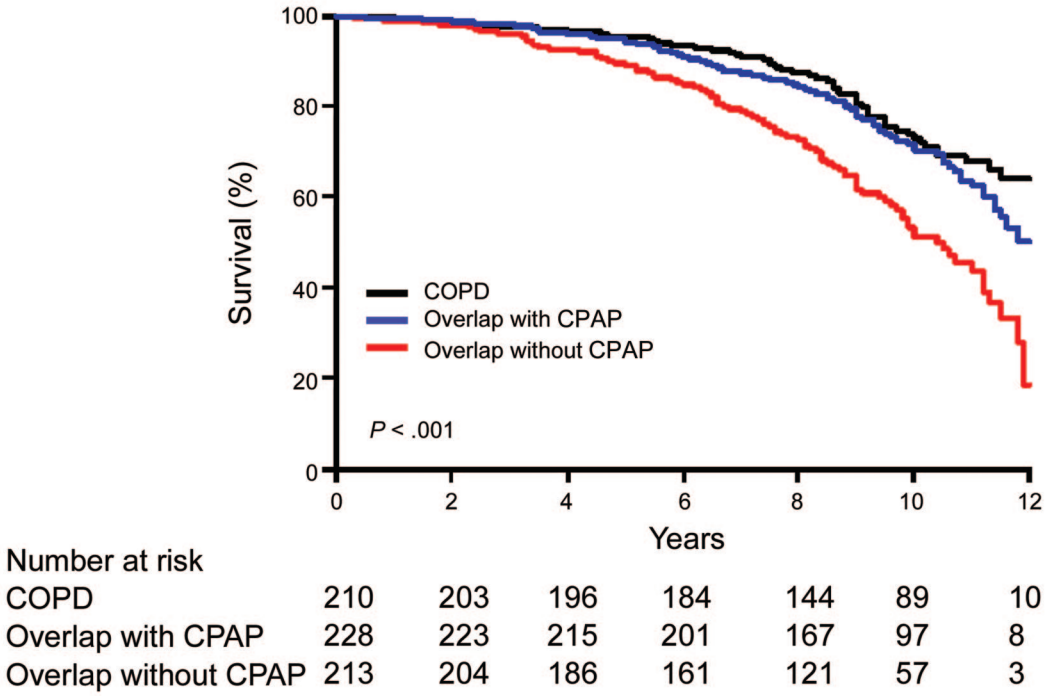

Fig. 3. Kaplan-Meier survival curves for outcomes among COPD patients, overlap patients on CPAP, and overlap patients not on CPAP. CPAP treatment was not randomly assigned, which is a source of potential bias, although markers of disease severity were similar, on average, in the treated and untreated groups. (Adapted from Reference 70, with permission.)

sistance, so, in theory, correction of repetitive airway collapse might improve pulmonary function.[27] Others have postulated that off-loading the respiratory muscles could decrease hypoventilation, oxygen consumption, or carbon dioxide production by the respiratory muscles. These muscles may be rested by CPAP, since it prevents the increase in upper-airway resistance that occurs during sleep. Alternatively, CPAP may offset intrinsic PEEP in severe COPD. In 8 COPD-only patients, Mezzanotte and colleagues applied CPAP for 1–3 weeks and assessed inspiratory force and endurance. They found significant improvements in maximum inspiratory force and 12-min walk test.[95] Improvements have also been observed in daytime oxygenation and hypercapnia,[96,97] and in the number of COPD-related hospital admissions following the start of CPAP treatment for OSA.[98]

Conflicting spirometry results have been seen when CPAP is used in the overlap syndrome. A few small nonrandomized studies have shown improvements in FEV_1, P_{aO_2}, P_{aCO_2}, and mean pulmonary artery pressure (measured via echocardiogram) after CPAP initiation.[96,99,100] For example, the largest study (55 patients), by de Miguel and colleagues, found significant improvements in FEV_1, FVC, and P_{aCO_2} after 6 months of nasal CPAP therapy. However, in that trial (and the recent report from Toraldo and colleagues) substantial weight loss (mean weight loss approximately 15 pounds) could also explain part of the improvement.[99,100] Conversely, in a retrospective trial, O'Brien found that the overlap patients who were most adherent to CPAP had the greatest decline in lung function.[101] This could reflect bias, since those patients with most progressive disease and symptoms may have used CPAP the most (or were urged to do so by their physicians).

Long-term follow-up and outcomes of CPAP therapy in the overlap syndrome have only recently been reported in 2 studies. First, Machado and colleagues reported their experience in a Brazilian cohort of COPD patients referred for long-term oxygen therapy (LTOT).[102] Patients with OSA symptoms were referred for polysomnography, and about 15% of LTOT COPD patients were confirmed to have the overlap syndrome. Although CPAP was prescribed for all of these patients, not all could afford the treatment (which may not be covered by insurance), some were not adherent to CPAP, and others refused treatment. Despite this source of potential bias,[103] the 5-year survival was 71% with CPAP and LTOT, versus 26% with LTOT alone. Marin and colleagues, in a Spanish cohort, reported that CPAP eliminated the additional mortality risk of OSA in overlap patients, compared to COPD-only patients (Fig. 3).[70] Again, CPAP was not provided in a randomized, blinded manner, but markers of both COPD and OSA severity were similar in the CPAP-treated and untreated groups.

Little is also known about morbidity data, although a single report shows that CPAP improves erectile dysfunction in those with the overlap syndrome, which might be a marker of endothelial function.[104]

Noninvasive Ventilation

There has been considerable interest in noninvasive ventilation (NIV) in stable hypercapnic COPD, with multiple (small) studies and inconsistent results over the years.[105] Overlap syndrome patients would seem to be the ideal candidates for NIV, since their standard treatment already involves the discomforts of positive airway pressure and they are chronically hypercapnic, yet their pulmonary function tests alone suggest that they could augment ventilation if needed. Two recent results deserve attention. The first by McEvoy and colleagues was a randomized control trial of NIV in patients with stable hypercapnic COPD, which showed a significant improvement in adjusted mortality.[106] There was little or no change in pulmonary function or daytime blood gases. The improvement in mortality with NIV was associated with a worse quality of life with NIV, which tempers enthusiasm for this approach. A second report by Windisch and colleagues also reported mortality improvements with NIV, though only compared to historical controls. However, those authors used what they call "high-intensity NIV," with very high driving pressure (average inspiratory pressure 28 cm H_2O, average expiratory pressure 5 cm H_2O) and a high respiratory rate (about 21 breaths/min). With those settings, which required in-hospital acclimatization, there were improvements in spirometry and blood gas abnormalities.[107]

The effects of bi-level PAP on overlap syndrome have not been specifically evaluated. However, one study that found benefit from NIV in hypercapnic COPD may have included overlap-syndrome patients.[108,109] Whether long-term NIV would improve outcomes in the overlap syndrome, compared to CPAP, perhaps in addition to supplemental oxygen, is unknown.

Summary

Because OSA and COPD are so common, overlap syndrome is also common. The morbidity and mortality of overlap syndrome is greater than that of either COPD or OSA alone. How the presence of OSA impacts the natural history of COPD is not yet known. When evaluating a patient with either OSA or COPD, a high index of suspicion is crucial to diagnose the overlap syndrome. Daytime hypercapnia and pulmonary hypertension in patients known to have only one disease (either OSA or COPD), mild in severity, should prompt assessment for the other disorder. Currently, CPAP with oxygen therapy as needed is the treatment of choice for overlap syndrome.

Many unanswered questions remain. What levels of OSA and COPD are clinically relevant? For example, at what AHI should a patient with COPD receive treatment with CPAP? Given that many patients with OSA are asymptomatic, which COPD patients without OSA symptoms should undergo a polysomnogram? How do OSA and COPD interact mechanistically to increase morbidity and mortality? Finally, an assessment of NIV in overlap patients is needed.

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Discussion

Dhand: Smoking seems to be a common correlate. Are there data on the effects of smoking on OSA? What would happen to their polysomnography findings if there were no COPD and patients with OSA quit smoking? Also, is there a difference in the effects of bronchodilator therapy on OSA? Beta-agonists or anticholinergics may have an effect on OSA. Do the anticholinergics, for example, have a greater effect on OSA than the beta-agonists?

Owens: Early studies on OSA risk factors identified cigarette smoking as a risk factor,[1] but that never really panned out in later studies. So, as attractive as it may be that smoking would lead to OSA, that's not been shown. If you have someone who was smoking and you did a polysomnography on them, and then they stopped smoking, what would they look like a month or 2 later? Unfortunately, I am not aware of any data to address that question. I think that ex-smokers may have some improvements because there'd be less upper-airway inflammation, but I think that these subjects might also gain weight. Any improvement they might have could be equally offset by change in weight.

About the different kinds of bronchodilators, most of the studies looking at sleep and COPD and bronchodilators completed formal polysomnographys on these patients.[2,3] While they reported nocturnal oxygen saturation and sleep architecture, they did not report AHI. Again, these were patients selected to be without OSA, and by design they were excluded if the baseline AHI was greater than 10 events per hour. So the improvements that they focus on are 2 to 3% improvements in oxygen saturation rather than AHI.

Ipratropium, tiotropium, and salmeterol have been studied.[4] The effects on oxygen saturation seem to be similar between the 2 classes of medication, and for both short and long-acting medications. However, we don't know their potential effect on OSA severity.

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Gay: I want to challenge you on the idea that the overlap syndrome hasn't been studied with NIV. In the mid-1990s we were chasing this holy grail for hypercapnic COPD patients. If you look at the study by Lin,[1] the study we did,[2] and the study by Nick Hill's group,[3] and then the one that was successful, by Meecham Jones's group,[4] you might argue that the last one was really treatment of overlap syndrome. There are some arguments about the way he ventilated them more aggressively than others, but it was still in the 15–18 cm H_2O IPAP [inspiratory positive airway pressure] range. The unique thing about that study was that he allowed those patients to have an AHI of around 10, so that there were mild overlap patients and their transcutaneous CO_2 would go up on oxygen. So I think these were actually overlap patients, and that's the reason that was successful in that so-called COPD group.

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Owens: I think you drew that same conclusion 5 years ago at a similar conference![1] I agree with you that it seems like overlap patients benefit from NIV, but I still think that the level of evidence right now is based on dividing already relatively small trials to get at this. In general, I think that bi-level will probably be effective for hypercapnic patients who "won't breathe"—like overlap patients—but less so for those who "can't breathe"—those with severe COPD. Alternatively, the overlap-syndrome patients might benefit anyway from CPAP alone, just by treating their OSA alone. Again, I think we need to compare CPAP to bi-level PAP in overlap patients to find out.

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Carlin: One of the symptoms is fatigability, particularly when you're looking at guidelines for how to detect patients with the overlap syndrome. Maybe that should be included as part of the expected symptomology, because a substantial percentage of people with COPD have fatigability. Is the fatigability related to their COPD and resultant debilitation, or is it related to the OSA?

Owens: I think your point emphasizes the difficulty of how to define the overlap syndrome, and whether all patients with the overlap syndrome are the same. I'm not sure that adding another relatively subjective criterion such as fatigability would be very helpful. I don't know that fatigue has been so well studied that we can definitively say that it is due to COPD alone or COPD and OSA. However, the number of COPD patients who report fatigue is much greater than the estimates we have for overlap syndrome prevalence. Also, if fatigue is mediated by inflammation or cytokines, either disorder alone could produce fatigue.

Pierson:[*] I think for the predominantly non-sleep-specialist readers of these proceedings your presentation is exceedingly important— for people who manage COPD without as much of a focus on sleep. The COPD patient who isn't doing very well over time should probably be evaluated for a sleep disorder.

Leila [Kheirandish-Gozal] mentioned yesterday the concept of simply trying auto-titration CPAP on patients who strongly met the demographics of OSA. And while we're maybe not there with the COPD patient, you mentioned the epidemiologic association, with maybe 10% of COPD patients having OSA and 10% of OSA patients having COPD. Among patients being followed for COPD who are having frequent exacerbations, and especially who are being readmitted frequently to the hospital—and getting back to Flenley's Venn diagram[1] with the old "blue-bloater" and "pink-puffer" distinction—it seems that the patients who fit into that frequent exacerbation and edema sort of thing would be expected to have a very high incidence of OSA, and that treatment of that in addition to continued treatment of their COPD might be more important.

1. Flenley DC. Sleep in chronic obstructive lung disease. Clin Chest Med 1985;6(4):651-661.

Owens: I agree. I think a key area of future research is the effect of OSA on COPD morbidity and mortality. There is indirect evidence that treatment of OSA reduced hospitalizations for COPD exacerbations,[1] but current guidelines call for polysomnography only for classic OSA symptoms, or for pulmonary hypertension out of proportion to the degree of airflow obstruction, not for exacerbations. I think that in the early studies that looked at COPD patients who showed up in the pulmonary clinics because their COPD was not under good control, the prevalence of overlap syndrome was exceedingly high and argues that OSA is probably important in these types of patients.

In my pulmonary clinic, sleep is the "low-hanging fruit": nobody asks these patients about their sleep. In some pul-

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monary clinics some healthcare providers may not want to know about sleep problems, because they may have limited treatment options. There is hesitancy to prescribe hypnotics, especially in hypercapnic patients—it's just a can of worms they don't want to open.

However, when I started sleep training I found that it was very rewarding to ask people about their sleep and actually make them better. Another reason nobody asks patients about sleep is the little training that most physicians receive in sleep medicine. Atul [Malhotra] and I have talked about this: in internal medicine residency I had no lectures about sleep or CPAP therapy, despite the fact that OSA is so common. I think we could do a better job both in internal medicine and in pulmonary medicine teaching these issues.

1. Peker Y, Hedner J, Johansson A, Bende M. Reduced hospitalization with cardiovascular and pulmonary disease in obstructive sleep apnea patients on nasal CPAP treatment. Sleep 1997;20(8):645-653.

Carlin: I think that holds true for many patients with cardiac disease as well. There has been little research, to my knowledge, on the interaction of OSA—or sleep in general—and COPD regarding symptoms in general. There has been some research in patients with cardiac disease who are undergoing cardiac rehabilitation. The subjective sleep patterns in those patients following completion of rehab were better than when they started the rehab program. Possibly the same is true for patients with COPD, but we really need research to answer that question.

Owens: In the NOTT [Nocturnal Oxygen Therapy Trial] I think they had a 3-week "stabilization" period during which they offered patients pulmonary rehab, and a number of them then no longer met the criteria for receiving oxygen, because their hypoxemia improved.[1] Along those lines, if a patient desaturates a lot during rehab and has an AHI of 8, I'm not sure I would want to diagnose them with either sleep-disordered breathing or overlap syndrome at that time. I agree that patients *after* rehab would be a good population to study, perhaps if they do not improve subjectively during that time, as you suggest. Regardless, I think figuring out what are the most meaningful outcome cut-offs (in terms of COPD or OSA severity) in this disease would be most helpful.

1. Continuous or nocturnal oxygen therapy in hypoxemic chronic obstructive lung disease: a clinical trial. Nocturnal Oxygen Therapy Trial Group. Ann Intern Med 1980; 93(3):391-398.

Quan: Do we have any idea of what adherence or compliance would be with overlap patients using CPAP? I see that sometimes COPD is discovered incidentally; this is the same group of people who have increased prevalence of insomnia, so you'd imagine that they might be less likely to adhere to a CPAP regimen. Do we have any evidence on this?

Owens: I don't know of any data specifically on adherence in that group. Classically, the sleep in patients with COPD is described as poor, with insomnia. In the Sleep Heart Health Study[1] the subjects generally had mild obstructive lung disease, and they tended not to have really substantial changes in their sleep quality. So perhaps their adherence may not be as bad as we think.

1. Sanders MH, Newman AB, Haggerty CL, Redline S, Lebowitz M, Samet J, et al; Sleep Heart Health Study. Sleep and sleep-disordered breathing in adults with predominantly mild obstructive airway disease. Am J Respir Crit Care Med 2003;167(1):7-14.