

**PHS PUBLIC ACCESS**

Author manuscript

*Respirology*. Author manuscript; available in PMC 2019 September 13.

Published in final edited form as:

*Respirology*. 2019 April ; 24(4): 338–344. doi:10.1111/resp.13441.**Effect of CPAP on airway reactivity and airway inflammation in children with moderate–severe asthma****Eduardo PRACA<sup>1</sup>, Hasnaa JALOU<sup>1</sup>, Nadia KRUPP<sup>1</sup>, Angela DELECARIS<sup>1</sup>, Joseph HATCH<sup>1</sup>, James SLAVEN<sup>2</sup>, Susan J. GUNST<sup>3</sup>, Robert S. TEPPER<sup>1</sup>**<sup>1</sup>Department of Pediatrics, Division of Pulmonology, James Whitcomb Riley Hospital for Children, Indiana University School of Medicine, Indianapolis, IN, USA;<sup>2</sup>Department of Biostatistics, Indiana University Schools of Medicine and Public Health, Indianapolis, IN, USA;<sup>3</sup>Department of Cellular and Integrative Physiology, Indiana University School of Medicine, Indianapolis, IN, USA**Abstract**

**Background and objective:** Asthma is characterized by airway hyperreactivity and airway inflammation. We previously demonstrated that adults with mild well-controlled asthma exhibited a marked decrease in airway reactivity (PC20 increased >2-fold) after using nocturnal continuous positive airway pressure (CPAP) for 1 week. If CPAP produces a similar suppression of airway reactivity in children with moderate–severe asthma, who require chronic use of corticosteroids, then this non-pharmacological therapy might provide a beneficial alternative or supplemental therapy in these subjects.

**Methods:** Children aged 8–17 years with moderate–severe asthma were treated with 4 weeks of nocturnal CPAP (8–10 cm H<sub>2</sub>O) or sham CPAP (<2 cm H<sub>2</sub>O). Adherence was monitored with a modem installed in the equipment or by memory cards. Airway reactivity, assessed by methacholine bronchial challenge, was measured prior to and following treatment.

**Results:** The percentage of subjects adherent to treatment was similar in both groups (19/27 CPAP vs 19/28 sham, ~70%). There was a tendency for PC20 to increase with treatment in both groups (3.0–5.3 mg/mL CPAP vs 3.2 to 4.3 mg/mL sham,  $P=0.083$ ); however, the change did not differ significantly between groups ( $P=0.569$ ).

**Conclusion:** We found that the 4-week treatment with nocturnal CPAP did not produce a twofold suppression of airway reactivity in children with moderate–severe asthma.

**Clinical trial registration:** at [ClinicalTrials.gov](http://ClinicalTrials.gov)

**Keywords**

bronchial challenge; chronic mechanical strain; induced sputum; lung function

Correspondence: Robert S. Tepper, Department of Pediatrics, Indiana University School of Medicine, James Whitcomb Riley Hospital for Children, University Medical Center, 702 Barnhill Drive, ROC 4270, Indianapolis, IN 46202 5225, USA. [rtepper@iupui.edu](mailto:rtepper@iupui.edu).

Data availability statement

Individual participant data will not be available for sharing.

## INTRODUCTION

Mechanical strain imposed on the lungs during breathing is an important modulator of airway responsiveness in vivo<sup>1</sup>; deep inspirations and tidal breathing decrease airway responsiveness in healthy adults and animals.<sup>2–6</sup> Our laboratory previously demonstrated in animals that sustained mechanical strain of the airways using continuous positive airway pressure (CPAP) decreased airway reactivity in vivo and ex vivo.<sup>7–9</sup> In a small clinical trial, we demonstrated that adults with mild well-controlled asthma exhibited a marked decrease in airway reactivity after using nocturnal CPAP for 1 week; the methacholine (MCh) concentration to decrease forced expiratory volume in 1 s (FEV<sub>1</sub>) by 20% more than doubled.<sup>10</sup> Currently, there are no studies evaluating whether CPAP suppresses airway reactivity in children, particularly those with moderate–severe disease, who require chronic use of inhaled corticosteroids (ICS) and systemic corticosteroids for frequent exacerbations. If CPAP markedly suppresses airway reactivity in these children, this non-pharmacological therapy might provide a beneficial alternative or supplemental therapy for children with high respiratory morbidity and risk of steroid associated growth suppression. Our recent in vitro studies have also demonstrated that mechanical strain of isolated airway smooth muscle (ASM) suppresses the inflammatory response of ASM to IL-13 stimulation<sup>11,12</sup>; however, there have been no in vivo studies. Therefore, we hypothesized that nocturnal CPAP for 4 weeks would markedly suppress airway reactivity, as well as airway inflammation, in children with moderate–severe asthma.

## METHODS

### Study population

Children aged 8–17 years with moderate–severe asthma, defined by National Asthma Education and Prevention Program/Expert Panel Report (NAEPP)/EPR III guidelines of treatment steps 4 and 5, were recruited at Riley Hospital for Children, Indianapolis, IN.<sup>13</sup> Study exclusion criteria included: body mass index (BMI) >95th percentile; other chronic lung disease; history of pneumothorax; congenital heart disease; obstructive sleep apnoea; baseline FEV<sub>1</sub> < 70% predicted; bronchial challenge test with an MCh concentration > 16 mg/mL to decrease FEV<sub>1</sub> by 20% (PC20).

The study was approved by the Institutional Review Board at Indiana University (ID# 1404809731). Subjects were recruited between 2015 and 2017. Informed parental consent and subject assent were obtained. The study was registered on [ClinicalTrials.gov](https://clinicaltrials.gov) ().

### Study design

**Treatment**—Subjects had two study visits (V1 and V2). The study was single-blinded (subjects were blinded to treatment group, but not all researchers). The research coordinator who performed the study measurements, as well as instructed subjects on use of the CPAP equipment, was not blinded to treatment. At V1, qualified subjects were alternately allocated to CPAP (8–10 cm H<sub>2</sub>O) or sham CPAP (<2 cm H<sub>2</sub>O) treatment and instructed to use the assigned treatment every night for a total of 28 ± 3 days. There was telephone follow-up in

the first 3 days to assess if parents had been able to set up the equipment at home, as well as weekly telephone follow-up. Assessment was repeated at V2.

Adherence to equipment use was assessed by the machine modem or memory card. For an asthma exacerbation requiring oral corticosteroids during the study period, CPAP or sham was extended for 21 days after the last corticosteroid dose. At V2, a subject was considered adherent with treatment if an average of 4 h/night and 5 days/week for all 4 weeks was achieved, and if treatment was used for 4 h on the two nights before V2.

**Measurements**—Asthma symptom score was assessed using the Asthma Control Test (ACT)<sup>14</sup>; higher scores indicate better control. Exhaled nitric oxide (eNO) was measured using a chemiluminescence analyser (NIOX; Aerocrine Inc., Morrisville, NC, USA).<sup>15</sup> Spirometry was obtained with bronchodilators withheld on the day of evaluation<sup>16</sup> (ComPAS; Morgan Scientific Inc., Haverhill, MA, USA). MCh bronchial challenge was performed using the 5-breath protocol (DeVilbiss646 with KoKo dosimeter: 9 µL/breath) with quadrupling concentrations starting with 0.0625 mg/mL and continuing until FEV<sub>1</sub> decreased by 20% (PC20) or MCh concentration of 16 mg/mL was inhaled.<sup>17</sup> Induced sputum was obtained after the MCh challenge and treatment with albuterol to return FEV<sub>1</sub> to 70% predicted. Subjects inhaled increasing concentrations of hypertonic saline (3%, 4%, 5% and 7%) at 5-min intervals using a breath actuated nebulizer (AeroEclipse; Monaghan, Plattsburgh, NY, USA) coupled with a device that generates oscillating positive expiratory pressure to improve lower airway clearance (Aerobika; Monaghan). Sputum was processed for total cell count and cell viability was determined by trypan blue exclusion. Only samples with cell viability ≥ 50% and squamous cells ≥ 20% were considered acceptable.<sup>18,19</sup> Cell-free supernatant was frozen for cytokine analysis (Luminex 200).

### Statistical analysis

The primary outcome was the change in airway reactivity (PC20) between V1 and V2. Sample size was calculated based on the difference of logPC20 changes between groups using our previous study in adults with mild asthma; there was a difference of change in logPC20 between CPAP and sham groups as 0.41, with an SD of 0.46.<sup>13</sup> With this effect size, variability and 10% subject dropout, we estimated that 30 subjects would result in more than 85% power to detect such a difference with a 5% Type I error rate using a two-sample t-test.

Secondary outcomes included the changes in airway inflammatory markers (eNO, % eosinophils and cytokine concentrations in induced sputum), FEV<sub>1</sub> (% predicted) and ACT scores. Demographic characteristics and baseline results of CPAP and sham groups were compared using Student's t-tests for continuous normal variables, Wilcoxon–Kruskal–Wallis non-parametric tests for non-normal variables, and chi-square tests for categorical variables. We utilized Generalized Linear Models (GLM) so that the analytic assumptions would be met, even when the data were not normally distributed. We tested the main effects of time (change between V1 and V2) and treatment group (CPAP/sham), as well as their interaction. Missing data were tested to ensure they were missing at random. The level of statistical

significance was set at 0.05. Statistical analysis was performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

## RESULTS

### Subjects

Eighty-four subjects were approached for the study; 25 were excluded based on screening criteria. Two subjects (one in each group) were lost to follow-up, two (one in each group) did not tolerate the equipment and two (one in each group) did not undergo MCh challenge at V2 due to the presence of asthma symptoms. The demographic characteristics, baseline measurements at V1 and type of asthma controller medication for those who completed follow-up (CPAP = 27; sham = 28) are summarized in Table 1. There were no statistically significant differences in age, sex, race or BMI; however, subjects in the sham group were significantly taller when height was expressed as z-scores. There were no statistically significant differences between groups in baseline FEV<sub>1</sub>, PC20, eNO and ACT score; however, the CPAP compared to sham group had a greater frequency of subjects in asthma treatment step 5 than in step 4.

### Primary outcome: PC20

Both groups tended to have an increase in PC20 (lower airway reactivity) between V1 and V2, but the change did not reach statistical significance ( $P=0.083$ ). While there was a tendency for greater increase in PC20 in the CPAP compared to sham group, the difference was not statistically significant ( $P>0.5$ ) (Table 2A, Fig. 1).

The CPAP group used the machine for an average of  $27.5 \pm 9.4$  days,  $5.7 \pm 1.2$  days/week and  $6.8 \pm 2.2$  h/night, whereas subjects in the sham group had averages of  $25.3 \pm 6.2$  days,  $5.8 \pm 1.1$  days/week and  $7.9 \pm 1.4$  h/night. There were no statistically significant differences in the average number of days or average days/week of machine use (Mann–Whitney U-test,  $P=0.397$  and  $P>0.5$ , respectively). However, on average, the CPAP group used the machine for significantly fewer hours/night over the course of the study compared to sham group (unpaired t-test,  $P=0.031$ ). Eight subjects in the CPAP group (29.6%) and nine subjects in the sham group (32.1%) did not meet the adherence criteria, which was not statistically different (chi-square test,  $P>0.5$ ).

The primary analysis was repeated adjusting for adherence by excluding the 17 non-adherent subjects, as well as adjusting for total hours of machine use, height z-scores and asthma treatment step. None of the subanalyses significantly altered the results.

**Adverse events**—There was no significant difference between groups for subjects with asthma exacerbations treated with oral corticosteroids (5 CPAP:3 sham; Fisher's exact test,  $P>0.5$ ). Repeating the primary analysis with the exclusion of these subjects did not significantly alter the results.

## Secondary outcomes

The overall success rate in obtaining quality sputum samples was 57%; however, only 12 sham and 10 CPAP subjects had quality samples at both study visits. At V1, there were no significant differences between the two groups in total cell count per gram of sputum ( $\times 10^6$ ) or % eosinophils (3.4 vs 4.6,  $P > 0.5$ ; and 6.2 vs 3.9,  $P > 0.5$ , respectively). While there was a tendency for % eosinophils to decrease in CPAP group and to increase in sham group, the changes for the groups were not significantly different ( $P = 0.130$ ) (Table 2B, Fig. 2).

Cytokines levels of IL-5, IL-13, IL-8, IL-10, interferon-gamma (IFN- $\gamma$ ) and TNF- $\alpha$  in the induced sputum supernatant did not change significantly with treatment and there were no significant differences in the changes between treatment groups (Table 3).

FEV<sub>1</sub>, eNO and ACT score did not change significantly with treatment and there were no significant differences in the changes between treatment groups (Table 4).

## DISCUSSION

We hypothesized that the 4-week treatment with nocturnal CPAP would markedly suppress airway reactivity, producing a twofold increase in PC20 in children with moderate–severe asthma, similar to that observed in adults with mild well-controlled asthma treated for 1 week. We did not find a significant effect of CPAP treatment in children with moderate–severe asthma, although there was a tendency for a greater increase in PC20 compared to sham-treated children. There was also a tendency for a decrease in airway inflammation in CPAP-treated subjects, which also did not reach statistical significance. Our findings suggest that the magnitude of suppression of airway reactivity following 1 month of CPAP treatment in children with moderate–severe asthma is much smaller than in adults with mild well-controlled asthma.<sup>13</sup>

There are several possible explanations for our current findings. The sample size for our children was based upon our previous adult data with an effect size required to double PC20. As there was no published data to obtain better estimates in children with moderate–severe asthma, we used data from our previous study of adults with mild asthma treated for 1 week to power the current study. A twofold magnitude of suppression of airway reactivity would be of a magnitude observed with pharmacological interventions,<sup>20–22</sup> and less than the PC20 variability reported for repeated measurements in children.<sup>23</sup> While 1-month intervention might result in greater variability than 1-week intervention, it might have also produced a greater treatment effect. We observed a much smaller potential effect size in children with moderate–severe asthma, which was not statistically significant with the number of subjects we evaluated. Our results indicate that children with moderate–severe asthma treated with CPAP for 1 month produces a much smaller suppression of airway reactivity than adults with mild well-controlled asthma treated for 1 week.

The smaller effect size we observed in children with moderate–severe asthma compared to adults with mild well-controlled asthma may relate to airway remodelling that often occurs with more severe disease.<sup>24</sup> Airway remodelling may increase airway stiffness, limiting the degree of mechanical strain CPAP delivers to the airways and ASM. This mechanism may

also explain the smaller bronchodilating effect produced by deep inspiration in adults with asthma compared to non-asthmatic controls.<sup>3</sup> The children in our study also used medium-high dose ICS, which might impair the molecular pathways by which mechanical strain suppresses ASM reactivity. In addition, differences in autonomic modulation between non-asthma and asthmatic children might contribute to suppression of in vivo airway reactivity.<sup>25</sup>

Lack of adherence to treatment can contribute to the absence of a treatment effect. A multicentre study evaluating adult subjects with mild well-controlled asthma found that CPAP for 12 weeks suppressed airway reactivity<sup>23</sup>; however, sham treatment had a similar effect. In that study, adherence to treatment was very low and significantly lower in CPAP (36%) versus sham (52%), which may have accounted for the absence of a significant difference between treatment groups. In our current study, we had good adherence for both groups (70%), which is higher than 50% adherence reported with regular asthma medications,<sup>26</sup> and our outcomes were similar when adjusted for adherence. Therefore, poor adherence does not appear to account for the absence of a CPAP effect in our study. However, adherence was defined as >4 h/night, derived from CPAP usage for obstructive sleep apnoea. It remains unclear as to the number of hours/night or length of CPAP treatment required to markedly suppress airway reactivity in subjects with moderate–severe asthma.

Our observation that CPAP and sham tend to suppress airway reactivity, but did not reach statistical significance, was similar to a larger multicentre study of adults.<sup>27</sup> In both studies, sham was used as the control treatment and no group used neither CPAP nor sham. Therefore, improvements with time may have been secondary to greater adherence with asthma medications during the study, due to the Hawthorne effect, or a potential benefit of nocturnal warm, humidified and filtered air provided by the equipment.

Sample size was important for our evaluation of whether mechanical strain suppressed airway inflammation, as observed previously in our in vitro studies.<sup>11,12</sup> We obtained 60% success rate for good quality sputum samples, similar to previous studies of children<sup>28,29</sup>; however, only a few children (10–12) had quality sputum at both visits. With limited longitudinal samples, we did not observe a significant decrease in airway inflammation with CPAP treatment; however, trends towards a suppression in airway inflammation provides important translational pilot data, which does not exist in the literature, to further test this novel hypothesis with a larger study population.

A strength of our study is that it is the first to evaluate CPAP therapy to suppress airway reactivity and inflammation in children, particularly those with moderate–severe asthma who would greatly benefit if corticosteroid use could be reduced. Another strength was the good adherence to treatment, particularly as we were evaluating children from 8 to 17 years of age.

Our study had several limitations. As we evaluated only children with moderate–severe asthma, the results cannot be extrapolated to children with mild or moderate asthma. A major limitation of our study was the limited number of subjects we could recruit from a single paediatric centre; however, we were able to evaluate whether this population

demonstrated a suppression of airway reactivity of a magnitude similar to what we previously observed in adults with mild well-controlled asthma. The smaller effect size in the current study would require 132 subjects/group to achieve statistical significance. Our evaluation of airway inflammation was limited to induced sputum rather than bronchoalveolar lavage, which would not have been an acceptable risk in our children.

In summary, 4 weeks of CPAP treatment for children with moderate–severe asthma did not markedly suppress airway reactivity to the degree we previously observed in adults with well-controlled mild asthma, nor did it significantly suppress airway inflammation.

## Acknowledgement

The National Institutes of Health funded this study through Grant # NHLBI-3R01HL048522–18S1.

## Abbreviations:

|                                |   |
|--------------------------------|---|
| <b>ACT</b>                     | Asthma Control Test   |
| <b>ASM</b>                     | airway smooth muscle  |
| <b>CPAP</b>                    | continuous positive airway pressure                           |
| <b>eNO</b>                     | exhaled nitric oxide  |
| <b>FEV<sub>1</sub></b>         | forced expiratory volume in 1 s                               |
| <b>ICS</b>                     | inhaled corticosteroid  |
| <b>IL</b>                      | interleukin   |
| <b>LABAs</b>                   | Long-Acting Beta Agonists                                     |
| <b>LTRA</b>                    | leukotriene receptor antagonists                              |
| <b>MCh</b>                     | methacholine  |
| <b>PC20</b>                    | provocative concentration to decrease FEV <sub>1</sub> by 20% |
| <b>TNF-<math>\alpha</math></b> | tumour necrosis factor alpha                                  |

## REFERENCES

1. Ding DJ, Martin JG, Macklem PT. Effects of lung volume on maximal methacholine induced bronchoconstriction in normal humans. *J. Appl. Physiol* 1987; 62: 1324–30. [PubMed: 3553143]
2. Gunst SJ, Shen X, Ramchandani R, Tepper RS. Bronchoprotective and bronchodilatory effects of deep inspiration in rabbits subjected to bronchial challenge. *J. Appl. Physiol* 2001; 91: 2511–6. [PubMed: 11717212]
3. Kapsali T, Permutt S, Laube B, Scichilone N, Togias A. Potent bronchoprotective effect of deep inspiration and its absence in asthma. *J. Appl. Physiol* 2000; 89: 711–20. [PubMed: 10926658]
4. Moore BJ, Verburgt LM, King GG, Pare PD. The effect of deep inspiration on methacholine dose-response curves in normal subjects. *Am. J. Respir. Crit. Care Med* 1997; 156: 1278–81. [PubMed: 9351635]

5. Shen X, Gunst S, Tepper RS. The effect of tidal ventilation on airway responsiveness to methacholine in rabbits. *Am. J. Respir. Crit. Care Med* 1997; 155: A544.
6. Skloot G, Permutt S, Togias A. Airway hyperresponsiveness in asthma: a problem of limited smooth muscle relaxation with inspiration. *J. Clin. Invest* 1995; 96: 2393–403. [PubMed: 7593627]
7. Xue Z, Yu Y, Gao H, Gunst SJ, Tepper RS. Chronic continuous positive airway pressure (CPAP) reduces airway reactivity in vivo in an allergen-induced rabbit model of asthma. *J. Appl. Physiol* 2011; 111: 353–7. [PubMed: 21493723]
8. Xue Z, Zhang L, Liu Y, Gunst SJ, Tepper RS. Chronic inflation of ferret lungs with CPAP reduces airway smooth muscle contractility in vivo and in vitro. *J. Appl. Physiol* 2008; 104: 610–5. [PubMed: 18096756]
9. Xue Z, Zhang L, Ramchandani R, Liu Y, Antony VB, Gunst SJ, Tepper RS. Respiratory system responsiveness in rabbits in vivo is reduced by prolonged continuous positive airway pressure. *J. Appl. Physiol* 2005; 99: 677–82. [PubMed: 15817724]
10. Busk M, Busk N, Puntenney P, Hutchins J, Yu Z, Gunst SJ, Tepper RS. Use of continuous positive airway pressure reduces airway reactivity in adults with asthma. *Eur. Respir. J* 2013; 41: 317–22. [PubMed: 22835615]
11. Desai LP, Wu Y, Tepper RS, Gunst SJ. Mechanical stimuli and IL-13 interact at integrin adhesion complexes to regulate expression of smooth muscle myosin heavy chain in airway smooth muscle tissue. *Am. J. Physiol. Lung Cell. Mol. Physiol* 2011; 301: L275–84. [PubMed: 21642449]
12. Wu Y, Huang Y, Gunst SJ. Focal adhesion kinase (FAK) and mechanical stimulation negatively regulate the transition of airway smooth muscle tissues to a synthetic phenotype. *Am. J. Physiol. Lung Cell. Mol. Physiol* 2016; 311: L893–1902. [PubMed: 27612967]
13. National Asthma Education and Prevention Program. Expert Panel Report 3 (EPR-3): Guidelines for the diagnosis and management of asthma-Summary Report 2007. *J. Allergy Clin. Immunol* 2007; 120: S94–138. [PubMed: 17983880]
14. Nathan RA, Sorkness CA, Kosinski M, Schatz M, Li JT, Marcus P, Murray JJ, Pendergraft TB. Development of the asthma control test: a survey for assessing asthma control. *J. Allergy Clin. Immunol* 2004; 113: 59–65. [PubMed: 14713908]
15. Dweik RA, Boggs PB, Erzurum SC, Irvin CG, Leigh MW, Lundberg JO, Olin AC, Plummer AL, Taylor DR. An official ATS clinical practice guideline: interpretation of exhaled nitric oxide levels (FENO) for clinical applications. *Am. J. Respir. Crit. Care Med* 2011; 184: 602–15. [PubMed: 21885636]
16. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, Crapo R, Enright P, van der Grinten CPM, Gustafsson P et al.; ATS/ERS Task Force. Standardisation of spirometry. *Eur. Respir. J* 2005; 26: 319–38. [PubMed: 16055882]
17. Crapo RO, Casaburi R, Coates AL, Enright PL, Hankinson JL, Irvin CG, MacIntyre NR, McKay RT, Wanger JS, Anderson SD et al. Guidelines for methacholine and exercise challenge testing-1999. This official statement of the American Thoracic Society was adopted by the ATS Board of Directors, July 1999. *Am. J. Respir. Crit. Care Med* 2000; 161: 309–29. [PubMed: 10619836]
18. Spanevello A, Confalonieri M, Sulotto F, Romano F, Balzano G, Migliori GB, Bianchi A, Michetti G. Induced sputum cellularity. Reference values and distribution in normal volunteers. *Am. J. Respir. Crit. Care Med* 2000; 162: 1172–4. [PubMed: 10988149]
19. Pizzichini E, Pizzichini MM, Efthimiadis A, Evans S, Morris MM, Squillace D, Gleich GJ, Dolovich J, Hargreave FE. Indices of airway inflammation in induced sputum: reproducibility and validity of cell and fluid-phase measurements. *Am. J. Respir. Crit. Care Med* 1996; 154: 308–17. [PubMed: 8756799]
20. van Grunsven PM, van Schayck CP, Molema J, Akkermans RP, van Weel C. Effect of inhaled corticosteroids on bronchial responsiveness in patients with “corticosteroid naive” mild asthma: a meta-analysis. *Thorax* 1999; 54: 316–22. [PubMed: 10092692]
21. Lim S, Jatakanon A, John M, Gilbey T, O’Connor BJ, Chung KF, Barnes PJ. Effect of inhaled budesonide on lung function and airway inflammation. *Am. J. Respir. Crit. Care Med* 1999; 159: 22–30. [PubMed: 9872813]



22. van Rensen ELJ, Straathof KCM, Veselic-Charvat MA, Zwinderman AH, Bel EH, Sterk PJ. Effect of inhaled steroids on airway hyperresponsiveness, sputum eosinophils, and exhaled nitric oxide levels in patients with asthma. *Thorax* 1999; 54: 403–8. [PubMed: 10212103]
23. Peat JK, Salome CM, Bauman A, Toelle BG, Wachinger SL, Woolcock AJ. Repeatability of histamine bronchial challenge and comparability with methacholine bronchial challenge in a population of Australian school children. *Am. Rev. Respir. Dis* 1991; 144: 338–43. [PubMed: 1859057]
24. Konradsen JR, James A, Nordlund B, Reinius LE, Soderhall C, Melen E, Wheelock AM, Lodrup Carlsen KC, Lidegran M, Verhoek M et al. The chitinase-like protein YKL-40: a possible biomarker of inflammation and airway remodeling in severe pediatric asthma. *J. Allergy Clin. Immunol* 2013; 132: 328–35.e5. [PubMed: 23628340]
25. de Freitas Dantas Gomes EL, Costa D, Germano SM, Borges PV, Sampaio LM. Effects of CPAP on clinical variables and autonomic modulation in children during an asthma attack. *Respir. Physiol. Neurobiol* 2013; 188: 66–70. [PubMed: 23681081]
26. Boulet LP, Vervloet D, Magar Y, Foster JM. Adherence: the goal to control asthma. *Clin. Chest Med* 2012; 33: 405–17. [PubMed: 22929091]
27. Holbrook JT, Sugar EA, Brown RH, Drye LT, Irvin CG, Schwartz AR, Tepper RS, Wise RA, Yasin RZ, Busk MF. Effect of continuous positive airway pressure on airway reactivity in asthma. A randomized, sham-controlled clinical trial. *Ann. Am. Thorac. Soc* 2016; 13: 1940–50. [PubMed: 27398992]
28. Wilson NM, Bridge P, Spanevello A, Silverman M. Induced sputum in children: feasibility, repeatability, and relation of findings to asthma severity. *Thorax* 2000; 55: 768–74. [PubMed: 10950896]
29. Jones PD, Hankin R, Simpson J, Gibson PG, Henry RL. The tolerability, safety, and success of sputum induction and combined hypertonic saline challenge in children. *Am. J. Respir. Crit. Care Med* 2001; 164: 1146–9. [PubMed: 11673200]

**SUMMARY AT A GLANCE**

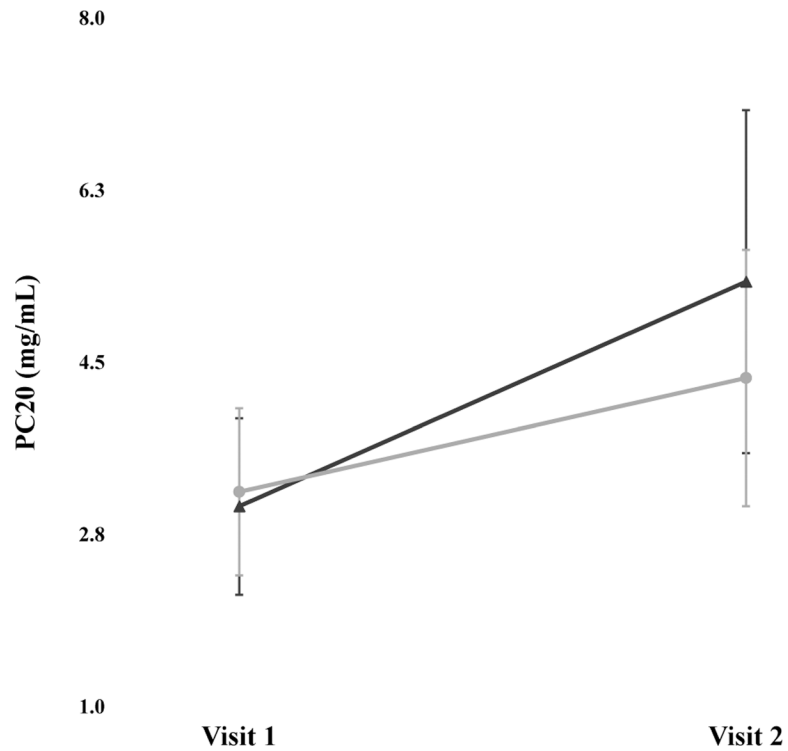
We compared 4 weeks of nocturnal continuous positive airway pressure (CPAP) versus sham to suppress airway reactivity and inflammation in children with moderate–severe asthma. There were no significant differences between treatments. The treatment effect in children with moderate–severe asthma was smaller than previously reported in adults with mild well-controlled asthma.

Author Manuscript

Author Manuscript

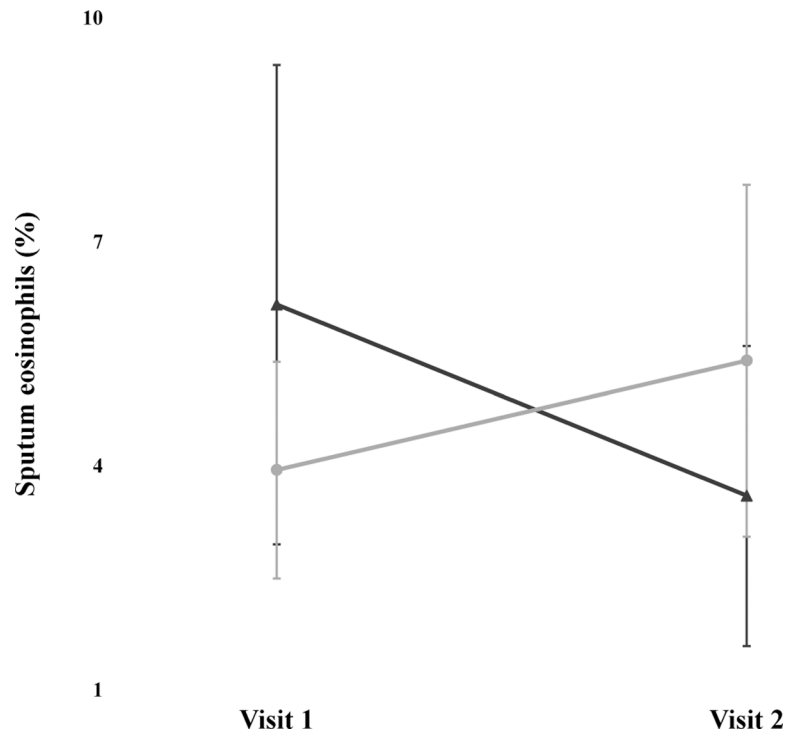
Author Manuscript

Author Manuscript



**Figure 1.**

Airway reactivity (PC20) at visit 1 and visit 2 for continuous positive airway pressure (CPAP; ▲,  $n = 26$ ) and (sham; ●,  $n = 27$ ) treated groups. There was no significant difference between treatment groups in baseline PC20 ( $P > 0.5$ ). Both groups tended to have an increase in PC20 (lower airway reactivity) between visit 1 and visit 2, which was not significant ( $P = 0.083$ ). While there was a tendency for greater increase in PC20 in the CPAP-treated group compared to the sham-treated group, the interaction term was not significant ( $P = 0.569$ ). Plots represent mean and SE.



**Figure 2.** Percentage of sputum eosinophils at visit 1 and visit 2 for continuous positive airway pressure (CPAP;  $\blacktriangle$ ,  $n = 10$ ) and (sham;  $\bullet$ ,  $n = 12$ ) treated groups. There was no significant difference between groups in baseline % sputum eosinophils ( $P > 0.5$ ). While there was a tendency for % sputum eosinophils to decrease in the CPAP group and increase in the sham group between visit 1 and visit 2, the interaction term was not significant ( $P = 0.130$ ). Plots represent mean and SE.

**Table 1**

## Demographic characteristics and baseline measurements

| Variable                             | CPAP         | Sham         | <i>P</i> -value <sup>†</sup> |
|--------------------------------------|--------------|--------------|------------------------------|
| Subjects (#)                         | 27           | 28           | –                            |
| Age (years)                          | 11.1 (2.5)   | 11.7 (2.5)   | 0.337                        |
| Males, #(%)                          | 17 (63)      | 16 (57)      | 0.660                        |
| Race, # African American (%)         | 10 (37)      | 8 (29)       | 0.531                        |
| Height (cm)                          | 142.9 (12.8) | 149.7 (13.1) | 0.055                        |
| Height (z-scores)                    | –0.3 (0.9)   | 0.3 (0.8)    | <b>0.009</b>                 |
| BMI (kg/m <sup>2</sup> )             | 18.6 (3.7)   | 20.5 (4.3)   | 0.081                        |
| BMI (z-scores)                       | 0.2 (1.1)    | 0.6 (1.1)    | 0.112                        |
| Baseline measurements                |              |              |                              |
| FEV <sub>1</sub> (% predicted)       | 88.0 (12.1)  | 86.8 (10.0)  | 0.694                        |
| PC20 (mg/mL)                         | 2.9 (4.5)    | 3.2 (4.3)    | 0.429                        |
| eNO (ppb)                            | 24.2 (25.8)  | 28.3 (22.5)  | 0.235                        |
| ACT score                            | 20.7 (3.8)   | 18.9 (3.9)   | 0.076                        |
| Asthma treatment step <sup>‡</sup>   |              |              | <b>0.014</b>                 |
| # of subjects (%)                    |              |              |                              |
| Step 4 (medium-dose ICS + LABA/LTRA) | 22 (81)      | 14 (50)      | –                            |
| Step 5 (high-dose ICS + LABA/LTRA)   | 5 (19)       | 14 (50)      | –                            |

Values are mean (SD) for all variables, except sex and race, which are represented by frequency and percentage of the given category.

<sup>†</sup>Unpaired t-test for continuous normal variables, Mann–Whitney U-test for non-normal variables and chi-square or Fisher's exact test for categorical variables.

<sup>‡</sup>According to the stepwise approach to asthma treatment proposed by the NAEPP/EPR III guidelines.

ACT, Asthma Control Test; BMI, body mass index; CPAP, continuous positive airway pressure; eNO, exhaled nitric oxide; FEV<sub>1</sub>, forced expiratory volume in 1 s; ICS, inhaled corticosteroid; LABAs, Long-Acting Beta Agonists; LTRA, leukotriene receptor antagonists; NAEPP/EPR, National Asthma Education and Prevention Program/Expert Panel Report; PC20, provocative concentration to decrease FEV<sub>1</sub> by 20%.

**Table 2**

(A) Airway reactivity (PC20) and (B) percentage of sputum eosinophils at visit 1 and visit 2 for CPAP- and sham-treated groups

| Variable                                | Group         | Study visit |           | Time  | Treatment group | Time × treatment group | P-value <sup>‡</sup> |
|---|---------------|-------------|-----------|-------|-----------------|------------------------|----------------------|
|   |               | 1           | 2         |       |                 |                        |                      |
| (A) <sup>‡</sup> PC20 (mg/mL)           | CPAP (n = 26) | 3.0 (4.6)   | 5.3 (8.9) | 0.083 | 0.837           | 0.569                  |                      |
|   | Sham (n = 27) | 3.2 (4.4)   | 4.3 (6.8) |       |                 |                        |                      |
| (B) <sup>§</sup> Sputum eosinophils (%) | CPAP (n = 10) | 6.2 (10.1)  | 3.6 (6.4) | 0.623 | 0.975           | 0.130                  |                      |
|   | Sham (n = 12) | 3.9 (5.0)   | 5.4 (8.2) |       |                 |                        |                      |

Values are mean (SD) for all variables.

<sup>‡</sup> Generalized Linear Model with repeated measures.

<sup>‡</sup> There was a tendency for greater increase in PC20 (lower airway reactivity) in the CPAP group, but the difference in change was not statistically significant.

<sup>§</sup> Sputum eosinophils tended to decrease in the CPAP group and increase in the sham group, but the difference in change was not statistically significant.

CPAP, continuous positive airway pressure; PC20, provocative concentration to decrease FEV<sub>1</sub> by 20%.

Cytokine concentrations in induced sputum at visit 1 and visit 2 for CPAP- and sham-treated groups. There were no statistically significant changes with treatment for any of the cytokines and no significant differences in the changes between CPAP and sham groups

**Table 3**

| Variable              | Study visit |            | Time        | P-value <sup>‡</sup> |                 |                        |
|-----------------------|-------------|------------|-------------|----------------------|-----------------|------------------------|
|                       | Group       | 1          |             | 2                    | Treatment group | Time × treatment group |
| IL-5 (pg/mL)          | CPAP        | 15 (8)     | 12 (4)      | 0.288                | 0.903           | 0.330                  |
|                       | Sham        | 14 (7)     | 14 (5)      |                      |                 |                        |
| IL-13 (pg/mL)         | CPAP        | 11 (3)     | 11 (1)      | 0.639                | 0.137           | 0.545                  |
|                       | Sham        | 12 (3)     | 14 (10)     |                      |                 |                        |
| IL-8 (pg/mL)          | CPAP        | 908 (1339) | 789 (1150)  | 0.637                | 0.558           | 0.293                  |
|                       | Sham        | 909 (1249) | 1296 (1581) |                      |                 |                        |
| IL-10 (pg/mL)         | CPAP        | 33 (14)    | 30 (8)      | 0.692                | 0.959           | 0.344                  |
|                       | Sham        | 30 (9)     | 32 (15)     |                      |                 |                        |
| IFN- $\gamma$ (pg/mL) | CPAP        | 10 (6)     | 7 (3)       | 0.489                | 0.801           | 0.125                  |
|                       | Sham        | 8 (5)      | 9 (4)       |                      |                 |                        |
| TNF- $\alpha$ (pg/mL) | CPAP        | 35 (47)    | 24 (25)     | 0.715                | 0.283           | 0.548                  |
|                       | Sham        | 42 (69)    | 47 (68)     |                      |                 |                        |

CPAP ( $n = 27$ ); sham ( $n = 28$ ).

Values are mean (SD) for all variables.

<sup>‡</sup> Generalized Linear Model with repeated measures.

CPAP, continuous positive airway pressure; IFN- $\gamma$ , interferon-gamma.

FEV<sub>1</sub> (% predicted), eNO (ppb) and ACT score at visit 1 and visit 2 for CPAP- and sham-treated groups. There were no statistically significant changes with treatment for any of these outcomes and no significant differences in the changes between CPAP and sham groups

**Table 4**

| Variable                       | Group | Study visit |         | Time  | Treatment group | Time × treatment group | P-value <sup>‡</sup> |
|--------------------------------|-------|-------------|---------|-------|-----------------|------------------------|----------------------|
|                                |       | 1           | 2       |       |                 |                        |                      |
| FEV <sub>1</sub> (% predicted) | CPAP  | 88 (12)     | 88 (13) | 0.887 | 0.702           | 0.914                  |                      |
|                                | Sham  | 87 (10)     | 87 (10) |       |                 |                        |                      |
| eNO (ppb)                      | CPAP  | 24 (26)     | 24 (28) | 0.565 | 0.680           | 0.497                  |                      |
|                                | Sham  | 28 (22)     | 26 (22) |       |                 |                        |                      |
| ACT (score)                    | CPAP  | 21 (4)      | 21 (3)  | 0.080 | 0.170           | 0.213                  |                      |
|                                | Sham  | 19 (4)      | 21 (4)  |       |                 |                        |                      |

CPAP (*n* = 27); sham (*n* = 28).

Values are mean (SD) for all variables.

<sup>‡</sup> Generalized Linear Model with repeated measures.

ACT, Asthma Control Test; CPAP, continuous positive airway pressure; eNO, exhaled nitric oxide; FEV<sub>1</sub>, forced expiratory volume in 1 s.