



The Egyptian Society of Chest Diseases and Tuberculosis
Egyptian Journal of Chest Diseases and Tuberculosis

www.elsevier.com/locate/ejcdt
www.sciencedirect.com



ORIGINAL ARTICLE

Overlap of obstructive sleep apnea and bronchial asthma: Effect on asthma control



Mohamed Zidan, Rasha Daabis *, Heba Gharraf

Dept. of Chest Diseases, Faculty of Medicine, Alexandria University, Egypt

Received 17 December 2014; accepted 18 January 2015

Available online 18 February 2015

KEYWORDS

Obstructive sleep apnea;
Bronchial asthma;
Asthma control;
Severity;
GERD;
Obesity

Abstract Obstructive sleep apnea (OSA) and asthma are highly prevalent respiratory disorders that share several risk factors and are frequently comorbid. Multiple mechanisms have been postulated to explain this frequent coexistence, which is recently referred to as the “alternative overlap syndrome”. Moreover, OSA is generally linked to worse asthma outcomes.

Objectives: First, to assess the prevalence of OSA in a group of asthmatics. Second, to evaluate the potential risk factors underlying the development of OSA in these patients. Third, to determine the effect of this overlap on asthma control.

Methods: Polysomnography was done for 30 asthmatics and 12 controls. Demographics, spirometry, comorbidities and clinical data were collected. Asthma control was assessed according to the latest GINA guidelines.

Results: OSA defined by an AHI of ≥ 5 events/h was present in 18 (60%) asthmatics and 2 (17%) controls. Regression analysis revealed that high body mass index (BMI), coexistent gastroesophageal reflux disease (GERD) and asthma severity (FEV1%) are significant independent predictors for the development of OSA in asthmatics ($p = 0.03$, 0.034 , and < 0.001 respectively). Moreover, the presence of OSA in asthmatic patients was significantly associated with worse asthma control ($p < 0.001$).

Conclusion: A high index of suspicion is warranted for the overlap of OSA and asthma, particularly in the presence of obesity, GERD, and in patients with severe asthma. Individualized therapy addressing these moderating factors is warranted for optimal health outcomes. Recognition and treatment of OSA in asthmatics is an important element in improving asthma control.

© 2015 Production and hosting by Elsevier B.V. on behalf of The Egyptian Society of Chest Diseases and Tuberculosis. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Obstructive sleep apnea (OSA) and asthma are highly prevalent chronic respiratory disorders that share several risk factors and are frequently comorbid [1]. Both symptoms of

OSA and diagnosed OSA are more frequent in clinical populations with asthma compared to other populations [2–4].

In addition to overlapping risk factors, multiple evidence-based and hypothetical mechanisms have been postulated to explain the frequent coexistence of OSA and asthma, also referred to as the “alternative overlap syndrome” [4–7].

* Corresponding author.

Peer review under responsibility of The Egyptian Society of Chest Diseases and Tuberculosis.

Asthma is an inflammatory disease of the lower respiratory tract, manifesting as intermittent constriction of the bronchial airways. Obstructive sleep apnea (OSA), on the other hand, is a state-dependent condition that is characterized by intermittent obstruction of the upper airway during sleep leading to hypoxemia and sleep fragmentation [8]. The pathophysiology of these two conditions seems to overlap significantly, as airway obstruction, inflammation, obesity, and several other factors are implicated in the development of both diseases [5]. On the other hand it has been suggested that asthma comorbidities, such as GERD, and medications may also contribute to the development of OSA [9]. In this setting, a more specific understanding of what increases predisposition for OSA in asthma could be useful.

Moreover, OSA is generally linked to worse asthma outcomes. The effects of the direct pathophysiologic consequences of OSA (e.g., chronic intermittent hypoxemia, circadian alteration of autonomic functions, and increased intrathoracic pressure swings related to the occluded upper airway) on the clinical severity of asthma are poorly understood [1]. Moreover, the National Asthma Education and Prevention Program Expert Panel Report recommends evaluating for OSA as a potential contributor to poor asthma control [10]. Thus, clarifying the nature of the relationship between OSAS and asthma is a critical area with important therapeutic implications.

Therefore, the aim of this study was: First, to assess the prevalence of OSA in a group of asthmatics. Second, to evaluate the potential risk factors underlying the development of OSA in these patients. Third, to determine the effect of this overlap on asthma control.

Patients and methods

30 patients with bronchial asthma were enrolled in the study. Participants were recruited from consecutive patients presenting to asthma clinics of Alexandria. We included adults (age ≥ 18 years) with a diagnosis of asthma of at least 12 month duration. Data were collected regarding demographic and clinical factors, spirometry, general health information including relevant comorbid conditions such as (Gastroesophageal reflux disease (GERD), rhinitis or sinusitis) and current asthma medication.

Patient control was assessed according to the latest GINA guidelines and the level of control was divided into well controlled, partly controlled or uncontrolled [11].

12 healthy adults matched for age, sex and BMI were included as a control group. No sleep-related information was used in the recruitment process.

Exclusion criteria for both groups included the following: current smoker or ex-smoker with a greater than 10 pack-year smoking history, comorbidities that could potentially interfere with the study or other pulmonary diseases.

Nocturnal sleep studies

All subjects underwent overnight polysomnography. The patients underwent polysomnography at a time of relative clinical stability, and at least 2 weeks after recovery from any exacerbation or intervention.

The analysis was carried out automatically and manually. Respiratory events were scored using standard criteria [12]. The apnea hypopnea index (AHI) was defined as the total number of apneas and hypopneas per hour of sleep. As indices of nocturnal hypoxemia we considered the oxygen desaturation index (this is the number of times that the oxygen saturation falls by more than 3 or 4 percent per hour of sleep), T90 (the fraction of sleep time spent below an oxygen saturation of 90%) and the minimal value recorded during sleep (minimal SaO₂). The OSA was defined as an AHI of ≥ 5 events/h.

Assessment of daytime sleepiness

The Epworth Sleepiness Scale (ESS) was used for assessing daytime sleepiness. This is a commonly used self-administered scale with eight items about how easily the respondent would fall asleep in different situations. The items are scored on a 0–3 scale, which are added to give an overall score of 0–24. Higher scores indicate more sleepiness. ESS score 2–10 is considered ‘normal’ and > 10 indicative of pathological sleepiness [13].

All subjects were enrolled in the study after a written informed consent according to a protocol approved by the Ethics Committee of the Hospital.

Results

Subjects' characteristics

30 asthmatic patients and 12 healthy controls matched for age, sex and BMI were enrolled in the study. Subjects' characteristics are shown in Table 1. Asthmatic patients showed significantly more comorbidities, snoring and ESS.

Polysomnographic respiratory parameters of the studied subjects

OSA, defined by an AHI of ≥ 5 events/h, was significantly more prevalent in the asthmatics in comparison with the control group ($p < 0.001$). The polysomnographic parameters of the studied subjects are shown in Table 2.

Table 1 Subjects' characteristics.

	Asthmatic patients	Control	<i>p</i>
Age	49.12 \pm 3.43	47.8 \pm 0.56	NS
Sex(M/F)	13/17	6/6	NS
BMI	28.13 \pm 4.22	26.88 \pm 2.42	NS
GERD n(%)	12(40)	2(15)	< 0.001*
Rhinitis/sinusitis	20(67)	3(25)	< 0.001***
ESS	8.89 \pm 2.8	4.85 \pm 2.15	< 0.01**

Variables are expressed as mean \pm standard deviation.

M = male, F = female, BMI = body mass index, GERD = gastroesophageal reflux disease, ESS = Epworth sleepiness scale, NS = not significant.

* Statistically significant at $p < 0.05$.

** Statistically significant at $p < 0.01$.

*** Statistically significant at $p < 0.001$.

Table 2 Polysomnographic respiratory parameters of the studied subjects.

	Asthmatic patients	Control	<i>p</i>
AHI ≥5	18(60)	1(8)	<0.001***
AHI	19.5 ± 12.2	3.11 ± 1.4	<0.001***
ODI	6.48 ± 7.8	1.6 ± 1.1	<0.01**
T90(% TST)	5.9 ± 3.2	0.8 ± 1.4	<0.021*
Mean SaO ₂	92.4 ± 2.6	95.7 ± 1.8	NS
Min. SaO ₂	87.1 ± 1.9	90.8 ± 1.03	NS

Variables are expressed as mean ± standard deviation.

AHI = apnea hypopnea index, ODI = oxygen desaturation index, NS = not significant .

* Statistically significant at *p* < 0.05.

** Statistically significant at *p* < 0.01.

*** Statistically significant at *p* < 0.001.

Comparison between asthmatic patients with and without OSA

Asthmatic patients with OSA had higher BMI, more comorbid GERD and worse FEV1% (Table 3).

Predictors of the occurrence of OSA (defined by an AHI of ≥5 events/h) in asthmatic patients

Regression analysis revealed that high body mass index (BMI), coexistent gastroesophageal reflux disease (GERD) and asthma severity (FEV1%) are significant independent predictors for the development of OSA in asthmatics, independent of each other (*p* = 0.03, 0.034, and <0.001 respectively) (Table 4).

Relation between the presence of OSA and the level of control in the asthmatic patients

The presence of OSA in asthmatic patients was significantly associated with worse asthma control (*p* < 0.001) (Table 5).

Discussion

The primary finding from this study was that asthmatics are more likely to develop OSA than non-asthmatics. Akhalil using overnight polysomnography, we found a strikingly high prevalence of OSA (defined by an AHI of >5/h) in our

Table 4 Linear regression model of factors predictive of the occurrence of OSA in asthmatics.

	β [#] ± SD	<i>p</i> value
BMI	0.058 ± 0.025	0.03*
GERD	1.192 ± 0.522	0.034*
FEV1	-0.128 ± 0.031	0.001**

The presence of OSA is the dependant variable. Adjusted R² = 0.744. #β = the regression coefficient.

BMI = body mass index, GERD = gastroesophageal reflux disease.

* Statistically significant at *p* < 0.05.

** Statistically significant at *p* < 0.01.

Table 5 Correlation between comorbid OSA and asthma control.

Control	Non OSA	OSA
Well controlled	50%	5.6%
Partly controlled	33.3%	61%
Uncontrolled	16.7%	33.3%
χ ²		39.2
<i>p</i>		<0.001***

χ² chi square test.

*** Statistically significant at *p* < 0.001.

asthmatic group in comparison with the control group (60% versus 17%, *p* < 0.001). A relationship between asthma and OSA was noted >25 years ago [8]. Earlier studies suggested that disturbed sleep in asthmatics was predominantly related to poorly controlled nocturnal asthma [14,15] however, more recent studies have found that symptoms of OSA, such as snoring and witnessed apneas [2,16–18], are common in this population. Furthermore, several studies have confirmed that asthmatic patients are more prone to develop OSAS symptoms than are members of the general population. In the European Community Health Respiratory Survey, self-reported habitual snoring and apnea were significantly more prevalent in asthmatics as compared with non-asthmatics [19].

The gold standard for the diagnosis of OSA remains an attended polysomnogram (PSG). However, there have been few studies using current polysomnographic techniques to assess OSAH prevalence among patients with asthma. Polysomnographic studies report a high prevalence of OSA

Table 3 Comparison between asthmatic patients with and without OSA.

	Patients with OSA(18)	Patients without OSA(12)	<i>p</i>
Age	52.1 ± 5.9	47.3 ± 9.21	NS
Sex(M/F)	6/12	7/5	NS
BMI	29.2 ± 3.28	25.4 ± 4.37	0.003**
GERD n(%)	10(56)	2(15)	0.023*
Rhinitis/sinusitis	12(67)	5(41)	NS
FEV ₁	72.8 ± 4.8	78.2 ± 2.62	<0.001***
ESS	10.22 ± 3.7	5.54 ± 2.15	<0.01**

Variables are expressed as mean ± standard deviation.

M = male, F = female, BMI = body mass index, GERD = gastroesophageal reflux disease, ESS = Epworth sleepiness scale, NS = not significant.

* Statistically significant at *p* < 0.05.

** Statistically significant at *p* < 0.01.

*** Statistically significant at *p* < 0.001.

with more severe asthma, regardless of the methodology used. In an earlier study of 22 difficult to-control asthma patients studied with laboratory based polysomnography, 21 (95.5%) were diagnosed with OSA (respiratory disturbance indices ≥ 5 with associated fatigue and EDS), and 9 (41%) had moderate-severe OSA (respiratory disturbance indices ≥ 20) [20]. In a more recent report using home-based complete overnight polysomnography, OSA, defined by an AHI ≥ 15 events/h of scored using Chicago criteria, was present in 88% patients with severe asthma, 58% patients with moderate asthma, and 31% controls without asthma ($\chi^2: p < 0.001$). Using the more restrictive scoring criteria applied in the Wisconsin cohort study, AHI ≥ 5 /h was present in 50% (severe), 23% (moderate), and 12% (control) of subjects ($p = 0.007$) [3]. In both studies, the very high prevalence of OSA in severe asthmatics was unexpected for the degree of excess bodyweight observed (mean BMI 29 and 27 kg/m², respectively).

Obstructive sleep apnea (OSA) and asthma are potentially linked at several levels. The pathophysiology of these two conditions seems to overlap significantly, as airway obstruction, inflammation, obesity, and several other factors are implicated in the development of both diseases [5]. Frequent nocturnal asthma attacks may result in sleep deprivation and fragmentation of sleep that could lead to increased upper airway collapsibility during sleep [21]. Recent data reporting a very high rate of OSA in a small group of severe asthmatic patients on chronic or intermittent systemic steroids suggest that the use of systemic steroids may increase upper airway collapsibility. Moreover, comorbid conditions which are closely associated with asthma such as Gastroesophageal reflux disease (GERD), obesity itself, cardiovascular complications, rhinitis and sinusitis are all complex contributory factors that provide hypothetical links [2,6].

In order to clarify the underlying factors predisposing to the occurrence of OSA in asthmatic patients, we compared different demographic and clinical factors as well as comorbid conditions and asthma severity between asthmatic patients with and without OSA. Furthermore, we performed a regression model to determine the underlying independent predictors for the occurrence of OSA in asthmatic patients. We have found that patients who had OSA had more coexistent GERD, higher BMI and worse FEV1% ($p < 0.001$) than other asthmatic patients. These factors were also found to be significant independent predictors of the occurrence of OSA in asthmatic patients in the regression model.

GERD is commonly encountered in asthma, in many cases being asymptomatic. 56% of asthmatic patients who had OSA had GERD symptoms in comparison with 15% in the non OSA group ($p = 0.023$). Moreover, GERD was found to be an independent predictor for the occurrence of OSA in these patients ($p = 0.034$). Pharyngeal spasm and mucosal exudative neurogenic inflammation occurring as a result of proximal migration of gastric acid and prolonged acid clearance during sleep could render the upper airway dysfunctional and prone to collapse during sleep [22]. Additionally, nocturnal GER can cause arousal during sleep leading to sleep fragmentation and upper airway edema promoting the expression of OSA [23]. All these mechanisms may set the scene for the development of OSA in these patients [1,7].

The mean BMI in our asthmatic group was 28.13 indicating that they were on average overweight and obesity, consistent

with previous reports of excess weight among asthmatics. Obesity is an independent risk factor for asthma and a dose response effect of increasing body mass index (BMI) on increasing risk of incident asthma has been shown [24]. Moreover, excess weight gain may occur in asthmatic, due to a limited ability to exercise, sleep deprivation with increased insulin resistance, depression, or the use of oral steroids [6]. In our previous study we have found a high prevalence of overweight and obesity in asthmatic patients (64% of the studied group) [25]. In this study, the BMI of asthmatic patients with OSA was significantly higher than those without (29.2 versus 25.4, $p = 0.003$). Moreover, excess weight (higher BMI) was found to be a significant independent predictor of the development of OSA in asthmatics ($p = 0.03$).

The rampant epidemic of obesity, particularly observed in asthma patients, is likely to promote OSA [9]. Obesity is the strongest risk factor for OSA and may affect breathing in several ways, including a change in structure or function (collapsibility) of the upper airway through increased fat deposition in the pharyngeal wall from weight gain, reductions in functional residual capacity, an increase in oxygen demand, and a change in the respiratory drive and load compensation relationship [5,6].

Relationships among obesity, OSA, and asthma are likely to be bidirectional and more complex than can be dissected in our correlational study.

Asthma severity as determined by spirometry, was found to be a strong predictor of OSA ($p < 0.001$), indicating that the increased prevalence of OSA in these patients is indeed linked to mechanisms related to asthma itself. Our results add to the evidence that asthma itself may lead to SDB, bronchoconstriction reduces total airway cross-sectional area and is associated with expiratory oropharyngeal and glottis constriction, possibly as a result of intrapulmonary and chest wall reflexes [7]. Another reason behind this reduction is the permanent airway mucosal inflammation observed in asthmatic patients. In fact, Collett et al found a significant reduction of upper airway dimension during inspiration and expiration during asthma flares [26]. Also, asthma could deleteriously impact the patency of the upper airway (UAW) through effects of sleep loss and fragmentation which can increase airway collapsibility. Moreover, greater reduction in lung volumes during sleep, particularly during REM sleep [27,28]; decreased pharyngeal transmural pressure related to nocturnal increase in air speed [29]; and systemic inflammation-related weakening of respiratory muscles, which could include the UAW dilators are additional mechanisms [30,31].

Recent studies suggest that airway disease can be a linked process (unified or linked airway) in selected patients. The coexistence and hypothetical link between Cough/asthma, Obesity/OSA, Rhinosinusitis, and Esophageal reflux was recently referred to as the "CORE" syndrome. In asthmatic patients refractory to therapy, CORE components must be considered in the management [5].

A very important finding in this study is that the presence of OSA in asthmatic patients was significantly associated with worse asthma control ($p < 0.001$).

Several pathways for OSA aggravation of asthma exist: OSA increases the resistive load on the lower airways, superimposed on an already challenged airway, especially during sleep [32]. Also, stimulation of upper airway receptors during the

Mueller maneuvers of obstructive events could augment the vagally mediated bronchoconstriction observed in asthmatics and worsen bronchial hyperresponsiveness (BHR) through alteration of the chemical arousal threshold or through resistive loading [33]. Moreover, hypoxia could impair arousal thresholds to resistive loading [34], cough [35], and asthma symptom perception [36], all of which are important defenses for these patients during sleep. OSA promotes GERD, which is a well-recognized trigger of asthma. GERD can lead to worsening of airway reactivity by directly inducing airway inflammation or indirectly by enhancing vagal tone [5]. Finally, inflammatory links may also be involved, where intermittent hypoxia and distally transmitted mechanical stress from snoring may exacerbate the lower airway inflammation in these patients. In OSA patients, inflammation of the upper airway has been well characterized, [37] while in the lower airway, a neutrophilic type of inflammation has been demonstrated in OSA patients, well correlated with disease severity [38]. Systemically, OSA gives rise to a persistent state of inflammation, which underlies its cardiovascular morbidity and also shares features with the systemic inflammation of asthma [39]. These observations raise the possibility that OSA, through local airway or systemic inflammation, may promote a non-eosinophilic phenotype increasingly recognized among patients with uncontrolled asthma [7,40,41].

In conclusion, a high index of suspicion is warranted for the overlap of OSA and asthma, particularly in the presence of obesity, GERD, and in patients with severe asthma. Individualized therapy addressing moderating factors as weight gain and GERD is warranted for optimal health outcomes. Recognition and treatment of OSA in asthmatics is an important element in improving asthma control. Further research is needed to examine the long-term impact of therapy for OSA on clinical outcomes in asthma.

Declaration of interest

I declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Funding

This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

References

- [1] B. Prasad, S.M. Nyenhuis, T.E. Weaver, Obstructive sleep apnea and asthma: associations and treatment implications, *Sleep Med. Rev.* 18 (2) (2014) 165–171.
- [2] D. Auckley, M. Moallem, Z. Shaman, M. Mustafa, Findings of a Berlin Questionnaire survey: comparison between patients seen in an asthma clinic versus internal medicine clinic, *Sleep Med.* 9 (2008) 494–499.
- [3] J.Y. Julien, J.G. Martin, P. Ernst, et al, Prevalence of obstructive sleep apnea-hypopnea in severe versus moderate asthma, *J. Allergy Clin. Immunol.* 124 (2009) 371–376.
- [4] M. Teodorescu, D.A. Polomis, S.V. Hall, M.C. Teodorescu, R.E. Gangnon, A.G. Peterson, et al, Association of obstructive sleep apnea risk with asthma control in adults, *Chest* 138 (2010) 543–550.
- [5] E. Kasasbeh, Krishnaswamy, Potential mechanisms connecting asthma, esophageal reflux, and obesity/sleep apnea complex: a hypothetical review, *Sleep Med. Rev.* 11 (1) (2009) 47–58.
- [6] M. Alkhalil, E. Schulman, J. Getsy, Obstructive sleep apnea syndrome and asthma: what are the links?, *J. Clin. Sleep Med.* 5 (2009) 71–78.
- [7] O.C. Ioachimescu, M. Teodorescu, Integrating the overlap of obstructive lung disease and obstructive sleep apnoea: OLDOSA syndrome, *Respirology* 18 (2013) 421–431.
- [8] R.K. Kakkar, R.B. Berry, Asthma and obstructive sleep apnea: at different ends of the same airway?, *Chest* 135 (2009) 1115–1116.
- [9] M. Teodorescu, F.B. Consens, W.F. Bria, M.J. Coffey, M.S. McMorris, K.J. Weatherwax, et al, Predictors of habitual snoring and obstructive sleep apnea risk in patients with asthma, *Chest* 135 (2009) 1125–1132.
- [10] US Department of Health and Human Services; National Institutes of Health; National Heart, Lung and Blood Institute; National Asthma Education and Prevention Program. Expert panel report 3 (EPR-3): guidelines for the diagnosis and management of asthma. Full report 2007. < <http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.pdf> > .
- [11] Global Strategy for Asthma Management and Prevention 2014 (revised). www.ginaasthma.org.
- [12] C. Iber, S. Ancoli-Israel, A. Chesson, S. Quan, For the American academy of sleep medicine, in: *The AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology and Technical Specifications*, first ed., American Academy of Sleep Medicine, Westchester, IL, 2007.
- [13] M.W. Johns, A new method for measuring daytime sleepiness: the Epworth sleepiness scale, *Sleep* 14 (1991) 540–545.
- [14] C. Janson, W. De Backer, T. Gislason, et al, Increased prevalence of sleep disturbances and daytime sleepiness in subjects with bronchial asthma: a population study of young adults in three European countries, *Eur. Respir. J.* 9 (1996) 2132–2138.
- [15] C. Janson, T. Gislason, G. Boman, et al, Sleep disturbances in patients with asthma, *Respir. Med.* 84 (1990) 37–42.
- [16] M. Teodorescu, F.B. Consens, W. Bria, et al, Correlates of daytime sleepiness in patients with asthma, *Sleep Med.* 7 (2006) 607–613.
- [17] L.G. Larsson, A. Lindberg, K.A. Franklin, et al, Symptoms related to obstructive sleep apnoea are common in subjects with asthma, chronic bronchitis and rhinitis in a general population, *Respir. Med.* 95 (2001) 423–429.
- [18] A. Ekici, M. Ekici, E. Kurtipek, et al, Association of asthma-related symptoms with snoring and apnea and effect on health-related quality of life, *Chest* 128 (2005) 3358–3363.
- [19] C. Janson, W. De Backer, T. Gislason, et al, Increased prevalence of sleep disturbances and daytime sleepiness in subjects with bronchial asthma: a population study of young adults in three European countries, *Eur. Respir. J.* 9 (1996) 2132–2138.
- [20] M. Yigla, N. Tov, A. Solomonov, et al, Difficult-to-control asthma and obstructive sleep apnea, *J. Asthma* 40 (2003) 865–871.
- [21] F. Series, N. Roy, I. Marc, Effects of sleep deprivation and sleep fragmentation on upper airway collapsibility in normal subjects, *Am. J. Respir. Crit. Care Med.* 150 (1994) 481–485.
- [22] W.C. Orr, S. Elsenbruch, M.J. Harnish, et al, Proximal migration of esophageal acid perfusions during waking and sleep, *Am. J. Gastroenterol.* 95 (2000) 37–42.
- [23] C. Jansson, H. Nordenstedt, M.A. Wallander, et al, A population-based study showing an association between gastroesophageal reflux disease and sleep problems, *Clin. Gastroenterol. Hepatol.* 7 (2009) 960–965.
- [24] C.A. Camargo Jr., S.T. Weiss, S. Zhang, W.C. Willett, F.E. Speizer, Prospective study of body mass index, weight change, and risk of adult-onset asthma in women, *Arch. Intern. Med.* 159 (1999) 2582–2588.
- [25] M. Zidan, R. Daabis, R. Ibrahim, Relation between body mass index and control of bronchial asthma among Egyptian adults with asthma, *World Allergy Organ. J.* 6 (Suppl. 1) (2013) P226.

- [26] P.W. Collett, A.P. Brancatisano, L.A. Engel, Upper airway dimensions and movements in bronchial asthma, *Am. Rev. Respir. Dis.* 133 (1986) 1143–1149.
- [27] F. Series, N. Roy, I. Marc, Effects of sleep deprivation and sleep fragmentation on upper airway collapsibility in normal subjects, *Am. J. Respir. Crit. Care Med.* 150 (1994) 481–485.
- [28] R.D. Ballard, C.G. Irvin, R.J. Martin, et al, Influence of sleep on lung volume in asthmatic patients and normal subjects, *J. Appl. Physiol.* 68 (1990) 2034–2041.
- [29] A.B. Bohadana, B. Hannhart, D.B. Teculescu, Nocturnal worsening of asthma and sleep-disordered breathing, *J. Asthma* 39 (2002) 85–100.
- [30] M. Silvestri, M. Bontempelli, M. Giacomelli, et al, High serum levels of tumour necrosis factor-alpha and interleukin-8 in severe asthma: markers of systemic inflammation?, *Clin. Exp. Allergy* 36 (2006) 1373–1381.
- [31] M.B. Reid, J. Lannergren, H. Westerblad, Respiratory and limb muscle weakness induced by tumor necrosis factor-alpha: involvement of muscle myofilaments, *Am. J. Respir. Crit. Care Med.* 166 (2002) 479–484.
- [32] R.D. Ballard, Sleep, respiratory physiology, and nocturnal asthma, *Chronobiol. Int.* 16 (1999) 565–580.
- [33] J.F. Morrison, S.B. Pearson, The parasympathetic nervous system and the diurnal variation of lung mechanics in asthma, *Respir. Med.* 85 (1991) 285–289.
- [34] M.C. Hlavac, P.G. Catcheside, R. McDonald, et al, Hypoxia impairs the arousal response to external resistive loading and airway occlusion during sleep, *Sleep* 29 (2006) 624–631.
- [35] D.J. Eckert, P.G. Catcheside, D.L. Stadler, et al, Acute sustained hypoxia suppresses the cough reflex in healthy subjects, *Am. J. Respir. Crit. Care Med.* 173 (2006) 506–511.
- [36] D.J. Eckert, P.G. Catcheside, J.H. Smith, et al, Hypoxia suppresses symptom perception in asthma, *Am. J. Respir. Crit. Care Med.* 169 (2004) 1224–1230.
- [37] C. Bergeron, J. Kimoff, Q. Hamid, Obstructive sleep apnea syndrome and inflammation, *J. Allergy Clin. Immunol.* 116 (2005) 1393–1396.
- [38] A.M. Li, E. Hung, T. Tsang, et al, Induced sputum inflammatory measures correlate with disease severity in children with obstructive sleep apnoea, *Thorax* 62 (2007) 75–79.
- [39] S. Ryan, W.T. McNicholas, Intermittent hypoxia and activation of inflammatory molecular pathways in OSAS, *Arch. Physiol. Biochem.* 114 (2008) 261–266.
- [40] P. Haldar, I.D. Pavord, Noneosinophilic asthma: a distinct clinical and pathologic phenotype, *J. Allergy Clin. Immunol.* 119 (2007) 1043–1052 (quiz 1053–44).
- [41] M. Teodorescu, D.A. Polomis, S.V. Hall, Association of obstructive sleep apnea risk with asthma control in adults, *Chest* 138 (3) (2010) 543–550.