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Nocturnal bilevel positive airway pressure for the treatment of asthma

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Abstract

Nocturnal worsening of asthma may be due to reduced lung volumes and fewer sigh breaths, which have been shown to increase airway resistance and bronchoreactivity. We hypothesized that mimicking deep inspiration using nocturnal mechanical support would improve symptoms in patients with asthma.

Subjects with asthma underwent usual care and bilevel positive airway pressure (PAP) therapy for 4 weeks, separated by 4 weeks, and methacholine challenge (PC_{20}) and subjective assessments.

13 patients with asthma alone and 8 with asthma + OSA completed the protocol. Change in bronchoreactivity (ratio of Post/Pre PC20) was not significantly different during usual care and bilevel PAP [0.86 (IQR 0.19, 1.82) vs 0.94 (IQR 0.56, 2.5), p = 0.88], nor was the change in Asthma Control Test different: 0.1±2.2 vs. −0.2±2.9, p = 0.79, respectively.

Bilevel PAP therapy for four weeks did not improve subjective or objective measures of asthma severity in patients with asthma or those with asthma and OSA, although there was heterogeneity in response.

Keywords

Asthma; sleep; lung volumes; obstructive sleep apnea; positive airway pressure

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DECLARATION OF INTEREST

RLO previously consulted for Philips Respironics. Philips Respironics provided the bilevel positive airway pressure machines and related equipment used in the study. As an Officer of the ATS, Dr. Malhotra relinquished all outside personal income in 2012. ResMed provided a philanthropic donation to UC San Diego for a Sleep Center. The other authors report no conflict of interest.

Registration: Clinicaltrials.gov NCT01154699

INTRODUCTION

Deep inspiration has an important role in bronchodilation. However, deep inspiration or sighs are relatively infrequent[1] during stable sleep and their impact on lower airway mechanics may be attenuated during sleep.[2] Nocturnal worsening of asthma has been recognized for centuries[3, 4], has persisted into the modern era[5–8] and is associated with morbidity and mortality, [9, 10] including daytime cognitive consequences.[11, 12]

The pathogenesis of nocturnal worsening of asthma is not known, although circadian rhythms influencing lung function or inflammation, local environmental factors (e.g. mattress dust mites), or co-morbidities associated with lying recumbent (e.g. gastro-esophageal reflux) are traditional explanations. However, several lines of evidence suggest that this nocturnal worsening of asthma symptoms is related to sleep specifically. First, although airway resistance increases throughout the night in awake asthma patients, it increases more when they also sleep.[13] Second, nocturnal asthma attacks seem stage dependent, with the greatest bronchoconstriction during REM sleep, rather than time of night dependent.[14] Thus, it seems that the sleep state might contribute to nocturnal worsening of asthma via mechanical changes, including reduced lung volumes and reduction in deep inspirations. During wakefulness, reductions in functional residual capacity and prevention of deep inspirations contribute to increased bronchoreactivity - within minutes - even in people without asthma.[15, 16]

Some investigators have used continuous positive airway pressure (CPAP), which increases lung volume, to reduce bronchoconstriction. For example, Tepper applied CPAP 8–10 cmH_20 for 7 nights to people with stable asthma, and found that bronchconstriction (as measured by the provocative concentration of methacholine to reduce FEV1 by 20%, PC_{20}) was improved compared to sham CPAP.[17] Another small study of CPAP for one week in severe asthma patients found reductions in nocturnal worsening of asthma and improvements in asthma control and quality of life[18]. Most recently, a large randomized, sham-controlled clinical trial of CPAP for 12 weeks found improvements in the PC_{20} and other markers of subjective and clinical asthma control, but this occurred in all groups (sham, low and high CPAP), possibly related to humidification.[19]

As both lung volumes and tidal lung stretch are thought to be important, we previously studied the effect of bilevel positive airway pressure, which should not only induce tonic mechanical strain but also increase tidal strain during inspiration. In our prior study, a single night of bilevel PAP did not produce major changes in bronchoreactivity.[20] Nor did bi-level PAP substantially alter sleep architecture in naïve subjects.

Therefore we conducted a pilot study of the effect of 4 weeks of bilevel PAP therapy on bronchoreactivity and subjective asthma control. Specifically, we applied bilevel PAP to asthma patients without obstructive sleep apnea and naïve to PAP therapy, and to asthma patients with OSA on CPAP. This latter group allowed us to assess the physiological impact of increases in tidal volume alone on bronchoreactivity and asthma quality of life in patients accustomed to PAP therapy. Moreover, although nocturnal asthma is a common problem, obstructive sleep apnea is the most common form of sleep disordered breathing

and prevalence has been reported to increase with increasing asthma severity.[21, 22] Complex interactions are thought to occur between asthma and OSA, although mechanistic data remain sparse. During obstructive apnea, transpulmonary pressure changes are minimal, perhaps contributing to bronchospasm via lack of lung stretch. Waking up gasping can occur with both OSA and nocturnal asthma, but given the high prevalence of undiagnosed OSA, careful physiological assessment would seem critical to draw meaningful conclusions.

METHODS

The study was approved by the Partners' Healthcare Institutional Review Board; all subjects were consented by the researchers and gave informed written consent. The study was registered at ClinicalTrials.gov (NCT01154699), and conducted at the Brigham and Women's Hospital Center for Clinical Investigation.

Patients

Patients aged 18–70 years with physician diagnosed asthma underwent a history and physical examination, and were excluded for: any lung disease other than asthma or OSA; current or >10 pack-year history of smoking; or severe asthma, defined as a recent exacerbation requiring a doctor or emergency room visit for asthma or oral steroid use in the last 4 weeks, or frequent exacerbations (>4 per year). Those on medications known to affect respiratory function (other than asthma or rhinitis medications), or those regularly taking medications for sleep were excluded.

A methacholine challenge test was performed in accordance with American Thoracic Society guidelines, and only subjects with a PC_{20} <12mg/mL were included. Subjects without known sleep apnea underwent home sleep testing with a level III portable monitor (ApneaLink, ResMed). Subjects were considered without OSA and continued with the study if the apnea hypopnea index (AHI) <10/hr without symptoms of OSA based on AASM criteria. Subjects with known OSA had to be compliant with CPAP therapy defined as >4 hours use per night on 4 out of 7 nights per week.

Study Protocol

This was a crossover trial of 4 weeks of nocturnal bilevel PAP vs usual care, in random order determined by coin flip, separated by a 4 week wash-out period (Figure 1). After a screening visit, subjects attended four study visits (before and after the bilevel PAP and usual care blocks) that consisted of written questionnaires and a methacholine challenge. Visits occurred during the day according to patient preference, thus, these occurred >1 hour after awakening. During the study, patients continued their usual asthma care. Peak flow measurements were made on awakening and before bedtime using a handheld peak flow meter (Asma-1, Vitalograph Inc.) and subjects recorded their symptoms in a written diary. The diary asked subjects the number of puffs of rescue medication used in the last 24 hours, and the number of nocturnal awakenings that required rescue medication.

Non OSA/PAP patients were fitted with a nasal mask and placed on Bilevel PAP (System One BiPAP Pro, Philips Respironics) at an inspiratory pressure of 10cmH_2O and an expiratory pressure of 4cmH_2O in a spontaneous mode. OSA subjects used their own masks

and were placed on an expiratory pressure equal to their therapeutic CPAP level, with an inspiratory pressure 6 cmH_2O above the expiratory pressure. Heated humidification was provided with all bilevel PAP devices, and adjusted by subjects as desired.

Outcomes

Adherence to bilevel PAP therapy was measured by device download of recorded usage hours.

Our primary objective outcome was the change in PC_{20} during each block. The main subjective outcome of the study was the change in the Asthma Control Test (ACT).[23] Secondary outcomes were: peak flow, the Short Form – 36, Pittsburgh Sleep Quality Index (PSQI), and the Epworth Sleepiness Score (ESS).

Data Analysis

Data were analyzed without knowledge of the treatment phase. Means (standard deviations) were calculated for the descriptive statistics such as baseline variables. PC_{20} is reported as a geometric mean. If the FEV1 did not decline by 20% at the maximum dose of methacholine (25mg/mL), the PC_{20} was assigned the value of the highest dose multiplied by 1.5. The main objective outcome was the change in PC_{20} during each block (usual care vs. bilevel PAP), expressed as the ratio PC_{20} at the end of the block/PC_{20} from the start of the block. Values greater than 1 would signal improvement in bronchoreactivity during that block; values less than 1 would represent worsening bronchoreactivity during that time. The Wilcoxon rank sum test was used to assess statistical difference.

The change (end of block – start of block value) in ACT were calculated for each block (usual care vs. bilevel PAP), and were compared using a two-tailed paired T-test. A similar analysis was performed with all of the questionnaire data. Secondary outcomes based on daily diary records and peak flows were averaged over all of the days between study visits prior to data analysis, providing a single mean value for each subject for each study block. The minimally important difference on the ACT has been estimated to be 3.[24] Thus, assuming a power of 0.80 (alpha = 0.05), at least 16 subjects would be needed. Values are presented as a mean ± standard deviation unless otherwise indicated.

RESULTS

Patients

In total, 20 patients with asthma and no known diagnosis of OSA underwent screening. 6 potential subjects did not have a PC_{20} <12 mg/dL. Another subject dropped out of the study after screening and was not randomized. The characteristics of the remaining 13 patients with asthma but not OSA are shown in Table 1. 7 subjects were randomly assigned to begin in the usual care arm. 1 asthma only subject had severe obstruction (FEV1 <35% predicted) and did not complete methacholine challenge testing.

13 patients with both asthma and CPAP treated OSA were screened. Of these, 8 met all inclusion criteria and were randomized. Baseline demographic information and CPAP usage are shown in Table 1. 6 subjects began in the usual care arm. Enrolment ceased once 20

subjects completed the protocol. Individual subject-level data, including baseline medication use, is available in Supplementary Table #1.

In both groups, as designed, asthma was well controlled but with remaining bronchoreactivity. There were two asthma exacerbations during the study (1 subject with asthma only, and 1 with asthma and OSA). Both exacerbations occurred during the bilevel PAP period. These subjects did not undergo methacholine challenges following their exacerbations; however, all available data are included.

Bilevel PAP use

Of the patients with asthma only and naïve to PAP, 2 reported difficulties and gave up therapy despite efforts at intensive support. The remaining subjects with asthma only used bilevel PAP an average of 4 hours 59 minutes per night ± 1 hour 31 minutes. Of note, three of the remaining 11 patients without OSA (AHI on home sleep testing was 4, 0, and 3/hour) had a residual apnea hypopnea index as measured by the bilevel devices of 18, 7.7, and 9.2 per hour, respectively. The majority of these events were central apneas.

Patients with OSA on CPAP used Bilevel PAP 4 hours 7 minutes per night ± 1 hour 29 minutes, compared to their average baseline CPAP use of 4 hours 24 minutes per night ± 1 hour 31 minutes.

Bronchoreactivity and Spirometry

Complete bronchoreactivity data were available in 17 subjects. (2 subjects had exacerbations, 1 had severe obstruction across all visits, and 1 had severe obstruction without any clear exacerbation on a single visit, precluding methacholine challenge.) Across all subjects, the change in bronchoreactivity (as measured by ratio Post/Pre PC_{20}) was not significantly different during usual care and bilevel PAP [0.86 (IQR 0.19, 1.82) vs 0.94 (IQR 0.56, 2.5), p=0.88]. See individual responses in Figure 2. There were no statistical differences when examined in the groups with and without OSA. Even excluding the 2 subjects who did not wear bilevel PAP, there was no difference in the change in PC_{20} during usual care vs. bilevel PAP (data not shown). Nor was any change seen in spirometry (Table 2).

Asthma quality of life

Across all subjects, there was no difference in the change in ACT during usual care vs. bilevel PAP (mean change 0.1±2.2 vs. −0.2±2.9, respectively, p=0.79). See individual responses in Figure 3. There was no statistical difference when examined in the groups with and without OSA.

Peak flow and daily asthma symptoms

As shown in Table 2, there were very small and not statistically significant changes in morning peak flow, %nocturnal decrease in peak flow, nocturnal awakenings, and rescue medication use during the bilevel PAP block.

Sleep quality

Changes in sleep quality, asthma control and quality of life were similar during the usual care and bilevel PAP blocks (Table 3). Of note, subjective sleep quality and quality of life did not decline with bilevel PAP.

DISCUSSION

We did not find evidence that 4 weeks of bilevel PAP improved our physiological measures including subjective or objective markers of asthma severity. Alternatively, the addition of bilevel PAP to non-apneic asthmatics did not worsen subjective sleep quality.

Our findings contrast with prior reports of subjective or objective improvements of asthma with PAP. There are several possible reasons for the discrepancy. First, other studies have focused on more severe asthma patients compared to our cohort.[28] Based on prior literature, we anticipated an improvement in bronchoreactivity that would be reflected in the PC_{20}, and recruited patients based on their PC_{20}. However, patients with more obstruction based on spirometry, or some other phenotype, might be more likely to respond to our intervention. Second, we rigorously screened for OSA. Older studies may have inadvertently treated OSA. Patients with asthma and OSA who begin treatment with CPAP have been reported to have improved asthma specific quality of life, although changes in objective measurements of asthma have been more difficult to show.[29] Recently Serrano found that 6 months of CPAP for OSA was associated with fewer asthma attacks, and small improvements in subjective asthma control and quality of life.[30] Although FEV1 was unchanged, fewer patients had positive bronchodilator tests after PAP therapy. Based on our data and the ALA CPAP trial, it seems likely that improvements in asthma by treating OSA are not clearly due to mechanical stretch. In theory, reported improvements in nocturnal dyspnea following application of positive pressure may reflect resolution of respiratory arousals (from OSA) rather than improved asthma control. Moreover, some nocturnal symptoms attributed to asthma may actually reflect unrecognized OSA. Third, we used low to moderate airway pressures, chosen to optimize comfort and adherence to therapy. If mechanical stretch is important, larger changes in resting lung volume and/or tidal stretch may be necessary.[31] However, even at the pressures used in the present study 3 of 11 adherent, PAP-naïve subjects demonstrated new onset central apneas that persisted throughout four weeks of therapy, which could worsen with higher pressures as a function of hypocapnia.[32–34]

Our findings add to the literature in an important way. Although the recent ALA publication showed no improvement in PC_{20} using CPAP compared to sham PAP, our use of bi-level PAP may mimic deep inspiration more than standard CPAP. Looking for reasons that neither study shows improvement, low adherence is one possible explanation. However, our subjects used CPAP ~4–5 hours per night on average, and higher levels of adherence would be difficult to achieve outside a laboratory setting. The timing of use of PAP use relative to the onset of bronchoconstriction during the night is likely important.[35] In theory, the greatest period of vulnerability for sleep-related bronchoconstriction may be the latter half of the night, when REM sleep is most likely to occur. Finally, it may be that PAP does have a beneficial effect on airway smooth muscle in asthma; however, that effect is small[36] and/or short-lived[37, 38] and we are not able to detect it in this small cohort. Moreover, the impact of

repeated deep inspiration may be hard to assess physiologically, given that deep inspiration precedes the standard measurement of FEV1 and FVC.[39] Nonetheless, we feel confident that we have excluded a major effect of our approach in unselected asthma patients.

Despite no discernible group effect, there were patients who asked to keep their bilevel PAP because of subjective improvement in asthma symptoms, which were matched by objective improvements in PC_{20}. While these improvements may be for reasons not related to PAP use, the possibility remains that future studies can help identify patient subgroups (based on asthma endophenotypes) who might benefit from this approach.[40] The current study cohort is too small to identify confidently predictors of response; however, responders were generally young, not obese, and had PC_{20} <1mg/mL. However, none of these factors reliably predicted favorable subjective or objective response to bilevel PAP. Predictors of response to PAP therapy might be explored in analysis of larger cohorts using sophisticated biomarkers and/or endophenotyping.

One novel aspect of our study was the use of bilevel PAP. While CPAP will induce tonic lung stretch and increase resting lung volumes during sleep, bilevel PAP has the potential to also increase tidal volumes. In the asthma + OSA group already on CPAP, there was no benefit in any parameter from the switch to bilevel PAP. In our prior single night physiological study we observed only a modest increase in tidal volumes (~50mL), presumably as pressure support offloaded respiratory muscles, rather than augmented tidal volume appreciably.[20, 33] Thus, application of bilevel PAP may not sufficiently induce enough tidal stretch with the settings used to mimic a deep inspiration. Of note, higher inspiratory pressures may cause or worsen central apneas via hypocapnia and could trigger arousals from sleep. Central apneas often appear during CPAP treatment of OSA and persist in a subset of patients; there is less known about the natural history of central apneas from bilevel PAP.[32, 41] Thus, in theory, optimal lung stretch may be beneficial during sleep for asthma control but perhaps poorly tolerated.

Our findings contrast with early studies in non-apneic asthma, which concluded that CPAP disrupted sleep architecture.[25] This finding likely reflects improvements in PAP technology, particularly interfaces. Recognizing that our subjects represent a well-motivated cohort, average daily PAP use was high compared with other trials of PAP therapy in patients without OSA.[19, 26] Clinically, there should be no increased concern about non-adherence to PAP therapy in asthma patients diagnosed with OSA. Indeed epidemiological studies have shown an increased incidence of new onset OSA in asthma, making our findings potentially important clinically.[27]

Limitations

Our patients were heterogeneous in terms of baseline medical therapy, with some on inhaled corticosteroids and others only receiving short acting bronchodilators. We designed the study to be broadly applicable to typical asthma patients and to address whether bilevel PAP as add-on therapy would improve asthma control in those with residual bronchoreactivity. Thus, our study design may have improved generalizability but could have failed to identify subsets of responders based on baseline pharmacology, baseline spirometry, or asthma endotype. Thus, further work is clearly necessary which we hope our findings will

encourage. Additionally, although the impact of lung volume manipulations and/or deep inspirations usually affect airway resistance and reactivity within minutes, the clinical effect of bilevel might take more than 4 weeks to become apparent.

Conclusions

Bilevel PAP therapy for four weeks with a goal of inducing lung stretch mimicking deep inspiration, although generally well tolerated, did not improve subjective or objective measures of asthma severity in patients with asthma or those with asthma and OSA. There was heterogeneity in response, which could be explored in future studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- - Nocturnal worsening of asthma might be due to sleep, with low lung volumes and few sigh breaths
- - Bilevel positive airway pressure (PAP) should improve lung volumes and mimic sigh breaths
- - But, 4 weeks of nocturnal bilevel PAP did not improve asthma symptoms or bronchoreactivity

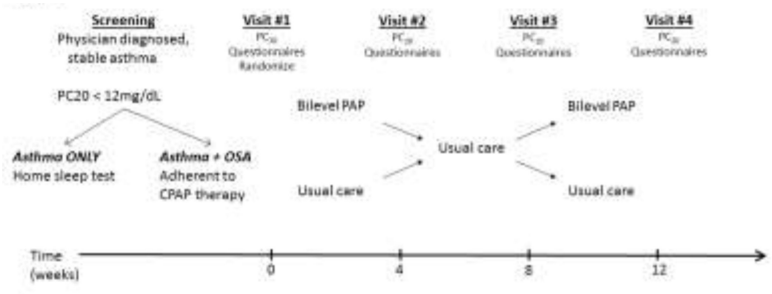

Figure 1.

Study design. After screening, subjects completed 4 weeks of usual care or Bilevel PAP, in random order, separated by 4 weeks of usual care. At each visit, subjects completed questionnaires and underwent methacholine challenge. In between visits, subjects completed diaries to record daily asthma symptoms.

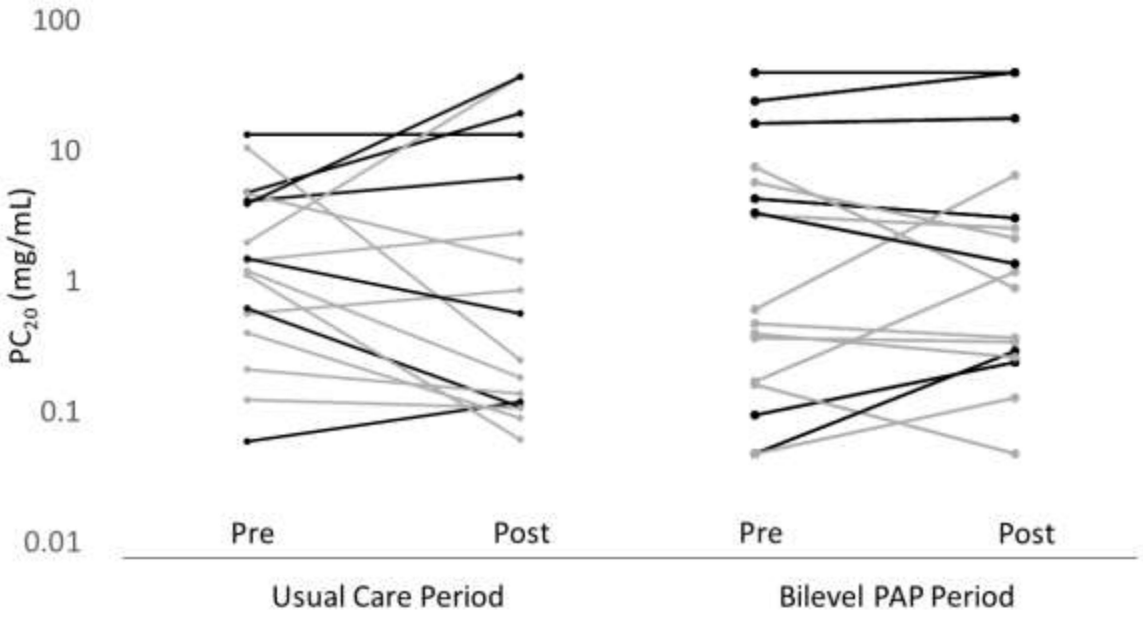

Figure 2.

Change in PC_{20}. Gray lines – asthma only, Black lines – asthma + OSA. If the FEV1 did not decline by 20% at the maximum dose of methacholine (25mg/mL), the PC20 was assigned the value of the highest dose multiplied by 1.5.

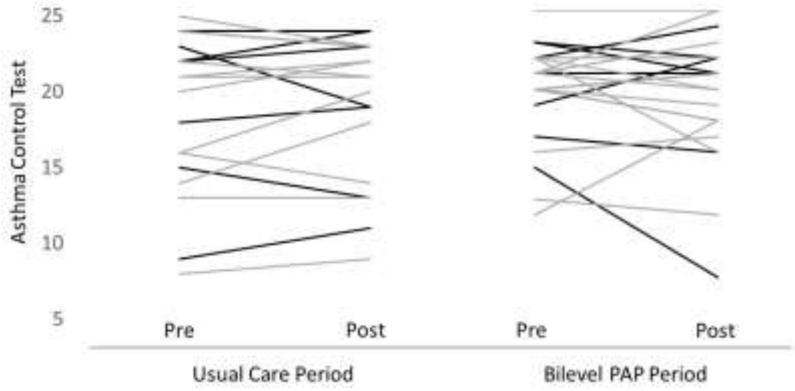

Figure 3.
Change in ACT. Gray lines – asthma only, Black lines – asthma + OSA.

Table 1.

Subject baseline demographics

	Asthma only N=13	**Asthma + OSA N=8**
Gender	9W: 4M	5W: 3M
Age *(years)*	43.2 ± 16.7	44.8 ± 10.5
BMI *(Kg/m^2)*	30.5 ± 7.4	36.4 ± 5.2
FEV1 %pred	90.2 ± 21.3	89.4 ± 21.0
FEV1/FVC	0.75 ± 0.09	0.75 ± 0.06
PC_{20} *(mg/mL)*[#]	1.5 (0.5)	1.8 (1.4)
ACT	19.4 ± 4.9	20.1 ± 3.6
AHI *(events/hour)*	2.5 ± 2.3	40.0 ± 30.1
CPAP pressure *(cmH_2O)*		11.6 ± 3.4
CPAP usage *(hours/day)*		4 hours 24 minutes ± 1 hour 36 minutes
ESS	7.4 ± 4.8	12.4 ± 5.2
PSQI	7.1 ± 4.5	7.3 ± 3.2
SF-36	73.3 ± 17.4	70.1 ± 13

[#]Data presented as geometric mean (SEM)

Apnea hypopnea index (AHI) in the Asthma only group from a home sleep test; AHI in the Asthma + OSA group is from their clinical study that qualified them for CPAP.

ACT – Asthma Control Test, 5–25, higher scores indicate better control.

ESS – Epworth Sleepiness Scale, 0–24, higher scores reflect greater sleepiness. 0–9 considered normal, ≥10 considered sleepy.

PSQI – Pittsburgh Sleep Quality Index, 0–21, higher scores indicate worse sleep. Scores > 5 considered poor sleep.

SF-36 – Short Form 36 Quality of Life, 0–100, higher score indicates better quality of life.

Table 2.

Asthma metrics during treatment blocks

	Asthma only		Asthma + OSA	
	Usual care	**Bilevel PAP**	**Usual care (CPAP)**	**Bilevel PAP**
Change in...				
FEV1 (*L*)	−0.074 ± 0.182	0.036 ± 0.136	0.125 ± 0.265	−0.149 ± 0.188
FEV1 %predicted	−3.08 ± 7.2	1.3 ± 4.9	4 ± 7.3	−5.5 ± 7.2
FVC (*L*)	−0.077 ± 0.200	−0.003 ± 0.438	0.109 ± 0.288	−0.180 ± 0.242
FVC %predicted	−2.8 ± 7.2	2.9 ± 9.5	2.9 ± 6.1	−5 ± 6.8
FEV1/FVC	−0.01 ± 0.04	−0.01 ± 0.05	0.01 ± 0.03	0.00 ± 0.02
Average...				
Morning Peak Flow *(L/min)*	365 ± 42	374 ± 42	371 ± 26.4	377 ± 29
Nocturnal drop in peak flow *(%)*	1.2 ± 1.9	−0.1 ± 2.6	2.7 ± 1.1	2.1 ± 1.7
Nocturnal awakenings requiring rescue medication	0.23 ± 0.15	0.09 ± 0.08	0.13 ± 0.13	0.14 ± 0.14
Total rescue medication use per day (median [IQR])	0.28 [0, 1.62]	0.21 [0, 0.64]	0.13 [0, 4]	0.12 [0, 1]

Spirometry measured at the start and end of treatment blocks.

Morning and evening peak flows and asthma diaries completed daily during treatment blocks.

Table 3.

Changes in sleep quality and quality of life. Values are averages +/− standard error.

	Asthma only		Asthma + OSA	
Change in...	**Usual care**	**Bilevel PAP**	**Usual care (CPAP)**	**Bilevel PAP**
ESS	0.7 ± 0.6	−0.4 ± 0.8	−0.4 ± 1.1	−1.3 ± 1.1
PSQI	−0.4 ± 0.8	−0.2 ± 0.9	−0.6 ± 0.7	0.1 ± 1.2
SF-36	0.6 ± 2.4	1.4 ± 2.4	−0.3 ± 4.1	−2.8 ± 4.6

ESS – Epworth Sleepiness Scale, 0–24, higher scores reflect greater sleepiness. 0–9 considered normal, ≥10 considered sleepy.

PSQI – Pittsburgh Sleep Quality Index, 0–21, higher scores indicate worse sleep. Scores > 5 considered poor sleep.

SF-36 – Short Form 36 Quality of Life, 0–100, higher score indicates better quality of life.