ORIGINAL ARTICLE AIRWAY DISEASES

Asthma outcomes improve with continuous positive airway pressure for obstructive sleep apnea

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Abstract

Background: Continuous positive airway pressure (CPAP) in asthma patients with concomitant obstructive sleep apnea syndrome (OSAS) seems to have a favorable impact on asthma, but data are inconsistent due to methodological limitations of previous studies.

Methods: Prospective, multicenter study. We examined asthma outcomes after 6 months of CPAP in 99 adult asthma patients (mean age 57 years) with OSAS (respiratory disturbance index ≥20). Asthma control and quality of life were assessed with the Asthma Control Questionnaire (ACQ) and the Mini Asthma Quality of Life Questionnaire (MiniAQLQ), respectively. Data were analyzed by intention-to-treat basis.

Results: The mean ± SD score of the ACQ decreased from 1.39 ± 0.91 at baseline to 1.0 ± 0.78 at 6 months ($P = 0.003$), the percentage of patients with uncontrolled asthma from 41.4% to 17.2% ($P = 0.006$), and the percentage of patients with asthma attacks in the 6 months before and after treatment from 35.4% to 17.2% ($P = 0.015$). The score of the mAQLQ increased from 5.12 ± 1.38 to 5.63 ± 1.17 ($P = 0.009$). There were also significant improvements in symptoms of gastroesophageal reflux and rhinitis, bronchial reversibility, and exhaled nitric oxide values (all $P < 0.05$). No significant changes were observed in drug therapy for asthma or their comorbidities nor in the patients' weight.

Conclusions: Asthma control (both actual and future risk), quality of life, and lung function improved after starting continuous positive airway pressure in asthmatics with moderate to severe obstructive sleep apnea syndrome.

The Global Burden of Disease Study estimates that there are 334 million asthmatics worldwide, and the global prevalence of obstructive sleep apnea syndrome (OSAS) exceeds 100 million patients (1, 2). In the developed world, between 5% and 10% of the adult population suffer from asthma (3). Depending on the criteria used for diagnosis, OSAS affects 2-4% of men and 1-2% of women in the United States (4), with an estimated prevalence of 3-6% in the general Spanish population (5). Being so prevalent, it is inevitable that a significant percentage of patients suffer from both diseases simultaneously. However, the relationship between asthma and OSAS appears to be more complex than a casual association. They share common risk factors and pathophysiological mechanisms and are also detrimental to each other (6).

OSAS is an important risk factor for uncontrolled asthma and for frequent exacerbations (7–11). In a prospective study of 22 patients with difficult-to-control asthma, a night polysomnography showed that all but one patient had OSAS (95.5% prevalence) (7). Also, it has been shown that the prevalence of OSAS increased progressively according to

severity of asthma (from 58% in moderate asthma to 88% in severe asthma) (9). In children with poorly controlled asthma and frequent asthmatic exacerbations, the prevalence of OSAS was markedly increased (63%) (10). Current asthma clinical practice guidelines already include OSAS as a possible comorbidity affecting asthma management, and recommend to investigate the presence of OSAS in the cases of severe or uncontrolled asthma (12, 13).

In patients with OSAS and concomitant asthma, application of continuous positive airway pressure (CPAP) has been reported to provide benefits for asthma, although, in general, these studies included a small number of subjects, lacked of a control arm, were retrospective, had relatively short follow-up times, and used heterogeneous criteria for the assessment of outcomes, which limit the consistency of their conclusions (14–18). In a recent survey among 1586 patients with OSAS of which 12.4% were asthmatics, long-term treatment with CPAP (mean of 5.7 ± 4.7 years) was effective in reducing asthma symptoms and improving asthma control in 152 patients (19).

To overcome some limitations of previous studies, we designed a prospective, multicenter study with a large number of asthma patients with OSAS, the objective of which was to examine the mid-term effect of CPAP on clinical and functional asthma outcomes, using objective diagnostic tests and validated questionnaires.

Methods

Study design

Between September 2011 and October 2014, a prospective multicentre study was carried out in 15 acute-care hospitals throughout Spain. The primary objective of the study was to assess the clinical and functional course of asthma in the mid-term (3 and 6 months) after starting treatment with CPAP in patients with moderate–severe OSAS, including variables of asthma control and health-related quality of life. As a secondary objective, possible differences in the clinical course of asthma according to severity of both asthma and OSAS were investigated. The study was conducted in accordance with the Declaration of Helsinki (6th World Medical Assembly 2013) and was approved by the Clinical Research Ethics Committee of the Balearic Islands (approval number IB 1616/11 PI) and registered at https://www.clinicaltrials.gov/ (NCT01374932). Written informed consent was obtained from all participants. Personal identification data were anonymized.

Participants

Patients previously diagnosed with asthma were consecutively enrolled from the outpatient clinics of the Pneumology Services involved in the study. Eligibility included men and women aged between 18 and 70 with moderate to severe OSAS (respiratory disturbance index ≥ 20). The diagnosis of asthma and the classification of disease severity were established according to the Global Initiative for Asthma (GINA) criteria (20). Patients were excluded in the presence of a severe, decompensated comorbid disease or when their treatment (ß-blockers, hypnotics, etc.) may interfere in the course of asthma and/or OSAS; other pulmonary diseases different from asthma with airflow limitation; cognitive impairment that could limit the comprehension or collaboration of the subject in the study; or a level of severity that, upon the investigator's judgment, prevented to apply the diagnostic and therapeutic protocol of the study. Patients with an asthma exacerbation episode between diagnosis of OSAS and the beginning of unattended domiciliary CPAP therapy were not eligible.

All subjects were naïve to CPAP. The CPAP equipments had hour meter recording systems, so that machine-on time hours could be checked at each clinical visit. During the first 3 months of study, changes in the pharmacological treatment for asthma were not allowed, except during exacerbation episodes when doses of inhaled bronchodilator treatment could be increased and oral glucocorticoids could be administered. All patients on CPAP treatment, independently on the compliance to CPAP therapy, remained in the study cohort.

Assessments and study procedures

A preestablished questionnaire was used to complete demographic variables; history and characteristics of asthma, including severity (categorized as intermittent, mild persistent, moderate persistent, and severe persistent), duration of asthma, pharmacological treatment, exacerbations, respiratory function tests, sensitization to common aeroallergens and comorbidities, including rhinitis, smoking status, obesity (defined as body mass index [BMI] ≥ 30 kg/m^2), and common subjective symptoms of gastroesophageal reflux disease (GERD) (heartburn and/or regurgitation) reported by the patients. Objective complementary examinations for the diagnosis of GERD at follow-up were not performed. Spanish-validated versions of the Epworth Sleepiness Scale (ESS) (21), the Asthma Control Questionnaire (ACQ) (22), and the Mini Asthma Quality of Life Questionnaire (MiniAQLQ) (23) were used to assess daytime sleepiness, asthma control, and asthma-related quality of life, respectively.

Pulmonary function tests (spirometry and fractional exhaled nitric oxide [FeNO]) were performed according to recommendations of the Spanish Society of Pneumology and Thoracic Surgery (SEPAR) (24, 25). Positive response to bronchodilator testing was considered if forced expiratory volume in one second (FEV_1) increased ≥12% and 200 mL as compared to baseline. Asthma exacerbations were defined as an increase in symptoms (dyspnea, cough, wheezing, chest tightness) needing unscheduled medical care of any type and/or a change in medication (including the prescription of systemic glucocorticoids). Well-controlled asthma was defined as an ACQ score ≤ 0.75 and not well-controlled asthma as an ACQ score ≥ 1.5 (26). The severity of rhinitis was graded according to ARIA guidelines (27).

The diagnosis of OSAS was made by conventional full polysomnography (30% of cases) or cardiorespiratory polygraphy (70%) that included, at least, the following parameters: oronasal flow (thermistor and nasal cannula), thoracoabdominal movements, and pulse oximetry. Sleep studies were

performed during a phase of at least 1 month of clinical stability of asthma. The different respiratory and electroencephalographic events included in the calculation of the respiratory disturbance index (RDI) were defined according to guidelines of the Sleep Group of the SEPAR (28) and the American Sleep Disorders Association (29). The intensity of OSAS was classified into two levels based on RDI (≤30, and >30 events/h). For each patient, titration of CPAP pressure was performed by conventional polysomnography (28) or using auto-CPAP equipment using a validated protocol (30). Once patients were adapted to CPAP therapy, conventional polysomnographies or nocturnal cardiorespiratory polygraphy with their CPAP machines was performed to assess efficacy. It was considered that patients followed adequately treatment with CPAP when the mean use of therapy was equal or higher than 4 h/night.

Statistical analysis

In order to detect minimal clinically relevant differences (0.5 points) in the ACQ and MiniAQLQ, for an α risk of 0.05 and a ß risk of 0.20, and assuming up to 40% losses at follow-up, a minimum of 90 patients were needed. Data were analyzed on an intention-to-treat (ITT) basis, including all 99 patients in whom titration of CPAP was performed. Therefore, in calculating proportions during the monitoring period, the value of the denominator was kept in the initial 99 cases. Categorical variables are expressed as frequencies and percentages, and quantitative variables as mean and SD. Proportions were compared with the chi-square (χ^2) test or the Fisher's exact test, and quantitative variables with the Student's *t*-test or the Mann–Whitney *U*-test, according to the normal or not normal distribution of data. The Student's *t*-test for paired data or the Wilcoxon rank-sum test was used for the comparison of repeated measures. A logistic regression analysis was performed to assess the possible influence of changes in comorbid diseases (rhinitis, GERD, obesity) and the patient's clinical condition (daytime sleepiness) on the course of asthma. Two regression models were fitted. In one model, a clinically relevant improvement in the control of asthma (decrease ≥ 0.5 points in the ACQ) was the dependent variable, with sex, decrease in BMI, reduction in the percentage of patients with rhinitis, and symptoms of GERD (heartburn and/or regurgitation) as binary independent variables (yes/no) and age as discrete independent variable. In the second model, a relevant increase in the score of the MiniAQLQ was the dependent variable, with age, sex, and decrease in BMI, reduction in the percentage of patients with rhinitis and GERD, and decrease in the score of the EES questionnaire as the independent variables. Statistical analysis was performed with the SPSS version 15.0.1 (Statistical Package for Social Sciences, SPSS, Inc., Chicago, IL, USA). Statistical significance was set at $P < 0.05$.

Results

The flowchart of study participants is shown in Fig. 1. Of the 121 patients who met the inclusion criteria, 22 were not included for the following reasons: refusal of CPAP therapy ($n = 3$), presence of an asthma exacerbation immediately before starting CPAP ($n = 2$), and CPAP titration not carried out for different reasons ($n = 17$). Therefore, the intention-to-treat study population included 99 patients (60 men and 39 women) with a mean age of 57.1 ± 11.4 years.

As shown in Table 1, significant differences between participants and nonparticipants were not observed, except for a higher cardiovascular comorbidity among participants. At follow-up, four patients failed to tolerate CPAP and discontinued the study and 13 patients were lost for different causes.

Baseline characteristics of the study population are shown in Table 2. Patients were all receiving asthma medications for at least 6 months (92% inhaled glucocorticoids). Patients with moderate–severe asthma as compared to those with intermittent–mild asthma had significantly lower values of FEV_1, higher frequency of positive bronchodilation test, more intense pharmacological treatment, and poorer asthma control and quality of life. Percentages of obese patients and patients with GERD symptoms were also significantly higher. However, differences in sleep parameters, daytime somnolence, and mean CPAP pressure were not observed. Seventy-five patients (75.8%) showed a RDI > 30 and 24 (24.2%) ≤30.

Clinical and functional characteristics of patients

At the end of the six-month follow-up period, no significant changes were observed in the mean values of FEV_1, in the mean weight of patients, or in the percentage of current smokers. Also, there were no significant differences in the pharmacological treatment for asthma, rhinitis, or GERD (Table 3) between 3 and 6 months and between baseline and 6 months. However, the percentage of patients with mild rhinitis, heartburn, and regurgitation decreased significantly, as well as the mean score of the ESS (Table 3). Finally, the mean fractional exhaled nitric oxide (FeNO) and the percentage of patients with positive bronchodilation test showed a significant decrease (Table 3).

Current asthma control and future risk of asthma-related events

The mean score of the ACQ at baseline of 1.39 ± 0.91 decreased to 1.11 ± 0.86 ($P = 0.032$) and 1.0 ± 0.78 ($P = 0.003$) at 3 and 6 months, respectively. Improvement in asthma control was also observed in all categories of both asthma and OSAS severity (Table 3), but only reached statistical significance in patients with moderate–severe asthma or severe OSAS (RDI > 30). In addition, the percentage of patients with well-controlled asthma increased from 28% to 38% at 6 months and the percentage of patients with not well-controlled asthma decreased from 41% to 17%. All these differences were statistically significant (Fig. 2).

Considering only clinically relevant ACQ changes (≥0.5 points), asthma control improved in 34.7% (34 of 98) of patients and worsened in only one patient.

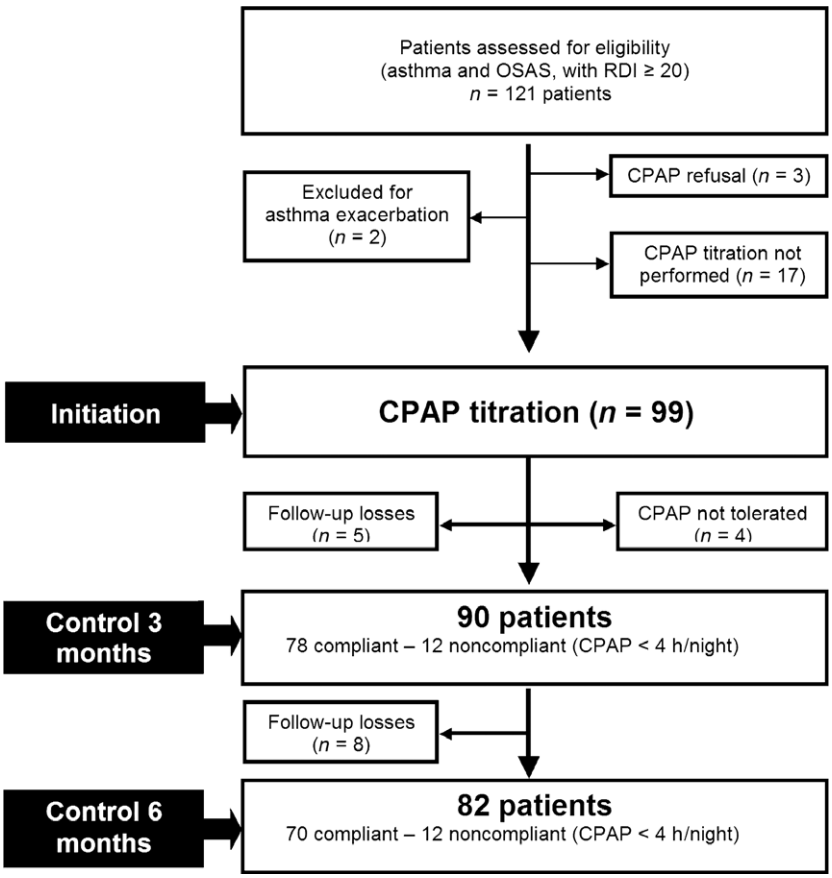

Figure 1 Flowchart of the study population. CPAP, continuous positive airway pressure; OSAS, obstructive sleep apnea syndrome; RDI, respiratory disturbance index.

According to the level of asthma control at baseline, improvement was recorded in 58.5% (24 of 41) of patients with not well-controlled asthma as compared to 7.1% (2 of 28) of those with well-controlled asthma ($P < 0.001$). In the multivariate analysis, decrease in body mass index (BMI) (odds ratio [OR] 0.76, 95% confidence interval [CI] 0.30-1.93), clinical improvement of rhinitis (OR 1.37, 95% CI 0.42-4.48), or GERD symptoms (OR 0.65, 95% CI 0.21-1.96) were not associated with better asthma control. On the other hand, 39 patients had a humidifier in CPAP at 3 months and 37 at 6 months, but differences in asthma control between those with CPAP with a humidifier compared with those with CPAP without a humidifier were not observed.

The percentage of patients with at least one asthma exacerbation decreased from 24.2% ($n = 24$) to 8.2% ($n = 8$) ($P = 0.004$) when the three-month pretreatment and post-treatment periods were compared, and from 35.4% ($n = 35$) to 17.2% ($n = 17$) ($P = 0.015$) when comparison was extended to the six-month pretreatment and post-treatment periods. During the first 3 months of follow-up, five patients with asthma exacerbation required treatment with oral glucocorticoids. No hospital admissions for asthma exacerbations were recorded during the study.

Quality of life

Asthma-related quality of life improved throughout the study. The mean score of the MiniAQLQ at baseline of 5.12 ± 1.38 increased to 5.53 ± 1.23 ($P = 0.032$) at 3 months and to 5.63 ± 1.17 ($P = 0.009$) at 6 months. Improvement in quality of life was recorded in all categories of both asthma and OSAS severity (Table 3). However, the differences only reached statistical significance in the groups of moderate–severe asthma or severe OSAS (RDI > 30).

Considering only clinically relevant MiniAQLQ changes (≥0.5 points), quality of life improved in 38.4% (38 of 99) of patients and worsened in 7.1% (7 of 99). Improvement in quality of life was recorded in 53.7% (22 of 41) of patients with not well-controlled asthma at baseline as compared to 14.3% (4 of 28) of those with well-controlled asthma. By contrast, decreases of ≥0.5 in the MiniAQLQ were more common among patients with well-controlled asthma (10.7% [4 of 28]) than among those with not well-controlled asthma (4.9% [2 of 41]).

In the multivariate analysis, female sex was an independent factor associated with an improvement in quality of life (OR 3.01, 95% CI 1.08-8.41, $P = 0.035$). However, a decrease in

Table 1 Comparison of characteristics of participants and nonparticipants

Variables	Participants (n = 99)	Nonparticipants (n = 22)	P value
Age, years, mean ± SD	57.1 ± 11.4	52.8 ± 16.7	0.259
Men/women, %	61/39	54/46	0.600
Body mass index, kg/m^2, mean ± SD	34.5 ± 6.0	35.8 ± 10.6	0.606
Smoking status, %			
Current smoker	8	14	0.360
Ex-smoker	39	50	
Never smoker	53	36	
Cardiovascular comorbidity, %	44	18	0.023
Severity of asthma, %			
Intermittent	11	14	0.915
Mild persistent	17	18	
Moderate persistent	48	50	
Severe persistent	24	18	
Respiratory disturbance index (RDI), mean ± SD	46.3 ± 20.8	42.7 ± 29.7	0.503
Epworth Sleepiness Scale, mean ± SD	12.8 ± 4.9	11.7 ± 5.9	0.370

BMI (OR 1.49, 95% CI 0.56-3.98), clinical improvement of rhinitis (OR 1.80, 95% CI 0.52-6.20) or GERD symptoms (OR 1.04, 95% CI 0.34-3.22), or reduction in daytime sleepiness (OR 3.72, 95% CI 0.67-20.65) was not associated with relevant improvements in quality of life.

Asthma control and quality of life according to compliance with CPAP

Asthma control and quality of life at 6 months were higher among patients compliant with CPAP (≥4 h/night) as compared to noncompliant subjects. Differences between baseline and final scores were only significant ($P < 0.001$) in the compliance group (Fig. 3).

Discussion

This study shows that after 6 months of treatment with CPAP, there was a decrease in the percentage of patients with positive bronchodilation test, a decrease in FeNO, and a reduction in the score of the ACQ. All these changes occurred without a significant modification of asthma drug therapy.

The beneficial effect of CPAP was associated with a better control of asthma, which was statistically significant and clinically relevant. The percentage of patients with not well-controlled asthma decreased from 41% at baseline to 27% at 3 months and 17% at 6 months. At the same time, a reduction in the number of asthma exacerbations was observed (from 35.4% to 17.2% during the six-month pretreatment and post-treatment periods). This favorable effect was also extended to a significant improvement in asthma-related quality of life, which was especially noticeable in the subset of patients with more severe diseases (OSAS and asthma) or poorly controlled asthma at baseline.

We believe our study adds significant evidence to previous authors, who reported a favorable impact of CPAP therapy in patients with OSAS. The first studies, carried out in the 1980s, consisted in series of 9-10 patients followed sometimes for only 2 weeks (14, 15). More recently, other groups have confirmed the positive effects of treating OSAS (in adults using CPAP and in children undergoing adenoidectomy and tonsillectomy) in the clinical course of asthma (10, 17–19). In contrast, the effects of CPAP therapy on pulmonary function of asthmatic patients with OSAS are less common and limited to small improvements in blood gases (16) or small increases (around 10%) in the peak expiratory flow rate (14).

In relation to pulmonary function, we found a favorable evolution in the degree of bronchial reversibility and a discrete, but significant, decrease in the mean value of FeNO. Other authors have evaluated the relationship between FeNO and OSAS, and the effects of CPAP therapy on FeNO, with relatively contradictory results (31–33). In nonasthmatic patients with OSAS, different studies have shown an increase in FeNO attributed to tissue inflammation of the upper airway directly related to the intensity of OSAS. After 1 to 3 months of CPAP therapy, FeNO levels usually normalized (31, 32). Other studies of shorter treatment periods did not found any improvement (33). The relationship between OSAS, obesity, local airways inflammation, and bronchial hyperresponsiveness (BHR) has also been extensively studied, as well as the response after CPAP therapy (33–38). In patients with asthma, a reduction in BHR has been reported in the majority of studies (34, 35). By contrast, in nonasthmatic patients with OSAS, BHR frequently increases (33, 36), although not always (37). In the present study, in which patients suffer from asthma and OSAS concurrently, it is possible that changes observed in FeNO values and bronchodilation test may represent a balance of the global effect of CPAP on both conditions.

Another interesting finding was the improvement in two diseases usually associated with asthma, rhinitis, and GERD, in the absence of relevant changes in their pharmacologic treatment or in the patients' weight. In this respect, immediate improvements of gastroesophageal reflux, after only one night of CPAP therapy, have been reported. These

Table 2 Demographic and clinical characteristics of patients according to asthma severity

	Total (n = 99)	Intermittent–Mild persistent asthma (n = 28)	Moderate–Severe persistent asthma (n = 71)	P value
Age, years, mean ± SD	57.1 ± 11.4	54.9 ± 14.2	58.0 ± 10.0	0.296
Men/women, %	61/39	64/36	59/41	0.638
Body weight, kg, mean ± SD	94.2 ± 15.6	89.3 ± 14.4	96.1 ± 15.7	0.049
Body mass index, kg/m^2, mean ± SD	34.5 ± 6.0	32.2 ± 5.5	35.5 ± 5.9	0.013
Body mass index ≥ 30, %	76	57	83	0.007
Smoking status, %				
Current smoker	8	4	10	0.706
Ex-smoker	39	43	38	
Never smoker	53	53	52	
Cardiovascular comorbidity, %	44	39	47	0.517
Rhinitis, %	54	57	52	0.651
Moderate–severe rhinitis, %	34	31	35	0.784
Nasal polyposis, %	18	14	20	0.528
Gastroesophageal reflux symptoms disease, %				
Heartburn	31	21	35	0.197
Regurgitation	19	4	25	0.016
Regular medical control of asthma, %	74	68	76	0.404
$FEV_{1,}$ % predicted, mean ± SD	83.6 ± 17.6	90.9 ± 14.4	80.8 ± 18.1	0.010
Positive bronchodilation test, %	36	21	42	0.052
FeNO, ppb, mean ± SD	29.9 ± 18.7	26.0 ± 21.1	31.0 ± 18.2	0.484
Sensitization to aeroallergens, %	59	57	60	0.739
Asthma Control Questionnaire (ACQ), score, mean ± SD	1.39 ± 0.91	0.88 ± 0.54	1.58 ± 0.95	<0.001
Control of asthma, %				
ACQ ≤ 0.75	28.6	48.1	21.1	0.002
ACQ 0.76-1.49	29.6	37.0	26.8	
ACQ ≥ 1.5	41.8	14.9	52.1	
Exacerbations previous 6 months, %	35	39	34	0.547
Pharmacological treatment, %				
Short-acting ß$_2$ adrenergic agonists	86	82	87	0.530
Long-acting ß2 adrenergic agonists	83	61	92	0.001
Inhaled glucocorticoids	92	75	99	0.001
Oral glucocorticoids	0	0	0	1.0
Leukotriene antagonists	35	32	37	0.675
Antacids	21	21	21	0.974
Nasal glucocorticoids	18	11	21	0.226
Equivalent doses of budesonide, mcg/day, mean ± SD	926 ± 716	517 ± 651	1048 ± 693	<0.001
MiniAQLQ score, mean ± SD	5.12 ± 1.38	5.77 ± 0.93	4.87 ± 1.45	0.001
Epworth Sleepiness Scale, mean ± SD	12.8 ± 4.9	13.6 ± 5.5	12.5 ± 4.7	0.310
Epworth Sleepiness Scale >11, %	60	61	59	0.887
Respiratory disturbance index, mean ± SD	46.3 ± 20.8	50.0 ± 20.4	44.8 ± 20.9	0.266
CT_{90}, mean ± SD	22.2 ± 24.7	26.1 ± 23.9	20.7 ± 25.1	0.135
CPAP pressure, cm H_2O, mean ± SD	9.0 ± 1.6	8.6 ± 1.5	9.1 ± 1.6	0.266
Respiratory disturbance index residual, mean ± SD	5.7 ± 5.6	5.2 ± 5.6	5.9 ± 5.7	0.691
CT_{90} residual, mean ± SD	5.5 ± 11.2	3.6 ± 8.0	6.2 ± 12.3	0.905

FEV_1, forced expiratory volume in one second; FeNO, exhaled nitric oxide fraction; MiniAQLQ, Mini Asthma Quality of Life Questionnaire; CT_{90}, percentage of time with arterial oxygen saturation <90%; CPAP, continuous positive airway pressure.

improvements in GERD have been confirmed by esophageal pH monitoring and esophageal manometry (15, 39).

The mechanisms by which treatment with CPAP may improve symptoms and asthma control are multiple. OSAS is associated with a systemic and local inflammation of the airways, as well as pulmonary vascular changes and release of endothelial factors (such as vascular endothelial growth factor) with proinflammatory effects (40). The use of CPAP reduces inflammation and its mediators (31). Improvement of gastroesophageal reflux may also be accompanied by a reduction in nocturnal asthma symptoms (15). Additionally, reduction in bronchial hyperresponsiveness produced by CPAP

Table 3 Changes in clinical and functional variables, asthma control, and quality of life after starting treatment with continuous positive airway pressure

	Baseline	Final six-month follow-up	*P* value
Clinical and functional characteristics			
Body mass index (BMI), kg/m^2, mean ± SD	34.5 ± 6.0	34.5 ± 5.7	0.938
Current smokers, %	8	2	0.100
Mild rhinitis, %	35.4	22.2	0.041
Moderate–severe rhinitis, %	18.2	15.2	0.567
Heartburn	30.3	10.1	<0.001
Regurgitation	18.2	5.1	0.007
FEV_1, % predicted, mean ± SD	83.6 ± 17.6	83.6 ± 16.6	0.977
Positive bronchodilation test, %	36.4	12.1	<0.001
FeNO, ppb, mean ± SD	29.9 ± 18.7	22.0 ± 12.5	0.041
Pharmacological treatment, %			
Inhaled glucocorticoids, equivalent doses of budesonide			
mcg/day, mean ± SD	926 ± 716	946 ± 765	0.988
≤400 mcg/day, %	39.6	37.3	0.826
401-800 mcg/day, %	24.2	28	
>800 mcg/day, %	36.3	34.7	
Leukotriene antagonists	35.4	32.3	0.652
Nasal glucocorticoids	18.2	20.2	0.718
Antihistamines	21.2	16.2	0.362
Antacids	21.2	19.2	0.723
Epworth Sleepiness Scale, mean ± SD	12.8 ± 4.9	6.9 ± 4.1	<0.001
Epworth Sleepiness Scale >11, %	59.6	13.1	<0.001
Control of asthma			
Asthma Control Questionnaire (ACQ) score, mean ± SD	1.39 ± 0.91	1.00 ± 0.78	0.003
ACQ score according to asthma severity, mean ± SD			
Intermittent–mild persistent	0.88 ± 0.54	0.71 ± 0.45	0.226
Moderate–severe persistent	1.58 ± 0.95	1.11 ± 0.85	0.003
ACQ score according to OSAS severity, mean ± SD			
RDI ≤ 30	1.47 ± 0.88	1.02 ± 0.88	0.113
RDI > 30	1.36 ± 0.92	0.99 ± 0.76	0.012
Asthma-related quality of life			
MiniAQLQ score, mean ± SD	5.12 ± 1.38	5.63 ± 1.17	0.009
MiniAQLQ score according to asthma severity, mean ± SD			
Intermittent–mild persistent	5.77 ± 0.93	6.04 ± 0.85	0.303
Moderate–severe persistent	4.87 ± 1.45	5.48 ± 1.24	0.012
MiniAQLQ score according to OSAS severity, mean ± SD			
RDI ≤ 30	5.23 ± 1.44	5.68 ± 1.41	0.324
RDI > 30	5.08 ± 1.37	5.62 ± 1.11	0.013

FeNO, exhaled nitric oxide fraction; OSAS, obstructive sleep apnea syndrome; MiniAQLQ, Mini Asthma Quality of Life Questionnaire; RDI, respiratory disturbance index.

(34) can be also associated with a clinical improvement of asthma.

An interesting finding was that female gender was an independent predictive factor for improvement in quality of life. Women as compared with men showed a lower proportion of severe persistent asthma (12.8% *vs* 54.6%, $P = 0.002$) and higher proportion of moderate persistent asthma (61.5% *vs* 38.3%, $P = 0.024$), lower mean baseline score of the MiniAQLQ (4.73 ± 1.64 *vs* 5.34 ± 1.12, $P = 0.049$), with a significantly higher increase in mean score of the MiniAQLQ at follow-up (0.84 ± 1.09 *vs* 0.35 ± 0.96, $P = 0.040$). Therefore, it is possible that a higher percentage of women with less severe asthma than men and lower baseline quality of life score may allow theoretically a greater margin for improvement.

Smokers and ex-smoker asthma patients were included in the study, so we cannot rule out the presence of ACOS (41) in some of them. Nevertheless, the impact of this circumstance in our results would be very small. Of the 99 patients included in the study, only 26 had persistent airflow limitation (never smokers: 13; ex-smokers: 12; and current smokers: 1). Therefore, the theoretical maximal percentage of patients with ACOS would be 13.1%, which should be further reduced after the exclusion of patients with a cumulative dose of tobacco exposure <10 pack years.

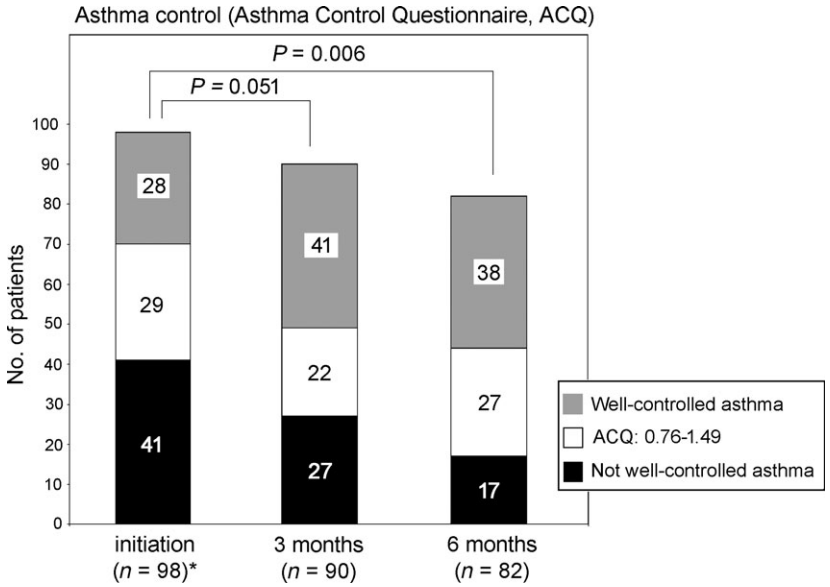

Figure 2 Number of patients with well-controlled asthma (ACQ score ≤ 0.75) and not well-controlled asthma (ACQ score ≥ 1.5) after starting continuous positive airway pressure. ACQ, Asthma Control Questionnaire. Expression of results and statistical analysis (χ^2) made by intention-to-treat basis; *one patient did not complete the ACQ.

The present study has strengths and limitations. Strengths include the prospective and multicentre design, the adequate sample size, the six-month duration of CPAP treatment, and the assessment of results using objective diagnostic tests and validated questionnaires. The observational nature of the study is one of its main limitations. In order to confirm definitively that the favorable clinical course of asthma in our patients was due to the use of CPAP, a randomized controlled trial might be considered necessary. But the execution of a randomized trial like that has considerable theoretical and practical difficulties. First, in addition to including a sham-CPAP arm, it would be also necessary to assess objectively patients' adherence to pharmacological treatment, including inhaled therapy for asthma. With respect to sham-CPAP, it is possible, moreover, that this procedure may not be a suitable placebo in patients with asthma. Busk et al. (34) studied the effect of CPAP in the short term (7–10 days) on BHR in asthmatic patients with low risk of OSAS. In the control group, with pressures of 0-2 cmH2O CPAP, the increase in the provocative concentration of methacholine causing a 20% fall in forced expiratory volume in 1 s (PC20) was lower than in the group using CPAP therapeutic pressures. However, although the mean variation in the PC20 did not reach statistical significance, 55% of patients who received sham-CPAP showed a decrease in the BHR. On the other hand, in patients with OSAS, it has been observed a significant difference after using sham-CPAP both in the degree of daytime hypersomnia and in several polysomnographic parameters: While hypersomnia improved (42), the quality of the sleep became worse (decreased sleep efficiency, increased time in stage 1 NREM sleep, and prolonged latency to REM sleep) (43). Therefore, taking into account the existing correlations between sleep quality, daytime hypersomnia, quality of life, and asthma control (44, 45), and the potential effect of sham-CPAP in BHR (34), it cannot be excluded that subtherapeutic CPAP pressures, used as a placebo in asthmatic patients with OSAS, may have relevant effects on asthma outcomes that would distort the results of a controlled study. Finally, there are ethical issues regarding keeping patients with OSAS without active treatment, in patients with two potentially severe diseases. All these considerations were taken into account in the final decision regarding the design of our study. However, an overall evaluation of all the results obtained is highly suggestive of a probable beneficial effect *per se* of the use of CPAP, with a progressive convergence in the improvement of the different study variables: asthma control, asthma-related quality of life, bronchial inflammation and response to bronchodilator test, as well as clinical symptoms of rhinitis and GERD. All of these findings occurred without significant changes in the mean weight of patients and in the pharmacological treatment for asthma or its comorbidities during the follow-up period. A significant association between clinically relevant changes in the evolution of asthma and improvement of comorbidity of OSAS and/or asthma was not observed. Finally, differences in ACQ and MiniAQLQ according to the level of compliance with CPAP treatment, with significant improvements only among good compliant patients, are also remarkable.

Conclusions

In patients with asthma and concomitant moderate–severe OSAS, we observed an improvement in current control of

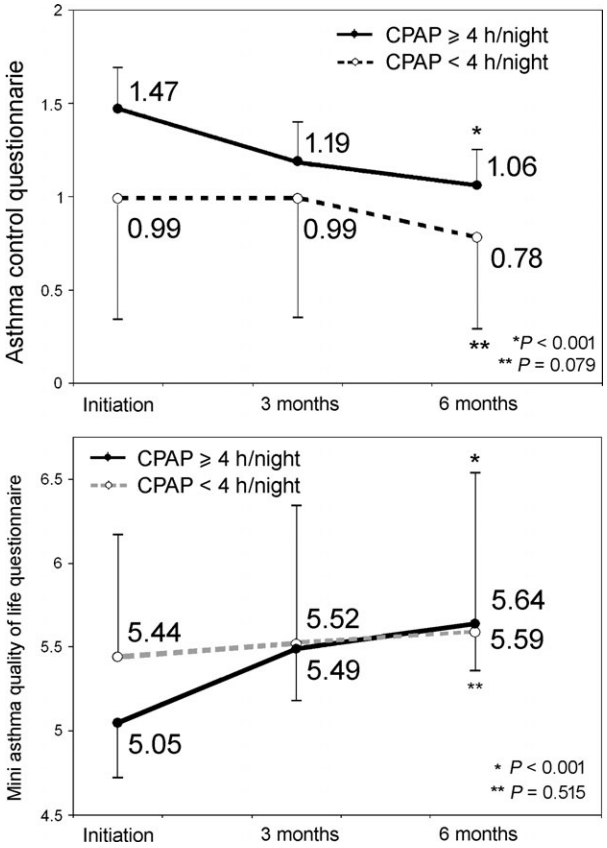

Figure 3 Changes in mean ± SD scores of Asthma Control Questionnaire and Mini Asthma Quality of Life Questionnaire during treatment with continuous positive airway pressure (CPAP) according to compliance with CPAP therapy. Values expressed as mean (circles) and SD (vertical lines); *vs* initiation, in CPAP-compliant patients; ***vs* initiation, in CPAP-noncompliant patients.

asthma and quality of life, together with a reduction in future risk, after starting CPAP therapy. This effect was stronger in patients with more severe asthma or OSAS, in those with uncontrolled asthma, and in patients compliant with CPAP. These observations provide further arguments to emphasize the need of screening and eventually treating OSAS in patients with severe or poorly controlled asthma.

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Author contributions

J. Serrano-Pariente involved in conception and design of the study; acquisition, analysis, and interpretation of data; and writing of the manuscript and is guarantor of the manuscript; V. Plaza involved in design of the study; acquisition, analysis, and interpretation of data; and writing of the manuscript; J.B. Soriano involved in design of the statistical analysis and interpretation of data and writing of the manuscript; M. Mayos and A. Lopez-Viña involved in design of the study; acquisition, analysis, and interpretation of data; and critical review of the content; C. Picado involved in design of the study; analysis and interpretation of data; and critical review of the content; L. Vigil involved in acquisition, analysis, and interpretation of data; and critical review of the content; all authors have seen and approved the final version of the manuscript; investigators of the CPASMA Trial Group involved in the collection of field data.

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Conflict of interest

The authors have no conflicts of interest to disclose.

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Appendix

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