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SLEEP BREATHING PHYSIOLOGY AND DISORDERS · ORIGINAL ARTICLE

Long-term CPAP treatment improves asthma control in patients with asthma and obstructive sleep apnoea

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Abstract

Purpose Both asthma and obstructive sleep apnoea cause sleep disturbance, daytime sleepiness and diminished quality of life. Continuous positive airway pressure (CPAP) is efficient in reducing symptoms related to sleep apnoea. Here we report the impact of long-term use of CPAP on asthma symptoms.

Methods A survey questionnaire was distributed to all of our obstructive sleep apnoea patients with CPAP therapy in 2013. We used the Finnish version of the Asthma Control Test™ (ACT) and a visual analogue scale (0 = no symptoms, 100 = severe asthma symptoms). Asthma was defined as self-reported physician-diagnosed disease and a special reimbursement for asthma medication by the Social Insurance Institution.

Results We sent 2577 questionnaires and received 1586 answers (61 %). One hundred ninety-seven patients were asthmatics with a prevalence of asthma among CPAP users of 13 %. We studied 152 patients (58 females) whose CPAP therapy was initiated after starting asthma medication. Their mean (SD) age was 62 (10) years, duration of CPAP 5.7 (4.7) years and their CPAP daily use was 6.3 (2.4) h. Self-reported asthma severity decreased significantly from 48.3 (29.6) to 33.1 (27.4) ($p < 0.001$), and ACT score increased significantly from 15.35 (5.3) to 19.8 (4.6) ($p < 0.001$) without a significant change in the body mass index (BMI). The percentage of patients using rescue medication daily reduced from 36 to 8 % with CPAP ($P < 0.001$).

Conclusions We noticed a significant decrease in asthma symptoms with long-term use of CPAP in patients with both asthma and obstructive sleep apnoea.

Keywords Asthma · Obstructive sleep apnoea · CPAP

Introduction

Symptoms of obstructive sleep apnoea (OSA), such as waking up at night with breathing difficulties, snoring and witnessed apnoeas, are common in patients with asthma [1–5]. However, the exact prevalence of OSA in asthmatic patients is not known but the incidence of OSA has been reported to be approximately 2.5 times greater in asthma patients than those without asthma [5, 6].

It has been suggested that OSA is an independent risk factor for asthma exacerbation [7], and it has been recommended that physicians evaluate symptoms that suggest OSA and consider differential diagnostics, especially in unstable, poorly controlled asthmatic patients, particularly those who are overweight or obese [8].

The first-line therapy for moderate to severe OSA is continuous positive airway pressure [CPAP], which is considered the most effective therapy to suppress sleep apnoea-related symptoms. Clinical improvement of symptoms after CPAP treatment is directly related to a major reduction in respiratory events and their related consequences during sleep. Specifically, CPAP eliminates or reduces the chronic intermittent hypoxia and sleep fragmentation observed during apnoeic events [9].

In asthmatics with concomitant OSA, CPAP has been shown in a prospective clinical study to have a positive impact on asthma outcome such as improvement in daytime and

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night-time asthma symptoms, reductions in nocturnal bronchodilator use and marked improvement in mean peak expiratory flow rates [6]. The aforementioned study was prospective but short and included a limited number of patients.

Although the number of studies on asthma, asthma and respiratory symptoms and OSA has been increasing, the consequences of CPAP therapy on asthma is not fully understood. The purpose of this study was to evaluate the prevalence of current asthma among CPAP users and describe the effect of long-term CPAP use on asthma symptoms.

Material and methods

This was a one-centre retrospective cross-sectional questionnaire study on respiratory symptoms and patient's perspective of CPAP therapy on respiratory symptoms in patients with concomitant asthma and OSA. All the patients with diagnosed obstructive sleep apnoea (OSA) ($N = 2577$) and current CPAP therapy of more than 3 months duration in the sleep unit in the Helsinki University Central Hospital were sent a questionnaire in June–July 2013 (diagnosed OSA, current CPAP therapy and self-reported physician diagnosed asthma formed the inclusion criteria) (Fig. 1). The exclusion criteria were asthma diagnosed after starting CPAP therapy, use of CPAP for less than 3 months and OSA without current CPAP therapy.

Asthma

Asthma was assessed as a self-reported physician-diagnosed disease. In Finland, asthma is diagnosed according to the international guidelines [10]. The criteria for reversible airway obstruction are either a bronchodilator response in spirometry (≥ 12 % and ≥ 200 ml) or moderate to severe bronchial
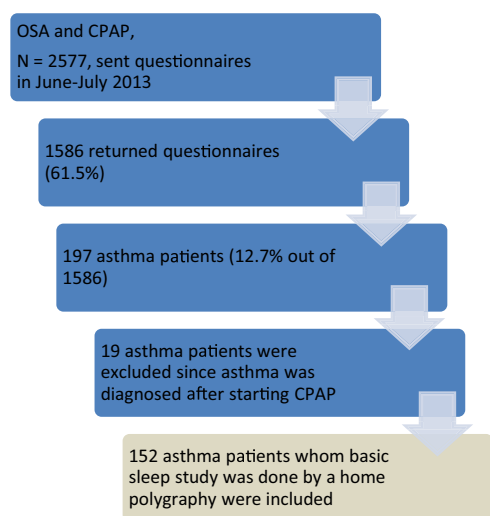
hyperreactivity or a bronchodilator response in peak expiratory flow (PEF) recording (≥ 15 %), a diurnal variation in PEF (≥ 20 %) or a FEV1/PEF decrease of ≥ 15 % in an exercise test [11, 12].

Asthma severity was assessed by a visual analogue scale (VAS) from 0 (no symptoms) to 100 (severe asthma symptoms). In addition, the patients fulfilled the Asthma Control Test® (ACT) concerning their symptoms (score between 5 and ≤ 19 uncontrolled asthma, 20–24 well-controlled asthma, and score = 25 totally controlled asthma). Patients reported their asthma symptoms retrospectively both before CPAP treatment and during the last 4 weeks using both ACT and VAS [13, 14]. ACT questions included use of asthma medication (During the past 4 weeks, how often have you used rescue inhaler or nebulizer medication?). The use of asthma medication was reported before of CPAP treatment and during the last 4 weeks. Asthma patients whose diagnosis was accomplished after starting CPAP therapy were excluded from the analyses.

Smoking status was assessed by the questionnaire. From the patient's file, we obtained values for body mass index and data concerning the use of CPAP and the chronology of asthma. We also analysed changes in body mass index (BMI) using the information on weight and height in the medical records at the time of starting CPAP therapy and at the time of the questionnaire study.

Obstructive sleep apnoea

The baseline sleep studies were mainly performed with the help of home polygraphy. In few cases, the diagnosis of OSA was done with the help of an in-lab polysomnography (PSG) or a home PSG. To avoid confusion related to the differences in OSA diagnostic method, we included in this study only patients with a home polygraphy. We offered CPAP therapy to patients with a respiratory event index (REI) >15/h during a sleep study (out-of-centre sleep test) and to patients with REI 5–14 and symptoms related to OSA [15]. The definition for apnoea was absence of nasal or buccal flow >10 s. The definition for hypopnoea was a decrease of nasal flow of at least 50 % for at least 10 s or a decrease of saturation of at least 3 % [16].

CPAP therapy was initiated mainly at home with an automatic PAP device (ResMed, Sydney, Australia), and titration was controlled by oximetry. The pressure was set to start automatically, from 4 cmH2O up to maximum of 20 cmH2O. The treatment effect was controlled by oximetry, and normalized results were considered if mean SPO$_2$ values were at least 95 % and ODI4 was less than five per hour [17]. The effect of CPAP therapy on OSA was controlled at 1 week, 3 months and then yearly as previously described [17]. For this study, we only used those who had had CPAP therapy for more than

Fig. 1 Flowchart of patient recruitment for sleep apnoea and asthma patients

3 months. Data were obtained from the memory of the CPAP device at each control visit.

The Helsinki University Central Hospital gave ethics permission (number §19 2/2013, date 25.5.2013) to organize the study, and the informed consent forms were included in the questionnaires.

Statistical analysis

Shapiro-Wilk's test ($p > 0.05$) and a visual inspection of their histograms, normal Q-Q plots and box plots showed that the exam scores were approximately normally distributed for the asthma control test score at baseline for both men and women, with a skewness of −0.287 (SE = 0.274) and a kurtosis of −0.960 (SE = 0.541) for men and a skewness of 0.366 (SE = 0.365) and a kurtosis of −0.421 (SE = 0.717) for women.

The ANOVA method was used to compare differences in ACT scores [13]. We used Student's t test for continuous variables with normal distribution and the chi-square tests for categorical variables. If the assumption, in the chi-square test, was violated, we used Fisher's exact test. A p value <0.05 was considered statistically significant.

The ACT scores before and after CPAP therapy were first analysed in the total study population and then in the subgroup of asthma patients. We divided patients according to the clinically significant modification in their ACT score into two groups: $\Delta ACT \geq 3$ group and $\Delta ACT < 3$ group [18].

A multivariate regression analysis was used to define factors that may predict modifications in asthma symptoms measured by the ACT. We run multivariate linear regressions for ΔACT using ACT baseline, CPAP daily use, age, gender, CPAP therapy duration, change in BMI, current smoking, chronic rhinitis, REI baseline, REI CPAP, BMI baseline and the baseline sleep study PSG or polygraphy.

IBM SPSS Statistics software (version 22.0.0.1) (IBM Corporate, New York, USA) was used to compute differences in demographic, clinical and measured variables.

Results

We received altogether 1586 answers (61.5 %). The responders (those who returned the questionnaire) were older than the non-responders (those who did not return the questionnaire), 60 (SD 13) vs. 58 (12) years, respectively ($p < 0.001$). Of the responders, 27 % were women and 45 patients had discontinued using CPAP therapy by the time of questioning. A total of 1530 patients had OSA and a current CPAP treatment (Fig. 1). Of these, 178 had a self-reported physician-diagnosed asthma with special reimbursement for asthma medication in whom asthma diagnosis had been done prior to CPAP therapy. We included 152 patients whose basic sleep study was done by a home polygraph. The mean age of the patients with both asthma

and OSA was 62 years (10 years), and 38 % of the patients were women. All the patients had used CPAP therapy a mean of 5.9 years (4.8) for 6.0 h/day (2.5), while the respective numbers for both asthma and OSA patients were 5.7 years (4.7) and 6.3 h/day (2.4) (p value ns). Minimum of the CPAP use was 0 h and maximum 10.2 h/day, median 6.90 h and percentiles of CPAP use were 5.5 (25th percentile), 6.90 (50th percentile) and 8.0 (75th percentile) in patients with asthma and OSA. CPAP treatment was effective in reducing the apnoea and hypopnoea index from 41.2 to 3.5/h.

We excluded 26 patients as their baseline sleep studies were performed with the help of an in-lab polysomnography (PSG) or home PSG. We found no significant differences between PSG and home polygraph groups regarding their age [$F(2, N = 178) = 0.15, p = 0.99$], gender [$\chi^2 (2, N = 178) = 2.83, p = 0.24$], CPAP daily use [$F(2, N = 178) = 0.25, p = 0.78$], scores of ACT baseline [$F(2, N = 178) = 0.39, p = 0.68$] or ACT with CPAP [$F(2, N = 178) = 0.10, p = 0.91$].

The severity of asthma symptoms measured by the VAS score decreased from 50.8 (SD 30.7) at baseline before CPAP treatment to 33.6 (25.9) with CPAP in women [$t (39) = 4.007, p = 0.000$]) and in men from 46.8 (29.1) to 32.9 (28.4) [$t (69) = 6.483, p = 0.000$]. In both women and men, it also decreased significantly from 48.3 (29.6) to 33.1 (27.4) [$t (109) = 7.311, p = 0.000$] (Fig. 2). We found the same trend concerning the self-reported asthma severity expressed by the ACT score. It increased significantly from the baseline at 15.3 (5.3) to 19.8 (4.2) with CPAP in women [$t (33) = −6.677, p = 0.000$] (Fig. 3) and in men from 17.2 (5.6) to 19.1 (4.9) [$t (67) = −4.373, p = 0.000$], respectively. Moreover, we found a significant correlation between the values of the ACT at baseline and those of the asthma severity at baseline [$r (102) = −0.721, p = 0.000$].

The mean baseline BMI was 37.2 (8.7) kg/m^2 in women and 33.8 (6.0) kg/m^2 in men. There was no statistically significant change in the BMI during the time course of CPAP therapy, neither in women nor in men [$t (145) = −0.277, p = 0.782$].

The percentage of patients reporting no night-time symptoms was 28 % at baseline and increased significantly [$\chi^2 (1, N = 103) = 19.232, p = 0.000$] ($p < 0.001$) with CPAP to 55 %. Moreover, we noticed a similar amelioration concerning the percentage of patients using rescue medication daily, with a significant reduction from 36 to 8 % with CPAP ($p < 0.001$).

As a value of 3 in the ACT score means a clinically significant change [18], we divided our patients into one group with an ACT change of three or more ($\Delta ACT \geq 3$) and another group with an ACT change of less than three ($\Delta ACT < 3$). We did not find a statistically significant association related to age, daily CPAP use, duration of CPAP therapy, severity of sleep apnoea, values of residual REI or values of BMI at baseline between these two groups. Moreover, the presence
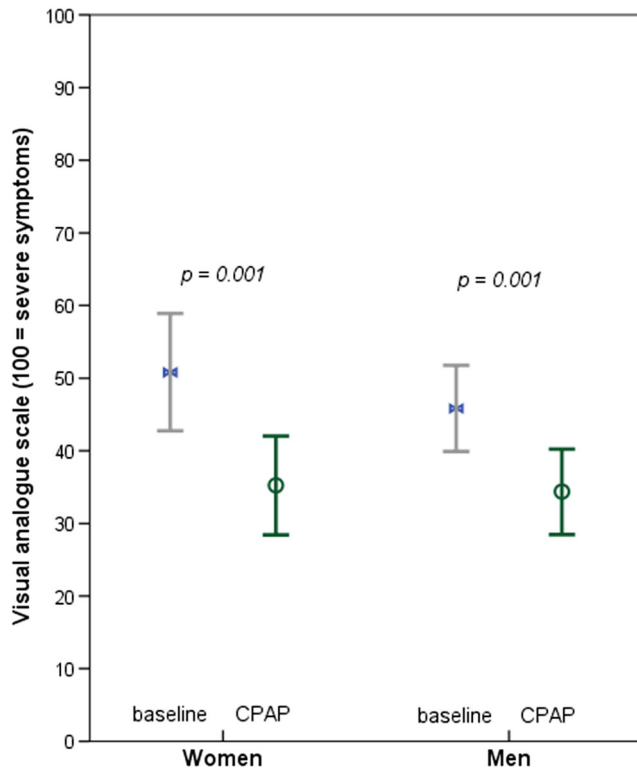
Fig. 2 Self-reported asthma severity on a visual analogue scale (0–100 mm) before and during CPAP treatment for OSA
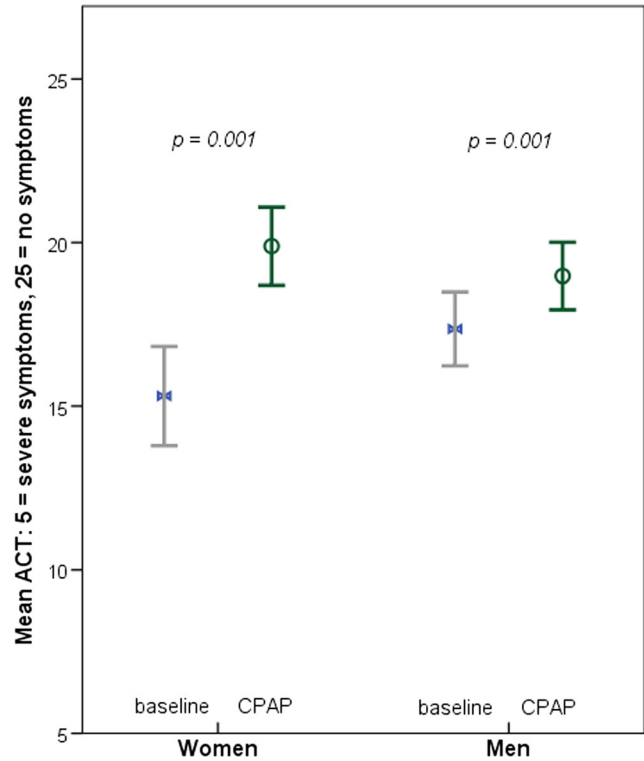

Fig. 3 Asthma control test score results before and during CPAP treatment

of current smoking, COPD or chronic rhinitis did not differ significantly between the $\Delta ACT \geq 3$ and $\Delta ACT < 3$ groups (Table 1). Interestingly, women were found significantly more often (49 %) in the $\Delta ACT \geq 3$ group compared to the $\Delta ACT < 3$ group (18 %) [χ^2 (1, $N = 102$) = 11.294, $p = 0.001$]. The same tendency was noticed in patients with a lower ACT score at baseline [t (100) = −6.222, $p = 0.000$] and in patients with a higher VAS asthma severity score [t (99) = 3.095, $p = 0.003$]. The absolute value of the BMI at baseline was not associated with the change in the ACT with CPAP [t (97) = 1.063, $p = 0.290$]. Nevertheless, a slight decrease in weight with CPAP (mean of −1.6 kg) was associated with a significant increase in the ACT with CPAP [t (97) = −2.740, $p = 0.007$].

We performed a multivariate regression analysis to define factors that may predict asthma symptom change measured by the ACT. Table 2 shows age, duration of CPAP therapy, daily CPAP use, change in bodyweight, smoking status, chronic rhinitis, severity of OSA measured by REI, or the efficacy of CPAP on AHI values or the type of the baseline sleep study (polysomnography or a polygraphy) did not show a significant relation to the ACT modification.

Meanwhile, the patient's gender (female), values of BMI at baseline and especially values of ACT at baseline were significant factors in predicting ACT modifications. The regression analysis showed that values of ACT at baseline could significantly predict

35 % of the ACT modification with long-term CPAP [$p = 0.000$, $R^2 = 0.346$]. The regression equation was $\hat{Y}\Delta ACT = 11.220 + (−0.502)$ ACT baseline.

Discussion

We found a prevalence of self-reported asthma of 13 % among long-term CPA users. In this population, long-term CPAP use reduced asthma symptoms measured both by a VAS and ACT significantly. Self-reported asthma severity decreased from 47.6 to 31.6 using the VAS scale during the CPAP treatment. Likewise, the self-reported ACT score increased from 16.5 to 19.3 during the CPAP treatment ($p < 0.001$), showing better asthma control during the CPAP treatment, whereas the BMI of the patients stayed unchanged.

This is the first study showing the long-term effect of CPAP on asthma symptoms in a large patient population. Further, the asthma diagnosis was based on both symptoms, airway reversibility shown in lung function measurements, as well as a response to asthma medication. On the other hand, the effect of CPAP treatment on bronchial hyperreactivity conflicts with reports of either a lack of effect on bronchial hyperreactivity [19] or even a negative effect [20]. In the latter study, bronchial

Table 1 Comparison of clinical characteristics, asthma severity, OSA severity and CPAP use in the group with ΔACT ≥ 3 vs. the group with ΔACT < 3

ACT difference (baseline − CPAP) = ΔACT

	≥3		<3				
	Mean	SD	Mean	SD	t	df	p value
Age, years	63.2	8.3	63.1	10.2	0.085	100	0.932
CPAP daily use (hours)	7.1	1.5	6.7	1.6	1.226	100	0.223
CPAP since (days)	2153	1682	2123	1692	0.089	100	0.929
REI baseline	42.0	26.0	40.2	25.7	0.338	93	0.736
REI residual	3.4	3.3	2.8	2.3	1.022	92	0.310
BMI baseline (kg/m^2)	35.1	7.7	33.7	5.6	1.063	97	0.290
Bodyweight change (CPAP − baseline, kg)	−1.6	11.0	3.5	6.8	−2.740	97	0.007
ACT baseline	13.6	4.0	19.5	5.4	−6.222	100	0.000
Asthma severity VAS baseline	56	27	39	28	3.095	99	0.003
	n (%)		n (%)		(χ2)	df	p value
Women	25 (49)		9 (18)		11.294	1	0.001
Current smoker	7 (14)		5 (10)		0.378	1	0.539
COPD	13 (26)		14 (28)		0.050	1	0.822
Chronic rhinitis	16 (31)		21 (41)		1.060	1	0.303

ACT means asthma control test: 5 = severe symptoms, 25 = no symptoms; asthma severity measured by a visual analogue scale, 0 = no symptoms, 100 = severe asthma symptoms

REI respiratory event index

hyperreactivity was increased in 57 OSA patients after 3 weeks of CPAP therapy compared to the baseline.

Previous studies on asthma and OSA have been smaller, including 9–50 patients, and have had a shorter duration of CPAP treatment ranging from 2 weeks to 6 months [19, 21–23], whereas we had altogether 178 patients with self-reported physician-diagnosed asthma and current CPAP treatment for OSA, whose CPAP therapy had continued for a mean of 5.5 years.

In the earlier studies, night-time asthma symptoms and nocturnal bronchodilator use were reported to be reduced by CPAP treatment in asthma patients [21, 22]. Further, daytime asthma symptoms have been reported to decrease and asthma-specific quality of life to improve due to CPAP therapy [19, 21, 23]. Our results were in accordance with the previous study results although our study was a retrospective questionnaire study without objective pulmonary function test measurements before and

Table 2 Predictors of amelioration of asthma symptoms with the long-term CPAP therapy with a multivariate regression analysis

Model	Unstandardized coefficients		Standardized coefficients	t	p value
	B	Std. error	Beta		
(Constant)	22.926	5.505		4.164	.000
Asthma control test, ACT (baseline)	−0.474	0.078	−0.543	−6.091	.000
CPAP daily use	0.253	0.272	0.081	0.932	.354
Age	−0.081	0.049	−0.156	−1.637	.106
Gender	−2.125	0.954	−0.211	−2.228	.029
CPAP treatment duration	0.000	0.000	−0.048	−0.537	.593
Change in body weight (baseline − CPAP)	−0.086	0.049	−0.173	−1.760	.082
Current smoking	0.224	1.330	0.015	0.168	.867
Chronic rhinitis	−0.054	0.897	−0.005	−0.060	.952
Respiratory event index, REI (baseline)	0.016	0.019	0.087	0.864	.390
REI (CPAP)	0.194	0.152	0.115	1.278	.205
Body mass index (baseline)	−0.197	0.078	−0.280	−2.530	.013

during CPAP therapy. Both VAS and the ACT test have been used when estimating asthma symptoms and asthma control even though sleep disturbance might be associated to either OSA or asthma or both. Here, the number of patients using rescue medication two to three times per week reduced significantly from 19 to 13 % with CPAP treatment, and those not needing rescue medication significantly increased from 33 to 36 % ($p < 0.001$) which was the level of asthma medication follow-up that was estimated possible when planning the study. In a prospective setting, a number of per oral steroid courses per year and a dose of inhaled corticosteroids should be followed. However, even if the asthma medication would be analysed further, it is according to patients' reports. The actual count of used medication is followed only in clinical trials and elsewhere (both in the medical records and in clinical studies), the information is based on the patient report. Since directly observed treatment is not used in asthma treatment, there is no absolute method for medication treatment adherence. Further, the 13 % prevalence of asthma among CPAP users in here is almost twice the reported prevalence of asthma patients with special reimbursement for medication in Finland (6.6 % in the year 2011) [24].

Neutrophilic inflammation of lower airways demonstrated by sputum samples has been reported in OSA patients without CPAP treatment [25]. Salerno et al. hypothesized that this might be caused by intermittent upper airway obstruction and mechanical mucosal stress. Further, neutrophilic lower airway inflammation would lead to airway obstruction. In the study of Salerno et al., BMI or obesity was not correlated to sputum neutrophilia but OSA was. Obesity and sleep apnoea are more likely to be associated with a neutrophilic asthma phenotype than an allergic and/or eosinophilic asthma phenotype, offering an explanation for the reduced probability of reaching an optimal asthma control level with traditional asthma therapy such as inhaled corticosteroids, long-acting bronchodilators and antileukotrienes [23, 26, 27]. Obesity has been associated with asthma both as a risk factor for asthma and as a modifying factor of the disease [28, 29]. Since this was a questionnaire study we did not have the option of studying sputum samples to differentiate between eosinophilic and neutrophilic asthma phenotypes. However, our results are in agreement with earlier ones [30] in which obese patients did not lose weight after the initiation of CPAP therapy. Further, the improvements in asthma control in our patients were not a result of weight loss.

The positive effect of CPAP on respiratory symptoms was greater in women and in those with poorer ACT and VAS values. Asthma is more common in women, and OSA is more often found in men [26]. Obesity is associated with both OSA and more severe asthma. OSA patients with concomitant asthma have probably more respiratory symptoms than patients with only OSA. These results are suggestive for and additive treatment option to traditional asthma medication in obese

asthmatic women and especially in patients with both asthma and OSA.

The benefits of CPAP treatment on asthma symptoms in asthma and OSA patients are multiple. CPAP therapy has been suggested to reduce systemic inflammation associated with OSA. CPAP treatment has been reported to decrease hypoxia and oxidative stress, to decrease neutrophil superoxide dismutase generation and superoxide release, and to lower CRP and vascular endothelial growth factor (VEGF) levels [6]. One of the mechanisms of CPAP therapy that may be effective in asthma is improving the acinar ventilation heterogeneity that has been shown to exist even during inhaled corticosteroid therapy [31]. Decreasing acinar ventilation heterogeneity might simply lead to improved ventilation but also secondarily decrease the local inflammation process. Further, improvements in reflux syndrome might contribute to reducing both any nighttime respiratory symptoms and also specifically nighttime asthma symptoms [6, 32].

In our study, none of the following variables (age, daily CPAP use, duration of CPAP therapy, severity of sleep apnoea, values of residual REI) were associated with an increase in ACT scores of three or more. Nevertheless, a slight decrease in BMI with CPAP was associated with a significant increase in ACT with CPAP, pointing to the role of body weight regulation in the pathogenesis of asthma symptoms. In addition, female gender, ACT baseline and BMI baseline values were predictive for a greater response (measured by ACT) to CPAP therapy.

The study has some limitations as it is a questionnaire study. Moreover, we did not report the effect on pulmonary function test results of CPAP therapy, nor comorbidity, which may influence asthma symptoms. We hypothesize that regular CPAP users are motivated patients, and motivation may also increase compliance to other treatments such as asthma medication. In addition, our reported results concerning asthma severity are both self-reported and retrospective, both of which include a possibility of recall bias. Thus, a prospective follow-up study with a control group should be performed to validate these study results. Those who answered our questionnaire were compliant CPAP users (6.3 h/day). The compliance in this study was greater than what we have reported previously (5.6 h ± 1.5) [33], probably because of high prevalence of asthma in this study. It is possible that asthma patients with OSA are more symptomatic and thus also more compliant than average CPAP users. This may have had a positive impact on their answers to asthma symptoms before and during CPAP therapy compared to those with OSA and asthma but no CPAP therapy. Further, our results cannot be generalized to the overall asthma population but only to those with concomitant sleep apnoea syndrome. However, a recent study on patients with severe asthma

by D'Amato et al. reported improvement in asthma control with CPAP therapy and reduction in PEF variability in patients without OSA [34]. In addition, these analyses and results are limited to the patients with OSA diagnosed with an ambulatory home polygraphy and thus may underestimate the true prevalence or severity of OSA in these patients [35]. Further, no formal in-lab CPAP titration was performed and instead CPAP therapy was initiated at home with an automatic PAP device and titration was controlled by oximetry. In a prospective setting, the use of an in-lab PSG and an in-lab CPAP titration would be more exact methods and thus recommended.

In conclusion, we noticed a statistically and clinically significant improvement in asthma control in patients using CPAP. This reduction in self-reported asthma severity could not be interpreted as a change in BMI. If asthma control is not achieved in obese patients, then the possibility of coexisting OSA should be assessed and CPAP therapy offered.

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