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Associations of Moderate to Severe Asthma with Obstructive Sleep Apnea

Min Kwang Byun,[1] Seon Cheol Park,[2] Yoon Soo Chang,[1,3] Young Sam Kim,[2,3] Se Kyu Kim,[2,3] Hyung Jung Kim,[1,3] Joon Chang,[2,3] Chul Min Ahn,[1,3] and Moo Suk Park[2,3]

[1]Division of Pulmonology, Department of Internal Medicine, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul;
[2]Division of Pulmonology, Department of Internal Medicine, Severance Hospital, Yonsei University College of Medicine, Seoul;
[3]The Institute of Chest Diseases, Yonsei University College of Medicine, Seoul, Korea.

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Corresponding author: Dr. Moo Suk Park, Division of Pulmonology, Department of Internal Medicine, Severance Hospital, Yonsei University College of Medicine, 50 Yonsei-ro, Seodaemun-gu, Seoul 120-752, Korea.
Tel: 82-2-2228-1974, Fax: 82-2-393-6884
E-mail: pms70@yuhs.ac

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Purpose: This study aimed to evaluate the correlation between associating factors of moderate to severe asthma with obstructive sleep apnea (OSA). **Materials and Methods:** One hundred and sixty-seven patients who visited the pulmonary and sleep clinic in Severance Hospital presenting with symptoms of sleep-disordered breathing were evaluated. All subjects were screened with ApneaLink. Thirty-two subjects with a high likelihood of having OSA were assessed with full polysomnography (PSG). **Results:** The mean age was 58.8±12.0 years and 58.7% of subjects were male. The mean ApneaLink apnea-hypopnea index (AHI) was 12.7±13.0/hr. The mean ApneaLink AHI for the 32 selected high risk patients of OSA was 22.3±13.2/hr, which was lower than the sleep laboratory-based PSG AHI of 39.1±20.5/hr. When OSA was defined at an ApneaLink AHI ≥5/hr, the positive correlating factors for OSA were age, male gender, and moderate to severe asthma. **Conclusion:** Moderate to severe asthma showed strong correlation with OSA when defined at an ApneaLink AHI ≥5/hr.

Key Words: Apnea-hypopnea index, ApneaLink, asthma, obstructive sleep apnea, sleep-disordered breathing

INTRODUCTION

Obstructive sleep apnea syndrome (OSA) is characterized by repeated episodes of upper airway obstruction that results in brief periods of breathing cessation (apnea) or a marked reduction in airflow (hypopnea) during sleep. OSA is the most severe form of obstructive sleep-disordered breathing (SDB). OSA is a common disorder with a prevalence estimated at 10-20%.[1,2] Risk factors for OSA include male gender, age, obesity, and nocturnal nasal congestion.[2] A population-based study in Korea reported the prevalence of OSA was 4.5% and 3.2% in men and women, respectively.[3]

Previous epidemiologic studies demonstrated that patients with asthma have an increased risk of OSA.[4-6] In an Australian longitudinal study, asthma was an independent risk factor for the development of habitual snoring.[7] A prospective cohort study showed a high prevalence of OSA in patients with difficult-to-control asth-

ma.[8] On the contrary, OSA may aggravate asthma because treatment for OSA has been shown to improve asthma symptoms.[9] The National Asthma Education and Prevention Program Expert Panel Report recommends OSA evaluation because it is a potential contributor to poor asthma control.[10] For such reasons, a more specific understanding of what increases a predisposition for OSA would be useful.

It has been suggested that gastroesophageal reflux disease (GERD), postnasal drip syndrome, and obesity may contribute to the development of OSA, but the role of each of these conditions in OSA has not been studied.[11,12] To date, many studies have investigated the risk or prevalence of OSA in asthma patients; however, there is lack of data concerning the prevalence of asthma in high-risk OSA patients. Therefore, we investigated the predisposing factors of moderate to severe asthma in high OSA risk patients and assessed possible associations to predict other risk factors for OSA.

Although sleep laboratory-based polysomnography (PSG) is currently regarded as the gold standard for the diagnosis of sleep apnea,[13] it is labor-intensive, costly, and has limited availability.[14] The use of a portable recording device such as the ApneaLink for screening sleep apnea has some potential advantages in terms of cost, convenience, and better sleep quality for patients.[15] Portable recording devices may be used as an alternative to PSG for the diagnosis of OSA in patients with a high pretest probability of moderate to severe OSA.[16] Recently, two studies validated the use of ApneaLink for the screening of sleep apnea compared with PSG.[17,18] As such, we used ApneaLink for OSA screening to estimate the predisposing factors of moderate to severe asthma in high OSA risk patients and to assess possible associations to predict other risk factors for OSA.

MATERIALS AND METHODS

Subjects

All subjects were adults age ≥18 years that visited the pulmonary and sleep clinic at Severance hospital from February 2007 to August 2008 with symptoms of daytime sleepiness, choking and gasping during sleep, recurrent awakenings from sleep, unrefreshed sleep, daytime fatigue, and impaired concentration.[13,19]

The enrolled patients were checked for diagnoses of lung and other comorbidities. Patients diagnosed with asthma were categorized by severity according to the American Thoracic Society criteria[20] and difficult asthma study.[21]

Severe asthma required at least one of the following major criteria: daily oral steroid use for >50% of the previous 12 months or a high-dose inhaled steroid (≥1000 mg/day fluticasone or equivalent) and at least one additional continuous add-on therapy for ≥12 months. Severe asthma also required at least two of the following minor criteria: use of a daily short-acting β-agonist, a persistent forced expiratory volume in one second (FEV_1) <70%, a predicted forced vital capacity (FEV_1/FVC) of <80%, at least one urgent visit or at least three steroid bursts in the last 12 months, prompt deterioration with <25% steroid dose reduction, or a previous near-fatal asthma attack within the last three years.

Moderate asthma was defined as well-controlled asthma symptoms, the use of a long-acting β-agonist at ≥200 mg/day and fluticasone (or an equivalent) at ≤1000 mg/day, at least two steroid bursts in the past year and none within the last three months, <30 total days on oral steroids within the last 12 months, a predicted FEV_1 of >70%, and at least one unscheduled clinical visit within the previous 12 months.

Asthma was defined as a positive response to 1) being diagnosed with asthma, 2) having wheezed in the last 12 months, 3) taking corticosteroids and objective evidence of variable airway obstruction, following the diagnostic criteria of Global Initiative for Asthma (GINA) guidelines. Additionally a demonstration of a positive bronchodilator test (increase in FEV_1 ≥12% and 200 mL) or a positive methacholine challenge test within the previous year was required.

Pregnant women and patients with significant cognitive impairment, a poorly controlled psychiatric disorder, or who had previous treatment for OSA were excluded.

All subjects provided informed consent to join the study. The Institutional Review Board of the Clinical Research Institute of Severance Hospital, Yonsei University College of Medicine, approved the study protocol (IRB number: 4-2011-0448).

Design

This was a cross-sectional study. Patients presented with symptoms of SDB were enrolled. All subjects agreed to use the ApneaLink device at home for one night after being instructed on the use of the device by an experienced sleep technician. Subjects returned the ApneaLink device to the pulmonary and sleep clinic the following morning, and the data were downloaded and analyzed. Patients with a high likelihood of having OSA were assessed with full PSG within 2 weeks after the ApneaLink study. We investigated all established diagnoses of lung and other comorbidities at en-

rollment, such as bronchial asthma, chronic obstructive pulmonary disease (COPD), GERD, rhinitis, diabetes, cardiovascular disease, and habitual snoring. Past smoking and body mass index (BMI) were also identified. In patients with asthma, current and previous asthma medications were recorded and recent spirometry data was collected to assess asthma severity.

Device

The ApneaLink™ device (ResMed, Sydney, Australia) is a portable single-channel screening tool for sleep apnea. The device consists of a nasal cannula attached to a small case that houses a pressure transducer. The ApneaLink software analyzes data generated by the flow signal, producing a report that provides information regarding snoring and inspiratory flow limitation; only the apnea-hypopnea index (AHI) information was used for this study. The ApneaLink default settings for apnea and hypopnea were used in this study. Apnea was defined as a decrease in airflow by 80% of baseline for at least 10 seconds and hypopnea was defined as a decrease in airflow by 50% to 80% of baseline for at least 10 seconds. The ApneaLink AHI was automatically analyzed by the ApneaLink software version 6.0.

The overnight in-lab diagnostic PSG (Comet-PLUS® XL, Grass Technologies, Warwick, RI, USA) included a recording electro-encephalogram (EEG), electrooculogram, submental electromyogram (EMG), bilateral anterior tibialis EMG, electrocardiogram, chest and abdominal wall movement by inductance plethysmography, and airflow measured by a nasal pressure transducer. The equipment was supplemented with an oral thermistor and finger pulse oximeter.[19,22] PSG scoring was performed according to internationally agreed criteria.[13] Apnea was defined as a cessation of nasal flow lasting 10 seconds or longer. Hypopnea was defined as a 50% decrease in nasal flow lasting at least 10 seconds or a discernible decrease leading to an at least 3% oxygen desaturation or an EEG arousal.

Statistical analysis

Data was analyzed using SPSS for windows, version 18.0 (SPSS Inc., Chicago, IL, USA). A Bland-Altman plot is a graphic representation of the observed differences between paired measurements. The differences between ApneaLink and PSG were plotted against the averages of the two methods. Results showing a mean difference close to zero indicate little systemic bias. Correlation analysis was carried out using Pearson correlation coefficients. The *p*-values of <0.05 were considered statistically significant. Multivariate logistic regression analysis was used to predict independent risk factors for OSA (age, gender, asthma, diabetes, cardiovascular disease, habitual snoring, and obesity) that demonstrated statistically significant univariate relationships. We defined mild OSA as 15>AHI≥5/hr, and moderate OSA as 30>AHI≥15/hr, and severe OSA as AHI≥30/hr, according to the severity criteria by an American Academy of Sleep Medicine.[13]

RESULTS

Patient characteristics

One hundred and sixty-seven subjects who visited the pulmonary and sleep clinics as well as complained of habitual snoring, OSA, and excessive daytime sleepiness completed the ApneaLink study. Of the 167 patients, 32 (19.2%) patients with a high likelihood of having OSA were assessed with full PSG within 2 weeks after the ApneaLink study. Thirty-two who patients performed PSG were selected by physician's decision according to definite symptoms of OSA without objective criteria. The characteristics of the

Table 1. Demographics and Characteristics of ApneaLink Screened 167 Patients

Characteristics	Total	ApneaLink screened patients (n=167)		
		AHI ≥5/hr	AHI <5/hr	*p* value
n (%)	167 (100)	111 (66.5)	56 (33.5)	-
Age, yrs (mean±SD)	58.8±12.0	60.1±9.9	56.0±14.9	0.070
Men, n (%)	98 (58.7)	80 (72.1)	18 (32.1)	<0.001
BMI, kg/m^2 (mean±SD)	25.3±3.8	25.5±4.1	24.8±3.3	0.311
Smoking				
Current of past smokers, n (%)	80 (47.9)	67 (60.4)	13 (23.2)	<0.001
Pack-yrs (mean±SD)	32.4±18.2	33.4±17.8	26.7±19.5	0.231
Habitual snoring, n (%)	91 (54.5)	63 (56.8)	28 (50.0)	0.408

AHI, apnea-hypopnea index; BMI, body mass index; Pack-years, (Packs smoked per day) × (years as a smoker); SD, standard deviation.
Data are presented as the mean±SD and No. (%).

167 patients who were screened with the ApneaLink study are shown in Table 1.

The mean age was 58.8±12.0 years and 58.7% were male. BMI scores were not different according to the presence of OSA. Of the 167 patients, 80 patients (47.9%) were either current or past smokers. The mean number of pack-years was 32.4±18.2. Of the current or past smokers, 67 patients (60.4%) had OSA (AHI ≥5/hr) and 13 patients (23.2%) did not. The presence of smoking history showed a difference between the OSA and non-OSA groups, but there was no difference in pack-years between groups. The prevalence of OSA depended on AHI cut-off values; AHI values of ≥5/hr, ≥10/hr, ≥15/hr and ≥30/hr corresponded to 111 (66%), 71 (42.5%), 52 (31%) and 20 (12%) patients, respectively. The mean ApneaLink AHI for the 167 screened patients was 12.7±13.0/hr. The mean ApneaLink AHI for the 32 selected high risk patients of OSA was 22.3±13.2/hr, which was lower than the sleep laboratory-based PSG AHI of (39.1±20.5/hr). The most common comorbidities in decreasing order were cardiovascular disease (50.3%), asthma (38.9%), COPD (21%), diabetes (14.4%), obesity (10.2%), postnasal drip syndrome (7.8%), and GERD (4.8%) (Table 2).

Associations of comorbidities and clinical parameters with OSA

Variables found to be associated with OSA on both univariate and multivariate analyses are shown in Table 3. When OSA was defined as AHI ≥5/hr, age, male gender, and moderate to severe asthma showed positive correlations with OSA on univariate and multivariate analyses (Table 3). All asthma severity groups, including mild asthma did not show correlations with OSA. Only moderate to severe asthma showed strong correlation with OSA. COPD was not associated with OSA, regardless of its severity according to FEV_1 (data not shown). Diabetes and habitual snoring were not found to be predictors. Although cardiovascular disease was the most common comorbid condition in this study, it was not associated. Postnasal drip syndrome and GERD were rare comorbid diseases in our study and consequently not showed positive correlations.

DISCUSSION

There are little data showing a correlation between asthma and OSA. According to several studies, patients with asth-

Table 2. Comorbidities of ApneaLink Screened 167 Patients

Characteristics	Total	ApneaLink screened patients (n=167)		
		AHI ≥5/hr	AHI <5/hr	*p* value
Cardiovascular diseases	84 (50.3)	56 (50.5)	28 (50.0)	0.956
Asthma	65 (38.9)	40 (35.1)	25 (41.1)	0.281
Moderate to severe asthma	44 (26.3)	37 (33.6)	7 (12.5)	0.004
COPD	31 (18.6)	23 (20.7)	8 (14.3)	0.313
Moderate to severe COPD	17 (10.2)	9 (8.1)	8 (14.3)	0.213
Diabetes	24 (14.4)	17 (15.3)	7 (12.5)	0.624
Obesity (BMI ≥30)	17 (10.2)	12 (10.8)	5 (8.9)	0.704
Postnasal drip syndrome	13 (7.8)	10 (9.0)	3 (5.4)	0.406
GERD	8 (4.8)	6 (5.4)	2 (3.6)	0.600

AHI, apnea-hypopnea index; COPD, chronic obstructive pulmonary disease; GERD, gastroesophageal reflux disease; BMI, body mass index.
Data are presented as No. (%).

Table 3. Univariate and Multivariate Analysis of Affecting Factors for the Presence of OSA (AHI ≥5/hr)

Variables	Unadjusted		Adjusted	
	OR (95% CI)	*p* value	OR (95% CI)*	*p* value
Age	1.03 (1.01-1.06)	0.041	1.04 (1.01-1.07)	0.043
Male gender	5.45 (2.71-10.94)	<0.001	7.14 (3.21-15.90)	<0.001
Moderate to severe asthma	3.22 (1.33-7.83)	0.001	4.25 (1.50-12.16)	0.007
Diabetes	1.27 (0.49-3.26)	0.631	1.80 (0.60-5.56)	0.306
Obesity	1.24 (0.41-3.70)	0.702	1.35 (0.40-4.65)	0.640
Habitual snoring	1.31 (0.69-2.50)	0.408	1.33 (0.63-2.80)	0.455

OR, odds ratio; CI, confidence intervals; OSA, obstructive sleep apnea; AHI, apnea-hypopnea index.
*Adjusted for all variables shown.

ma have a higher prevalence of snoring and witnessed apnea relative to patients without asthma,[4,23] but the prevalence of asthma in patients with OSA was only investigated in one small and uncontrolled study.[24]

We investigated the associating factors thought to increase predisposition for OSA, including well-known factors such as male gender, age, and obesity and additional possible factors including asthma, GERD, postnasal drip syndrome, cardiovascular disease, diabetes, smoking, habitual snoring, and COPD. Factors with a positive correlation with OSA were age, male gender, and moderate to severe asthma when OSA was defined at an AHI ≥5/hr. We identified factors associated with moderate to severe asthma that showed positive correlations with OSA. Most patients with moderate to severe asthma had uncontrolled asthma. Irrespective of severity, asthma was not an independent predictor of OSA. Yigla, et al.[8] found that 21 of 22 (96%) patients with severe asthma demonstrated OSA in complete PSG testing. Julien, et al.[25] demonstrated a high prevalence of OSA among patients with severe asthma, compared to patients with moderate asthma or without asthma. Several plausible hypotheses have been proposed to explain the association of asthma and OSA including anatomic abnormalities of upper air way related to obesity, nasal disease or GERD related upper airway inflammation, chronic systemic corticosteroid use, and airway patency of lung volume reduction during sleep in asthmatics.[12,26,27] However, these proposed mechanisms need to be studied further. The interaction of OSA and asthma could be reciprocal in that asthma-related factors could also contribute to OSA deterioration. Nocturnal hypoxemia could be aggravated by asthma-related lung function impairment. Poor sleep quality could also be a factor because it has been associated with severe asthma in previous studies.[28,29] In our study, 32 subjects who performed PSG completed the sleep questionnaire of the Epworth Sleepiness Scale (ESS). The ESS mean score was over the upper limits of the normal range at 10.38±4.85, with approximately 62.5% showing excessive daytime sleepiness, defined as an ESS score greater than 10.[30]

COPD was not a predicting factor, regardless of severity, categorized by FEV_1 (data not shown). Cardiovascular disease was also not associated with OSA, contrary to previous studies.[31,32] We presumed that cardiovascular disease has not been well characterized in this study. Moreover, hypertension was the most common condition; not heart failure, stroke, or coronary heart disease (Table 4). Postnasal drip syndrome and GERD were comorbid in very small patients (9%, 5% respectively) in our study and showed no correlations with OSA. Obesity did not show positive correlations with OSA on univariate and multivariate analyses. Ip, et al.[33] reported that obesity is prevalent and a strong risk factor for OSA in white populations but is relatively uncommon in Asians. They hypothesized that other strong OSA risk factors, such as craniofacial features, are prevalent in Asians, and clinical observational studies of Asian patients with OSA support this hypothesis.[34-36] In this study, the number of obese patients was very small. The prevalence of obesity, defined as western cut-off (BMI ≥30 kg/m^2), was only 4.6% in our population.[3] Obesity was not correlated with OSA in our study and this is similar to a recent study of ethnic differences in craniofacial structures and obesity.[37]

Previous studies have validated ApneaLink as an appropriate screening tool for OSA.[17,18] Diagnostic accuracy of the ApneaLink for OSA detection was evaluated and compared with PSG. The ApneaLink device was highly sensitive and specific in quantifying AHI when compared with the AHI obtained from the lab-based PSG. In our study, 32 patients completed both ApneaLink and PSG studies, and ApneaLink AHI and PSG AHI were closely correlated (Pearson's correlation coefficient r=0.613) (Fig. 1). The ApneaLink tended to underestimate the AHI score, which is similar to previous studies.[17,18] Erman, et al.[18] applied ApneaLink a screening tool in comparison with the sleep-laboratory based PSG. ApneaLink was highly sensitive and specific in calculating AHI when compared with AHI obtained from PSG.[18] Ng, et al.[17] evaluated the diagnostic accuracy of the ApneaLink device in detecting sleep apnea compared

Table 4. Subgroup Analyses of 84 Patients with Cardiovascular Diseases

	Total	AHI ≥5/hr	AHI <5/hr	*p* value
Hypertension only	55	37	18	0.511
Coronary artery diseases	15	12	3	0.192
Non-coronary artery diseases	15	8	7	0.198
Heart failure	2	1	1	0.560

AHI, apnea-hypopnea index.
Patients with one more cardiovascular disease are present. Non-coronary artery diseases are arrhythmia, hypertrophic cardiomyopathy and valvular heart disease.

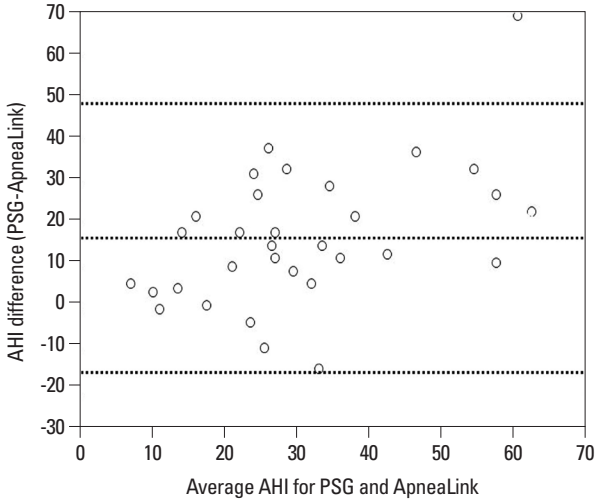

Fig. 1. Bland-Altman plot of ApneaLink apnea-hypopnea index (AHI) and polysomnography (PSG) AHI data.

to PSG and showed that the ApneaLink device was highly sensitive and specific at AHI values ≥10/hr and ≥20/hr when quantifying AHI in symptomatic OSA patients. These data support the use of ApneaLink for OSA screening studies in subjects with a high probability and suggest that ApneaLink is a useful tool for determining the presence or absence of sleep apnea. Our study has some limitations. First, a small number of subjects (32 patients), completed PSG along with ApneaLink, compared to 167 patients who were screened with ApneaLink. However, all subjects were at a high probability of having OSA when presenting with symptoms of SDB, and ApneaLink was well correlated with PSG in 32 patients. Second, this study was a cross-sectional study and the study population and clinical setting were selective and limited; therefore, it is difficult to generalize our results to other settings. Third, asthma severity was evaluated using clinical and spirometry data without an objective measurement for severity, such as an asthma control questionnaire.[38,39]

In summary, moderate to severe asthma showed strong correlations with OSA when defined at an AHI ≥5/hr in addition to the well-known predictors of age and male gender. ApneaLink was used for the screening of OSA in subjects with a high probability of having OSA instead of the laboratory-based PSG testing. Obesity was not associated with OSA in our study.

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