

Use of Continuous Positive Airway Pressure Reduces Airway Reactivity in Adults with Asthma

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Running Head: CPAP Reduces Airway Responsiveness

Supported by NIH grants HL48522

ABSTRACT

Asthma is characterized by airway hyper-reactivity, which is primarily treated with beta-adrenergic bronchodilators and anti-inflammatory agents. However, mechanical strain during breathing is an important modulator of airway responsiveness and we have previously demonstrated in animal models that continuous positive airway pressure (CPAP) resulted in lower *in vivo* airway reactivity. We now evaluated whether using nocturnal CPAP decreased airway reactivity in clinically-stable adults with asthma.

Adults with stable asthma and normal spirometry used nocturnal CPAP (8-10 cmH₂O) or SHAM (0-2 cmH₂O) for 7-days. Spirometry and bronchial challenges were obtained before and after treatment. The primary outcome was PC₂₀, the methacholine concentration that decreased FEV₁ by 20%.

CPAP group (N=16) had a significant decrease in airway reactivity ($\Delta\log PC_{20} = +0.406$; $p < 0.0017$), while SHAM group (N=9) had no significant change in airway reactivity ($\Delta\log PC_{20} = 0.003$; $p = 0.9850$). There was a significant difference in the change in airway reactivity for CPAP vs. SHAM groups ($+0.41$; $p < 0.043$). Our findings indicate that chronic mechanical strain of the lungs produced using nocturnal CPAP for 7-days reduced airway reactivity in clinically stable asthmatics. Future studies of longer duration are required to determine whether CPAP can also decrease asthma symptoms and/or medication usage.

keywords: Bronchial challenge; Chronic mechanical strain; Continuous positive airway pressure; Lung function

INTRODUCTION

Asthma, which is characterized by repeated episodes of reversible airway obstruction, airway hyper-reactivity, and airway inflammation, is primarily treated with beta-adrenergic bronchodilators and anti-inflammatory agents. These therapies are effective in prevention of symptoms for the vast majority of asthmatics; however, they are limited by high cost, poor adherence, and increasing concern about long-term adverse effects. Thus, there is a compelling need for new, safe and effective approaches to the treatment of asthma. The mechanical strain imposed on the lungs during breathing is an important modulator of airway responsiveness *in vivo*(1). Deep inspirations and tidal breathing decrease airway responsiveness in healthy adults and animals, while the absence of a deep inspiration or tidal breathing increases airway responsiveness(2-6). However, in humans, the bronchoprotective effect of acute mechanical strain lasts for only 10 - 20 minutes, and it is less effective in patients with asthma(3, 4).

The application of chronic mechanical strain to airway tissues *in vitro* has also been shown to induce changes in their active and passive physiologic properties(7, 8). Using *in vivo* animal models our laboratory has demonstrated that chronic mechanical strain of the lung produced by continuous positive airway pressure (CPAP) can result in lower airway reactivity *in vivo* and *in vitro*(9, 10). We recently reported that the administration of High CPAP (6-cmH₂O) to rabbits for 4-days followed by 1-day of Low CPAP (0-cmH₂O) resulted in a persistent reduction of *in vivo* airway responsiveness compared to rabbits treated with Low CPAP for 5-days(11). In addition, the positive effects of High CPAP in rabbits could also be obtained by using only nocturnal High

CPAP for the same time period(11). Lastly, chronic High CPAP also suppressed *in vivo* airway reactivity in the presence of allergic airway inflammation, rabbits sensitized and challenged with OVA(11). As the pre-clinical studies suggested that nocturnal CPAP might decrease airway reactivity in patients with asthma, we hypothesized that the use of nocturnal CPAP for 7-days by clinically stable patients with asthma would decrease airway reactivity.

METHODS

Subjects

Adults with clinically stable asthma were recruited to participate in the study. Subjects were recruited from the database maintained by the Asthma Clinical Research Center (ACRC) at Indiana University, as well as from clinics at Indiana University, and by local advertisements.

Inclusion criteria:

- 1) physician diagnosed asthma
- 2) FEV₁ greater than 70% predicted
- 3) greater than 15% increase in FEV₁ following an inhaled bronchodilator
- 4) clinically stable asthma with Juniper score < 1.5(12)
- 5) PC₂₀ less than 16 mg/ml

Exclusion criteria:

- 1) smoked cigarettes or cigars,
- 2) acute respiratory illness or use of systemic corticosteroids in the previous 2-months,

- 3) gastro-esophageal reflux requiring medical management, chronic obstructive pulmonary disease, ischemic heart disease or hypertension requiring treatment with medications other than diuretics.
- 4) Berlin Questionnaire for Sleep apnea with a positive score in two or more categories.(13)

The study was approved by Indiana University Institutional Review Board and informed written consent was obtained from all subjects. The study was registered at NIH Clinical Trials.

Study Design

The primary objective of the study was to determine whether CPAP treatment produced a greater decrease in airway reactivity assessed by methacholine challenge compared to SHAM treatment in adults with stable asthma. At a screening visit to determine eligibility, an Asthma Score (Juniper) was obtained to determine clinical stability; subjects were included only if the score ≤ 1.5 (12). In addition, to minimize the inclusion of subjects with obstructive sleep apnea, the Berlin Questionnaire for Sleep apnea was administered; subjects with a positive score in two or more categories were excluded(13). Exhaled nitric oxide (eNO) was measured using portable Niox equipment (Aerocrine, Inc. NJ, USA) to evaluate whether CPAP treatment might affect eNO, as an index of airway inflammation. Spirometry was performed using the KoKo spirometer and subjects with $FEV_1 < 70\%$ predicted were excluded from the study and no further testing was performed. Those subjects with $FEV_1 \geq 70\%$ predicted performed a bronchial challenge with inhaled methacholine (MCh) using the 5-breath dosimeter protocol

recommended by ATS(14). Initial inhalation for the bronchial challenge was saline as a control, and then followed by increasing MCh concentration of 0.0625, 0.25, 1.0, 4.0 and 16.0 mg/ml until there was a decrease of FEV₁ by 20% from baseline or the final dose was inhaled. The provocative concentration of MCh that decreased FEV₁ by 20% from baseline (PC₂₀) was calculated by linear interpolation from the dose response curve. Subjects who completed the bronchial challenge at the screening visit without a 20% decrease in FEV₁ by the final dose were excluded from the study. At the follow-up visit after treatment with CPAP or Sham, the bronchial challenge was repeated at the same time of day as the initial bronchial challenge. Subjects at the follow-up visit who did not exhibit a 20% decrease in FEV₁ by a MCh dose of 16 mg/ml were assigned a PC₂₀ of 32 mg/ml.

CPAP and SHAM Treatment: An experienced laboratory technician fitted the subject with an appropriate sized face mask and instructed the subject on the use of the equipment. CPAP treatment was set at 8 - 10 cmH₂O, which depended upon subject tolerance. SHAM equipment was provided by ResMed (Bella Vista, Australia); a leak was created at the connector to the facemask, which resulted in a mask pressure between 0 and 2 cmH₂O. Subjects used the CPAP or SHAM between 7 – 10 nights, which included the night prior to the follow-up assessment of spirometry and MCh bronchial challenge. The laboratory technician was available by telephone to address questions related to use of the facemask and equipment. Use of the CPAP and SHAM equipment was evaluated by downloading the recorded information from machines at the follow-up visit.

ANALYSIS

The primary outcome was comparison of the pre and post change in log transformed PC₂₀ (log PC₂₀) for CPAP and SHAM treated subjects, which was assessed by an un-paired t-test. Similar comparisons were performed for FEV₁, eNO, and Asthma Score. Demographic characteristics were summarized and compared between CPAP and Sham treated subjects using two-sample t-test or Pearson's Chi-square test as appropriate. We evaluate the change of FEV₁, logPC₂₀, eNO at each group and compare the change between two groups using a repeated-measurement ANOVA model with group (CPAP vs. Sham), time (pre and post), and their interaction as predictors. A significant interaction represents a significant difference of changes between groups. The change of logPC₂₀ at each group was tested under this model too. StatView software version 5.0.1 and SAS 9.3 (SAS Institute, Inc, Cary, NC) was used to conduct all of the analysis.

RESULTS

Subjects

There were 27 subjects (8 male, 19 female) between 19 and 38 years of age enrolled into the study; however, 2 treated subjects did not return for the follow-up assessment. Table 1 summarizes the 25 subjects who completed the study. There were no significant differences between the CPAP group (N=16) and SHAM group (N=9) for age or gender. Upon entry to the study there were no significant differences between the CPAP and SHAM groups for use of asthma controller medications (p = 0.69), Asthma Score (0.85 vs. 0.72; p = 0.39), FEV₁ (86.8 vs. 89.6%; p = 0.46), logPC₂₀ (0.36

vs. 0.73; $p = 0.12$) or eNO (48 vs. 28; $p = 0.17$). All the subjects used CPAP for at least 7 days and ≥ 4 hours per night. In addition, all the subjects used the CPAP or SHAM equipment the night before the post-treatment follow-up visit.

CPAP group (N=16) had a significant decrease in airway reactivity ($\Delta\log PC_{20} = +0.406$; $p < 0.0017$), while Sham group (N=9) had no significant change in airway reactivity ($\Delta\log PC_{20} = 0.003$; $p = 0.9850$) (Figure 1). The post-pre change in $\log PC_{20}$ with treatment was significantly greater for the CPAP compared to Sham group (0.41; $p < 0.043$). In addition, 15 of 16 subjects in CPAP treatment group demonstrated an increase in PC_{20} compared to 5 of 9 in the SHAM treatment group; this difference in the frequency for an increase in PC_{20} was significant by Fisher's exact test ($p < 0.05$).

Neither the CPAP nor the SHAM treated groups demonstrated a significant change with treatment for Asthma Score and there was not a significant difference for the change in Asthma score between treatments (Figure 2A). None of the subjects changed the use of inhaled corticosteroids during the study period. Similarly, there were no significant changes in FEV_1 or eNO with treatment for either group and there were not significant differences for the changes in FEV_1 or eNO between treatments (Figures 2B, C).

DISCUSSION

Our study demonstrated that short-term use of nocturnal CPAP by clinically stable adults with asthma can reduce airway reactivity, as assessed by methacholine bronchial challenge. These current findings extends to humans our previous work demonstrating that nocturnal CPAP decreases airway reactivity in animal models(11).

As heightened airway reactivity is a phenotypic characteristic of patients with asthma, our study in adult asthmatics suggests that CPAP has the potential as a non-pharmacologic intervention to decrease airway reactivity. However, more prolonged treatment will be required to determine whether CPAP can decrease asthma symptoms and/or the use of medication, which would then make CPAP a novel therapy for patients with asthma.

We evaluated clinically stable patients with asthma to determine whether the short-term use of nocturnal CPAP could decrease airway reactivity, as we had previously observed in an animal model of allergic pulmonary inflammation(11). In our animal studies, we used CPAP of 6-cmH₂O, which was well tolerated and placed the end-expiratory volume (EEV) in the mid-lung range. As adult humans have stiffer chest walls compared to rabbits and ferrets, in the current study, we used CPAP of 8-10 cmH₂O, which should also place EEV above functional residual capacity and in the mid-lung volume range. In adults with obstructive sleep apnea (OSA), this level of CPAP is often the starting pressure for treatment and is relatively well tolerated by subjects. From our study we are not able to determine whether there is a dose-response effect of CPAP upon airway reactivity.

We screened our subjects to exclude those with a history of OSA; however, we did not obtain sleep studies to confirm the absence of OSA. As we were primarily interested in the effects of CPAP upon airway reactivity, we excluded 2 recruited subjects who did not respond to our methacholine bronchial challenge protocol with a decrease of FEV₁ by 20%. This was done as we would not have been able to detect a further decrease in airway reactivity with the abbreviated bronchial challenge protocol

we used. In addition, it would have evaluated subjects with very low degrees of airway reactivity. For those subjects that received CPAP or SHAM, but at follow-up did not respond during the bronchial challenge with a 20% decrease in FEV₁ by a MCh dose of 16 mg/ml, we assigned a PC₂₀ of 32 mg/ml. Although this is an artificial PC₂₀, as this dose was never delivered, we obtained the same results when a non-parametric analysis was employed; CPAP, but not SHAM treated subjects demonstrated a significant decrease in airway reactivity.

We did not find that nocturnal CPAP changed the Asthma Score; however, this was not surprising, as we evaluated a clinically stable group of asthmatics for a relatively short period of time. Our patient selection created a relatively homogenous group of clinically stable asthmatics without significant other health problems. Therefore, we are not able to extrapolate our findings to subjects with more severe asthma symptoms. Importantly, we also do not know whether a decrease in airway reactivity secondary to CPAP treatment has a clinical impact upon asthma symptoms; this question will require a much longer period of treatment to evaluate.

We evaluated whether CPAP treatment might alter eNO to provide some potential insight into its mechanism of action. Wearing a facemask during sleep could potentially reduce allergen exposure of the lung during sleep and thus decrease NO production by decreasing allergic inflammation. Alternatively, we previously demonstrated that mechanical strain of cultured bronchial epithelial cells increases nitric oxide production(15). Therefore, if mechanical strain of the lung by CPAP treatment increased NO production, the increased NO in the airway could have a bronchoprotective effect upon airway reactivity(16). We did not find that CPAP or SHAM

treatment affected eNO; therefore, alterations in NO production do not appear to account for the effect of CPAP on airway reactivity.

CPAP and SHAM treatments had no significant effect upon FEV₁; however, our subjects did not exhibit evidence of severe airway obstruction, as all subjects had FEV₁ > 70% predicted. A greater magnitude of chronic mechanical strain or the application of CPAP for longer periods of time could potentially initiate remodeling of the lung. Chronic CPAP treatment for several weeks has been demonstrated to increase lung volume in animals, and mechanical strain has been proposed as a potential treatment for congenital pulmonary hypoplasia(17, 18). We previously found that ferrets treated with CPAP of 6 cmH₂O not only increased lung volume, but also increased cross-sectional area of the conducting airways, when assessed by CT scan(9). In these animal studies, there were no differences in the amount of airway smooth muscle (ASM) in the airway wall(10), which suggests that the lower airway reactivity *in vivo* may be related to the marked plasticity of the contractile properties of ASM, as well as the airway wall, rather than to a decrease in the quantity of ASM. The effects of mechanical loads on the contractility of isolated tracheal muscle tissues *in vitro* have been attributed to reorganization of cytoskeletal and contractile proteins(19-22). These processes may be initiated by mechano-sensitive protein complexes that localize to smooth muscle cell cytoskeletal/extracellular matrix junctions(22-25); however, it remains unclear whether these processes occur *in vivo*, particularly in asthmatic subjects.

There are only a few studies that have previously assessed the effect of CPAP treatment on airway reactivity in patients with asthma. Lin and coworkers used CPAP to evaluate the relatively acute effects of mechanical strain on airway reactivity. Clinically

stable asthmatics treated with CPAP of 8 cm H₂O for 10 minutes had a reduction of airway reactivity assessed by bronchial challenge(26). Our findings are consistent with those of Lin; however, we greatly extended the CPAP treatment from 10 minutes to 1-week. Ciftci and colleagues evaluated the effect of CPAP treatment for 2 months on adults with asthma and obstructive sleep apnea (OSA)(27). These investigators selected the level of CPAP to minimize OSA based upon each subject's polysomnogram (PSG) study. As a group, there was a significant decrease in asthma nighttime symptoms with 2-months of CPAP treatment and no change in FEV₁; however, airway responsiveness was not assessed and there was no control or Sham treatment group. Chan and coworkers(28) evaluated the effects of a 2-week period of nocturnal CPAP on peak expiratory flows, asthma symptoms, and bronchodilator usage in 9 patients with OSA and unstable asthma. CPAP compared to no CPAP was associated with improvement in pre- and post-bronchodilator peak expiratory flows, and a decrease in asthma symptoms, although airway reactivity was not directly assessed by bronchial challenge testing. In a study of only 4 subjects with OSA and airway hyper-reactivity by bronchial challenge, Lin and coworkers reported that all 4 subjects had a decrease in airway reactivity following 2-months of CPAP treatment(29). Lastly, Lafond and coworkers evaluated patients with OSA and stable asthma who were treated for 6-weeks with a level of CPAP determined by PSG to treat their OSA(30). These investigators found that nocturnal CPAP improved the asthma quality of life score, but there was no effect upon airway reactivity assessed by bronchial challenge. These studies vary greatly in study design, types of subjects evaluated, level and duration of CPAP treatment, and outcome parameters (peak flow, airway reactivity, asthma

symptoms, medication usage); however, their cumulative findings, along with our current study, as well as our pre-clinical animal models, strongly suggest that CPAP may provide an effective therapy for subjects with asthma.

In summary, 7-days of nocturnal CPAP decreased airway reactivity in adults with asthma. Future studies of longer duration are required to determine whether chronic CPAP can also decrease asthma symptoms and/or medication usage, as well as identify asthmatic subjects that can best be treated with CPAP.

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TABLE 1: **Demographics**

Subject	Treatment	Age (yrs)	Race	Sex	Inhaled Steroid	Leukotriene inhibitor
1	CPAP	27	Caucasian	M	Y	N
2	CPAP	22	Caucasian	F	N	N
3	CPAP	25	Caucasian	M	N	N
4	CPAP	30	Caucasian	F	N	N
5	CPAP	38	Caucasian	F	Y	Y
6	CPAP	26	Caucasian	F	Y	N
7	CPAP	29	Caucasian	M	N	N
8	CPAP	24	Caucasian	F	N	N
9	CPAP	19	Caucasian	M	Y	Y
10	CPAP	21	Non-Caucasian	F	N	N
11	CPAP	29	Non-Caucasian	M	N	Y
12	CPAP	29	Non-Caucasian	F	N	N
13	CPAP	36	Caucasian	F	Y	Y
14	CPAP	24	Caucasian	F	Y	N
15	CPAP	21	Caucasian	F	Y	N
16	CPAP	36	Caucasian	F	N	N
1	Sham	20	Caucasian	M	Y	N
2	Sham	36	Caucasian	F	Y	N

3	Sham	30	Non-Caucasian	F	Y	N
4	Sham	40	Caucasian	F	N	N
5	Sham	48	Caucasian	M	Y	N
6	Sham	24	Caucasian	F	N	Y
7	Sham	25	Caucasian	F	N	N
8	Sham	24	Caucasian	M	N	N
9	Sham	32	Non-Caucasian	F	Y	N

FIGURE LEGENDS

Figure 1: Change in LogPC₂₀ with Treatment (Individual subjects and group means)

LogPC₂₀ increased (airway reactivity decreased) significantly with CPAP treatment ($p < 0.004$), but not with SHAM treatment ($p = 0.988$). The change in logPC₂₀ was significantly greater for the CPAP compared to Sham group ($p < 0.043$).

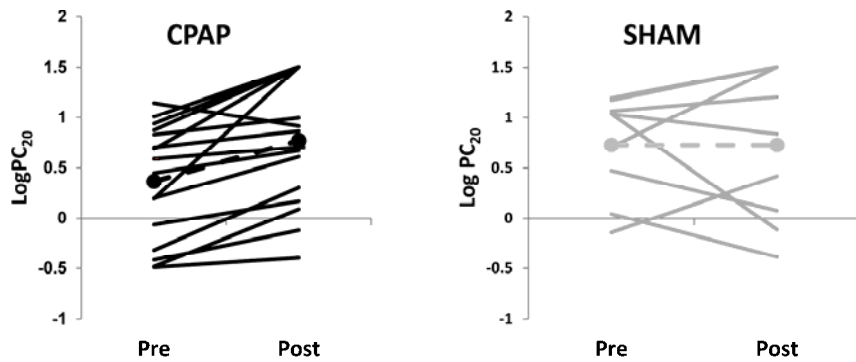


Figure 2A: Change in Asthma Score with Treatment (Individual subjects and group means)

There were no significant changes in Asthma Score with CPAP treatment ($p < 0.147$) or SHAM treatment ($p = 0.594$).

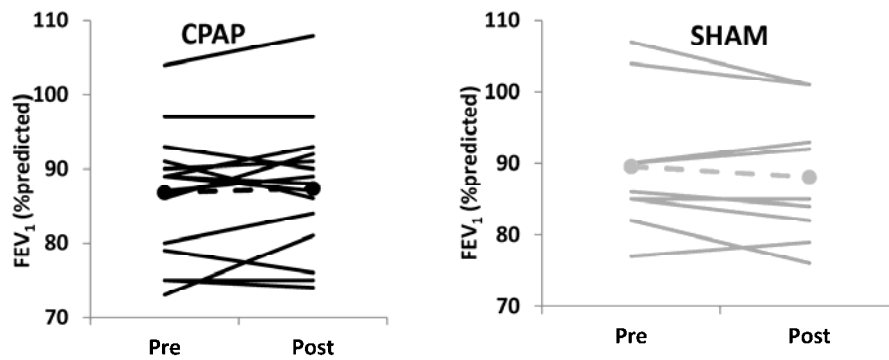


Figure 2B: Change in FEV₁ with Treatment (Individual subjects and group means)

There were no significant changes in FEV₁ with CPAP treatment ($p < 0.567$) or SHAM treatment ($p = 0.238$).

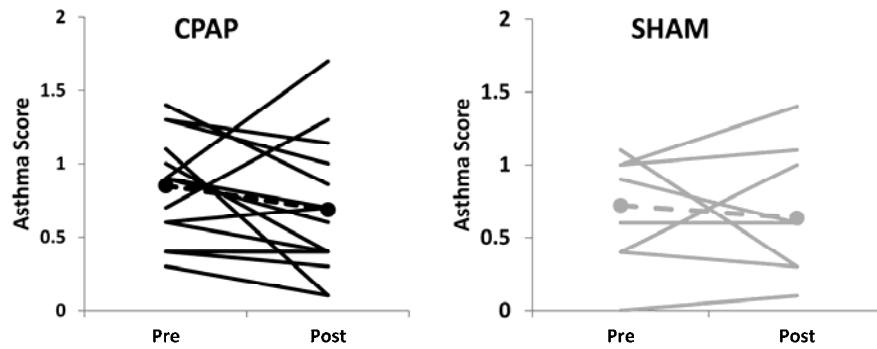


Figure 2C: Change in eNO with Treatment (Individual subjects and group means)

There were no significant changes in eNO with CPAP treatment ($p < 0.326$) or SHAM treatment ($p = 0.523$).

