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Effects of Inhaled Fluticasone on Upper Airway during Sleep and Wakefulness in Asthma: A Pilot Study

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Study Objective: Obstructive sleep apnea is prevalent among people with asthma, but underlying mechanisms remain unknown. Inhaled corticosteroids may contribute. We tested the effects of orally inhaled fluticasone propionate (FP) on upper airway (UAW) during sleep and wakefulness.

Study design: 16-week single-arm study.

Participants: 18 (14 females, mean [± SD] age 26 ± 6 years) corticosteroid-naïve subjects with mild asthma (FEV_1 89 ± 8% predicted).

Interventions: High dose (1,760 mcg/day) inhaled FP.

Measurements: (1) UAW collapsibility (passive critical closing pressure [Pcrit]); (2) tongue strength (maximum isometric pressure—Pmax, in KPa) and endurance—time (in seconds) able to maintain 50% Pmax across 3 trials (Ttot)—at anterior and posterior locations; (3) fat fraction and volume around UAW, measured by magnetic resonance imaging in three subjects.

Results: Pcrit overall improved (became more negative) (mean ± SE) (-8.2 ± 1.1 vs. -12.2 ± 2.2 cm H_2O, p = 0.04); the response was dependent upon baseline characteristics, with older, male gender, and worse asthma control predicting Pcrit deterioration (less negative). Overall, Pmax increased (anterior p = 0.02; posterior p = 0.002), but Ttot generally subsided (anterior p = 0.0007; posterior p = 0.06), unrelated to Pcrit response. In subjects studied with MRI, fat fraction and volume increased by 20.6% and 15.4%, respectively, without Pcrit changes, while asthma control appeared improved.

Conclusions: In this study of young, predominantly female, otherwise healthy subjects with well-controlled asthma and stiff upper airways, 16-week high dose FP treatment elicited Pcrit changes which may be dependent upon baseline characteristics, and determined by synchronous and reciprocally counteracting local and lower airway effects. The long-term implications of these changes on sleep disordered breathing severity remain to be determined.

Keywords: Asthma, lung, inhaled corticosteroid, genioglossus, sleep apnea, obstructive

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SCIENTIFIC INVESTIGATIONS

Growing evidence suggests that asthma patients have an increased predisposition for obstructive sleep apnea (OSA). Studies consistently find higher prevalence of OSA symptoms among asthma patients.[1-5] In a 14-year longitudinal study, asthma emerged as an independent risk factor for incident habitual snoring when adjusting for relevant confounders, including body mass index (BMI) at baseline and its change in time.[6] Likewise, the prevalence of OSA diagnosed on polysomnography (PSG) is high (88% to 95.5%) in difficult-to-control asthma,[7,8] and follows asthma severity with 58% in moderate asthma versus 12% in controls.[7]

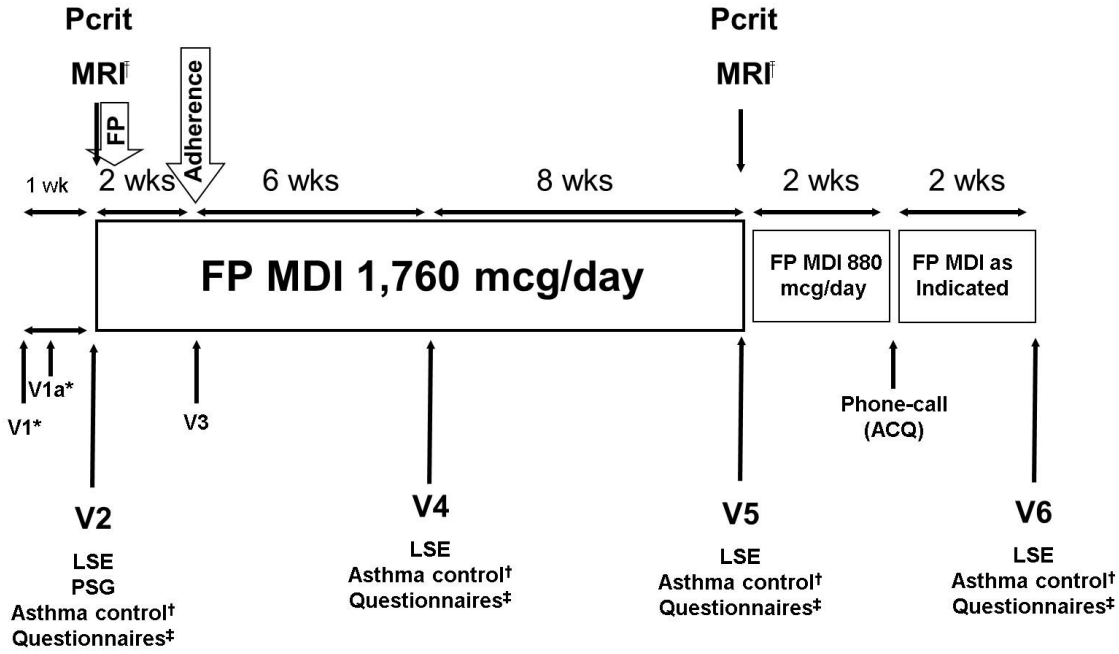
The mechanisms underlying this increased risk for OSA in asthma remain unknown. Apart from traditional OSA risk factors,

BRIEF SUMMARY

Current Knowledge/Study Rationale: Obstructive sleep apnea is more prevalent among people with asthma of increasing severity, but underlying mechanisms remain unknown. Inhaled corticosteroids may play a role.

Study Impact: Sixteen-week treatment with inhaled fluticasone elicited individual responses in upper airway collapsibility dependent upon baseline characteristics, with older age, male gender and worse asthma control predicting deterioration in the upper airway collapsibility, and a pattern of changes in wakefulness tongue function similar to that observed in individuals with obstructive sleep apnea. The long-term implications of these changes on sleep-disordered breathing severity and other upper airway functions, such as swallowing, remain to be determined.

Figure 1—Study outline and procedures performed.



*Visits for phenotyping/eligibility assessment. †Asthma control was assessed with the Asthma Control Questionnaire (ACQ), standardized asthma quality of life questionnaire (AQLQs), spirometry and diaries (except at V2). ‡Questionnaires included: 1) the Sleep Apnea scale of the Sleep Disorders Questionnaire (SA-SDQ), 2) Pittsburgh Sleep Quality Index (PSQI), and 3) Epworth Sleepiness Scale (ESS). Scans were obtained in the last three subjects. V, visit; Pcrit, critical closing pressure of the upper airway; MRI, magnetic resonance imaging; FP, inhaled fluticasone propionate; MDI, metered dose inhaler; LSE, lingual strength and endurance, measured using the Iowa Oral Performance Instrument; ACQ, Asthma Control Questionnaire (symptoms and rescue use) which was administered via phone.

asthma patients have a unique set of predisposing characteristics related to the pathophysiology of asthma itself, its comorbidities and treatment with corticosteroids.[9,10] The association of OSA with corticosteroids was initially suggested by the high prevalence of OSA (50%) observed in patients with Cushing's, conditions characterized by sustained hypercortisolism.[11] Also, more severe OSA was reported in patients with difficult-to-control asthma requiring continuous versus bursts of oral corticosteroids.[8] In our clinic survey of 244 asthma patients, we found that inhaled corticosteroid (ICS) therapy was associated with a dose-dependent increase in the risk of habitual snoring and OSA, independent of asthma severity, and other known risk factors, including excess weight.[12] While the available literature on the association of OSA and corticosteroid use is limited by cross-sectional designs, collectively, these studies raise the possibility that ICS treatment may negatively affect the dynamic between the upper and lower airway, rendering people with asthma vulnerable to OSA.

Myopathy and weight gain/centripetal fat redistribution are known side effects of corticosteroids. ICS are known to cause dysphonia which has been attributed to myopathic changes of the vocal cord adductors and occurs dose-dependently.[13] It is possible that ICS therapy may deleteriously influence pharyngeal upper airway (UAW) patency by: (1) producing myopathy of its dilators, particularly the genioglossus, analogous to the myopathy of vocal cord adductors, and (2) weight gain/fat redistribution to the neck area, owing to their systemic absorption.[14] Dilator muscle dysfunction may be problematic, particularly in the face of narrowed UAW by enhanced extraluminal fat-imposed pressure. All these anatomical and mechanical deficiencies could render the UAW more vulnerable to occlusion during sleep, predisposing to OSA.

Fluticasone propionate (FP) is the most potent[14] and most commonly prescribed ICS to treat asthma. We aimed to test the effects of inhaled FP on UAW collapsibility during sleep, and to assess tongue function changes and fat redistribution around UAW as potential underlying mechanisms. We hypothesized that inhaled FP would: (1) increase UAW collapsibility during sleep; (2) be associated with reduced wakefulness tongue strength and endurance and increased fat content around UAW structures. Preliminary results of this study were published in abstract form.[15]

METHODS

Subjects

Subjects aged 18-65 years with a history of asthma were recruited from University of Wisconsin (UW) Allergy/Asthma/Pulmonary Research database. The inclusion and exclusion criteria are presented in the supplemental material. The protocol was IRB-approved and all subjects signed informed consent (Registered: www.clinicaltrials.gov: NCT01184118).

Study Design

This was a prospective, single group and center study (**Figure 1**). After the baseline studies, subjects initiated 16-week treatment with inhaled FP metered dose inhaler (MDI) (GlaxoSmithKline, NC), 220 mcg/inhalation, 4 inhalations twice/day. Adherence to medication was electronically

Table 1—Baseline demographic, pulmonary physiologic, and clinical characteristics of n = 18 subjects who completed the protocol.

Characteristic	Mean ± SD or Number (%)
Age (years)	25.9 ± 6.3
Gender (female)	14 (77.8%)
BMI (kg/m^2)	26.8 ± 5.3
Neck circumference (inches)	13.9 ± 1.6
Duration of asthma (years since first MD diagnosis)	14.4 ± 10.2
ACQ short (symptoms and rescue β_2-agonist use)*	1.2 ± 0.5
Pre-bronchodilator FEV_1 (% predicted)	88.8 ± 8.2
Pre-bronchodilator FEV_1 (L)	3.4 ± 0.7
Pre-bronchodilator FVC (L)	4.3 ± 0.8
Pre-bronchodilator FEV_1 (*100)/FVC	79.2 ± 7.0
FEF_{25-75} (L/sec)	3.1 ± 0.9
Methacholine PC20 (mg/ml) (n = 17)	1.4 ± 2.2
AQLQ(s)†	5.7 ± 0.5
History of rhinitis	10 (56%)
History of chronic sinusitis	0
History of nasal polyps	1 (6%)
Medication (asthma/allergy) use (at Visit 1)	
LABA	0 (0%)
Short-acting β_2-agonists	0 (0%)
Oral β_2-agonists	0 (0%)
Long-acting anticholinergics	0 (0%)
Short-acting anticholinergics	0 (0%)
Leukotriene modifiers	0 (0%)
Oral antihistamines	4 (22%)
Nasal corticosteroids	1 (6%)

SD, standard deviation; BMI, body mass index; ACQ, Asthma Control Questionnaire; FEV_1, forced expiratory volume in first second of FVC maneuver; FVC, forced vital capacity; FEF_{25-75}, forced expiratory flow between 25% and 75% of vital capacity; PC20, the provocative concentration of methacholine, necessary to produce a 20% fall in FEV_1; AQLQ(s), standardized version of the Asthma Quality of Life Questionnaire; LABA, long acting β_2-agonist. *Scores on the ACQ range from 0 to 6, with a higher score indicating worse asthma control; the minimal clinically important difference (MID) is 0.5.[19] †Scores on the AQLQ(s) range from 1 to 7, with a higher score indicating a better quality of life; the MID is 0.5.[49]

Table 2—Baseline sleep and tongue function characteristics of n = 18 subjects who completed the protocol.

Characteristic	Mean ± SD or Number (%)
Total sleep time (hours)	7.4 ± 1.1
Sleep efficiency (%)	0.9 ± 0.1
AHI (events/hour)	1.2 ± 2.0
OSA (AHI ≥ 5 events/hour)	1 (6%)
RDI (events/hour)	2.9 ± 4.4
Average sleep O_2 saturation (%)	94.5 ± 2.6
Minimum sleep O_2 saturation (%)	92.7 ± 4.7
Pcrit (derived) (cm H_2O)	-8.2 ± 4.7
Holding pressure (cm H_2O)	5.3 ± 1.7
Anterior tongue strength (KPa)	52.9 ± 15.8
Posterior tongue strength (KPa)	40.9 ± 15.3
Anterior tongue endurance (T1) (seconds)	39.8 ± 26.9
Anterior tongue endurance (T_{tot}) (seconds)	113.0 ± 71.1
Posterior tongue endurance (T1) (seconds)	26.4 ± 13.9
Posterior tongue endurance (T_{tot}) (seconds)	73.3 ± 33.9
Self-reported snoring	
Any	12 (67%)
Habitual (≥ 3 nights/week)	5 (28%)
Self-reported nocturnal nasal congestion	
Any	11 (61%)
Habitual (≥ 3 nights/week)	6 (33%)
SA-SDQ score*	21.2 ± 3.9
High OSA risk*	0 (0%)
PSQI score†	4.9 ± 2.6
ESS scores‡	7.9 ± 4.4

SD, standard deviation; AHI, apnea-hypopnea index; OSA, obstructive sleep apnea; RDI, respiratory disturbance index; Pcrit, critical closing pressure of the upper airway; SA-SDQ, Sleep Apnea scale of the Sleep Disorders Questionnaire; PSQI, Pittsburgh Sleep Quality Index; ESS, Epworth Sleepiness Scale. *Scores on SA-SDQ range from 12 to 60, higher scores indicating increased risk for OSA; scores ≥ 36 for men and ≥ 32 for women have been validated with polysomnography as High OSA risk.[16] †Scores on PSQI range 0 to 21 with higher scores indicating worse sleep quality; scores > 5 distinguish good from poor sleepers.[18] ‡Scores on the ESS range from 0 to 24, with a higher score indicating worse sleepiness.[17]

recorded via DOSER (Meditrack Products, MA). Only subjects with an initial 2-week dosing adherence ≥ 75% continued in the protocol. The treatment phase was followed by a 4-week run-out, to step down FP dose (see supplemental material), with subsequent transition to clinical care.

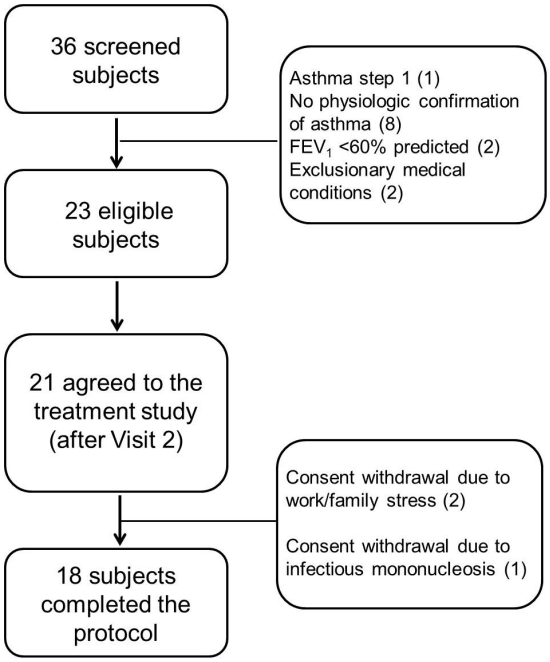
Outcomes Measures

The primary outcome was UAW collapsibility, as measured by passive critical closing pressure (Pcrit) during sleep. Secondary outcomes were wakefulness tongue strength and endurance, OSA risk measured by the Sleep Apnea scale of the Sleep Disorders Questionnaire (SA-SDQ),[16] Epworth Sleepiness Scale (ESS),[17] and Pittsburgh Sleep Quality Index (PSQI).[18] Due to a new funding opportunity that became available late in the study, only the last 3 subjects could undergo UAW magnetic resonance imaging (MRI). Asthma control was monitored with the Asthma Control Questionnaire (ACQ—version with symptoms and rescue bronchodilator use),[19] spirometry (FEV_1% predicted)[20] and standardized Asthma Quality of Life Questionnaire (AQLQs).[21] The ranges, validated discriminative cutoffs and interpretations of the questionnaires are presented in the legends of **Tables 1** and **2**. Subjects also kept a diary of daytime and nighttime symptoms, rescue β_2-agonist use, and peak expiratory flows (PEF).

Experimental Protocol for Polysomnogram (PSG) and Pcrit Studies

A standard montage was used for the PSG[22] performed only at baseline; for Pcrit studies, we used a set-up analogous to our previous report[23] (see supplemental material).

Figure 2—Flow diagram of subjects through the study.



Lingual Strength and Endurance (LSE) Assessment

Measurements were performed at anterior and posterior locations, as previously published (see supplemental material).[24] Tongue strength was determined as the maximum pressure (in KiloPascals) generated during an isometric task (Pmax). Endurance was determined as the time (in seconds) subjects maintained 50% of the Pmax obtained at each visit; as previously reported,[25] 3 trials were obtained at each location and 2 endurance indices were generated: (1) the duration of the first trial (T_1), and (2) the total time of all 3 trials (T_{tot} = T1 + T2 + T3).

Magnetic Resonance Imaging

High-resolution anatomic images progressing from the roof of the hard palate to the tip of the epiglottis[26] were acquired using the Iterative Decomposition of water and fat with echo asymmetry and least squares estimation fast spin-echo (IDEAL-FSE) method,[27] to allow in vivo determination of total fat volume and fat fraction in the structures surrounding the pharyngeal UAW (see supplemental material for details). Scans were obtained on 3 participants.

Data Analysis

Sleep and Pcrit data were analyzed using established criteria (see supplemental material).[22,23] Details on MRI data analysis are also presented in the supplemental material.

Statistical analyses were performed using SAS software, version 9.3 (SAS Institute, NC). Descriptive data are expressed as mean ± standard deviation (SD) for continuous variables, and percentages for categorical variables (**Tables 1** and **2**). Mean ± standard errors (SE) are presented in the text and where statistical comparisons are being made in **Figures 3-5** and **Tables 3-5**. Pearson tests were used to assess correlations as needed. Changes in Pcrit were analyzed with a paired t-test. Using the Pcrit change cutoff of ≥ 3 cm H_2O, proposed as the minimally significant change necessary to assess the effect of an intervention,[28] subjects were divided in 3 subgroups: improved (more negative Pcrit), unchanged, or worsened (less negative). To compare these groups on baseline and change in time in continuous and categorical variables, univariate generalized linear models with post hoc contrast statements (with adjustment within each model for multiple pairwise comparisons using the studentized maximum modulus method[29]) and Fisher exact tests, respectively, were used. Paired-t tests were used to compare changes from baseline in variables of interest for the subjects who underwent MRI scanning.

The other measurements, which were collected at multiple time-points were analyzed separately, for the main treatment and for the run-out period, using mixed-effects linear models with visit number as the fixed within subject factor of interest.[30] For the run-out, percent reduction in cumulative FP dose used relative to the treatment period was included as a covariate. Relationships between changes in Pcrit and other variables were tested using linear regression models. McNemar test was used to assess changes in categorical variables.[31] Two-sided p-values < 0.05 indicated statistical significance.

RESULTS

The study flow chart is presented in **Figure 2**. Eighteen subjects completed the full protocol, and the last 3 subjects also underwent MRI studies.

Baseline Characteristics

Table 1 presents the subjects' baseline demographic and asthma clinical characteristics. Sleep and tongue measures are presented in **Table 2**. On average, subjects were young, predominantly female, slightly overweight, with well-controlled asthma symptoms, without significant lower airways obstruction, and without controller therapy. They had stiff UAWs, minimal sleep disordered breathing (SDB) (none had OAI > 10 events/h or desaturation < 70%), and normal ESS and PSQI scores.

Changes in Pcrit and Predictors of Response during the Treatment Phase

The overall FP dosing adherence was (mean ± SE) 91.2% ± 1.7%. **Table 3** presents the changes in asthma control indices, which as expected, improved significantly with treatment.

Figure 3 depicts the change in Pcrit with FP treatment. In contrast to our hypothesis, overall, Pcrit improved (became more negative) from -8.2 ± 1.1 at baseline to -12.2 ± 2.2 cm H_2O (mean change -4.00 with 95% CI [-7.73, -0.23], p = 0.04, supplemental material, **Table S2**). However, as noted (**Figure 3**), the response was variable, and when stratified by a change ≥ 3 cm H_2O, 8 subjects significantly improved (Pcrit change: -10.02 ± 2.68 cm H_2O, p = 0.007), 8 remained unchanged (0.08 ± 0.50, p = 0.88), and 2 worsened (4.0 ± 0.30, p = 0.047). Comparison of baseline characteristics between these subgroups identified older age, male gender, and worse asthma control (by ACQ) as predictors of deterioration in Pcrit (**Table 4**) with both subjects in this latter subgroup having all 3 characteristics. Trends in other baseline variables, such as higher BMI, larger necks, worse SDB (RDI, minimum SpO_2), and FEV_1 (% of predicted) and more frequent habitual

Table 3—Changes over time in asthma control indices with fluticasone treatment.

	Pre-treatment (Mean ± SE)	Post-treatment (Mean ± SE)	Effect Change (95% CI)	p-value
ACQ short (symptoms and rescue β_2-agonist use)	1.2 ± 0.1	0.4 ± 0.1	-0.81 (-1.05, -0.58)	< 0.0001
FEV_1% predicted	88.8 ± 1.9	94.1 ± 1.9	5.28 (2.46, 8.10)	0.001
FEV_1 (L)	3.3 ± 0.1	3.5 ± 0.1	0.18 (0.07, 0.29)	0.002
FVC (L)	4.2 ± 0.2	4.2 ± 0.1	0.01 (-0.10, 0.12)	0.86
FEV_1(*100)/FVC	79.2 ± 1.7	83.4 ± 1.3	4.25 (2.10, 6.40)	0.0007
FEF_{25-75} (L/s)	3.1 ± 0.2	3.6 ± 0.2	0.54 (0.32, 0.77)	< 0.0001
AQLQs	5.7 ± 0.1	6.6 ± 0.1	0.84 (0.61, 1.06)	< 0.0001

SE, standard error; ACQ, Asthma Control Questionnaire; FEV_1, forced expiratory volume in first second of FVC maneuver; FVC, forced vital capacity; FEF_{25-75}, forced expiratory flow between 25% and 75% of vital capacity; AQLQ(s), standardized version of the Asthma Quality of Life Questionnaire.

nocturnal nasal congestion emerged, but no statistical significance was reached.

Changes in Wakefulness Tongue Function and Other Parameters during Treatment Phase

Figures 4 and **5** show changes in tongue function for the entire group, while **Table S2** adds changes in other sleep parameters and anthropometrics. Tongue strength improved at both, anterior and posterior locations (**Figures 4A** and **4B**, respectively); endurance generally subsided at anterior (**Figures 5A** and **5B**) and posterior locations (**Figures 5C** and **5D**).

The subgroups of Pcrit responses showed no differences in baseline tongue parameters (**Table 4**) or in their changes with treatment (**Table 5**). Similar to above Pcrit changes, the holding pressure increased in the subgroup whose Pcrit worsened vs. those who improved ($p = 0.03$). No differential subgroup responses were noted in the other variables recorded, including asthma control indices, scores on sleep questionnaires, and anthropometrics (**Table 5**).

Magnetic Resonance Imaging Results

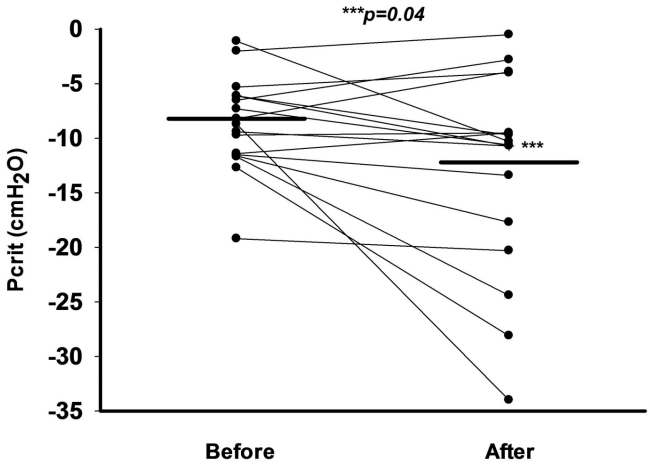
The last 3 consecutive subjects (all females, 22 ± 1 year old) underwent upper airway MRI. Fat fraction and total fat volume in the surrounding UAW structures increased after 16 weeks of FP by 20.6% and 15.4%, respectively; BMI and neck sizes did not seem to change (**Table 6**). These subjects, on average, showed no change in Pcrit (mean change ± SE: 0.13 ± 0.81 cm H_2O), and an apparent improvement in asthma control as seen in FEV_1% predicted (6.33 ± 3.84) and in ACQ scores (-0.50 ± 0.42) was seen. None of these subjects reported nocturnal nasal congestion either at baseline or at their repeat visit. Tongue strength increased (anterior 3.67 ± 2.85; posterior 5.00 ± 0.58 KPa), whereas endurance (Ttot) subsided particularly at anterior location (anterior -16.00 ± 25.58; posterior -2.33 ± 17.57 seconds). With the exception of significantly increased posterior tongue strength ($p = 0.01$), none of the changes in these parameters reached statistical significance, likely a result of the small sample size.

Results for the Run-Out Phase

Per protocol, at the last visit of the treatment phase (V5), all subjects had their FP reduced to half (880 mcg/day) for the ensuing 2 weeks. Only 11 (61%) of subjects had been tapered off FP by study completion. Overall dose adherence was not significantly different for the run-out relative to the treatment period (88.1% ± 2.7% vs. 91.2% ± 1.7%, $p = 0.21$). The percent reduction in the cumulative FP dose used throughout run-out, relative to the treatment period was 87.8% ± 1.3%.

Changes in asthma and outcome variables measured during run-out relative to the treatment period, with adjustment for percent reduction in cumulative FP dose are shown in the supplemental material (**Table S3**). On average, as the subjects shifted from the treatment to the run-out period, asthma control was maintained. Likewise, tongue function changes persisted and scores on the sleep questionnaires and anthropometrics remained not significantly changed.

Figure 3—Group and individual data showing the change in Pcrit with inhaled fluticasone treatment.



Following treatment, overall the Pcrit significantly improved on average ($p = 0.04$). However, variability in the response was noted, as some subjects improved (Pcrit became more negative), others remained unchanged and others deteriorated (Pcrit became less negative). Data are presented as mean ± standard error (SE).

DISCUSSION

Summary of Findings

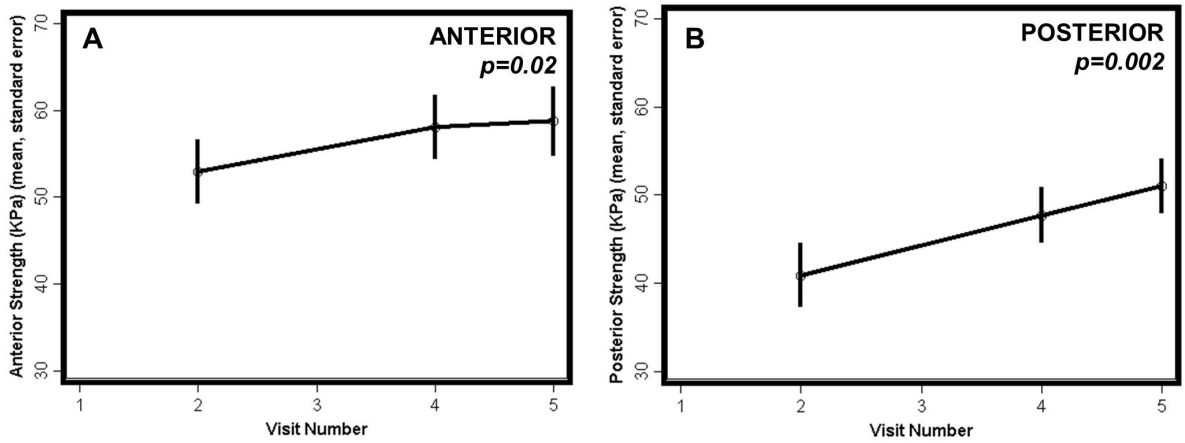
This is the first study to test the effects of an orally inhaled corticosteroid on UAW during sleep and wakefulness. After 16 weeks of high-dose FP treatment: (1) Pcrit overall improved

Table 4—Univariate analyses of baseline demographic, sleep, tongue and asthma measures by Pcrit response groups.

Baseline Variable (Visit)	Improved (n = 8)	Unchanged (n = 8)	Worsened (n = 2)
Age	24.63 ± 1.45	24.70 ± 2.45	35.92 ± 1.44*†
Gender (Male)	1 (13%)	1 (13%)	2 (100%)‡
BMI (kg/m^2) (V1)	24.15 ± 1.83	28.37 ± 1.70	30.76 ± 3.61
Neck circumference (inches) (V2)	13.34 ± 0.44	13.88 ± 0.55	16.00 ± 1.50
Pcrit (cm H_2O) (V2)	-8.16 ± 1.36	-8.51 ± 2.18	-7.35 ± 0.85
Holding pressure (cm H_2O) (V2)	5.37 ± 0.75	5.13 ± 0.58	5.50 ± 0.50
AHI (events/h) (V2)	0.51 ± 0.48	1.64 ± 0.79	2.40 ± 2.40
RDI (events/h) (V2)	2.19 ± 1.78	2.55 ± 0.92	6.85 ± 5.95
Average sleep O_2 saturation % (V2)	95.30 ± 0.87	93.64 ± 1.03	94.75 ± 1.05
Minimum sleep O_2 saturation % (V2)	93.40 ± 1.03	92.75 ± 2.19	89.5 ± 3.50
SA-SDQ	19.38 ± 0.98	22.00 ± 1.40	25.00 ± 4.00
ACQ short (symptoms and rescue β_2-agonist use)	1.13 ± 0.15	1.06 ± 0.18	1.92 ± 0.08*†
FEV_1% predicted (V1)	90.75 ± 2.52	89.13 ± 2.66	80.00 ± 10.00
FEV_1(*100)/FVC (V1)	77.03 ± 2.12	77.03 ± 5.99	75.04 ± 5.90
FEF_{25-75} (L/s) (V1)	2.91 ± 0.28	3.29 ± 0.93	2.97 ± 1.12
Self-reported nocturnal nasal congestion (V1)			
Any	5 (62.5%)	5 (62.5%)	1 (50%)
Habitual (≥ 3 nights/week)	3 (37.5%)	3 (37.5%)	1 (50%)
Anterior tongue strength (KPa) (V2)	52.25 ± 4.59	53.00 ± 7.36	55.00 ± 2.00
Posterior tongue strength (KPa) (V2)	39.75 ± 4.17	45.13 ± 6.35	28.5 ± 12.5
Anterior tongue endurance (seconds) (T1) (V2)	27.50 ± 4.08	54.00 ± 11.66	32.50 ± 20.50
Anterior tongue endurance (seconds) (T_{tot}) (V2)	86.75 ± 16.37	141.0 ± 31.04	106.00 ± 50.00
Posterior tongue endurance (seconds) (T1) (V2)	22.88 ± 5.53	29.13 ± 4.80	30.00 ± 6.00
Posterior tongue endurance (seconds) (T_{tot}) (V2)	77.75 ± 15.06	69.38 ± 10.81	71.00 ± 2.00

Data are presented as mean ± SE or number (%); *p < 0.05 for worsened vs. improvement groups; †p < 0.05 for worsened vs. unchanged groups; ‡Fisher exact p = 0.039. Pcrit, critical closing pressure of the upper airway (derived); BMI, body mass index; AHI, apnea-hypopnea index; RDI, respiratory disturbance index; SA-SDQ, Sleep Apnea scale of the Sleep Disorders Questionnaire; ACQ, Asthma Control Questionnaire; FEV_1, forced expiratory volume in first second of FVC maneuver; FVC, forced vital capacity; FEF_{25-75}, forced expiratory flow between 25% and 75% of vital capacity.

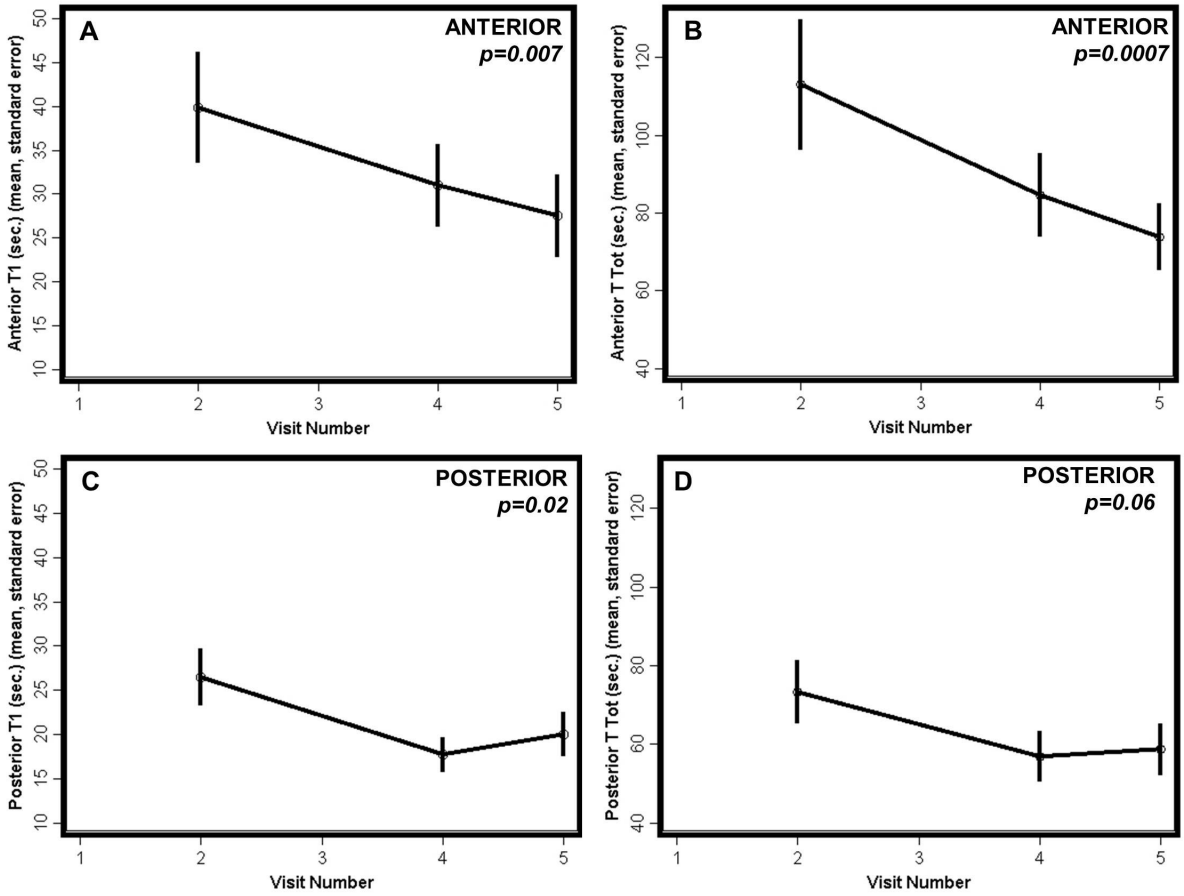
Figure 4—Changes in tongue strength with inhaled fluticasone treatment, at anterior **(A)** and posterior **(B)** locations.



A significant improvement in strength was seen with treatment at both anterior **(A)** (p = 0.02) and posterior **(B)** (p = 0.002) locations. Data are presented as mean ± standard error (SE).

(**Figure 3**, **Table S2**); (2) the individual response was dependent upon each subject's baseline characteristics, with older age, male gender and worse asthma control predicting a Pcrit deterioration (**Table 4**); (3) a pattern of changes in wakefulness tongue function similar to that observed in OSA patients, i.e., increased strength and reduced endurance emerged (**Figures 4** and **5**, **Table S2**), was unrelated to Pcrit response (**Tables 4** and **5**) and persisted with FP dose reduction (**Table S3**); (4) in 3 unselected subjects studied with MRI, fat content around the UAW structures increased but there were no changes in Pcrit

Figure 5—Changes in tongue endurance (first trial—T_1 and the sum of all 3 trials—T_{tot}) with inhaled fluticasone treatment, at anterior (A and B) and posterior (C and D) locations.



Tongue endurance significantly subsided at anterior location **(A)** (p = 0.007) and **(B)** (p = 0.0007); likewise, at the posterior location, endurance generally subsided **(C)** (p = 0.02) and **(D)** (p = 0.06). Data are presented as mean ± standard error (SE).

Table 5—Univariate analyses of changes from baseline in demographic, sleep, tongue and asthma measures, by Pcrit response groups.

Variable	Improved (n = 8)	Unchanged (n = 8)	Worsened (n = 2)
Pcrit (cm H_2O)	-10.02 ± 2.68	0.08 ± 0.50	4.0 ± 0.30*†
Holding pressure (cm H_2O)	-0.38 ± 0.64	0.13 ± 0.64	3.0 ± 1.27*
Anterior tongue strength (KPa)	7.63 ± 3.57	5.75 ± 3.09	-1.00 ± 16.00
Posterior tongue strength (KPa)	10.0 ± 5.36	7.88 ± 1.77	19.5 ± 11.5
Anterior tongue endurance (seconds) (T1)	-7.38 ± 3.86	-18.88 ± 9.77	-6.00 ± 15.0
Anterior tongue endurance (seconds) (T_{tot})	-25.38 ± 10.25	-56.88 ± 23.41	-25.00 ± 39.00
Posterior tongue endurance (seconds) (T1)	-3.88 ± 5.53	-7.25 ± 5.38	-13.50 ± 12.50
Posterior tongue endurance (seconds) (T_{tot})	-18.75 ± 17.11	-9.88 ± 10.70	-17.00 ± 14.00
ACQ short (symptoms and rescue β_2-agonist use)	-0.83 ± 0.09	-0.71 ± 0.21	-1.17 ± 0.50
FEV_1% predicted	5.00 ± 1.95	5.50 ± 1.66	5.50 ± 9.50
FEV_1(*100)/FVC	6.08 ± 1.51	2.99 ± 1.50	1.90 ± 2.69
FEF_{25-75} (L/s)	0.64 ± 0.12	0.49 ± 0.19	0.34 ± 0.47
SA-SDQ	-1.75 ± 0.77	1.00 ± 0.98	4.44 ± 2.0
BMI (kg/m^2)	0.13 ± 0.39	0.08 ± 0.30	-1.23 ± 0.05
Neck circumference (inches)	0.19 ± 0.07	0.10 ± 0.22	0.05 ± 0.05

Data are presented as mean ± SE; *p < 0.05 for worsened vs. improvement groups; †p < 0.05 for worsened vs. unchanged groups. Pcrit, critical closing pressure of the upper airway (derived); ACQ, Asthma Control Questionnaire; FEV_1, forced expiratory volume in first second of FVC maneuver; FVC, forced vital capacity; FEF_{25-75}, forced expiratory flow between 25% and 75% of vital capacity; SA-SDQ, Sleep Apnea scale of the Sleep Disorders Questionnaire; BMI, body mass index.

Table 6—Changes from baseline with FP treatment in fat content around the UAW structures, anthopometrics, Pcrit, asthma control indices, and tongue measures in the three subjects studied with MRI.

	Subject 1		Subject 2		Subject 3	
Variable	**Before**	**After**	**Before**	**After**	**Before**	**After**
Airway fat fraction (%)	20.7	22.6	19.3	21.9	14	20.6
Airway fat volume (mm^3)	35,532.3	36,321.4	30,346.2	31,911.7	16,777.5	27,164.8
BMI (kg/m^2)	34.43	34.87	35.30	34.54	27.46	26.78
Neck circumference (inches)	13.75	13.3	15.25	16.5	14	13.55
Pcrit (cm H_2O)	-9.4	-10.7	-2	-0.5	-9.7	-9.5
ACQ short (symptoms and rescue β_2-agonist use)	1.17	0.17	1.17	0.33	0.83	1.17
FEV_1% predicted	100	102	85	99	99	102
Anterior tongue strength (KPa)	62	69	84	90	66	64
Posterior tongue strength (KPa)	53	58	72	76	54	60
Anterior tongue endurance (seconds) (T_{tot})	75	53	48	79	129	72
Posterior tongue endurance (seconds) (T_{tot})	39	49	32	52	79	42

(**Table 6**). These findings suggest UAW responses to FP are dependent upon baseline characteristics, and determined by concomitant but reciprocally counteracting local and lower airway changes.

Patterns of Pcrit Responses to FP Therapy and Possible Explanations

We observed an overall improvement (more negative) in Pcrit with orally inhaled FP for 16 weeks. Although somewhat surprising, this observation provided us an opportunity to get more insight into the dynamic influences of FP on upper and lower airway function, as not all subjects responded the same, i.e., some improved, some remained unchanged and some deteriorated. These changes might not occur randomly but rather relate to various degrees of synchronous changes in the forces that regulate the upper airway patency during sleep[32,33]: (1) an improvement in UAW collapsibility may result from anti-inflammatory effects of FP, in the nose and in the lower airways. It is known that increased nasal resistance results in more negative intrapharyngeal pressure during inspiration which predisposes to oropharyngeal collapse.[34] It is possible that FP via either a topical effect (propulsion of residual particles to the nose, via mucociliary clearance) or systemic absorption[14] may have attenuated the nasal inflammation, and thereby the nasal resistance. Meanwhile, the improved lower airways obstruction, as suggested by asthma control indices including spirometric measures (**Tables 3** and **5**) would unload the UAW. During nocturnal asthma, the forced inspiration accentuates the negative intraluminal pressure, "sucking closed" the deformable UAW.[35] Additionally, the active contraction of the respiratory muscles during forced expiration could increase the pressure in the UAW surrounding tissues, causing the airway to collapse.[36,37] The observed improvement in lung mechanics could attenuate these effects, decreasing the Pcrit. Secondly, it could reduce the degree of hyperinflation, since resistance to airflow is inversely related to lung volumes.[38] Patients with nocturnal asthma, who start the night hyperinflated relative to controls, experience an augmented decline in functional residual capacity (FRC) to levels comparable to those of control subjects during REM sleep.[39] It is thus possible that the improved lung mechanics with FP also attenuated the degree of decline in FRC during sleep; the resultant increase in pharyngeal UAW tethering via tracheal tug could have rendered it stiffer,[40] thereby also improving the Pcrit. Further studies accounting for nasal resistance and sleep related changes in lower airway mechanics will be needed; (2) an unchanged Pcrit could result from above changes being offset by deleterious effects, discussed next; (3) a deterioration in Pcrit could result from a predominant increase in the surrounding tissue pressure, including fat accumulation, and from changes in the properties of UAW muscle, as suggested by our findings on the tongue discussed below. As shown by our MRI data (**Table 6**), FP may cause regional fat redistribution around the UAW, probably as a result of systemic absorption which has been shown particularly with the highly lipophilic fluorinated compounds.[14,41] And then, why did our subjects show different responses to the same treatment? The outcome might be determined yet by an interaction with several baseline predictors.

Predictors of Pcrit Response to FP

We observed a relationship of Pcrit response with age, such that older age (only 36 years on average!) was a predictor of Pcrit deterioration (**Table 4**). Likewise, male gender predicted Pcrit deterioration, while none of those young females with stiff UAW seemed deleteriously affected by FP. There is clear recognition of male gender predominance of OSA and that women, while protected when premenopausal (as all our female patients were), catch up in OSA risk at menopause[42]; however, why men unfortunately suffer a "double hit" when exposed to FP, and how the many asthmatic women on ICS change around the menopause remains to be studied. Also, baseline asthma control, defined by ACQ score—a composite measure that includes daytime and nighttime symptoms—related to worsening Pcrit (**Table 4**). These observations suggest the UAW of older, male, and of those individuals with less controlled asthma may be more prone to detrimental FP effects. The lack of significant associations of Pcrit response with other demographics (BMI, neck size), baseline PSG and spirometric measures does not negate their potential role (especially as trends already emerged—**Table 4**), and rather reflects small sample size

and variability inherent to human physiology and differences between sleep vs. wakefulness lung measures, which could be better understood in larger studies.

Changes in the Tongue Function in Response to FP Therapy and Possible Mechanisms

FP increased tongue strength and reduced its endurance (**Figures 4** and **5**, **Table S2**), which persisted during the run-out period (**Table S3**). We believe a dual effect underlies these findings: (1) the improved strength may be related to some degree of transient muscle fiber hypertrophy. Tongue hypertrophy has been reported in children treated with ICS,[43,44] as soon as 4-7 weeks into treatment.[44] This effect is believed to be partly due to muscle fiber hypertrophy[43,44]; (2) the reduced endurance could reflect incipient functional deficits, building-up as a result of differential effects on the tissue compartments comprising the tongue, such as (a) unmasked preexistent inflammation-induced remodeling/dysfunction, and/or (b) a direct drug effect on the muscle fibers. Patients with asthma frequently have UAW inflammation, which often extends distally to the pharyngeal area. Inflammation in the pharyngeal UAW has been linked to profibrotic cytokines and collagen deposition.[45] Collectively, these observations suggest that sustained inflammation leads to UAW remodeling which could adversely affect tissue compliance and/or its mechanical coupling, translating into impaired ability to sustain increased demands.[45]

How ICS impact the structure and function of skeletal muscles, such as those of the pharyngeal UAW, remains to be studied. However, a myopathic effect of the vocal cords adductors is believed to underlie the bowing of the vocal cords on phonation observed in patients with ICS-induced dysphonia.[13] In the only prospective study to date, such an effect on this small muscle developed in 7-12 weeks, was dose-dependent, resolved in one month, but resumed with reinitiating the drug.[13] This finding may mirror other UAW muscles alterations in response to our intervention with FP. Interestingly, a more recent study of untreated OSA patients reported a pattern of wakefulness tongue function changes[46] similar to that observed in our study, i.e., these patients, relative to controls, demonstrated greater maximal protrusive force but shorter time to task failure. These functional alterations have as histological substrate a shift from type I (slow twitch—low force, fatigue resistant) to type II (fast twitch—high force, fatigue prone) muscle fibers,[47,48] and are believed to be an adaptive mechanism to the increased contractile demands on the dilator.[46] Was a similar pathology involved in our subjects? Further work needs to be done to answer this question.

Possible Long-Term Interactions of FP Effects

We only investigated the UAW collapsibility at a point when subjects had received 16 weeks of ICS treatment, which is relatively short comparing to clinical practice where this therapy is usually chronic, in some cases lifelong. Corroborating with the overall effects on the tongue (**Figures 4** and **5**) and their lack of an association with Pcrit responses (**Tables 4** and **5**), and the fat accumulation observed in the 3 subjects (**Table 6**) lends us to speculate that, in time, the pharyngeal UAW patency may overall shift towards a detrimental pattern with important clinical implications, such that: (1) short-term, anti-inflammatory effects and transient muscle fiber hypertrophy may predominate, and these "protective processes" maintain the UAW patent. However, fiber atrophy and shifts in the type of fibers comprising the genioglossus (and possibly other UAW dilators), along with surrounding UAW fat, concomitantly start to build-up, resulting in some functional deficits as observed in the present study; and (2) long-term, these "non-protective processes" along with the airway remodeling, may eventually take a more prominent role overall, rendering the muscle less efficient to compensate when faced with increased demands particularly during sleep, setting the stage for SDB/OSA. Additionally, these latter changes could have implications for other UAW functions, such as mastication and deglutition, functions of particular importance to the respiratory patient.

Limitations of the Study

Despite our study's novelty, we acknowledge a number of limitations. First, we were unsuccessful at securing placebo MDI, and the lack of a control group raises the possibility that our findings may reflect natural history of UAW in asthma. However, we doubt that this encompasses spontaneous improvement in UAW mechanics over four months. Furthermore, the night-to-night variability in passive Pcrit measurement has been shown to be nonsignificant,[28] such that, we believe the Pcrit changes we observed are due to the FP intervention. Additionally, we note that, albeit at a lower dose, FP has been continued throughout run-out in nearly half of subjects; although the LSE changes may seem to have continued during this phase (**Table S3**), their magnitude was less than that achieved during the treatment (**Table S2**), and not significantly different from the treatment period (**Table S2**). These observations indicate that the ICS dose used during run-out may have been sufficient to maintain the tongue functional changes, and perhaps, once established, the FP effect may no longer be dose-dependent. Certainly, future studies should step up the efforts for randomizing to a placebo or other control group. Second, the characteristics of the sample, with a narrow range of critical demographics, i.e., age, BMI, and "healthy" baseline characteristics (Pcrit, ACQ and FEV_1), precludes extension of these findings to asthma subjects who are older, male, heavier, and have less controlled asthma and physiology, and who are also more likely to receive ICS therapy. Our subgroup data, albeit small, suggest these patients are most vulnerable to detrimental UAW effects. Further studies including a wider range of such characteristics, will be needed. Third, we recognize that four months of therapy is relatively brief considering the prolonged duration of treatment that is generally provided to patients with asthma suffering from chronic airway inflammation. Thus, we can only speculate and refrain from drawing any firm conclusions regarding what many years of ICS therapy may do to the pharyngeal UAW. The duration of treatment may prove to be important in this interaction. It may also explain the somewhat discrepant previous dose-dependent association of ICS with habitual snoring and OSA risk noted in a clinic-based sample,[12] where ICS exposure may have been much longer than the four months tested in this study. We certainly encourage longer-term studies to assess these effects and underlying mechanisms. Last, the clinical impact of these changes on severity of SDB was not tested. Thus, gaining understanding of clinical significance of these physiologic and anatomic findings remains an

interesting area of investigation. Despite these limitations, this initial pilot study opens the door for an array of clinical and mechanistic investigations. Such studies will be most feasible with multicenter efforts, owing to the inherent challenges to recruitment in sufficient numbers of subjects suitable for this kind of research.

In summary, this first, short-term study of otherwise healthy, young subjects with mild asthma and stiff UAW, suggests responses in the UAW collapsibility during sleep may be dependent upon baseline characteristics, and underlined by anti-inflammatory, direct tissue/muscle effects, and fat redistribution to the neck. We wish to caution that no firm conclusions can be drawn from these data; however, they are intriguing enough to lay the foundation for future larger and longer studies including patients with wider range of important baseline characteristics and detailed upper and lower airway assessments, to better understand these effects, as well as their long-term impact on OSA risk and other UAW functions.

ABBREVIATIONS

ACQ, Asthma Control Questionnaire
AQLQs, Standardized Asthma Quality of Life Questionnaire
AHI, apnea-hypopnea index
BMI, body mass index (in kilograms per meter squared)
CI, confidence interval
CPAP, continuous positive airway pressure
ESS, Epworth Sleepiness Scale
FEF_{25-75}, forced expiratory flow between 25% and 75% of vital capacity
FEV_1, forced expiratory volume in first second
FP, orally inhaled fluticasone propionate via metered dose inhaler
FVC, forced vital capacity
FRC, functional residual capacity
ICS, inhaled corticosteroid
IDEAL-FSE, iterative decomposition of water and fat with echo asymmetry and least squares estimation fast spin-echo (imaging method for fat)
IOPI, Iowa Oral Performance Instrument
KPa, Kilopascals
LABA, long-acting β_2-agonist
LSE, lingual strength and endurance, measured with the IOPI
MDI, metered dose inhaler
MID, minimal clinically important difference
MRI, magnetic resonance imaging of the upper airway
NAEPP, National Asthma Education and Prevention Program
OAI, obstructive apnea index
OR, odds ratio
OSA, obstructive sleep apnea
PEF, peak expiratory flow rate
PC20, the provocative concentration of methacholine, necessary to produce a 20% fall in FEV_1
Pcrit, critical closing pressure of the upper airway (passive)
Pmax, maximum isometric pressure of the tongue
PSG, polysomnography (laboratory-based sleep study)
PSQI, Pittsburgh Sleep Quality Index
SA-SDQ, Sleep Apnea scale of the Sleep Disorders Questionnaire
SD, standard deviation
SDB, sleep disordered breathing
SE, standard error of the mean
Ttot, Time (in seconds) able to maintain 50% Pmax across 3 trials (T1+T2+T3)
UAW, upper airway

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Supplemental Material

METHODS

Subject Inclusion and Exclusion Criteria

Subjects with an asthma diagnosis were enrolled. This diagnosis was confirmed either by bronchodilator reversibility (≥ 12% improvement in FEV_1 following 2 puffs of albuterol) or a provocative concentration of methacholine needed to produce a 20% fall in FEV_1 (PC20) ≤ 8 mg/mL. Subjects had symptoms consistent with National Asthma Education and Prevention Program (NAEPP) asthma severity step ≥ 2,[1] and an FEV_1 ≥ 60% predicted.

Exclusion criteria included: 1) use of inhaled corticosteroid for > 2 weeks at a time during the prior 6 months, or any use in the last 6 weeks; 2) any oral or systemic corticosteroid use in the last 6 months; 3) as needed use of nasal steroids in the prior 6 months; 4) recent exacerbation or respiratory tract infection; 5) diagnosed osteopenia or osteoporosis; 6) unstable medical or psychiatric illness; 7) BMI > 40 kg/m^2; 7) treated OSA or new diagnosis of OSA (obstructive apnea index [OAI] > 10 events/h or desaturation < 70% on PSG); 8) established diagnosis of neuromuscular disease; 9) medications affecting breathing control; 10) current smoking or overall tobacco use ≥ 10 pack-years.

Step-Down Schedule in the Inhaled Fluticasone Propionate (FP) Dose during the Run-Out Period

At the end of 16-week treatment phase, in all subjects, the FP dose was reduced to 880 mcg/day. Subjects continued this dose for the following 2 weeks. Thereafter, the doses were further adjusted based on the ACQ score, using the validated cutoffs for level of control.[2] At the 2-week phone-call, the dose was adjusted based on the score on ACQ (version with symptoms and rescue bronchodilator use)[3] administered via phone, according to the following schedule: (1) if ACQ was ≤ 0.75, the FP was discontinued; (2) for ACQ > 0.75 and < 1.5, the FP dose was reduced to 440 mcg/day; (3) for ACQ ≥ 1.5, the FP 880 mcg/day was maintained. These doses were prescribed for the reminder of the study.

At the exit visit (V6), the dose was adjusted based on full ACQ (symptoms, rescue bronchodilator use and FEV_1%) and subjects were transitioned to clinical care.[4] For those who had been off FP and remained well controlled (ACQ ≤ 0.75) at this visit, no further therapeutic steps were taken. For those in whom FP had not been discontinued during run-out, if at V6: (1) control has been maintained (ACQ ≤ 0.75), no FP was prescribed; (2) ACQ > 0.75 and < 1.5, FP 440 mcg/day was prescribed; and (3) ACQ remained ≥ 1.5, the FP was maintained/changed to 880 mcg/day.

Experimental Set-Up for Sleep Studies

Nocturnal polysomnogram (PSG) was obtained only at baseline (V2), for the purpose of evaluating subjects' eligibility. It was recorded on Grass Technologies systems (Astro-Med, Inc., West Warwick, RI), following standard criteria.[5] The montage included electroencephalogram (F3-A2, F4-A1, C3-A2, C4-A1, O1-A2, and O2-A1), bilateral electroculograms, bipolar chin and anterior tibialis electromyograms, 2 electrocardiographic (ECG) leads, snore microphone, nasal and oral airflow (thermocouples), nasal pressure cannula (Pro-Tech, Woodinville, WA), thoracic and abdominal excursions (Pro-Tech zRIP system, Pro-Tech Services, Inc., Mukilteo, WA), and finger oximetry.

For Pcrit studies, we used a previously described set-up,[6] with the exception that subjects wore a tight-fitting nasal mask (Respironics, Inc., Murrysville, PA) connected to a modified CPAP device (Respironics Inc. Murrysville, PA) that delivered both negative and positive (-20 to 20 cm H_2O) pressures. For each subject, the same mask was applied with each study. If mouth breathing occurred, this was further prevented by sealing the mouth with waterproof tape. To prevent rebreathing, a leak was induced by inserting a leak valve in series above the pneumotachometer. Prior to each study, oxymetazoline hydrochloride 0.05%, 2 sprays in each nostril, was applied to reduce nasal congestion, and as previously reported, zolpidem 10 mg was administered to facilitate sleep and to suppress arousals.[6] To assure comparable conditions, for each subject, the same nasal and hypnotic treatments were administered at the post-treatment study. A recent study with a benzodiazepine systemic sedative (midazolam) demonstrated similar Pcrit measurements during natural and drug-induced sleep (-0.82 ± -3.44 and -0.97 ± -3.21 cm H_2O, p = 0.663), which were highly associated (intraclass correlation coefficient = 0.92; 95% confidence interval, 0.78-0.97, p < 0.001), and both measurements similarly correlated with obstructive sleep apnea severity.[7] We measured Pcrit during stable N2 and N3 sleep, as we previously reported,[6] and also in light of the fact that a previous study has shown no significant influences of N2 vs. slow wave sleep on Pcrit.[8] Measurements were obtained with the subject supine, and the head in a contoured pillow to assure constant position.

Experimental Protocol for Pcrit Studies

As in our previous report,[6] CPAP was incremented by 1 cm H_2O/min during stable NREM sleep, to eliminate flow limitation. This (holding) pressure was maintained or adjusted as necessary during the study. Following 5 min of stable N2-N3 sleep, the nasal pressure was lowered during exhalation by 1 cm H_2O for 5-6 breaths, and then returned to the holding pressure for one minute before dropping to the next lower level. We repeated this sequence until airflow ceased (Pcrit) or arousal occurred. Another set of measurements was then taken by gradually increasing the mask pressure from Pcrit (i.e., Pcrit+1; Pcrit+2 cm H_2O), back up to initial pressure drop.[9] Multiple trials were attempted in each subject, each night.[6]

Lingual Strength and Endurance (LSE) Assessment

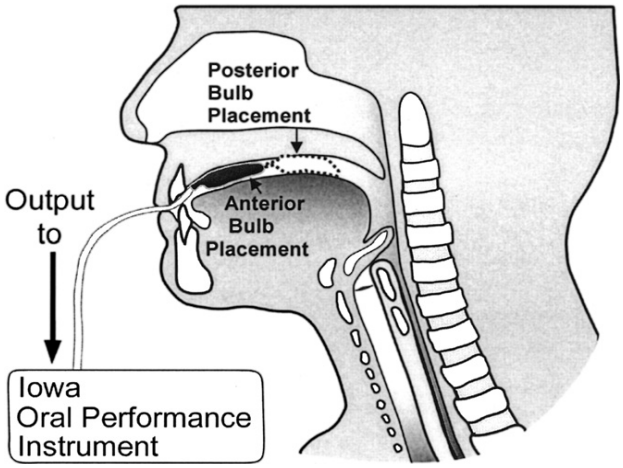
Measurements were performed as previously published,[10] using the Iowa Oral Performance Instrument (IOPI) (IOPI Medical LLC, Carnation, WA). In brief, the IOPI has a standard-sized air-filled polymer balloon, called tongue sensor or bulb, which is inserted between the tongue blade and the roof of the mouth. The tube is connected by a tube to the IOPI device. The pressure generated (measured in KiloPascals) is displayed on a large, easy to read vertical array of colored light-emitting diodes (LED) screen. During endurance testing, visual feedback is provided to subjects by these

lights which signify linear increments, such that the uppermost red light represents the maximum pressure boundary, and the middle green light represents 50% of the pressure scale. Subjects were seated upright with the torso and neck erect. Measurements at the anterior (operationally defined as 10 mm posterior to the tongue tip) and posterior (operationally defined as 10 mm anterior to the most posterior circumvallate papilla) portions of the tongue (**Figure S1**)[11] were obtained, to account for regional differences in tongue muscle composition, marked by a greater percentage of muscle tissue in the posterior tongue.

For tongue strength, subjects were asked to "press your tongue against the bulb as hard as possible…push, push, push." Sets of 3 trials were collected, first at anterior tongue location, and subjects were allowed to rest approximately 30 sec between trials. Subject's maximum pressure (Pmax) was identified as the highest value from 2 sets with the averages of the sets differing by ≤ 5%, to account for natural variability. If the trials were not within 5% of each other, further trials were allowed until 2 values within 5% were to be produced. The average (± SE) number of trials performed across all visits was 2.3 ± 0.1 and 2.6 ± 0.2, at anterior and posterior locations, respectively; no subject required more than 4 trials at each location, on any of the study visit.

After the tongue strength was determined, the bulb was repositioned to the anterior tongue to measure its endurance. Tongue endurance was defined as the time (in seconds) that subject maintained 50% of the Pmax. The maximum pressure on IOPI was set to the Pmax obtained at each location during

Figure S1—Positioning of the IOPI air-filled bulb at the anterior and posterior tongue locations.



Reproduced from Robbins J, et al.[11] with permission from The American Congress of Rehabilitation Medicine.

Table S1—Magnetic resolution imaging scans parameters

T1/T2	Plane	TR/TE (milliseconds)	FOV (cm)	Thickness/ Gap (mm)
T1	Axial	4000/12	22 × 20	4.0/1.0
	Sagittal	5455/12	22 × 22	4.0/1.0
T2	Axial	10909/96.3	22 × 20	4.0/1.0
	Sagittal	7059/96.3	22 × 20	4.0/1.0

TR, repetition time; TE, echo time; FOV, field of view.

Table S2—Changes pre/post treatment in Pcrit, and for the entire treatment period in sleep and tongue variables, and anthropometrics

	Pre-treatment Mean ± SE or n (%)	Post-treatment (% change from pre-treatment) Mean ± SE or n (%)	Effect Change (95% CI)*	p-value
Pcrit (cmH_2O)	-8.2 ± 1.1	-12.2 ± 2.2 (77.8 ± 48.8)	-4.00 (-7.73, -0.23)	0.04
SA-SDQ	21.2 ± 0.9	20.8 ± 1.3 (-1.4 ± 3.0)	-0.17 (-1.39, 1.05)	0.33
PSQI	4.9 ± 0.6	4.1 ± 0.6 (-15.1 ± 10.8)	-0.83 (-1.73, 0.06)	0.10
ESS	7.9 ± 1.0	6.4 ± 1.1 (-13.6 ± 10.6)	-1.44 (-2.64, -0.25)	0.12
Anterior tongue strength (KPa)	52.9 ± 3.7	58.7 ± 4.0 (14.6 ± 5.9)	5.83 (1.61, 10.06)	0.02
Posterior tongue strength (KPa)	40.9 ± 3.6	51.0 ± 3.1 (35.8 ± 11.5)	10.11 (4.85, 15.37)	0.002
Anterior tongue endurance (T1) (seconds)	39.8 ± 6.3	27.5 ± 4.7 (-18.4 ± 10.3)	-12.33 (-19.94, -4.73)	0.007
Anterior tongue endurance (T_{tot}) (seconds)	113.0 ± 16.8	73.7 ± 8.6 (-22.5 ± 8.7)	-39.33 (-58.70, -19.96)	0.0007
Posterior tongue endurance (T1) (seconds)	26.4 ± 3.3	20.0 ± 2.5 (-12.5 ± 10.5)	-6.44 (-12.52, 0.36)	0.02
Posterior tongue endurance (T_{tot}) (seconds)	73.3 ± 8.0	58.7 ± 6.6 (-10.6 ± 9.9)	-14.61 (-29.67, 0.45)	0.06
BMI (kg/m^2)	26.8 ± 1.3	26.7 ± 1.3 (0.1 ± 1.2)	0.11 (-0.32, 0.54)	0.96
Neck circumference (inches)	13.9 ± 0.4	14.0 ± 0.4 (1.0 ± 0.7)	0.14 (-0.06, 0.33)	0.50
Self-reported snoring				
Any	12 (67%)	8 (44%)	-	0.10
Habitual (≥ 3 nights/week)	5 (28%)	2 (11%)	-	0.08
Self-reported nocturnal nasal congestion				
Any	11 (61%)	7 (39%)	-	0.05
Habitual (≥ 3 nights/week)	6 (33%)	3 (17%)	-	0.08

SE, standard error; Pcrit, critical closing pressure of the upper airway (derived); SA-SDQ, Sleep Apnea scale of the Sleep Disorders Questionnaire; PSQI, Pittsburgh Sleep Quality Index; ESS, Epworth Sleepiness Scale. *Changes for continuous variables across the entire period.

Table S3—Changes in scores on asthma control indices, sleep questionnaires, tongue measures, and anthropometrics during the run-out relative to the treatment period

Variable	Post-treatment, at V5 Mean ± SE or n (%)	Final run-out, at V6 (% change from V5) Mean ± SE or n (%)	Changes relative to the treatment period*		
			Estimate	SE	p-value
ACQ short (symptoms and rescue β_2-agonist use)	0.4 ± 0.1	0.4 ± 0.1 (-17.3 ± 13.6)	-0.38	0.34	0.27
AM PEF (L/min) (diary)	481.2 ± 17.9	481.7 ± 16.9 (-0.2 ± 0.8)	0.40	54.62	0.99
PM PEF (L/min) (diary)	479.4 ± 17.3	483.6 ± 17.3 (0.7 ± 0.6)	10.97	53.88	0.84
PEF variability	4.7 ± 0.6	3.6 ± 0.4 (-3.9 ± 8.2)	-2.99	2.13	0.17
AM symptoms (diary)	0.4 ± 0.2	0.3 ± 0.2 (26.9 ± 18.7)	0.03	0.58	0.96
PM symptoms (diary)	0.5 ± 0.2	0.4 ± 0.1 (-4.7 ± 10.5)	-0.34	0.72	0.64
Rescue β2-agonist (# actuations) (diary)	0.1 ± 0.1	0.1 ± 0.1 (-6.3 ± 7.2)	0.18	0.25	0.47
FEV_1 (%)	94.1 ± 1.9	93.3 ± 2.2 (-1.0 ± 0.9)	-1.67	4.79	0.73
FEV_1 (L)	3.5 ± 0.1	3.5 ± 0.1 (-0.9 ± 0.9)	-0.06	0.24	0.81
FVC (L)	4.2 ± 0.1	4.2 ± 0.1 (1.0 ± 0.9)	0.02	0.33	0.96
FEV_1/FVC	83.4 ± 1.3	81.8 ± 1.2 (-1.9 ± 0.7)	-2.03	3.36	0.55
FEF_{2575} (L/s)	3.6 ± 0.2	3.5 ± 0.2 (-4.2 ± 1.8)	-0.21	0.46	0.65
AQLQ	6.6 ± 0.1	6.6 ± 0.1 (0.02 ± 1.1)	0.26	0.30	0.39
SA-SDQ	20.8 ± 1.3	20.0 ± 1.2 (-2.8 ± 3.8)	-1.61	4.47	0.72
PSQI score	4.1 ± 0.6	3.6 ± 0.5 (11.4 ± 17.1)	-1.29	2.15	0.55
ESS score	6.4 ± 1.1	6.1 ± 0.9 (5.8 ± 18.0)	-2.33	3.35	0.49
Anterior tongue strength (KPa)	58.7 ± 4.0	61.0 ± 3.6 (5.2 ± 2.4)	5.22	9.23	0.57
Posterior tongue strength (KPa)	51.0 ± 3.1	54.7 ± 2.6 (9.4 ± 3.4)	10.67	7.75	0.17
Anterior tongue endurance (T1) (seconds)	27.5 ± 4.7	22.8 ± 2.4 (-7.1 ± 5.3)	-12.80	12.06	0.29
Anterior tongue endurance (T_{tot}) (seconds)	73.7 ± 8.6	65.5 ± 5.6 (-6.4 ± 3.9)	-27.23	28.29	0.34
Posterior tongue endurance (T1) (seconds)	20.0 ± 2.5	16.1 ± 1.4 (-6.0 ± 6.6)	-5.61	6.02	0.35
Posterior tongue endurance (T_{tot}) (seconds)	58.7 ± 6.6	47.8 ± 4.1 (-10.7 ± 4.7)	-20.19	15.93	0.21
BMI (kg/m^2)	26.7 ± 1.3	25.5 ± 1.8 (-0.5 ± 0.5)	-0.55	4.23	0.90
Neck circumference (inches)	14.0 ± 0.4	14.0 ± 0.4 (-0.2 ± 0.7)	0.01	1.27	0.99
Self-reported snoring					
Any	8 (44%)	7 (39%)	0.06	0.39	0.71
Habitual (≥ 3 nights/week)	2 (11%)	3 (17%)	0.00	0.32	0.56
Self-reported nocturnal nasal congestion					
Any	7 (39%)	8 (44%)	0.00	0.40	0.56
Habitual (≥ 3 nights/week)	3 (17%)	4 (22%)	-0.11	0.35	0.32

*With adjustment for % reduction in cumulative fluticasone dose used relative to the treatment period. SE, standard error; ACQ, Asthma Control Questionnaire; PEF, peak expiratory flow; FEV_1, forced expiratory volume in first second of FVC maneuver; FVC, forced vital capacity; FEF_{25-75}, forced expiratory flow between 25% and 75% of vital capacity; AQLQ(s), standardized version of the Asthma Quality of Life Questionnaire; SA-SDQ, Sleep Apnea scale of the Sleep Disorders Questionnaire; PSQI, Pittsburgh Sleep Quality Index; ESS, Epworth Sleepiness Scale; BMI, body mass index.

that session, such that the middle green LED on the IOPI was programmed to represent the target 50% value. Subjects were read each time to "press your tongue against the bulb keeping the green light on as long as possible. As soon as you drop below the green light, stop pressing and relax." Three trials separated by 30 seconds of rest were obtained at each location.[12]

Magnetic Resonance Imaging (MRI)

Iterative decomposition of water and fat with echo asymmetry and least squares estimation fast spin-echo (IDEAL-FSE) is a chemical shift based fat-water separation method our group has developed to delineate fat-containing anatomy. As compared with conventional MRI, this technique provided robust water-fat separation in multiple regions of the body, including in the head, neck, and tongue.[13-17]

The method acquires three images at slightly different echo times and uses an iterative algorithm to estimate the local inhomogeneity in the magnetic field. Phase shifts created by the field inhomogeneity are then demodulated from the three images and finally, a least squares pseudoinverse operation is performed to make final estimates of water and fat, free from the effects of field inhomogeneities. The separated water and fat images are perfectly co-registered and can be recombined into "in-phase" (water+fat), and "out-of-phase" (water-fat) images. Separate fat fraction axial images are then computed for T2-weighted IDEAL images.

Scans were acquired on a 3.0 Tesla MR750 scanner (GE Healthcare, Waukesha, WI) with an 8-channel neurovascular phased array coil. Sagittal and axial T1 and T2 end-expiratory gated images were obtained with a 4.0-mm thickness (and

1.0-mm skip), a 384 × 224 matrix, ± 41.7 kHz bandwidth and the other parameters for each plane shown in **Table S1**. Subjects were positioned supine with the head in neutral anatomic Frankfort plane,[18] while the coil ensured no head movement. Studies were performed during wakefulness, ensured by frequent communication. Earphones provided a computer-generated sound to coach the subjects who were instructed to breathe exclusively through the nose with the mouth closed, and to avoid swallowing, speaking, or movements. On return visits, studies were replicated with the subject in the same position, using the same set-up and anatomical landmarks.

PSG Scoring and Pcrit Data Analysis

Sleep (in 30-sec epochs) and respiration were scored according to standard criteria.[5] Obstructive apnea was defined as cessation or decrease in airflow by 90% for ≥ 10 sec associated with continued or increased inspiratory effort. Central apnea was separated based on absence of inspiratory effort. Hypopnea was defined as a decrease in nasal pressure signal excursions ≥ 50% for ≥ 10 sec, associated with an arousal and/or oxygen desaturation ≥ 3%. Respiratory effort-related arousal (RERA) was scored when in the absence of a hypopnea, a sequence of breaths occurs, lasting at least 10 sec characterized by increasing respiratory effort or flattening of nasal pressure waveform leading to an arousal. Standard parameters (apnea-hypopnea index—AHI, RDI respiratory disturbance index—RDI and minimum oxygen saturation) were generated.

Data from Pcrit studies was processed off-line using custom made software, as previously described.[6] Absolute Pcrit, defined as the mask pressure which induced apnea, was achieved in 13 (72%) subjects on both pre- and post-treatment studies. In all subjects, the derived Pcrit was determined from peak inspiratory flow-UAW pressure relationships, as we previously published.[6] Peak inspiratory flow from each of the 3rd to 5th breaths with unambiguous flow limitation during reduction in CPAP was plotted against the measured mask pressure. Pcrit was derived by the zero-flow intercept from the least-square linear regression of maximal flow vs. mask pressure. For each study, data were collected from flow-limited breaths with no associated arousal, obtained from all Pcrit trials. The derived and absolute Pcrit were highly correlated (*rho* = 0.95, $p < 0.0001$), and since derived Pcrit was available in all subjects, it was used as the outcome measure in all subsequent analyses.

MRI Data Analysis

Using the Amira software (Visualization Sciences Group, Burlington, MA) and water image for anatomical demarcation, a rectangular region of interest (ROI) was fitted on each axial slice anterior to the vertebral bodies, posterior to the base of the tongue and medial to the mandibles. This ROI was superimposed on the fat fraction image and then the image analysis software computed a mean fat fraction for the ROI. This was averaged across all applicable slices to determine the mean fat fraction for the entire structure. To assess total UAW fat volume, we computed the area of fat in each slice by multiplying the mean fat fraction by area of the ROI. The total fat volume was derived via summation of the individual slice fat areas multiplied by slice thickness. For consistency, on repeat studies, the same ROI was replicated on each slice, a feature that the software allows.

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