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Obstructive Airway Disease and Obstructive Sleep Apnea: Effect of Pulmonary Function

Bhavneesh Sharma

Division of Sleep Medicine, Harvard Medical School/Brigham and Women's Hospital, Boston, MA 02115, USA

Division of Sleep Disorders Research, Harvard Medical School/Brigham and Women's Hospital, 221 Longwood Avenue, BLI 035M, Boston, MA 02115, USA

Steven Feinsilver

Division of Pulmonary and Critical Care Medicine, New York University School of Medicine, New York, NY 10016, USA

Robert L. Owens

Divisions of Pulmonary and Critical Care and Sleep Medicine, Harvard Medical School/Brigham and Women's Hospital, Boston, MA 02115, USA

Atul Malhotra

Divisions of Pulmonary and Critical Care and Sleep Medicine, Harvard Medical School/Brigham and Women's Hospital, Boston, MA 02115, USA

David McSharry

Division of Sleep Medicine, Harvard Medical School/Brigham and Women's Hospital, Boston, MA 02115, USA

Stephen Karbowitz

Division of Pulmonary and Critical Care Medicine, Weill Cornell Medical College/New York Hospital Queens, Flushing, NY 11355, USA

Abstract

This study sought to determine whether reduced pulmonary function in obstructive airway disease (OAD) is an independent risk factor for obstructive sleep apnea (OSA). This was a prospective observational study conducted at an outpatient pulmonary clinic. Adults with a known diagnosis of COPD/asthma were enrolled as OAD group. Family members without a history of COPD/asthma who accompanied these patients to the clinic were enrolled as a control group. The Berlin Questionnaire (BQ) was used to assess OSA risk in the OAD group and controls. Forced expiratory volume in 1 second (FEV₁ % predicted) was determined from spirometry. The subjects at high risk for OSA were referred for a full overnight polysomnogram (PSG). The prevalence of patients with a high risk of OSA was 55.2% in the OAD group, which was higher than in the controls (7.5%, $p < 0.0001$). OAD subjects had a higher body mass index (BMI) and larger neck circumference than controls ($p < 0.01$). There was no difference in FEV₁ % predicted between the OAD patients at high risk and low risk of OSA. On receiver operator curve (ROC) analysis, FEV₁ % predicted was not a significant predictor of high OSA risk. Using logistic regression, FEV₁ % predicted had no association with OSA risk. There was no correlation between FEV₁ % predicted and total apnea-hypopnea index (AHI), oxygen desaturation index, % time spent below oxygen saturation 90%, and mean oxygen saturation on multiple regression analysis. OSA appears to be

common in patients with COPD or asthma in an urban outpatient pulmonary clinic. However, the high prevalence of OSA in OAD patients appears to be due to obesity, and reduced pulmonary function is not an independent risk factor for OSA.

Keywords

Asthma; Chronic obstructive pulmonary disease; COPD; Lung; Obstructive sleep apnea; OSA; Pulmonary function

Introduction

Obstructive sleep apnea (OSA) is a common disease with a prevalence estimated at 10–20% in the adult population [1, 2]. Several studies have investigated the association between OSA and obstructive airway disease (OAD), including both asthma and chronic obstructive airway disease (COPD). A high prevalence of OSA has been reported in asthma clinics [3], and asthma may also be common in OSA [4]. Several reports stress that OSA may somehow contribute to asthma symptoms and severity. First, OSA is common in a difficult-to-control asthma clinic. Second, OSA prevalence increases with asthma severity [5], being particularly common in difficult-to-control asthma patients receiving chronic oral corticosteroid therapy [6]. Third, OSA appears to be a risk factor for frequent asthma exacerbations [7]. However, asymptomatic asthma decreased the likelihood of OSA in a pediatric population [8]. Thus, the association between asthma and OSA has been inconsistent in the literature.

The coexistence of COPD and OSA in patients has been termed the overlap syndrome [9]. Early small studies showed a high prevalence of OSA in COPD and vice versa [10, 11]. However, these studies may have had selection bias. The more recent Sleep Heart Health Study (SHHS), a large community-based cohort study, showed no increase in prevalence of OSA in mostly mild OAD patients compared to the general population [12]. Similar results were shown by Bednarek et al. [13] in a Polish cohort with predominantly mild COPD. Regardless of whether the two diseases are mechanistically linked, overlap syndrome patients have more severe nocturnal hypoxemia, hyper-capnia, and pulmonary hypertension than OSA-alone patients, which likely has important clinical consequences [13]. For example, it was recently reported that overlap syndrome patients have greater mortality compared with either OSA alone or COPD alone [14].

Thus, although clinically relevant, an independent association between OAD and OSA has not been proven, and it is not known if reduced pulmonary function in OAD is an independent risk factor for OSA. We performed a pulmonary clinic-based study to test the hypothesis that reduced pulmonary function due to OAD is an independent risk factor for OSA.

Methods

Adults 18 years or older and with a known diagnosis of COPD or asthma, excluding pregnant women, who attended our pulmonary clinic between September 2008 and February 2010 were approached for enrollment in our study as members of the OAD group. Adult family members who were 18 years or older and with no known history of COPD or asthma (excluding pregnant women) who accompanied the OAD patients to the clinic were approached for enrollment in the study as a control group. OAD patients and control subjects with known OSA were excluded. The study was approved by the institutional review board and all participants gave their informed written consent.

After informed written consent was obtained, the Berlin Questionnaire (BQ) [15] was used to assess OSA risk in OAD and control subjects. The subject was considered to be at high risk for OSA if two of three categories of questions were positive in the BQ. Focused physical examination to determine any upper-airway abnormalities and measurement of neck circumference and body mass index (BMI) was performed. All subjects and controls also filled out a questionnaire regarding duration of OAD, smoking history, duration of OSA symptoms, other comorbid conditions, and medications.

Forced expiratory volume in 1 second (FEV₁ % predicted) was determined from spirometry done within the prior 6 months in the OAD group. If a subject did not have spirometric data available within the prior 6 months, repeat spirometry was done according to the guidelines of the American Thoracic Society [16].

Only the subjects found to be at high risk for OSA were referred for full overnight polysomnogram (PSG). Each subject was instrumented for recording beginning 1 h before their normal bedtime. Each subject was recorded for at least 8 h during the night. Sleep was monitored and staged using standard electroencephalogram (EEG), electromyogram (EMG), and electro-oculogram (EOG) techniques. During the polysomnogram, nasal and oral airflow (using thermistor), nasal pressure (using transducer), chest and abdominal wall motion (using piezo electrodes), electrocardiogram (EKG), anterior tibialis EMG, and arterial oxygen saturation were monitored. All signals were acquired using the computerized sleep recording system Morpheus™ (SleepMed Inc., Columbia, SC). Apneas and hypopneas were defined using the American Academy of Sleep Medicine (AASM) criteria [17]. Hypopneas were defined as airflow reduction ≥30% and desaturation ≥4%. Each 30-s epoch was scored by a registered polysomnographic technologist (RPSGT), and the polysomnogram was interpreted by a board-certified sleep specialist. OSA was considered to be present if the apnea–hypopnea index (AHI) was ≥15/h or ≥5/h with documented symptoms of excessive daytime sleepiness, impaired cognition, mood disorders or insomnia, or documented hypertension, ischemic heart disease, or history of stroke.

Statistical Analysis

The differences in proportions between the groups were compared using Fisher's exact test. The differences in means between the groups were compared using the independent *t* test (if the data had Gaussian distribution) or the Mann-Whitney *U* test (if the data had non-Gaussian distribution). Receiver operator curve (ROC) analysis using the log-rank test was done to determine the correlation of FEV₁ with OSA risk and AHI. Logistic regression analysis was done with age, BMI, neck circumference, duration of OAD, duration of smoking, and FEV₁ as independent variables, and OSA risk as the dependent variable. All *p* values less than 0.05 were considered significant. All analyses were performed using Medcalc ver. 11.3 (Medcalc software, Mariakerke, Belgium).

Results

Eighty-five subjects with a known history of OAD were eligible for participation in our study. Sixty-seven subjects consented to participate in the study and were included in the analysis as the OAD group. The OAD group had 38 COPD subjects (56.7%) and 29 asthma subjects (43.3%). The mean FEV₁ (% predicted) in the OAD group was 70.9% (95% CI = 66.7–75%). Seventy-five family members were eligible for the control group; 40 consented to participate in the study and were included in the analysis as controls. The characteristics of the study groups are given in Table 1.

The OAD subjects were older and had a higher body mass index (BMI) and larger neck circumference than the controls (*p* < 0.001). The prevalence of subjects with a high risk of

OSA in the OAD group was higher than in the control group (55.2 vs. 7.5%, $p < 0.0001$). Even when considered separately, both COPD (50 vs. 7.5%, $p < 0.0001$) and asthma groups (62.1 vs. 7.5%, $p < 0.0001$) had a higher prevalence of high-OSA-risk subjects than control subjects. The mean duration of onset of OSA symptoms in OAD subjects was 5.3 years.

Correlation Between OAD and OSA Risk

There was no difference in FEV₁ % predicted between the OAD subjects at high risk and at low risk of OSA (72.5 vs. 69.5%, $p = 0.55$). Even when the COPD (67.1 vs. 66.7%, $p = 0.85$) or the asthma (77.2 vs. 74.3%, $p = 0.67$) group was analyzed separately, there was no difference in FEV₁ % predicted between subjects at high risk and at low risk of OSA.

On ROC analysis by log-rank test in the OAD group (both COPD and asthma), FEV₁ % predicted (area under curve [AUC] = 0.49, $p = 0.88$) was not a significant predictor of high OSA risk (Fig. 1). Even when the asthma group (AUC = 0.55, $p = 0.67$) or the COPD group (AUC = 0.52, $p = 0.85$) was analyzed separately, FEV₁ % predicted did not correlate with OSA risk on ROC analysis.

Using logistic regression, FEV₁ % predicted had no association with OSA risk (odds ratio [OR] = 1.0, coefficient = 0.004, $p = 0.81$) (Table 2). BMI was the only factor that had a significant association with OSA risk (OR = 1.19, $p = 0.009$).

PSG Data

Patients found to be at high risk for OSA were subsequently referred for PSG testing. PSG data was available for 26 of 37 OAD patients (both COPD and asthma) who were found by the BQ to be at high risk for OSA. PSG testing was not performed on all subjects (such as those with low risk by BQ) due to cost. Of the 26 high-OSA-risk patients who had PSG done, PSG was diagnostic of OSA in 24 patients but was negative for OSA in 2 patients. The mean total AHI in the OSA group was 17.1/h. Predominantly rapid eye movement (REM)-related AHI was seen in 16 patients (61.5%). The positive predictive value of the BQ to diagnose OSA in our OAD group was 92.3%.

There was no correlation between FEV₁ % predicted and total AHI ($p = 0.69$), % time spent below oxygen saturation 90% ($p = 0.3$), oxygen desaturation index ($p = 0.14$), and mean oxygen saturation ($p = 0.23$) on multiple regression analysis.

Discussion

There are two major findings of our study. First, patients in an urban outpatient pulmonary clinic with OAD are very frequently at high risk for OSA. Second, our data did not support our hypothesis that the degree of airway obstruction as measured by spirometry predicted OSA risk or OSA severity.

Poor sleep has classically been reported among both COPD and asthma patients [18]. Therefore, many practitioners may attribute sleep difficulties or sleep symptoms to these respiratory diseases rather than investigate for obstructive sleep apnea. In particular, asthma guidelines (e.g., Global Initiative for Asthma [GINA]) [19] stress treatment escalation for nocturnal awakening but do not give clear guidelines for PSG referral. These assumptions may explain the long delay between symptom onset and OSA diagnosis in our cohort. Patients, too, may have a tendency to under-report poor sleep symptoms (possibly attributing them to underlying lung disease), or there may be a tendency among pulmonologists not to pay close attention to sleep-related symptoms in general. Of note in the SHHS, those with mostly mild OAD (but no OSA) did not have substantial impairment

of sleep quality. Thus, sleep symptoms should not automatically be attributed to OAD, particularly if OAD appears otherwise well controlled.

Because, as discussed earlier, OSA may contribute to asthma and COPD morbidity and mortality, our study has resulted in a paradigm shift in our pulmonary clinic. OSA is now a common disease in our pulmonary clinic as these patients are now seen regularly for their OSA treatment as well. Thus, we hope that our study has resulted in improved clinical care and perhaps better prognosis in these OAD patients. Our study suggests that OSA is common in COPD or asthma patients in outpatient pulmonary clinics, and pulmonologists should consider screening for OSA symptoms in these patients.

The BQ had not been validated earlier in outpatient COPD or asthma patients. As evident from our study, the BQ has high positive predictive value (92.3%) to diagnose OSA in COPD/asthma patients in an urban, outpatient pulmonary clinic. Even simple screening using the BQ, which takes only a few minutes to administer, can help diagnose OAD patients as high-OSA-risk patients. Because our low-risk patients did not undergo PSG testing, we are unable to assess the negative predictive value of this tool in this patient population.

Despite our a priori hypothesis, we did not find an association between pulmonary function and OSA (using OSA risk by BQ as well as total AHI in the subset with confirmed OSA). The data available have shown conflicting results so far, with one study showing an association between severity of asthma and OSA prevalence in asthma patients [5], while another study in asthma patients showed a negative association between pulmonary function and OSA [3].

If there is a link between OSA and OAD, it appears not to be mediated via airway obstruction per se. It is interesting to speculate then on other possible mechanistic links. The OAD group had higher BMI and larger neck circumference compared to controls, and thus the high prevalence of OSA in our OAD group could be attributed to obesity [20]. Obesity could be an effect of OAD or OAD treatment. COPD or asthma patients may be less physically active due to respiratory symptoms. Also, a high prevalence of obesity in these patients could be weight gain related to high doses of inhaled corticosteroids or oral corticosteroids. In fact, inhaled corticosteroid dose is an independent predictor for snoring in asthma [21]. Inhaled corticosteroids may also contribute to OSA in COPD or asthma patients by causing upper airway myopathy or, alternatively, extrapulmonary inflammation may impair upper airway reflexes or neuromuscular responses [22, 23]. Increased end-expiratory lung volume can tether open the upper airway through caudal traction forces [24], which would be predicted to improve apnea in patients with hyperinflation due to severe OAD. Could hyperinflation due to severe OAD be a protective mechanism from the standpoint of OSA? On the other hand, loss of lung elastic recoil may reduce the effectiveness of lung volume stabilizing the upper airway, at least in patients with emphysematous changes. Further investigation into all these mechanisms is clearly needed.

Our study has some limitations. First, it included selected patients from a single medical center, which could affect our generalizability. Thus, our conclusions are limited to the sample studied; however, we believe that our results are probably applicable to most urban outpatient pulmonary clinics. Similarly, the study subjects were enrolled from a referral pulmonary clinic. In theory, this could suggest more severely symptomatic patients (thus requiring specialty clinic care), or those receiving more optimum care than those managed by primary-care providers alone. Second, we estimated OSA risk using the BQ, and PSG was not done in all OAD patients due to cost. Although the BQ had not been validated earlier for OSA diagnosis specifically in COPD or asthma patients, the high-risk group using

the BQ predicted a respiratory disturbance index (RDI) greater than 5 with a sensitivity of 0.86, a specificity of 0.77, a positive predictive value of 0.89, and a likelihood ratio of 3.79 in another study [3]. Moreover, the BQ had a 92.3% positive predictive value to diagnose OSA in our OAD study group (with the limitation that not all of our high-risk BQ patients underwent gold-standard testing). Finally, our subjects had generally mild and/or well-controlled OAD, so that we are unable to assess the relationship between severe untreated OAD and OSA.

In conclusion, this study shows that OSA appears to be common in patients with COPD or asthma in an urban outpatient pulmonary clinic. However, the high prevalence of OSA in OAD patients appears to be due to obesity since reduced pulmonary function is not an independent risk factor for OSA. Further mechanistic research is needed to determine other factors that contribute to OSA in OAD patients.

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Fig. 1. Receiver operator curve analysis showing negative association between FEV% and OSA risk in obstructive airway disease patients (including both COPD and asthma). *COPD* chronic obstructive pulmonary disease, *FEV₁* forced expiratory volume in 1 s, OSA obstructive sleep apnea

Table 1

Characteristics of the study subjects

Characteristic	OAD group (<i>n</i> = 67)	COPD (<i>n</i> = 38)	Asthma (<i>n</i> = 29)	Control subjects (<i>n</i> = 40)
Age (years)	57.7 (54.2–61.2)	61.34 (56.5–66.1)	52.2 (47.4–57.1)	52.2 (48.8–55.5)
Male sex (%)	26.8	34.2	16.7	32.5
BMI (kg/m ²)	32.9 (30.8–34.9)	31.1 (28.9–33.3)	35.1 (31.3–38.7)	26.7 (25.4–28.1)
Neck circumference, inches	16.5 (16.3–16.7)	16.5 (16.2–16.7)	17 (16.1–17.9)	15.3 (15.1–15.5)
Past smokers (%)	65.7	89.5	23.3	20
Pack-years of smoking (<i>n</i>)	23.3 (18.4–28.3)	21.9 (16.5–16.7)	3.6 (0.3–7)	8.1 (6.3–10.5)
High OSA risk (%)	55.2	50	62.1	7.5

Data is presented as mean (confidence interval)

BMI body mass index, *COPD* chronic obstructive pulmonary disease, *OAD* obstructive airway disease, *OSA* obstructive sleep apnea

Table 2

Logistic regression analysis using age, BMI, duration of OAD, duration of smoking, FEV%, and neck circumference as independent variables and OSA risk as dependent variable (there was no association between FEV% and OSA risk)

Variable	Odds ratio	95% CI	<i>p</i> value
Age	0.99	0.95–1.04	0.87
BMI	1.19	1.04–1.35	0.009*
Duration of OAD	1.01	0.95–1.07	0.69
Duration of smoking	0.98	0.95–1.02	0.46
FEV1%	1.0	0.97–1.04	0.81
Neck circumference	1.22	0.89–1.45	0.76

CI confidence interval, *BMI* body mass index, *FEV1* forced expiratory volume in 1 s, *OAD* obstructive airway disease

* Significant *p* value