Effect of Continuous Positive Airway Pressure on Airway Reactivity in Asthma

A Randomized, Sham-controlled Clinical Trial

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Abstract

Rationale: Studies have demonstrated that application of stress suppresses airway smooth muscle contractility. In animal models of asthma, continuous positive airway pressure (CPAP) reduced airway reactivity. Short-term studies of CPAP in patients with asthma showed reductions in airway reactivity.

Objectives: To evaluate whether nocturnal CPAP decreased the provocative concentration of methacholine to reduce FEV₁ by 20% (PC₂₀).

Methods: One hundred ninety-four individuals with asthma were randomized (1:1:1) to use CPAP with warmed, filtered, humidified air at night at pressures either less than 1 cm H₂O (sham) or at 5 cm H₂O or 10 cm H₂O. The primary outcome was change in PC₂₀ after 12 weeks.

Measurements and Main Results: Adherence to CPAP was low in all groups. Regardless, all groups had a significant improvement in PC₂₀, with 12 weeks/baseline PC₂₀ ratios of 2.12, 1.73, and 1.78 for the

sham, 5 cm H₂O, and 10 cm H₂O groups, respectively, and no significant differences between the active and sham groups. Changes in FEV₁ and exhaled nitric oxide were minimal in all groups. The sham group had larger improvements in most patient-reported outcomes measuring asthma symptoms and quality of life, as well as sinus symptoms, than the 5 cm H₂O group. The 10 cm H₂O group showed similar but less consistent improvements in scores, which were not different from improvements in the sham group.

Conclusions: Adherence to nocturnal CPAP was low. There was no evidence to support positive pressure as being effective for reducing airway reactivity in people with well-controlled asthma. Regardless, airway reactivity was improved in all groups, which may represent an effect of participating in a study and/or an effect of warm, humid, filtered air on airway reactivity.

Clinical trial registered with www.clinicaltrials.gov (NCT01629823).

Keywords: asthma; CPAP; airway reactivity; methacholine; PC₂₀

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*A complete list of members may be found before the beginning of the REFERENCES.

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Asthma is characterized by increased airway smooth muscle constriction to nonspecific agonists, a characteristic that is correlated with asthma severity (1). It is well established that failure to apply a constant or oscillating strain to airway smooth muscle leads to a change in the biomechanics of the muscle that is characterized by shortened resting length and increased sensitivity to pharmacologic constrictors (2–14). Patients with asthma have physiologic airway characteristics that recapitulate this condition: increased airway tone and increased sensitivity to methacholine.

Our underlying hypothesis is that airway reactivity is promoted by decreased stretching of airways during recumbent sleep (15). If true, treatments that stretch the airways should suppress airway reactivity. Continuous positive airway pressure (CPAP) increases stretching of the airways during sleep and prevents a fall in end-expiratory lung volume that could lead to closure of airways in dependent regions of the lung. Keeping airways open permits tidal breathing to apply strain to the airways.

In animals, sustained mechanical strain of the airways using CPAP, including nocturnal administration, produced decreases in airway reactivity (16, 17). CPAP also decreased airway reactivity in a rabbit model of asthma with atopic airway inflammation and airway hyperreactivity (18). Preliminary data derived from 16 individuals with asthma showed that 1 week of nocturnal 10 cm H₂O CPAP was associated with a greater than twofold increase in the concentration of methacholine required to cause a 20% fall in FEV₁ (PC₂₀), as compared with 9 individuals with asthma who received sham CPAP (19).

To determine whether the effect of CPAP could be reproduced and sustained for a longer time, we conducted a randomized, sham-controlled, parallel-group, multicenter trial of 5 cm H₂O and 10 cm H₂O CPAP to assess whether 12 weeks of treatment with nocturnal CPAP could decrease airway reactivity and improve asthma symptoms. We used a sham treatment to isolate the effects of positive pressure while controlling for the effect of warm, humidified, filtered air by providing conditioned air to all groups. To evaluate the tolerability of treatment, we measured adherence using device-monitoring software and participant self-reports.

Evaluation of efficacy among adherent participants was also a stated objective of the trial. We excluded people at high risk for sleep apnea to ensure that any positive effect of CPAP was not due to improvements in sleep apnea having an indirect benefit for asthma.

Methods

Study Design

We conducted a multicenter, randomized, three-parallel-arm, sham-controlled clinical trial in which individuals with asthma were instructed to use a CPAP device for 12 consecutive weeks. The study was conducted at 18 centers of the American Lung Association Airways Clinical Research Centers Network. All study centers received approval from their respective institutional review boards. This clinical trial is registered at www.clinicaltrials.gov (NCT01629823).

The study included six clinic visits and one phone call. After randomization, participants were instructed to use the device for 12 weeks, with clinic visits scheduled at weeks 1, 6, and 12, and, after a 2-week washout period, 14 weeks (Figure 1). The phone call was scheduled for 1–3 days after randomization to ensure that the initial setup and use of the CPAP device went smoothly. More details on the conduct of the trial are included in the online supplement.

Eligibility

Major eligibility criteria included (1) a physician's diagnosis of asthma, (2) treatment for asthma for the past

12 months, (3) stable asthma treatment for a minimum of 8 weeks, (4) FEV₁ of 75% predicted or greater, (5) methacholine bronchial challenge with PC₂₀ of 8 mg/ml or less, (6) body mass index less than 35 kg/m², (7) no history of sleep apnea by self-report, (8) absence or low risk of less than 20% probability score of sleep apnea as assessed using the Multivariable Apnea Prediction Index (20), (9) no other known sleep disorders under treatment by a sleep specialist, (10) no current pregnancy, and (11) no prior use of CPAP. All participants provided signed consent statements approved by the clinical centers' institutional reviews boards.

Study Treatment

Allocations were concealed prior to randomization. Participant were randomly allocated in a 1:1:1 ratio stratified by clinic with a permuted block randomization scheme to be provided with a CPAP device (ResMed S9 device with heated humidifier; ResMed Ltd., Bella Vista, Australia) that delivered either less than 1 cm H₂O (sham) or 5 cm H₂O or 10 cm H₂O via a nasal mask fitted by a trained research coordinator. The manufacturer set the pressure level and masked the display that provided information on pressure. Factory calibration of the pressure level was done to ensure that all devices delivered the assigned pressure within a narrow (± 1 -cm) range. Clinical personnel and participants were not told which setting a participant was assigned to receive. Sham devices had intake flow rates and noise levels similar to those of the nonsham devices. All devices had 6 ft of ClimateLineAir heated tubing

Figure 1. Study design diagram. Participants were screened at V1 (0–4 d before randomization) and randomized at V2. V3 and V4 were conducted early to troubleshoot problems with continuous positive airway pressure (CPAP) initiation or adherence. Methacholine challenge tests were done at V1, V5 (6 wk), V6 (12 wk), and V7 (14 wk; 2 wk after CPAP use discontinued).

Figure 2. Consolidated Standards of Reporting Trials diagram of the study. Of the 1,952 participants screened, 1,743 were excluded before enrollment or during the run-in period. Two hundred nine participants were randomized to receive one of the three treatments. Data from one clinic (15 patients) were excluded from the analysis because of data irregularities. Methacholine (MeCh) challenge tests were obtained for 194 participants at baseline, 158 participants at 6 weeks, 158 participants at 12 weeks, and 152 participants after washout. One hundred ninety-four participants were included in the analysis for the trial period, and 165 participants were included in the analysis for the washout period. *Other reasons included those categories with less than 5% (refused or unable to do study procedures [$n = 66$], previous use of continuous positive airway pressure [CPAP] [$n = 44$], history or high risk of sleep apnea [$\geq 20\%$ by Multivariable Apnea Prediction Index] [$n = 35$], sleeps < 6 h/night on average [$n = 17$], not fluent in English or Spanish [$n = 14$], compensation [$n = 6$], multiple reasons given [$n = 39$], and no reason specified [$n = 768$]). BMI = body mass index; PC_{20} = concentration of methacholine required to cause a 20% fall in FEV_1 .

Table 1. Baseline characteristics of randomized participants

	Treatment Groups			Total (n = 194)
	Sham <1 cm H ₂ O (n = 66)	5 cm H ₂ O (n = 69)	10 cm H ₂ O (n = 59)	
Age, yr, median (Q1–Q3)	33 (23–47)	31 (20–40)	25 (18–39)	31 (20–41)
Age <18 yr, n (%)	9 (14%)	14 (20%)	13 (22%)	36 (19%)
Male sex, n (%)	24 (36%)	34 (49%)	23 (39%)	81 (42%)
Racial or ethnic group, n (%)				
White	27 (41%)	27 (39%)	31 (53%)	85 (43%)
Black	20 (30%)	28 (41%)	14 (24%)	62 (32%)
Hispanic	16 (24%)	11 (16%)	9 (15%)	36 (19%)
Other	3 (5%)	3 (4%)	5 (8%)	11 (6%)
BMI, kg/m ² , median (Q1–Q3)	25.8 (23.0–29.8)	26.2 (22.3–28.9)	24.1 (22.0–28.8)	25.7 (22.3–29.0)
Former smoker, n (%)	12 (18%)	6 (9%)	5 (8%)	23 (12%)
Secondhand smoke exposure, n (%)	9 (14%)	19 (28%)	20 (34%)	48 (25%)
Asthma characteristics				
Age at onset, yr, median (Q1–Q3)	10 (3–24)	6 (3–12)	7 (3–12)	8 (3–15)
≥1 Unscheduled health care visits for asthma in previous 12 mo, n (%)	14 (21%)	19 (28%)	13 (22%)	46 (24%)
≥1 Course of oral corticosteroids in previous 12 mo, n (%)	12 (18%)	14 (20%)	13 (22%)	39 (20%)
Use of inhaled short-acting β-agonist ≥2 times/wk, n (%)	20 (30%)	20 (29%)	22 (37%)	62 (32%)
Daily use of ICS, n (%)	11 (17%)	10 (14%)	10 (17%)	31 (16%)
Daily use of ICS/LABA, n (%)	18 (27%)	23 (33%)	13 (22%)	54 (28%)
Daily use of antileukotriene, n (%)	8 (12%)	9 (13%)	5 (8%)	22 (11%)
Patient-reported outcome, median (Q1–Q3)				
ASUI score (†) (range, 0–1)	0.89 (0.83–0.94)	0.94 (0.85–1.00)	0.92 (0.86–0.98)	0.92 (0.84–0.98)
ACT score (†) (range, 5–25)	21 (19–23)	22 (20–24)	22 (20–23)	22 (20–23)
ACT score ≤19, n (%)	19 (29%)	15 (22%)	12 (20%)	46 (24%)
Marks AQLQ (‡) (range, 0–80)	9 (5–21)	7 (3–11)	6 (3–10)	7 (4–12)
SNQ-6 (‡) (range, 0–3)	0.8 (0.6–1.6)	0.8 (0.4–1.4)	0.8 (0.4–1.2)	0.8 (0.4–1.4)
Lung function, median (Q1–Q3)				
PC ₂₀ , mg/ml	1.06 (0.47–2.95)	0.96 (0.30–2.66)	0.89 (0.28–2.33)	0.98 (0.33–2.74)
FEV ₁ , L	2.9 (2.4–3.5)	3.1 (2.6–3.7)	3.0 (2.7–3.4)	3.1 (2.6–3.6)
Percent predicted FEV ₁ *	90 (84–96)	91 (82–100)	92 (81–98)	91 (83–98)
FVC, L	3.9 (3.3–4.5)	4.2 (3.5–4.9)	3.9 (3.4–4.5)	4.1 (3.4–4.7)
Percent predicted FVC*	101 (92–108)	103 (91–110)	100 (91–107)	101 (91–108)
Peak flow, L/min	425 (350–510)	430 (360–500)	410 (360–475)	430 (350–500)
Percent predicted peak flow*	92 (81–104)	92 (80–104)	90 (82–105)	91 (81–104)
Biomarkers, median (Q1–Q3)				
F _{ENO} , ppb	29.0 (18.3–49.5)	32.8 (18.5–55.5)	33.0 (20.0–55.5)	31.5 (18.5–55.5)
Eosinophil counts, cells/μl	200 (120–500)	260 (126–369)	221 (161–400)	214 (138–400)
Sleep questionnaire scores				
Multivariable Apnea Prediction Index, %, median (Q1–Q3)	1.2 (0.4–3.1)	0.9 (0.5–2.3)	0.8 (0.2–1.3)	0.9 (0.4–2.3)
Berlin Questionnaire, high risk, n (%)	19 (29)	11 (16)	9 (15)	39 (20)
Pittsburg Sleep Quality Index, median (Q1–Q3)	5 (3–7)	4 (3–7)	5 (3–8)	5 (3–7)
Other self-reported conditions, n (%)				
Eczema	9 (14%)	15 (22%)	11 (19%)	35 (18%)
Rhinitis	40 (61%)	37 (54%)	36 (61%)	113 (58%)
Food allergies	14 (21%)	19 (28%)	15 (25%)	48 (25%)
Allergies worsened asthma	55 (83%)	56 (81%)	41 (69%)	152 (78%)

Definition of abbreviations: ACT = Asthma Control Test; AQLQ = Asthma Quality of Life Questionnaire; ASUI = Asthma Symptom Utility Index; BMI = body mass index; F_{ENO} = fractional exhaled nitric oxide; ICS = inhaled corticosteroid; LABA = long-acting β-agonist; PC₂₀ = concentration of methacholine required to cause a 20% fall in FEV₁; Q1 = first quartile; Q3 = third quartile; SNQ-6 = sinonasal questionnaire.

*Predicted values of Hankinson and colleagues (22).

(ResMed Ltd.) to ensure that air stayed warm after exiting the humidifier unit, and participants were allowed to adjust the air temperature. Participants were provided a choice of nasal masks or pillows. Devices were set to ramp up to the designated pressure over a 15-minute period. Participants were

instructed to use the machine nightly and to continue their routine asthma care, including drug therapy and environmental interventions.

Participants were contacted by phone 1–3 days after randomization to ensure that they were able to set up the devices and use them properly. A second in-person visit

was conducted at 1 week to troubleshoot problems with the use of the device and to collect data on use. Coordinators reviewed use patterns at every visit to encourage participants to commence use at the start and to maintain continuous and consistent use throughout the trial.

Adherence to treatment was assessed on the basis of three measures: machine run-time, data obtained from SD cards, and participant diary cards. For analyses based on overall adherence, we used machine run-time as the primary measure of adherence. For sensitivity analyses based on windows around PC₂₀ measurements, we used diary cards and SD cards to classify adherence prior to tests.

Outcome Measures

The primary outcome measure was the change in PC₂₀ from baseline to 12 weeks. Modified American Thoracic Society guidelines were followed for prebronchodilator spirometry and methacholine challenge testing using the five-breath dosimeter technique (21). Spirometry reference values used were

those of Hankinson and colleagues from the National Health and Nutrition Examination Survey (22). Up to 11 doses, each a doubling concentration of methacholine (Provocholine; Methapharm, Brantford, ON, Canada), were inhaled, starting at 0.03 mg/ml until a 20% or greater fall in FEV₁ occurred. The maximum dose used was 32 mg/ml. Breaths of methacholine were inhaled from a calibrated DeVilbiss 646 nebulizer (DeVilbiss Healthcare, Somerset, PA).

Secondary outcomes included prebronchodilator measures of lung function based on the Asthma Control Test (ACT; score range, 5–25) (23), the Asthma Symptom Utility Index (ASUI; score range, 0–1.0) (24, 25), the Marks Asthma Quality of Life Questionnaire (AQLQ; score range, 0–80) (26), and the 6-week sinonasal

questionnaire (SNQ-6) score (range, 0–3) (27). Other outcomes included asthma diaries for symptom-free days (28). Also measured were fractional exhaled nitric oxide (F_{ENO}) and peripheral blood eosinophil counts. The detailed study schema and data collection schedule are provided in the online supplement.

Sample Size

In the pilot study, 1 week of CPAP at 8–10 cm H₂O showed a 2.4-fold increase in PC₂₀ as compared with the group using sham devices (19). A total sample size of 201 (67 per group) provided 80% power to detect a smaller difference in mean change in PC₂₀ (1.7-fold increase) for each of the CPAP groups as compared with the sham group, with a two-sided type I error rate of 0.025, assuming 60% adherence and an SD of 3.3. The sample size was inflated 15% to account for missing data. There was more than 95% power to detect a twofold increase in the CPAP groups as compared with the sham group.

Data Analysis

The primary statistical analysis was an unadjusted comparison of 12-week change in PC₂₀ between each of the active groups and the sham treatment group. Generalized estimating equations were used to model the change in log PC₂₀ over time, and the results were transformed back to the original scale. A saturated means model with adjustment for the correlation among repeated measures and an unstructured covariance structure were used (29). This approach also offers protection against missing data by incorporating all the available PC₂₀ measurements in the analyses. For participants whose FEV₁ did not decline by 20% at the highest dose of methacholine, the PC₂₀ was assigned the value of the highest dose (32 mg/ml) multiplied by 1.5. Sensitivity analyses included multiple imputation for missing PC₂₀ and limiting the analysis to participants who were adherent to CPAP.

Analyses of secondary outcomes (FEV₁, asthma diary data, asthma control, and inflammatory biomarkers) were similar to those used for the primary outcome. F_{ENO} and eosinophil data were log transformed for analyses because these data were skewed rightward. Analyses were performed using SAS software (SAS Institute, Cary, NC).

Table 2. Comparison of concentrations of methacholine required to cause a 20% fall in FEV₁ over time between treatment groups

	Estimated Median* (95% CI)		
	Treatment Assignments		
	Sham <1 cm H ₂ O	5 cm H ₂ O	10 cm H ₂ O
Trial PC₂₀			
Visit PC ₂₀ , mg/ml			
Randomization (n = 194 [†])	1.01 (0.71–1.42)	0.86 (0.62–1.19)	0.81 (0.58–1.12)
6 wk (n = 158 [†])	1.95 (1.19–3.20)	1.31 (0.86–1.98)	1.91 (1.21–3.03)
12 wk (n = 158 [†])	2.13 (1.30–3.49)	1.48 (0.96–2.28)	1.44 (0.91–2.27)
Ratio of follow-up compared with baseline			
6 wk	1.94 (1.28–2.94)	1.53 (1.05–2.22)	2.37 (1.64–3.42)
12 wk	2.12 (1.38–3.26)	1.73 (1.12–2.66)	1.78 (1.19–2.67)
Treatment effect estimates compared with sham			
6 wk	N/A	0.79 (0.45–1.38)	1.22 (0.70–2.12)
P value [‡]		0.40	0.48
12 wk	N/A	0.81 (0.44–1.50)	0.84 (0.47–1.52)
P value [‡]		0.51	0.57
Washout PC₂₀			
Visit PC ₂₀ , mg/ml			
14 wk (n = 152 [†])	1.60 (0.96–2.69)	1.37 (0.91–2.07)	1.27 (0.81–2.01)
Ratio of washout compared with 12 wk			
14 wk	0.69 (0.48–0.98)	0.83 (0.59–1.13)	0.90 (0.64–1.27)
Treatment effect estimates compared with sham	N/A	1.19 (0.74–1.91)	1.31 (0.80–2.14)
P value [‡]		0.49	0.28

Definition of abbreviations: CI = confidence interval; N/A = not applicable; PC₂₀ = concentration of methacholine required to cause a 20% fall in FEV₁.

*Parametric estimates were calculated using generalized estimating equations with log-transformed PC₂₀ values assuming an unstructured covariance structure for the within-person replicate measurements with robust standard errors. The treatment effect differences were calculated on the logarithmic scale and transformed to give the ratio of the estimates of the 12th week divided by baseline for pairs of treatments. Values above 1 favored the treatment in the numerator. The models for 14 weeks were constructed in the same way but included only Week 12 and Week 14 data. The effect estimates are ratios of Week 14/Week 12 for pairs of treatments.

[†]Number with observed PC₂₀ values at each visit.

[‡]P values are for the comparison of 5 cm H₂O or 10 cm H₂O group with the sham group.

The primary measure of adherence was evaluated on the basis of total run-time hours, which was recorded cumulatively on each device. A participant with a mean CPAP use of 4 hours per night was considered adherent. We categorized individuals as adherers (≥ 4 h/night) or nonadherers (< 4 h/night).

Results

Study Enrollment and Follow-Up

Participants were recruited from July 2012 through July 2014 (Figure 2). We screened 1,952 participants for eligibility, of whom 1,743 were excluded before enrollment or during the run-in period. Two hundred nine participants were randomized to receive sham, 5 cm H₂O, or 10 cm H₂O of CPAP. Data from one clinical site were excluded from the analysis because of significant data irregularities. Methacholine challenge tests were obtained for 194 participants at baseline, 158 at 6 weeks, 158 at 12 weeks, and 152 at the washout visit.

Participant Characteristics

The participants' median age was 31 years, the majority were female (58%), and there was a diverse minority representation (Table 1). The participants assigned to the 10 cm H₂O group were younger and more likely to be white, and participants assigned to the 5 cm H₂O group were more likely to be male. Regardless, participants in all three groups had well-controlled asthma and similar lung function and airway reactivity at baseline: The median ACT score was 22 (an ACT score > 19 indicates well-controlled asthma); the median percent predicted FEV₁ was 90.6%; and the median PC₂₀ was 0.98 mg/ml. Figures E1–E4 in the online supplement display the distribution of percent predicted prebronchodilator FEV₁ and scores derived from the ACT, ASUI, and AQLQ at baseline. The risk of obstructive sleep apnea, as measured by the Multivariable Apnea Prediction Index and the Berlin Questionnaire, was relatively low in all groups but tended to be higher in the sham group.

There were no differences among the groups in sleep quality. About 40% of participants in each group had a Pittsburgh Sleep Quality Index score of 5 or greater, which signifies poor sleep quality (30). Almost 20% of participants missed the

Week 12 visit. Participants with missing data were more likely to be female (78% vs. 55%; $P = 0.04$), to have signs of worse asthma control (FEV₁ percent predicted, 86% vs. 91%; $P = 0.04$), a lower median ACT score (20 vs. 22; $P = 0.06$), and more sinus symptoms (SNQ-6 score, 0.8 vs. 1.2; $P = 0.02$) than those who completed the Week 12 visit. The median PC₂₀ values were similar (1.0 in both groups; $P = 0.60$).

Primary Outcome

There were no significant differences in airway reactivity improvement among the three treatment groups at 6 or 12 weeks (Table 2). All three groups had a significant increase in PC₂₀ from baseline at 6 and 12 weeks (Figure 3, Table 2). These effects diminished after the 2-week washout period, significantly in the sham group (Table 2). The results were similar for the models in which missing values were replaced with multiply imputed PC₂₀ values.

Secondary Outcomes

No significant changes were seen in lung function measures or FE_{NO} within or between groups, but there was a significant reduction in eosinophil counts in the sham group as compared with the 5 cm H₂O group (Table 3).

Patient-reported asthma outcomes (ACT, ASUI, and AQLQ) improved from baseline in the sham group, and the 10 cm H₂O group had similar but less consistent

improvements. The scores in the 5 cm H₂O group did not change from baseline (Table 4). The improvements in the sham group were significantly greater than those in the 5 cm H₂O group for the ASUI and AQLQ scores, and there were no significant differences in the degree of improvement between the sham and 10 cm H₂O groups. Patient-reported sinonasal symptoms (based on SNQ-6 responses) showed a similar pattern of differences (Table 4).

Adherence to Study Treatment

CPAP use was low in all groups, with median durations of use of 4.2, 3.0, and 2.5 hours per night in the sham, 5 cm H₂O, and 10 cm H₂O groups, respectively (Table 5, Table E1). The proportions of participants who met our definition of adherence (average use, ≥ 4 h/night) were 52%, 41%, and 36% in the sham, 5 cm H₂O, and 10 cm H₂O groups, respectively. Adherence was highest at the beginning of the study and degraded throughout follow-up in all groups. There was a statistically significant difference in use ($P = 0.02$) and in the proportion of adherers ($P = 0.05$), with the sham group having the best adherence. There were no significant differences in the change in PC₂₀ between the sham group and the 5 cm H₂O or 10 cm H₂O group in the subgroups defined as adherent ($P = 0.55$ and $P = 0.36$, respectively), nor was there a difference in response rates, defined as at least a doubling in the PC₂₀ value or

Figure 3. Change in concentration of methacholine required to cause a 20% fall in FEV₁ (PC₂₀), by treatment. Median of ratio of PC₂₀ relative to baseline and 95% confidence intervals (CIs) over time by treatment group with 95% CI in the trial period (baseline and Weeks 6 and 12).

Table 3. Comparison of effect continuous positive airway pressure versus sham on lung function and biomarkers

	Estimated Median (95% CI)		
	Treatment Groups		
	Sham <1 cm H ₂ O (n = 54)	5 cm H ₂ O (n = 57)	10 cm H ₂ O (n = 51)
	Mean (95% CI)		
FEV ₁ , L*			
Change from baseline	−0.03 (−0.11, 0.04)	−0.05 (−0.11, 0.01)	−0.07 (−0.15, 0.01)
P value [†]		0.75	0.51
FVC, L*			
Change from baseline	−0.04 (−0.09, 0.02)	−0.06 (−0.11, −0.001)	−0.09 (−0.17, −0.01)
P value [†]		0.66	0.24
Ratio FEV ₁ /FVC*			
Change from baseline	−0.001 (−0.014, 0.012)	−0.001 (−0.011, 0.009)	−0.0002 (−0.017, 0.017)
P value [†]		0.98	0.94
FEV ₁ , % predicted*			
Change from baseline	−1.03 (−3.17, 1.11)	−1.14 (−2.70, 0.42)	−2.43 (−4.59, −0.28)
P value [†]		0.94	0.36
FVC, % predicted*			
Change from baseline	−1.08 (−2.35, 0.19)	−1.05 (−2.37, 0.27)	−2.58 (−4.45, −0.70)
P value [†]		0.98	0.19
	Median (95% CI)		
FE _{NO} , ppb [‡]			
Ratio to baseline	0.87 (0.73–1.04)	1.04 (0.89–1.20)	0.91 (0.79–1.06)
P value [†]		0.13	0.67
Eosinophils, cells/μl [§]			
Ratio to baseline	0.59 (0.38–0.89)	1.11 (0.84–1.48)	0.89 (0.71–1.11)
P value [†]		0.011	0.08

Definition of abbreviations: CI = confidence interval; FE_{NO} = fractional exhaled nitric oxide.

*Model-based estimates were calculated using generalized estimating equations assuming an exchangeable correlation structure for the within-person replicate measurements with robust standard errors.

[†]P values are for the comparison of 5 cm H₂O or 10 cm H₂O group with the sham group.

[‡]FE_{NO} (sham, n = 53; 5 cm H₂O, n = 54; 10 cm H₂O, n = 53). Model-based estimates were calculated using generalized estimating equations with a log-transformed FE_{NO} value assuming an unstructured correlation structure for the within-person replicate measurements with robust standard errors. The treatment effect differences were calculated on the logarithmic scale and transformed to give the ratio of the estimates of the 12th week divided by baseline for pairs of treatments. Values above 1 favored the treatment in the numerator.

[§]Eosinophil (sham, n = 51; 5 cm H₂O, n = 53; 10 cm H₂O, n = 51).

median change in log PC₂₀, between adherent and nonadherent participants (Tables E2 and E3).

Treatment-related Adverse Events and Symptoms

Few serious adverse events were reported for the three treatment groups. The most commonly reported moderate or severe symptoms were nasal congestion (cumulative proportions: 36% sham, 36% 5 cm H₂O, and 20% 10 cm H₂O) and headaches (cumulative proportions: 21% sham, 13% 5 cm H₂O, and 15% 10 cm H₂O) (Table E4). There were no significant differences between treatment groups in emergent symptoms ($P > 0.10$ for all symptoms). Three serious adverse events occurred during the study (one hospitalization due to kidney infection [sham], one stroke [sham], and one hospitalization for chronic blood loss and fatigue [5 cm H₂O]).

Discussion

We conducted a randomized, sham-controlled clinical trial to determine whether CPAP improved airway reactivity in individuals with asthma who were at low risk for having obstructive sleep apnea. Our study population was not representative of the adolescent and adult population with asthma. Excluding people at high risk of sleep apnea led to exclusion of many people who were obese or older. Furthermore, we had to implement several recruitment strategies to meet the recruitment goal. Many of the over 1,700 individuals screened (Figure 2) contacted clinics by telephone or e-mail, and data regarding their eligibility are limited; most did not recontact the clinics after their initial expression of interest.

In this younger population with more than 80% classified as having good asthma control (Table 1), the main findings are that CPAP was not well accepted and that

there was no evidence suggesting an improvement in airway reactivity caused by CPAP. Although poor adherence to CPAP may have diminished a treatment effect, it is unlikely that the hypothesized treatment effect of a 1.7-fold increase in PC₂₀ compared with sham was missed entirely because the upper bound of the 95% confidence intervals for the treatment effects was below 1.5 in both the 5 cm H₂O and 10 cm H₂O groups, which excludes the hypothesized treatment effect (Table 2). There also was no evidence of treatment effects in the subgroups of adherent participants (Tables E2 and E3).

Despite significant efforts to provide participants with early and frequent feedback on adherence and training on ways to minimize potential side effects such as dry airways, adherence was poor in all groups and declined with follow-up time. The best adherence was found in the sham group.

Table 4. Comparison of effect continuous positive airway pressure versus sham on patient-reported outcomes

	Treatment Groups		
	Sham <1 cm H ₂ O (n = 56)	5 cm H ₂ O (n = 58)	10 cm H ₂ O (n = 54)*
	Mean (95% CI)		
ACT (†) (range, 5–25)			
Change from baseline [†]	1.14 (0.38, 1.90)	0.40 (−0.32, 1.12)	1.29 (0.62, 1.97)
P value [‡]		0.16	0.76
ASUI (†) (range, 0–1)			
Change from baseline [†]	0.05 (0.02–0.08)	−0.003 (−0.03, 0.03)	0.03 (−0.006, 0.06)
P value [‡]		0.01	0.22
SNQ-6 (‡) (range, 0–3)			
Change from baseline [†]	−0.19 (−0.33, −0.06)	0.001 (−0.15, 0.15)	−0.08 (−0.23, 0.07)
P value [‡]		0.045	0.24
AQLQ (‡) (range, 0–80)			
Change from baseline [†]	−3.76 (−6.05, −1.47)	−0.41 (−2.33, 1.50)	−2.29 (−4.65, 0.07)
P value [‡]		0.028	0.38

Definition of abbreviations: ACT = Asthma Control Test; AQLQ = Asthma Quality of Life Questionnaire; ASUI = Asthma Symptom Utility Index; CI = confidence interval; SNQ-6 = sinonasal questionnaire.

Higher values (†) indicate less severe disease; lower values (‡) indicate less severe disease.

*Asthma Quality of Life Questionnaire (n = 53) for the 10 cm H₂O group.

[†]Model-based estimates were calculated using generalized estimating equations assuming an unstructured correlation structure for the within-person replicate measurements with robust standard errors.

[‡]P values are for the comparison of 5 cm H₂O or 10 cm H₂O group with the sham group.

The median use of 3.2 hours per night was less than the mean use in studies of patients with obstructive sleep apnea, reported previously as 4.88 and 3.3 hours per night in two different studies (31, 32). Our participants' low level of adherence probably represents near-optimal adherence because we actively tried to promote adherence. Adherence to more conventional treatments for asthma is also low (33), so it is not surprising that our participants' adherence was poor.

Regardless, there was a notable and statistically significant improvement in airway reactivity in all three treatment

groups. This improvement of PC₂₀ was in excess of the variability of PC₂₀ that we reported in a previous study (34). The improvement in airway reactivity was approximately one doubling dose in the sham group and was accompanied by improvements in patient-reported outcomes, including asthma control scores, but no effect on FEV₁ was seen. No or smaller improvements in patient-reported outcomes were noted in the 5 cm H₂O and 10 cm H₂O treatment groups, respectively. There are several potential explanations for decreased airway reactivity in all groups. One possibility is regression to the mean

because we selected people who had high levels of airway reactivity; however, a previous study of patients with similar initial levels of airway reactivity did not show similar decreases (34).

Another possibility is a positive effect of participating in a clinical trial with regular attention (i.e., a Hawthorne effect [35]). Typically, Hawthorne or placebo effects are limited to more subjective outcomes and are less likely to affect lung function measures such as airway reactivity (36, 37). Regardless, participation in a clinical trial may have promoted better adherence to asthma therapies in all groups, which may have decreased airway reactivity. Our sham devices did have a small amount of pressure, and these participants were more adherent, so there may have been physiologic effects of very low, more consistent exposure to pressure, but this seems unlikely (38). The eosinophil result is puzzling and may represent a false-positive result (type I error), or perhaps it indicated a reduction in allergen exposure during the treatment period.

A mechanistic explanation for our findings is that the use of a mask with filtered air reduced exposure to inhaled perennial household allergens such as house dust mites or animal dander. Also, warmed humidified air might have altered the osmolality of the airway lining fluid, thereby altering airway reactivity (39, 40). Finally, wearing a mask might have changed the pattern of breathing, which could alter airway reactivity (41–43). In support of this conditioned air hypothesis, our study showed that, after 2 weeks of washout, airway reactivity returned toward baseline and was not significantly different from the baseline measures. However, change in PC₂₀ from

Table 5. Treatment adherence based on machine run-time

	Treatment Assignment						<i>P</i> Value [†]
	Sham <1 cm H ₂ O (<i>n</i> = 58)*		5 cm H ₂ O (<i>n</i> = 61)*		10 cm H ₂ O (<i>n</i> = 56)*		
Daily machine run-time, h/night, median (Q1–Q3)	4.2	(2.1–6.2)	3.0	(1.0–5.6)	2.5	(0.7–4.8)	0.05
Total h of machine run-time, median (Q1–Q3)	336	(181–506)	243	(87–460)	204	(57–371)	0.02
Number of follow-up d, [‡] median (Q1–Q3)	82	(71–89)	82	(75–90)	83	(71–89)	
Participants with average machine run-time ≥4 h/night, <i>n</i> (%)	30	(52%)	25	(41%)	20	(36%)	0.05

Definition of abbreviations: Q1 = first quartile; Q3 = third quartile.

*Participants were included if they had at least one follow-up visit and returned the machine.

[†]P value for differences among the three groups, which was calculated using the Kruskal-Wallis test for continuous measures.

[‡]Randomization to Week 12.

baseline at 12 weeks was not associated with adherence, which does not support a treatment effect of conditioned air.

Strengths and Limitations

This study had several strengths. First, it was a sham-controlled, randomized, multicenter trial. Methacholine challenge testing, the primary outcome, was conducted by a trained coordinator using standardized procedures and equipment, and 94% of tests were considered of excellent quality on the basis of central review. We made substantial efforts to encourage CPAP initiation and to maintain continuous and consistent adherence that included electronic monitoring with regular feedback, special attention to proper mask selection and fitting, and motivational interviewing.

The study had limitations. We selected participants largely on the basis of a diagnosis of asthma, presence of airway reactivity, and low risk for obstructive sleep apnea. Most participants had well-controlled asthma and were relatively lean. Hence, our results cannot be extended to obese patients with asthma or patients with more symptomatic asthma. Obesity is common among patients with asthma and has been associated with reduced lung volumes (44, 45), which may lead to decreased airway stretch and greater hyperresponsiveness (46). Therefore, the effects of CPAP may be more pronounced in obese patients with asthma.

Another limitation was poor adherence to CPAP. Adherence may have been improved if we had asked participants to use CPAP for at least 4 hours any time during the day or night. Anecdotally, we did encourage participants to start using CPAP while watching television or reading before falling asleep. We encouraged participants, with limited success, to commence using CPAP and to have continuous and consistent use throughout the study. Most participants did initiate CPAP use, but relatively few used it for 4 hours each night consistently throughout the study. CPAP could be beneficial in highly adherent participants, but we could not confirm this in subgroup analyses of adherent participants.

Other limitations include the lack of a usual-care group, which could have served as a control group for the effects of conditioned air. Finally, almost 20% of the primary outcome data were missing, and participants with missing data had signs of

worse asthma. Most of these data were missing because participants failed to return for a visit. Our statistical methods allowed us to incorporate all enrolled participants' data collected during the trial, which may have reduced the impact of missing data. In addition, we did several sensitivity analyses using multiple imputations to address the impact of missing data.

Conclusions

Our findings are in conflict with preliminary data that showed improvement in airway reactivity after 1 week in individuals with asthma and no effect in a nonconcurrent sham population (19). Possible explanations for this difference are that there is only a short-term benefit of CPAP and that better adherence in the previous study yielded more improvement in airway reactivity.

In conclusion, we noted a positive association of filtered, humidified, warmed air delivered by sham CPAP with improved airway reactivity and patient-reported outcomes. The addition of positive pressure did not augment this response. A well-controlled trial of nocturnal breathing of conditioned air would be necessary to confirm this finding. ■

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