ELSEVIER

Effect of nasal continuous positive airway pressure in uncontrolled nocturnal asthmatic patients with obstructive sleep apnea syndrome

Tansu Ulukavak Ciftci[a],*, Bulent Ciftci[b], Selma Firat Guven[b],
Oguz Kokturk[a], Haluk Turktas[a]

[a]Department of Pulmonary Disease, Faculty of Medicine, Gazi University, Ankara
[b]Ataturk Chest Disease and Chest Surgery Hospital, Department of Pulmonary Disease, Ankara

Summary   The mechanisms of nocturnal asthma are intimately related to circadian rhythms, which influence inflammatory cells and mediators, hormone levels and cholinergic tone. Nocturnal airway narrowing in asthma is sometimes associated with sleep disorders, such as obstructive sleep apnea syndrome (OSAS). The aims of this study were to evaluate the association of nocturnal asthma and OSAS, and investigate the influence of continuous positive airway pressure (CPAP) therapy to improve nighttime symptoms in asthmatic patients with OSAS. Forty-three asthmatic patients who had nocturnal symptoms in spite of the optimal medical treatment according to the Global Initiative for Asthma guidelines and associated with snoring were studied. Pulmonary function tests (PFTs), asthma nighttime symptom scores, and polysomnography were performed on all patients. We treated the patients with an apnea-hypopnea index (AHI) $\geqslant 15$ (moderate–severe OSAS) ($n = 16$) with CPAP during 2 months. After 2 months, PFT, asthma nighttime symptom scores were reperformed. There was no significant difference in PFT values before and after CPAP treatment in OSAS patients. Asthma nighttime symptom scores were improved significantly ($P < 0.05$) after CPAP treatment. In conclusion, in some patients with nocturnal asthma, OSAS may be responsible disease for nocturnal symptoms. In this condition, CPAP improves nocturnal symptoms without amelioration in PFT abnormalities.
© 2004 Elsevier Ltd. All rights reserved.

Introduction

Asthma is a chronic inflammatory disease of the airways, characterized by hyperresponsiveness to a

*Corresponding author. Tel.: +90 312 2026119; fax: +90 312 2129019.
E-mail address: tansu.ciftci@gazi.edu.tr (T.U. Ciftci).

variety of stimuli. It affects at least 5% of the population at least sometime during their lives.[1]

Nocturnal asthma is not a different condition from asthma and is defined as a variable nighttime exacerbation of the underlying asthma condition associated with increases in symptoms and need for more medication, increased airway responsiveness and/or worsening of lung function.[2]

The occurrence of nocturnal asthma is associated with increased morbidity and inadequate of asthma control. The mechanisms by which nocturnal asthma develops remain unclear and may vary from patient to patient.[3] The main mechanism is related to circadian rhythms. Most normal people also have circadian changes in airway caliber with mild nocturnal bronchoconstriction. Although circadian changes in flow rate are synchronous in asthmatic patients and normal subjects, asthmatic patients have a far greater variation in their peak flow rates. Nocturnal bronchoconstriction in asthma appears to be an exaggeration of the normal circadian changes in airway caliber. Other factors that have been proposed as possible causes for overnight bronchoconstriction are interruption of bronchodilator or other treatment, allergens in bedding, airway cooling, supine posture, and gastroesophageal reflux (GER). In addition, mucociliary clearance is impaired during sleep, and the accumulation of mucus in the airways could contribute to nocturnal airway narrowing.[4–6]

Appropriate and adequate medical treatment should be the first step for asthmatic patients with nighttime symptoms. But, nighttime symptoms may continue in some patients, against optimal medical treatment. In this condition, other factors responsible the nighttime symptoms should be investigated. The relatively uncommon cause of nocturnal asthma beyond ones mentioned above is obstructive sleep apnea syndrome (OSAS).

In present study, we aim to evaluate the association of OSAS in asthmatic patients who had nighttime symptoms in spite of the optimal medical treatment and investigate the influence of continuous positive airway pressure (CPAP) therapy to improve nighttime symptoms in asthmatic patients with OSAS.

Material method

Patient population

Study was performed on asthmatic patients who had nighttime symptoms in spite of the optimal medication according to Global Initiative for Asthma (GINA) guidelines during 6 months and suffered from habitual snoring. Patients with GER symptoms were treated under the control of a gastroenterologist during this period. Patients who had nighttime symptoms after GER treatment were included in the study.

Inclusion criteria: (1) At least one nocturnal awakening or early morning awakening caused by asthmatic symptoms (cough, wheeze, chest tightness, and breathlessness) and (2) habitual snoring. Patients with cardiac failure, cerebrovascular disease or a lung disease except asthma were excluded.

Two sleep studies were performed: one to assess the diagnosis of OSAS and other to determine the adequate pressure level of CPAP for patients with OSAS. After diagnostic sleep study, patients with sleep disorders except OSAS were excluded.

Patients were asked to check on the agenda when they had nighttime symptoms each morning on awakening during 2 months before and 2 months after sleep studies.

All patients gave written informed consent to the procedure. The study was carried out in accordance with the Declarations of Helsinki.

Nocturnal asthma status

Physiologic parameters were expressed as the patient's best measure of forced expiratory volume in first second (FEV_1), forced vital capacity (FVC), FEV_1/FVC ratio, and forced expiratory flow between 25% and 75% of vital capacity (FEF_{25-75}) in percentage of the predicted value, measured with a wedge spirometer, which fulfilled the requirements of the American Thoracic Society. Pulmonary function test (PFT) was performed before sleep study and after 2 months of CPAP treatment.

Nighttime symptoms were quantified as a score according to the frequency of symptoms based on GINA guidelines. According to patients' agenda, sums of the days with nighttime symptoms were calculated and nocturnal asthma scores were recorded as follows:

0:	No symptom,
1:	$\leqslant 2$ times a month,
2:	>2 times a month,
3:	<1 time a week,
4:	Frequent.

Sleep study

Overnight polysomnography (PSG) was performed in all patients by a computerized system

(Rembrandt; Medcare, Holland) and included the following variables: electrooculogram (two channels), electroencephalogram (four channels), electromyelogram of submental muscles (two channels), electromyelogram of the anterior tibialis muscle of both legs (two channels); electrocardiogram and airflow (with an oro-nasal thermistor). Chest and abdominal efforts (two channels) were recorded using inductive plethysmography, arterial oxyhemoglobin saturation (SaO_2: one channel) by pulse oximetry with a finger probe. The recordings were conducted at a paper speed of 10 mm/s, and sleep stages were scored according to the standard criteria of Rechtschaffen and Kales.[7] Arousals were scored according to accepted definitions.[8] Apneas were defined as complete cessation of airflow $\geqslant 10$ s. Hypopneas were defined as a reduction of $>50\%$ in one of three respiratory signals, airflow signal or either respiratory or abdominal signals of respiratory inductance plethysmography, with an associated fell of $\geqslant 3\%$ in oxygen saturation or an arousal. The apnea-hypopnea index (AHI) was defined as the number of apneas and hypopneas per hour of sleep. Patients with $AHI \geqslant 5$ were considered OSAS.

Patients were grouped by their total AHI. These groups were AHI of 0–4.9 (normal), 5–14.9 (mild OSAS), 15–29.9 (moderate OSAS), and $\geqslant 30$ (severe OSAS) as used in other studies.[9] Those with AHI of 5–14.9 were followed with general recommendation such as weight loss, etc. Those with AHI of $\geqslant 15$ were offered a trial of nasal CPAP (nCPAP) treatment and included in the subgroup of study.

Nasal continuous positive airway pressure study

The appropriate level of CPAP for each patient with an $AHI \geqslant 15$ was determined during an all-night CPAP pressure determination study. A polysomnographic study was performed with the same setup as the diagnostic study, except that nCPAP was applied during sleep. Attended CPAP titration was performed with the CPAP auto-titrating device (AutoSet; Resmed, Sydney, Australia) on the second night of the study in our hospital. All patients were prescribed the use CPAP device (Vector Plus CPAP devices; Hoffrichter, Germany), which automatically turned on when the mask was removed. Four patients used CPAP with heated humidifier according to their desire. We measured compliance by the mean rate of CPAP use (hours per day). Acceptable duration was considered $\geqslant 4$ h/night. Optimal medication according to GINA guidelines was continued during CPAP treatment.

Statistical analysis

Means and standard errors of measurement (SEM) were determined for continuous variables and percentage for categorical variables. Differences in nighttime symptom scores and PFT values between baseline and after CPAP treatment were tested using the Wilcoxon signed-rank test. Differences between two groups were analyzed with the Mann–Whitney U-test.

All statistical analyses were carried out using statistical software (SPSS, version 11.0 for Windows; SPSS Inc., Chicago, IL). Differences were considered significant at $P < 0.05$.

Results

Forty-three asthmatic patients who had nighttime symptoms in spite of the optimal medical treatment according to the GINA guidelines and associated with snoring were studied. According to PSG data, 21 of 43 patients (48.83%) had OSAS with an $AHI > 5$. Nineteen of 21 OSAS patients who had an $AHI > 15$ were candidate for CPAP treatment. Sixteen of 19 patients completed the study. The reasons for the withdrawal of three patients were: intolerance the CPAP treatment (one patient) and insufficient duration of CPAP use (two patients).

Table 1 shows the demographics, PFT values, SaO_2, nighttime symptom scores, and diagnostic PSG results for 43 patients included in the analysis. No statistical differences were found in the two groups (with and without OSAS) except for stages I and IV percents. Stage I percents were found higher and stage IV percents were found lower in asthmatic patients with OSAS, comparing with patients without asthma. Therefore, sleep is more superficial and poorer in quality in asthmatics with OSAS.

Table 2 shows comparison of PFT values and nighttime symptom scores at baseline and after CPAP treatment of 16 OSAS patients. Nighttime symptom scores were improved significantly after CPAP treatment (scores were found lower after CPAP in 10 patients comparing with scores before CPAP, while were found higher in two patients and found similar in four patients) ($P = 0.04$). There was no significant difference in PFT values before and after CPAP treatment.

Discussion

Nocturnal airway narrowing in asthma is often associated with episodes of nocturnal and early

Table 1 Demographics, PFT values, and diagnostic PSG results of the patients.

	Patients without OSAS (n = 22)	Patients with OSAS (AHI > 15 and completed the study) (n = 16)	P-value
Age (years)	43.86 ± 8.32	45.94 ± 7.69	0.4
Sex (F/M)	19/13	9/7	
Body mass index (kg/m^2)	33.1 ± 7.06	34.38 ± 6.08	0.39
FEV$_1$ (% predicted)	65.52 ± 17.37	70.25 ± 21.17	0.61
FVC (% predicted)	83.21 ± 15.03	83.68 ± 17.93	0.85
FEV$_1$/FVC	64.94 ± 14.3	66.68 ± 15.64	0.94
FEF$_{25-75}$ (% predicted)	35.4 ± 16.72	39.87 ± 24.7	0.76
Nighttime symptom scores	1.77 ± 0.97	2.19 ± 1.07	0.22
AHI	3.9 ± 3.72	44.25 ± 50.82	0.000[*]
Mean of the awakening SaO$_2$ (%)	95.5 ± 3.4	95.06 ± 2.64	0.28
Mean of the SaO$_2$ during sleep (%)	91.54 ± 6.2	89.06 ± 6.09	0.08
Mean of the minimum SaO$_2$ during sleep (%)	82.31 ± 8.17	64.87 ± 20.37	0.003[*]
Stage I (%)	6.8 ± 3.7	10.8 ± 4.86	0.01[*]
Stage II (%)	37.95 ± 10.68	45.56 ± 9.5	0.06
Stage III (%)	5.13 ± 3.37	4.5 ± 2.3	0.5
Stage IV (%)	7.68 ± 6.53	3.5 ± 4.5	0.03[*]
REM (%)	14.09 ± 6.02	15.12 ± 6.3	0.8
Sleep efficiency (total sleep time/total time in bed) (%)	68.86 ± 16.81	74.12 ± 13.9	0.35

Note: Values are mean ± SD.
[*]$P < 0.05$

Table 2 PFT values and nighttime symptoms scores of asthmatic patients with OSAS, before and after CPAP treatment.

	Baseline no. 16	After 2 months of CPAP treatment no. 16	P-value
FEV$_1$ (% of predicted value)	70.25 ± 21.17	71.25 ± 21.85	0.64
FVC (% of predicted value)	83.68 ± 17.93	88.81 ± 20.64	0.34
FEV$_1$/FVC	66.68 ± 15.64	70.75 ± 15.37	0.12
FEF$_{25-75}$ (% of predicted value)	39.87 ± 24.7	40.4 ± 20.77	0.14
Nighttime symptom scores	2.19 ± 1.07	1.44 ± 1.15	0.04[*]

[*]$P < 0.05$

morning awakening, difficulty in maintaining sleep, and daytime sleepiness. But, besides the impairing of sleep quality by nocturnal asthma itself, an association has been documented between nocturnal sleep-disordered breathing and asthma or bronchial hyperreactivity.[4,10–12] OSAS is the most common sleep-disordered breathing and snoring is one of the major symptoms of OSAS. While snoring is present in more than 90% of the patients with OSAS, OSAS can be determined in 8–10% of the subjects with habitual snoring.[1] In our study, patients with both nocturnal asthma and snoring were included and OSAS was identified in 21 of 43 (48.83%). This rate is higher than the OSAS rate reported in healthy subjects with snoring and

suggests that OSAS may be one of the causes of the nocturnal asthma, which is not improved with medical treatment. Another important result of our study was the improvement of nocturnal asthma symptoms with CPAP. When the OSAS's role on development of nocturnal asthma is established, the cause of its improvement with CPAP will also be understood.

Several circadian rhythms may be important in nocturnal asthma such as circadian changes in bronchial hyperresponsiveness and inflammation.[1,3,4,6,13] The changes in parasympathetic tonus are responsible for the circadian changes in bronchial hyperresponsiveness. Parasympathetic tone is increased during sleep. The increase in

vagal output is thought to affect the muscarinic receptors located in the central airways and contribute to bronchoconstriction. Increased parasympathetic bronchoconstrictor tone and decreased nonadrenergic, noncholinergic broncho-dilator function in the early morning may significantly contribute to nocturnal asthma exacerbations.[3,4,13] On the other hand, patients with OSAS have increased vagal tone during sleep. It was documented that Muller maneuver was involved in the development of the known sleep-related hemodynamic changes noted with obstruc-tive apnea or hypopnea. Atropine and other anticholinergic medications, or autonomic nervous system lesions eliminate the cardiovascular changes associated with partial or complete upper airway obstruction during sleep, which are mediated through marked vagal stimulation. A possibility exists that the increased vagal tone could also produce bronchoconstriction. Guillemi-nault et al.[14] showed that combined with the local effects of snoring, and increased vagal stimulation would be a precipitating factor in nocturnal asthma attacks and concluded that CPAP reduced vagal tone in asthmatic patients with OSAS and this was the cause for the improvement in their nocturnal asthma.

According to another hypothesis suggested by Chan et al.[15] recurrent upper airway obstruction in OSAS and snoring may be important triggering mechanisms of nocturnal asthma attacks. The recurrent episodes of airway obstruction and snoring act as a chronic irritant that when eliminated by CPAP therapy improved the asth-matic symptoms. Neural receptors at the glottic inlet and in the laryngeal region have been shown to have potent bronchoconstrictive reflex activity. Thus, with the repeated stimulation from snoring and apnea of the oropharynx and glottic inlet or larynx during the night, a neural reflex arc could be initiated, producing bronchoconstriction. CPAP may stabilize the upper airway and remove the chronic nightly irritation to the oropharyngeal area, with subsequent elimination of the reflex bronchocon-striction.[15] In another study suggesting that OSAS can cause nocturnal asthma, Bohadana et al.[16] reported that recurrent upper airway obstruction causes bronchoconstriction by means of negative intrathoracic pressure changes.

Chronic inflammation of the airway is the major underlying mechanism of airway damage and bronchoconstriction. Most importantly, bronchoal-veolar lavage fluid in patients with nocturnal asthma compared with asthma patients without nighttime symptoms shows marked increase in neutrophil and eosinophil counts at nighttime than in the daytime. Patients with nocturnal asthma seem to have more exaggerated inflammatory response during the nighttime.[4,6,13] Although the pathogenesis of OSAS is not clearly understood, various anatomic, mechanical, and neurologic, components appear to contribute to relaxation and closure of the pharyngeal airway during sleep. Along with these, recently, upper airway inflamma-tion has been suggested frequently in the patho-genesis. Snoring is caused by vibration, which occurs in uvula, soft palate and upper airway wall while passing turbulent air into these tissues. Inflammation and edema occur in upper airway related to snoring and increasing upper airway resistance. Moreover, Carpagnano et al.[17] showed the presence of an upper airway inflammation after sleep in patients with OSAS correlated with severity of the disease. On the other hand, in OSAS, cyclical alterations of arterial oxygen saturation are ob-served with oxygen desaturation developing in response to apnea followed by the resumption of oxygen saturation during hyperventilation. This phenomenon has been referred to as hypoxia/reoxygenation. Hypoxia functions as a danger signal for the immune system by inducing the synthesis of inflammatory cytokines. Some authors have re-ported that systemic biomarkers of inflammation has increased in patients with sleep apnea suggest-ing a possible role in the pathologic consequences of OSAS.[18,19] This information demonstrates that, inflammation exists in both asthma and OSAS, and these two disorders may interact negatively.

Another issue needs attention in the matter of association between nocturnal asthma and OSAS is GER. Increased intrathoracic pressure caused by upper airway obstruction in OSAS patients results in GER through increasing pressure gradient between stomach and eosephagus.[1] On the other hand, in GER, respiratory tract irritation resulted from microaspiration of stomach content causes reflex bronchoconstriction directly and acid irritation in lower end of eosephagus by vagal pathway.[20] Consequently, the hypothesis of OSAS causes GER and GER causes nocturnal asthma can be proposed. But, in our study, patients with GER symptoms were received GER treatment along with asthma treat-ment.

Present study showed that nocturnal asthma symptoms could be treated with CPAP therapy without amelioration on PFT values. Patients included in our study have nocturnal symptoms in spite of optimal medical treatment and OSAS was identified in approximately half of these patients. When considering OSAS is a disorder related to sleep and influences only nocturnal symptoms pertaining to asthma, nocturnal improvement with

CPAP and not affecting functional parameters should be accepted logical. Being different from our study, Chan et al.[15] demonstrated that both daytime and nighttime PEFR improved in patients with concomitant OSAS and asthma when nocturnal CPAP was applied. But, only nine subjects were included in this study and asthma treatment given together with CPAP did not mentioned.

On the other hand, it can be considered that, if CPAP would improve nocturnal asthma in patients without sleep apnea. The Martin and Pak[21] study showed that nCPAP was poorly tolerated in asthmatic patients without concomitant sleep apnea and did not improve nor lung function neither nocturnal symptoms. CPAP given to patients with nocturnal asthma who do not have OSAS does not appear to be beneficial and was associated with significant sleep disruption.

In present study, it is showed that 2 months of CPAP treatment improved significantly nighttime symptoms without changes in PFT values in patients with nocturnal asthma associated OSAS. These findings suggested that OSAS might be responsible disease for nighttime symptoms. Further studies are needed to investigate longtime effect of CPAP treatment. In conclusion, it is important to enquire as to the presence of symptoms of OSAS in patients presenting with nocturnal asthma, because treatment with CPAP may effect a substantial improvement in asthma. Snoring in patients with asthma raise clinical suspicion of OSAS but it must be remembered that, excessive daytime sleepiness resulted from poor quality sleeping due to nocturnal asthma symptoms is also an important symptom of OSAS. In these conditions, PSG is the only definitive way to document objective evidence of OSAS and is also helpful in prescribing proper treatment.

References

1. Douglas NJ. Nocturnal asthma. In: McNicholas WT, Phillipson EA, editors. *Breathing disorders in sleep*. London: W.B. Saunders; 2002. p. 291–8.

2. Skloot GS. Nocturnal asthma: mechanisms and management. *Mt Sinai J Med* 2002;**69**(3):140–7.

3. Calhoun WJ. Nocturnal asthma. *Chest* 2003;**123**:399S–405S.

4. Douglas NJ. Asthma. In: Kryger MH, Roth T, Dement WC, et al., editors. *Principles and practice of sleep medicine*. 3rd ed. Philadelphia: W.B. Saunders; 2000. p. 955–96.

5. Cibella F, Giuseppina C. Nocturnal asthma and gastroesophageal reflux. *Am J Med* 2001;**111**:31–6.

6. Calhoun WJ. Nocturnal asthma. *Chest* 2003;**123**:399S–405S.

7. Rechtschaffen A, Kales A. *A manual of standardized terminology, techniques, and scoring system for sleep stages in human subjects*. Los Angeles, CA: Brain Information Service, VCLA; 1968.

8. EEG arousals, scoring rules and examples: a preliminary report from the Sleep Disorders Atlas Task Force of the ASDA American Sleep Disorders Association. *Sleep* 1992;**15**:173–84.

9. Loube DI, Gay PC, Strohl KP, et al. Indications for positive airway pressure treatment of adult obstructive sleep apnea. *Chest* 1999;**115**:863–6.

10. Fitzpatrick MF, Jokic R. Nocturnal asthma. In: McNicholas WT, editor. Respiratory disorders during sleep. *Eur Respir Monograph* 1998;**3**:285–302.

11. Fitzpatrick MF, Martin K, Fossey E, et al. Snoring, asthma and sleep disturbance in Britain: a community-based survey. *Eur Respir J* 1993;**6**(4):531–5.

12. Lin CC, Lin CY. Obstructive sleep apnea syndrome and bronchial hyperreactivity. *Lung* 1995;**173**(2):117–26.

13. Bonekat HW, Hardin KA. Severe upper airway obstruction during sleep. *Clin Rev Allergy Immunol* 2003;**25**:191–210.

14. Guilleminault C, Quera-Salva MA, Powell N, et al. Nocturnal asthma: snoring, small pharynx and nasal CPAP. *Eur Respir J* 1988;**1**(10):902–7.

15. Chan CS, Woolcock AJ, Sullivan CE. Nocturnal asthma: role of snoring and obstructive sleep apnea. *Am Rev Respir Dis* 1988;**137**(6):1502–4.

16. Bohadana AB, Hannhar B, Teculescu DB. Nocturnal worsening of asthma and sleep disordered breathing. *J Asthma* 2002;**39**(2):85–100.

17. Carpagnano GE, Kharitonov SA, Resta O, et al. Increased 8-isoprostane and interleukin-6 in breath condensate of obstructive sleep apnea patients. *Chest* 2002;**122**:1162–7.

18. Vgontzas An, Bixler EO, Papanicolaou DA, et al. Chronic systemic inflammation in overweight and obese adults. *JAMA* 2000;**283**:2235–6.

19. Visser M, Bouter LM, McQuillan GM, et al. Elevated C-reactive protein levels in overweight and obese adults. *JAMA* 1999;**282**:2131–5.

20. Martin RJ. Nocturnal asthma. *Clin Chest Med* 1992;**13**(3):533–50.

21. Martin RJ, Pak J. Nasal CPAP in nonapneic nocturnal asthma. *Chest* 1991;**100**(4):1024–7.