Title
High prevalence of obstructive sleep apnea in patients with moderate to severe chronic obstructive pulmonary disease

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**Abstract**

**Rationale:** When obstructive sleep apnea (OSA) and chronic obstructive pulmonary disease (COPD) coexist in the so-called “overlap” syndrome, a high risk for mortality and morbidity has been reported. There is controversy about the prevalence of OSA in people affected by COPD.

**Objectives:** The purpose of this study was to investigate objective measures of sleep-disordered breathing in patients with moderate to severe COPD to test the hypothesis that COPD is associated with an increased prevalence of OSA.

**Methods:** Fifty-four patients (54% men) with moderate to severe COPD were enrolled prospectively (mean ± SD, FEV₁ = 42.8 ± 19.8% predicted, and FEV₁/FVC = 42.3 ± 13.1). Twenty patients (37%) were on supplemental oxygen at baseline. Exercise tolerance; questionnaires related to symptoms, sleep, and quality of life; and home polysomnography were obtained.

**Measurements and Main Results:** Forty-four patients had full polysomnography suitable for analysis. OSA (apnea-hypopnea index > 5/h) was present in 29 subjects (65.9%). Sleep efficiency was poor in 45% of subjects.

**Conclusions:** OSA is highly prevalent in patients with moderate to severe COPD referred to pulmonary rehabilitation. Sleep quality is also poor among this selected group. These patients have greater-than-expected sleep-disordered breathing, which could be an important contributory factor to morbidity and mortality. Pulmonary rehabilitation programs should consider including a sleep assessment in patients with moderate to severe COPD and interventions when indicated to help reduce the impact of OSA in COPD.

**Keywords:** obstructive sleep apnea; overlap; sleep-disordered breathing; emphysema; chronic obstructive pulmonary disease; pulmonary rehabilitation
awareness and somewhat vague symptoms, COPD is underappreciated and underdiagnosed.

Obstructive sleep apnea (OSA) is a form of sleep-disordered breathing (SDB) clinically recognized 4 decades ago (7) and defined by total or partial intermittent collapse of the upper airway resulting in nocturnal hypoxemia and arousals from sleep (8). Recent data (2007–2010) indicate an increasing trend, with 26% of adults estimated to have mild to severe OSA (apnea–hypopnea index [AHI] ≥ 5/h) (9).

Prevalence of OSA increases with age, probably similar to COPD (1, 10, 11). Also, COPD as well as OSA symptoms appear slowly over time and therefore can be easily overlooked. Furthermore, the detrimental cardio vascular effects of OSA are well recognized and can be present even in patients without daytime sleepiness (12–14).

The presence of both OSA and COPD was termed the “overlap” syndrome by Flenley (15). The prevalence of OSA among patients with COPD varies across different studies (16, 17). Some epidemiologic studies have reported OSA to be present in about 10 to 15% of patients with COPD, similar to the general population (18–22).

Little is known about the pathophysiological and clinical consequences of having concomitant COPD and OSA. Recent studies have demonstrated that patients with COPD–OSA have a high risk of death as well as increased risk of exacerbations if OSA remains untreated (23, 24). Also, people with COPD–OSA have more profound hypoxemia (both day and night) than patients having either condition alone and may be predisposed to pulmonary hypertension (19). In patients with OSA, the presence of COPD increases the risk of death sevenfold (25). Therefore, evaluating the presence of OSA in patients with advanced COPD seems logical, as concurrence of these diseases may potentially explain the high cardiovascular morbidity and mortality in these patients.

Pulmonary rehabilitation, a well-established treatment for patients with chronic lung diseases, enhances standard therapy and helps to control and alleviate symptoms, optimize function, and reduce medical and economic burdens of disease (26–33). Patients are typically referred for rehabilitation at advanced stages of the disease with associated comorbid conditions.

The prevalence of the overlap syndrome in this at-risk population is unknown. To that end, we investigated sleep characteristics of patients enrolling in a single-site pulmonary rehabilitation program to determine the prevalence and nature of disordered sleep.

Methods

Patients and Study Design

This was a prospective, observational study of patients enrolled in the University of California, San Diego (UCSD) Pulmonary Rehabilitation Program during a 2-year period from September 2010 to August 2012 (Figure 1). Patients presenting sequentially were screened and enrolled based on the following selection criteria: age 40 years or older, diagnosis of COPD confirmed by pulmonary function tests, and important smoke exposure (>10 pack-years accumulated). Experienced staff performed a comprehensive pulmonary rehabilitation assessment. Participants had an overnight full sleep study (polysomnography [PSG]) at home to capture objective measures of sleep. Patients with a previous diagnosis of OSA or those using supplemental oxygen were included. The UCSD Human Subjects Protection Program approved the protocol, and written informed consent was obtained from all subjects.

Measurements

Information obtained from the pulmonary rehabilitation evaluation included: demographics; body mass index (BMI), comorbidities (systemic hypertension, past diagnosis of OSA by self-report, depression, diabetes, and dyslipidemia), current use of medications and supplemental oxygen, and available pulmonary function tests. Exercise tolerance was evaluated with a 6-minute-walk test.

The Pittsburgh Sleep Questionnaire Index (PSQI) was used to assess the quality of sleep. The PSQI consists of 19 items and provides a well-validated global index of sleep quality over the previous 1-month time interval. PSQI greater than 5 is generally considered to be an indicator of poor sleep quality (34). Health-related quality of life was evaluated using the Short Form-36 Health Survey (SF-36), a general health profile. The SF-36 contains 36 items used to evaluate subjects in eight subscales (35). Physical and mental composite summary scores were calculated from the subscales.

An assessment of dyspnea was performed using the UCSD Shortness of Breath Questionnaire, which asks patients to rate the severity of their breathlessness experienced with various daily activities (36). We also measured subjective confidence in exercise capacity using the self-efficacy for walking tool, (37). Self-efficacy for walking was measured with

![Figure 1. Study workflow for patients referred to pulmonary rehabilitation enrolled in the study. COPD = chronic obstructive pulmonary disease.](image-url)
a questionnaire modified from that developed by Kaplan and collaborators (37). The questionnaire assesses efficacy expectations associated with the physical activity of walking. A more detailed explanation about those measures is available in the online supplement.

Objective sleep architecture was measured with a full unattended home overnight PSG with 16-channel portable system (Somte PSG; Compumedics Limited, Abbotsford, Victoria, Australia) to evaluate sleep efficiency and architecture, OSA, and nocturnal oxygen desaturations. The International 10–20 system of electrode placement was used. EEG recordings were critical for the proposed project, because nocturnal oxygen desaturations, arousals, and sleep efficiency are important outcome measures. Based on our data on more than 300 subjects in the Sleep Health and Knowledge in U.S. Hispanics study, we anticipated ∼10% of initial sleep recordings to be deficient. Our laboratory has experience with this procedure and has recorded well over 400 home recordings using the Somte. All data were scored by a blinded certified Registered Polysomnographic Technologist using the 2007 American Academy of Sleep Medicine (AASM) criteria (38).

Criteria from the Sleep Heart Health Study were used to determine the quality of PSG recordings (39). Each record was graded in six categories from Outstanding to Unsatisfactory. Poor and Unsatisfactory grade recordings were not used for analyses. An intrascorer and interscorer reliability was used to validate the findings. Sleep efficiency and apneas were calculated. To identify all physiologically important respiratory events, the 2007 AASM alternative hypopnea definition was used to define hypopneas (i.e., a 50% reduction of airflow amplitude from baseline lasting ≥10 s associated with a ≥3% oxyhemoglobin desaturation and/or an arousal terminating the respiratory event). Arousals were divided into movement, respiratory, and spontaneous (40).

For patients who slept using supplemental oxygen via nasal cannula, the hypopnea definition was modified to also include periods of unequivocal airflow reduction lasting 10 seconds or more regardless of desaturation with or without an arousal. Mean nocturnal oxygen saturation, oxygen desaturation index (drops ≥3% in oxygen saturation, ≥10 seconds, <180 s), and percentage of recorded time spent at an oxygen saturation level less than 90% were recorded. OSA was defined as an AHI greater than or equal to 5/h.

Statistical Analysis
Descriptive statistics were used to characterize measures at baseline. Comparisons of outcomes between subgroups were evaluated by t tests. The relationships among baseline measures of sleep, lung function, exercise tolerance, and psychosocial function were evaluated initially with a correlation matrix. Mean values are presented ±SD. Candidate variables (P < 0.15) were then evaluated further using stepwise, multivariate regression models to explore the interrelationships and independence among these various measures. A P value less than 0.05 was considered statistically significant. All data analyses were conducted using the SPSS 17.0 software package, (SPSS Inc., Chicago, IL).

Results
Fifty-four patients completed the baseline assessment. The participants were generally elderly (age, 67.2 ± 8.1 yr), 54% were men, spirometry demonstrated on average moderate to severe COPD, and 37% had been prescribed long-term supplemental oxygen at the time of the study. Three participants consented but dropped out during initial evaluation due to: COPD exacerbation (n = 2) or declined polysomnography (n = 1). Seven PSG studies (13%) were not suitable for analysis: sleep duration less than 4 hours (n = 2), loss of EEG signal (n = 2), and lost raw data in a hardware malfunction (n = 3). A final sample of 44 subjects was included in the analyses.

Baseline demographic, anthropometric, and spirometric data are presented in Table 1 for all subjects who completed the study. There were no demographic differences between patients who dropped out of the study or had inadequate PSG data. Subjects with COPD-OSA had increased BMI and larger neck circumference, but these measures were not significantly different from those without OSA (P = 0.13 and P = 0.21 respectively). Smoking history was not different between patients with COPD-OSA and OSA only (P = 0.33). OSA (AHI greater than or equal to 5/h) was present in 29 of 44 subjects (65.9%). Only six subjects at baseline (11%) reported having OSA by self-report. Of these, we confirmed OSA in four (severe: n = 2, moderate: n = 2); one subject with a prior OSA diagnosis dropped out of the study because of a COPD exacerbation, and one had loss of EEG signal during polysomnography. New OSA cases represented 85.2% of subjects (23 new cases, 4 previously reported OSA confirmed in our study, and 2 reported OSA but no available PSG).

Mean sleep efficiency was low at 80.8 ± 14.2% (normal, >85%) (41–43). Also, we found abnormal sleep architecture in both groups. As expected, stage 1 sleep was significantly higher in subjects with COPD-OSA than subjects with COPD only (P = 0.04), Table 2.

Table 1. Demographic, anthropometric, and spirometric data (N = 44)

<table>
<thead>
<tr>
<th></th>
<th>All Patients (N = 44)</th>
<th>COPD and OSA (n = 29)</th>
<th>COPD no OSA (n = 15)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/female, %</td>
<td>59/41</td>
<td>62/38</td>
<td>53/47</td>
<td>0.58</td>
</tr>
<tr>
<td>Age, yr</td>
<td>67.8 ± 8.4</td>
<td>68.1 ± 7.6</td>
<td>67.0 ± 10.0</td>
<td>0.68</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>26.9 ± 5.4</td>
<td>27.7 ± 5.2</td>
<td>25.2 ± 5.4</td>
<td>0.13</td>
</tr>
<tr>
<td>Neck circumference, cm</td>
<td>38.4 ± 4.9</td>
<td>39.2 ± 4.7</td>
<td>37.0 ± 5.2</td>
<td>0.21</td>
</tr>
<tr>
<td>Smoking, pack-years</td>
<td>41.8 ± 24.4</td>
<td>44.6 ± 24.5</td>
<td>36.8 ± 24.4</td>
<td>0.33</td>
</tr>
<tr>
<td>Spirometry</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FVC, % predicted</td>
<td>75.5 ± 18.4</td>
<td>76.8 ± 20.0</td>
<td>73.1 ± 15.2</td>
<td>0.53</td>
</tr>
<tr>
<td>FEV₁, % predicted</td>
<td>41.0 ± 18.2</td>
<td>41.6 ± 18.8</td>
<td>39.8 ± 17.8</td>
<td>0.76</td>
</tr>
<tr>
<td>FEV₁/FVC, %</td>
<td>41.5 ± 12.7</td>
<td>41.7 ± 12.4</td>
<td>41.3 ± 13.7</td>
<td>0.94</td>
</tr>
</tbody>
</table>

Definition of abbreviations: BMI = body mass index; COPD = chronic obstructive pulmonary disease; OSA = obstructive sleep apnea.

Data presented as mean ± SD unless otherwise noted.
There were no differences in measures of dyspnea, exercise tolerance, health-related quality of life, quality of sleep, and sleepiness between patients with COPD only and patients with COPD-OSA “overlap.” Overall, subjective sleep quality was poor (mean PSQI, 8.3 ± 4.3; normal ≤ 5).

Results are presented in Table 3. Table 4 reports the sleep data of patients stratified by BMI. As expected, OSA was significantly more prevalent among overweight individuals (77.8% if BMI ≥ 25 kg/m² and 47.1% for BMI < 25 kg/m²; P = 0.04).

Table 5 reports sleep data of patients stratified by use of supplemental oxygen. Those using supplemental oxygen had an AHI greater than or equal to 5/h marginally less frequently than patients who slept on room air (50 vs. 76.9%, P = 0.06, for oxygen use and room air, respectively).

OSA was also marginally more prevalent among younger subjects (age > 65 years, 37% and ≤65 years, 69%; P = 0.06). The presence of OSA was not correlated with the Epworth Sleepiness Scale, insomnia index, sleep quality, dyspnea scale, anxiety/depression scales, exercise tolerance, BODE index (Body-mass index, airflow Obstruction, Dyspnea scale, and Exercise capacity index) (44), or FEV₁. However, BMI did correlate with OSA (r = 0.33, P = 0.03).

Discussion

We observed a high prevalence of SDB in patients with moderate to severe COPD referred to our pulmonary rehabilitation program. The presence of both COPD and OSA coexisting was termed by Flenny as the “overlap” syndrome (15). We have further identified poor sleep quality based on both PSQI questionnaire and low sleep efficiency in full polysomnography in these patients undergoing pulmonary rehabilitation. These findings may be important causative risk factors among patients with COPD (e.g., increased cardiovascular events, reduced quality of life) in afflicted individuals. Furthermore, our study demonstrated that the majority of subjects were naive to the OSA diagnosis, which may be clinically important.

The literature regarding sleep in COPD is somewhat mixed. The Sleep Heart Health study, for example, found no major increase in OSA risk among patients with COPD compared with matched control subjects (18). However, the authors studied a community sample of patients with mild subclinical disease, and thus the findings may not generalize to clinical cohorts. On the other hand, Sharma and coworkers found a high risk of OSA in patients with COPD, but the authors failed to use gold standard polysomnography, and thus the results may be biased by misclassification (45).

In addition to the causes of abnormal sleep seen in a general population and in patients with other chronic diseases, patients with COPD may have particular problems that contribute to poor sleep. More profound arterial hypoxemia (and perhaps associated hypercapnia) are found in patients with COPD-OSA than those with OSA alone (46, 47). In addition, changes during sleep in chemoreceptor sensitivity and ventilatory control, respiratory mechanics, respiratory muscle function, and symptoms such as cough and sputum production may occur in these patients (48–56). Patients with severe emphysema are known to have poor sleep quality. Krachman and collaborators studied 25 patients with COPD and emphysema and found that sleep quality was poor, nocturnal oxygenation desaturations were common, and the measurements of respiratory mechanics and function as well as nocturnal oxygenation desaturations were important predictors of sleep quality (57). It is certainly reasonable to speculate that poor sleep quality is an important contributing factor to the markedly impaired quality of life seen in patients with COPD.

Multiple mechanisms may be implicated in the link between OSA and...
COPD. End-expiratory lung volume has an important impact on pharyngeal mechanics, and thus the hyperinflation associated with COPD may protect against upper airway collapse (58). Conversely, because lung elastic recoil is believed to be important, the dilation and destruction of lung parenchyma seen in emphysema may reduce caudal traction forces believed to stabilize the upper airway.

Regarding body weight, we found a weak correlation ($r = 0.33$) between OSA and BMI, confirming the results of previously published studies demonstrating a relationship between weight and OSA (9, 59). However, in our study, one out of two subjects with a BMI less than 25 kg/m² were found to have OSA, and therefore OSA should be also suspected among nonobese patients with COPD. Although end-stage COPD can be associated with cachexia, which might be predicted to protect against OSA, patients often gain weight after smoking cessation or with systemic glucocorticoid use and, thus, may be predisposed to OSA. As a result, the uncertainty in the literature may reflect differences in study populations, including stages of disease as well as prior pharmacological therapy.

Despite the strengths of our study, we also acknowledge a number of limitations. First, the scoring criteria for SDB in COPD are imperfect. For example, a 3-minute reduction in breathing would be counted as one hypopnea even though it may have serious clinical implications. Thus, we used the gold standard criteria as defined by AASM but recognize the need for further research in this area (38, 60).

Second, although this is the first in-depth report of SDB in patients presenting for pulmonary rehabilitation, our sample size was modest compared with some prior reports in more general COPD populations. We studied a relatively sick homogeneous cohort of pulmonary rehabilitation participants, and thus our findings should not be seen as generalizable to all patients with COPD, specifically those having mild disease. Larger-scale studies are warranted based on our results.

Third, a number of our participants were using oxygen, which could affect the sensitivity of nasal cannula to judge hypopneas. In addition, based on the shape of the oxy-hemoglobin saturation curve, the sensitivity of the pulse oximeter for desaturation may be reduced depending on the baseline saturations while on therapy. The observation that oxygen-treated patients had marginally significant less OSA than those not on oxygen could reflect these methodological limitations but could equally occur as a result of beneficial effects of oxygen on ventilatory control instability (i.e., loop gain) (61).

A selection bias could have occurred, as patients referred to pulmonary rehabilitation have usually more severe disease than those who are managed in regular COPD clinics. However, our intent was to study patients with more advanced disease, as mild COPD has been previously researched. The participants in our research have typical demographic and anthropometric data compared with our usual outpatient COPD clinics. We have also previously observed that patients with advanced COPD do not describe classic OSA symptoms, and thus we doubt that patients with sleep apnea symptoms were more motivated to participate in our study or preferentially enrolled. However, we acknowledge the need for further research in this area to assess the generalizability of our findings. Despite these limitations, we are confident that our findings add to the existing literature.

In summary, in this study we found that a high percentage of patients with moderate to severe COPD referred to pulmonary rehabilitation had OSA, poor sleep efficiency, and poor sleep quality. Supplemental oxygen may be protective in this group of patients. Pulmonary rehabilitation programs may provide unique platforms to incorporate measures of sleep assessment that could eventually benefit this highly selected group of patients.

Table 4. Body mass index and age, apnea-hypopnea index, oxygen desaturation index, and obstructive sleep apnea

<table>
<thead>
<tr>
<th></th>
<th>BMI &gt; 25 kg/m² (n = 27)</th>
<th>BMI &lt; 25 kg/m² (n = 17)</th>
<th>P Value*</th>
<th>All (N = 44)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>66.3 ± 8.2</td>
<td>70.1 ± 8.4</td>
<td>0.15</td>
<td>67.8 ± 8.4</td>
</tr>
<tr>
<td>AHI, events/h</td>
<td>22.8 ± 22.1</td>
<td>11.0 ± 16.8</td>
<td>0.07</td>
<td>18.3 ± 20.8</td>
</tr>
<tr>
<td>ODI, events/h</td>
<td>15.3 ± 20.3</td>
<td>6.0 ± 13.1</td>
<td>0.10</td>
<td>11.7 ± 18.3</td>
</tr>
<tr>
<td>OSA†, %</td>
<td>77.8</td>
<td>47.1</td>
<td>0.04</td>
<td>65.9</td>
</tr>
</tbody>
</table>

Definition of abbreviations: AHI = apnea–hypopnea index; BMI = body mass index; ODI = oxygen desaturation index; OSA = obstructive sleep apnea.

Data are presented as mean ± SD.

*Chi-square test.

Table 5. Apnea-hypopnea index, obstructive sleep apnea, and oxygen desaturation index in patients with and without long-term oxygen therapy.

<table>
<thead>
<tr>
<th></th>
<th>No Supplemental O₂ (n = 26)</th>
<th>Supplemental O₂ (n = 18)</th>
<th>P Value*</th>
<th>All (N = 44)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AHI, events/h</td>
<td>21.6 ± 22.8</td>
<td>13.5 ± 17.0</td>
<td>0.21</td>
<td>18.3 ± 20.8</td>
</tr>
<tr>
<td>OSA†, %</td>
<td>76.9</td>
<td>50.0</td>
<td>0.06</td>
<td>65.9</td>
</tr>
<tr>
<td>ODI, events/h</td>
<td>15.2 ± 18.6</td>
<td>6.6 ± 16.9</td>
<td>0.13</td>
<td>11.7 ± 18.3</td>
</tr>
</tbody>
</table>

Definition of abbreviations: AHI = apnea–hypopnea index; ODI = oxygen desaturation index; OSA = obstructive sleep apnea.

Data are presented as mean ± SD.

*Chi-square test.

†Prevalence using AHI.
References


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