Use of continuous positive airway pressure reduces airway reactivity in adults with asthma

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ABSTRACT: Asthma is characterised by airway hyperreactivity, which is primarily treated with β-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 cmH$_2$O) or sham treatment (0–2 cmH$_2$O) for 7 days. Spirometry and bronchial challenges were obtained before and after treatment. The primary outcome was the provocative concentration of methacholine causing a 20% fall in forced expiratory volume in 1 s (PC$_{20}$).

The CPAP group (n=16) had a significant decrease in airway reactivity (change in (Δ)logPC$_{20}$ 0.406, p<0.0017) while the sham group (n=9) had no significant change in airway reactivity (ΔlogPC$_{20}$ 0.003, p=0.9850). There was a significant difference in the change in airway reactivity for the CPAP *versus* the sham group (ΔlogPC$_{20}$ 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

Asthma, which is characterised by repeated episodes of reversible airway obstruction, airway hyperreactivity and airway inflammation, is primarily treated with β-adrenergic bronchodilators and anti-inflammatory agents. These therapies are effective in the 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 min 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 physiological 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 cmH$_2$O) to rabbits for 4 days followed by 1 day of low CPAP (0 cmH$_2$O) resulted in a persistent reduction of *in vivo* airway responsiveness compared with 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 sensitised and challenged with ovalbumin [11]. As the pre-clinical studies suggested that nocturnal CPAP might decrease airway reactivity in patients with asthma, we hypothesised 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 at Indiana University (Indianapolis, IN, USA), from clinics at Indiana University and by local advertisements.

Inclusion criteria were: 1) physician-diagnosed asthma; 2) forced expiratory volume in 1 s (FEV_1) >70% predicted; 3) >15% increase in FEV_1 following an inhaled bronchodilator; 4) clinically stable asthma with Juniper score <1.5 [12]; and 5) provocative concentration of methacholine causing a 20% fall in FEV_1 (PC_{20}) <16 mg·mL^{-1}. Exclusion criteria were: 1) smoking cigarettes or cigars; 2) acute respiratory illness or use of systemic corticosteroids in the previous 2 months; 3) gastro-oesophageal reflux requiring medical management, chronic obstructive pulmonary disease, ischaemic heart disease or hypertension requiring treatment with medications other than diuretics; and 4) Berlin Questionnaire for sleep apnoea with a positive score in two or more categories [13].

The study was approved by the Indiana University Institutional Review Board and informed written consent was obtained from all subjects.

Study design

The primary objective of the study was to determine whether CPAP treatment produced a greater decrease in airway reactivity assessed by methacholine (MCh) challenge compared with 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 was ⩽1.5 [12]. In addition, to minimise the inclusion of subjects with obstructive sleep apnoea (OSA), the Berlin Questionnaire 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., Morrisville, NC, USA) to evaluate whether CPAP treatment might affect eNO, an index of airway inflammation. Spirometry was performed using the KoKo® spirometer (nSpire Health Inc., Longmont, CO, USA) and subjects with FEV_1 <70% pred were excluded from the study and no further testing was performed. Those subjects with FEV_1 ⩾70% pred performed a bronchial challenge with inhaled MCh using the five-breath dosimeter protocol recommended by the American Thoracic Society [14]. Initial inhalation for the bronchial challenge was saline as a control, followed by increasing MCh concentrations of 0.0625, 0.25, 1.0, 4.0 and 16.0 mg·mL^{-1} until there was a fall in FEV_1 of 20% from baseline or the final dose was inhaled. PC_{20} 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 FEV_1 by the final dose were excluded from the study. At the follow-up visit after CPAP or sham treatment, 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 FEV_1 with a MCh dose of 16 mg·mL^{-1} were assigned a PC_{20} of 32 mg·mL^{-1}.

CPAP and sham treatment

An experienced laboratory technician fitted the subject with an appropriately sized face mask and instructed the subject on the use of the equipment. CPAP treatment was set at 8–10 cmH$_2$O, which depended upon subject tolerance. Sham equipment was provided by ResMed (Bella Vista, Australia); a leak was created at the connector to the face mask, which resulted in a mask pressure between 0 and 2 cmH$_2$O. Subjects used the CPAP or sham treatment between seven and 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 face mask 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 change in (Δ) log transformed PC_{20} (logPC_{20}) for CPAP- and sham-treated subjects, which was assessed by an unpaired t-test. Similar comparisons were performed for FEV_1, eNO and Asthma Score. Demographic characteristics were summarised and compared between CPAP- and sham-treated subjects using a two-sample t-test or Pearson's Chi-squared test as appropriate. We evaluated ΔFEV_1, ΔlogPC_{20} and change in eNO in each group, and compared the change between two groups using a repeated-measurement ANOVA model with group (CPAP versus sham), time (before and after) and their interaction as predictors. A significant interaction represents a significant difference of changes between groups. ΔlogPC_{20} in each group was tested in this model too. StatView 5.0.1 (Adept Scientific, Letchworth Garden City, UK) and SAS 9.3 (SAS Institute Inc., Cary, NC, USA) were used to conduct all of the analysis.

RESULTS

Subjects

There were 27 subjects (eight males and 19 females) between 19 and 38 yrs of age enrolled into the study; however, two treated subjects did not return for the follow-up assessment. Table 1 summarises 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 sex. 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 versus 0.72, p=0.39), FEV_1 (86.8 versus 89.6%, p=0.46), logPC_{20} (0.36 versus 0.73, p=0.12) or eNO (48 versus 28, p=0.17). All the subjects used CPAP for ⩾7 days and ⩾4 h per night. In addition, all the subjects used the CPAP or sham equipment the night before the post-treatment follow-up visit.

The CPAP group (n=16) had a significant decrease in airway reactivity (ΔlogPC_{20} 0.406, p<0.0017) while sham group (n=9) had no significant change in airway reactivity (ΔlogPC_{20} 0.003, p=0.9850) (fig. 1). ΔlogPC_{20} with treatment was significantly greater for the CPAP compared with the sham group (ΔlogPC_{20} 0.41, p<0.043). In addition, 15 out of 16 subjects in the CPAP

| TABLE 1	Demographics					
Treatment	Subject	Age yrs	Race	Sex	Inhaled steroid	Leukotriene inhibitor
CPAP	1	27	Caucasian	M	Y	N
CPAP	2	22	Caucasian	F	N	N
CPAP	3	25	Caucasian	M	N	N
CPAP	4	30	Caucasian	F	N	N
CPAP	5	38	Caucasian	F	Y	Y
CPAP	6	26	Caucasian	F	Y	N
CPAP	7	29	Caucasian	M	N	N
CPAP	8	24	Caucasian	F	N	N
CPAP	9	19	Caucasian	M	Y	Y
CPAP	10	21	Non-Caucasian	F	N	N
CPAP	11	29	Non-Caucasian	M	N	Y
CPAP	12	29	Non-Caucasian	F	N	N
CPAP	13	36	Caucasian	F	Y	Y
CPAP	14	24	Caucasian	F	Y	N
CPAP	15	21	Caucasian	F	Y	N
CPAP	16	36	Caucasian	F	N	N
Sham	1	20	Caucasian	M	Y	N
Sham	2	36	Caucasian	F	Y	N
Sham	3	30	Non-Caucasian	F	Y	N
Sham	4	40	Caucasian	F	N	N
Sham	5	48	Caucasian	M	Y	N
Sham	6	24	Caucasian	F	N	Y
Sham	7	25	Caucasian	F	N	N
Sham	8	24	Caucasian	M	N	N
Sham	9	32	Non-Caucasian	F	Y	N

CPAP: continuous positive airway pressure; M: male: F: female; Y: yes; N: no.

treatment group demonstrated an increase in PC_{20} compared with five out of nine 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 in Asthma Score with treatment and there was no significant difference for the change in Asthma score between treatments (fig. 2a and b). None of the subjects
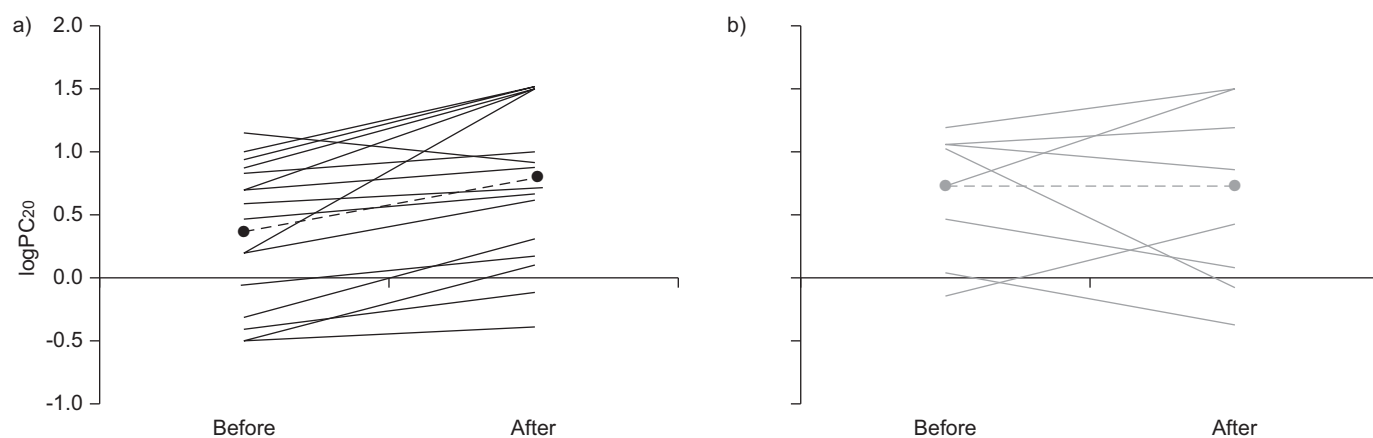
FIGURE 1. Change in log-transformed provocative concentration of methacholine causing a 20% fall in forced expiratory volume in 1 s (PC_{20}) with treatment. $logPC_{20}$ increased (airway reactivity decreased) significantly with a) continuous positive airway pressure (CPAP) treatment ($p<0.004$), but not with b) sham treatment ($p=0.988$). The change in $logPC_{20}$ was significantly greater for the CPAP compared with the sham group ($p<0.043$). Solid lines represent individual subjects, and circles and dashed lines represent group means.
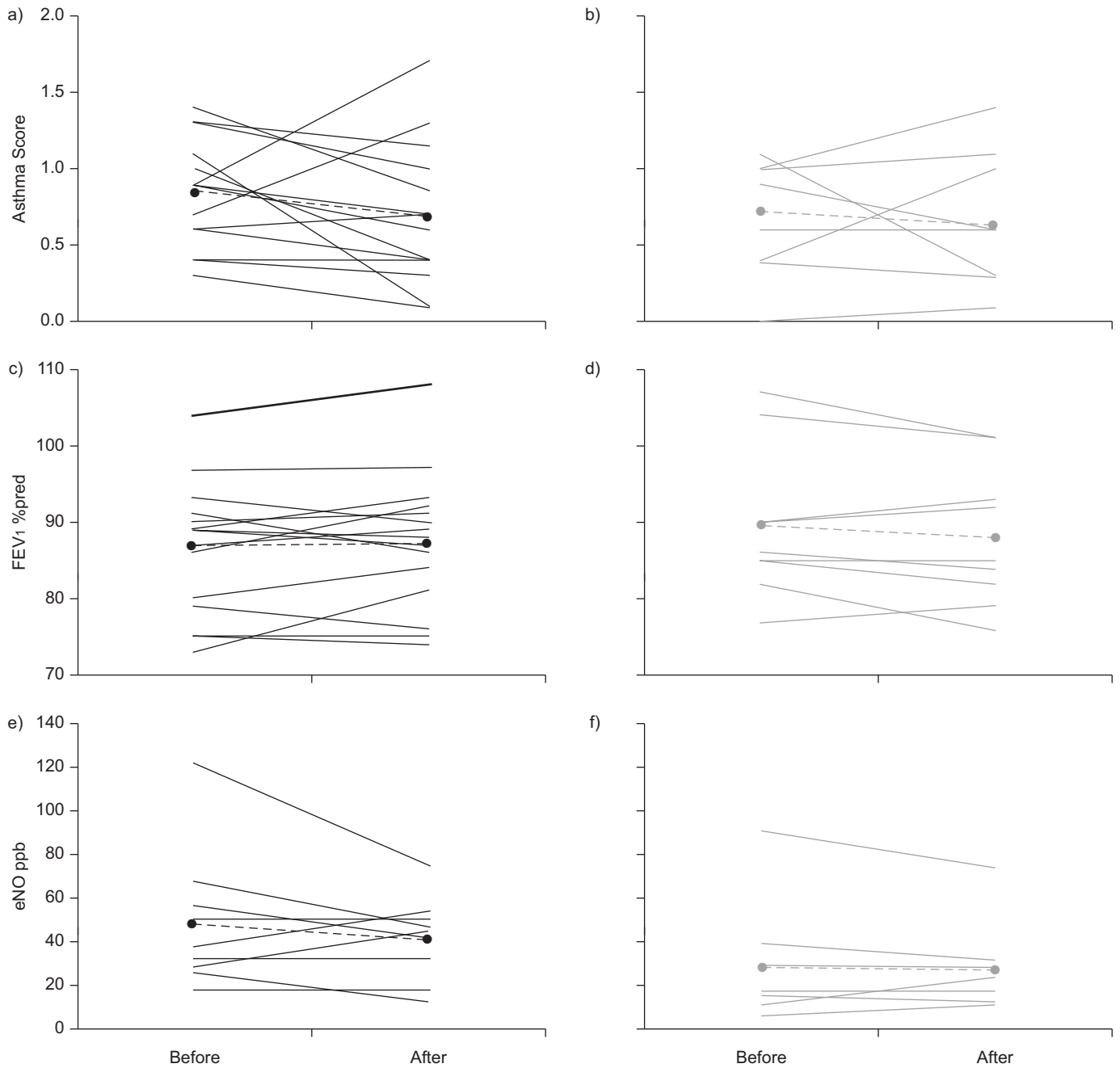
FIGURE 2. a, b) Change in Asthma Score with treatment. There were no significant changes in Asthma Score with a) continuous positive airway pressure (CPAP) treatment (p<0.147) or b) sham treatment (p=0.594). c, d) Change in forced expiratory volume in 1 s (FEV1) with treatment. There were no significant changes in FEV1 with c) CPAP treatment (p<0.567) or d) sham treatment (p=0.238). e, f) Change in exhaled nitric oxide (eNO) with treatment. There were no significant changes in eNO with e) CPAP treatment (p<0.326) or f) sham treatment (p=0.523). Solid lines represent individual subjects, and circles and dashed lines represent group means. % pred: % predicted.

changed their use of inhaled corticosteroids during the study period. Similarly, there were no significant changes in FEV1 or eNO with treatment for either group and there were no significant differences for the changes in FEV1 or eNO between treatments (fig. 2c–f).

DISCUSSION

Our study demonstrated that short-term use of nocturnal CPAP by clinically stable adults with asthma can reduce airway reactivity, as assessed by MCh bronchial challenge. These current findings extend 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 nonpharmacological 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 cmH$_2$O, which was well tolerated and placed the end-expiratory volume (EEV) in the mid-lung range. As adult humans have stiffer chest walls than rabbits and ferrets, in the current study, we used CPAP of 8–10 cmH$_2$O, which should also place EEV above functional residual capacity and in the mid-lung volume range. In adults with 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 perform sleep studies to confirm the absence of OSA. As we were primarily interested in the effects of CPAP upon airway reactivity, we excluded two recruited subjects who did not respond to our MCh bronchial challenge protocol with a decrease in FEV1 of 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 treatment, 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^{-1}, we assigned a PC20 of 32 mg·mL^{-1}. Although this is an artificial PC20, as this dose was never delivered, we obtained the same results when a nonparametric 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 other significant 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 nitric oxide production, the increased nitric oxide 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 nitric oxide 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% pred. A greater magnitude of chronic mechanical strain or the application of CPAP for longer periods of time could potentially initiate remodelling 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 cmH$_2$O not only increased lung volume, but also increased cross-sectional area of the conducting airways, when assessed by computed tomography 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 reorganisation of cytoskeletal and contractile proteins [19–22]. These processes may be initiated by mechanosensitive protein complexes that localise 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 *et al.* [26] used CPAP to evaluate the relatively acute effects of mechanical strain on airway reactivity. Clinically stable asthmatics treated with CPAP of 8 cmH$_2$O for 10 min had a reduction of airway reactivity assessed by bronchial challenge [26]. Our findings are consistent with those of LIN *et al.* [26]; however, we greatly extended the CPAP treatment from 10 min to 1 week. CIFTCI *et al.* [27] evaluated the effect of CPAP treatment for 2 months on adults with asthma and OSA. These investigators selected the level of CPAP to minimise OSA based upon each subject's polysomnography (PSG) study. As a group, there was a significant decrease in asthma night-time 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 *et al.* [28] evaluated the effects of a 2-week period of nocturnal CPAP on peak expiratory flows, asthma symptoms and bronchodilator usage in nine patients with OSA and unstable asthma. CPAP, compared with 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 four subjects with OSA and airway hyperreactivity assessed by bronchial challenge, LIN and LIN [29] reported that all four subjects had a decrease in airway reactivity following 2 months of CPAP treatment. Lastly, LAFOND *et al.* [30] 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. 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 and 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.

CLINICAL TRIAL
This study is registered at www.clinicaltrials.gov with identifier number NCT00592631.

STATEMENT OF INTEREST
A statement of interest for M. Busk can be found at www.erj. ersjournals.com/site/misc/statements.xhtml

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