

Comparative effects of hydrofluoroalkane and chlorofluorocarbon beclomethasone dipropionate inhalation on small airways: Assessment with functional helical thin-section computed tomography

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A double-blind, randomized, parallel-group pilot study compared the relative efficacy of hydrofluoroalkane-134a beclomethasone dipropionate (HFA-BDP [QVAR]); mass median aerodynamic diameter, 0.8-1.2 μ m) versus chlorofluorocarbon-11/12 BDP (CFC-BDP [Beclonvent]; mass median aerodynamic diameter, 3.5-4.0 μ m) in 31 steroid naive patients with mild to moderate asthma (PC_{20} , 4 mg/mL). Functional high-resolution computed tomography was used to assess the relative efficacy of HFA-BDP and CFC-BDP on regional air trapping, as an indirect measure of small airways function and on regional hyperactivity. Pretreatment functional computed tomography was performed at residual volume before and after methacholine challenge. After 4 weeks of treatment, functional imaging was repeated before and after the same concentration of methacholine that was administered before the treatment ($n = 19$ patients). Quantitative assessment of changes in distribution of lung attenuation was performed. After 4 weeks of treatment, the HFA-BDP group showed significantly more improvement in air trapping overall (a shift in the lung attenuation curve at residual volume toward more attenuation) on the posttreatment computed tomography scan ($P < .05$; Fisher's Exact Test). After an equal constrictor stimulus (methacholine concentration), subjects treated with HFA-BDP ($n = 10$ patients) showed less increase in air trapping overall than subjects treated with CFC-BDP ($n = 9$ patients) on the posttreatment scans compared with the pretreatment scans ($P < .001$; Fisher's Exact Test). No significant difference was demonstrated between the 2 treatment groups with respect to improvement in symptoms, spirometry, or methacholine responsiveness assessed by FEV_1 , except for a greater reduction in breathlessness in the HFA-BDP group ($P < .05$). We conclude that HFA-BDP may have greater efficacy in the peripheral airways and that this effect is better assessed with functional imaging computed tomography techniques than with conventional physiologic tests. (*J Allergy Clin Immunol* 1999;104:S258-67.)

Key words: Hydrofluoroalkane, chlorofluorocarbon, beclomethasone dipropionate, asthma, small airways, thin-section computed tomography

Inhaled corticosteroids are recognized as the premiere therapeutic agents for the control of persistent asthma.¹ However, the effectiveness of these agents is often compromised by poor adherence and incorrect inhaler technique that results in inadequate drug delivery to the lung.² Moreover, even with optimal technique, only approximately 10% of steroid aerosols generated from chlorofluorocarbon-based metered dose inhalers reach the lower respiratory tract, and most of the medication delivered to the lung is deposited in the large central airways.³ These observations suggest that conventional inhaled corticosteroids may have limited effectiveness in suppressing inflammation in and improving patency of the small airways in asthma.

The small airways (defined as bronchial passages less than 2 mm in diameter, located beyond the 7th or 8th generation of the tracheobronchial tree) are now recognized to be significantly affected in asthma. Wagner et al⁴ demonstrated more than 7-fold increases in small airways resistance even in asymptomatic asthma with normal spirometry and normal plethysmographic airway resistance. Synek et al⁵ documented the presence of significant inflammation in both large and small airways. Airway-wall remodeling, potentially leading to a component of fixed airflow obstruction, has also been shown to occur in small airways.^{6,7} Although the full clinical significance of the small airways in asthma is not yet known, it is possible that poorly controlled inflammation in peripheral airways that are not penetrated by conventional inhaled corticosteroids could contribute to the accelerated decline in lung function with age that has been documented in asthma.⁸

The small airways cannot be visualized directly with current radiographic techniques. However, they can be assessed indirectly with high-resolution computed tomography (HRCT).^{9,10} Obstruction of small airways, even in mild asthma, results in air trapping and regional hyperinflation. Regional hyperinflation can be assessed through dynamic HRCT analysis of lung attenuation

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TABLE I. Study design*

Tests and procedures	Screening visits		Treatment phase	
	1	2 (Day 1)	3 (Day 15)	4 (Day 29)
Visits				
Screening procedures	X	—	—	—
Spirometry	X	X	—	X
Methacholine challenge	X	X	—	X
Training in press and breathe inhaler technique	X	—	—	—
HRCT for quantitation of regional air trapping	—	X	—	X
Diaries/peak expiratory flow rate	X	X	X	X

X, performed at visit.

*Double-blind, placebo-controlled, double-dummy.

Abbreviations used

CFC-BDP:	Chlorofluorocarbon–beclomethasone dipropionate
FOV:	Field of view
FRC:	Functional residual capacity
HFA-BDP:	Hydrofluoroalkane–beclomethasone dipropionate
HRCT:	High-resolution computed tomography
LAC:	Lung attenuation curve
MMAD:	Mass median aerodynamic diameter
RV:	Residual volume

curves (LACs), which depict the distribution of lung attenuation in a region of interest. Acquired during different phases of suspended respiration or under different physiologic conditions, LACs represent a new method for studying the relationships between airway structure, function, and therapeutic efficacy. A shift in the LAC at a given standardized lung volume (usually residual volume [RV]) to the left (ie, to lower attenuation) reflects air trapping, whereas a shift to the right (ie, to higher attenuation) reflects improvement in air trapping that in the correct setting can be attributed to therapeutic efficacy. LAC measures have recently been shown to be more sensitive than traditional spirometry in the detection of peripheral airways dysfunction and hyperreactivity and regional changes in small airways function.¹⁰

Beclomethasone (BDP) reformulated with the alternative propellant, hydrofluoroalkane-134a (HFA), results in a solution preparation that delivers an aerosol with a much smaller particle size (mass median aerodynamic diameter [MMAD], 0.8–1.2 μ m) than that of the suspension aerosols generated by conventional chlorofluorocarbon 11/12 (CFC)-based metered dose inhalers of BDP (MMAD, 3.5–4 μ m). Mathematical models predict that the extra-fine particles of the HFA preparation would deposit more peripherally in the lung than the coarser particles of the CFC-generated aerosols, as supported by lung deposition studies.¹¹ The availability of an extra-fine corticosteroid aerosol raises the possibility of more effective delivery of inhaled anti-inflammatory medication to the lung periphery in asthmatic patients and thus more effective suppression of inflammation and improved function of the small airways in asthma.

We hypothesized that, compared with a CFC-based inhaled corticosteroid (BDP [Beclovent]), HFA-BDP (QVAR) administered in the same low dose (50 μ g/puff ex-valve, 2 puffs twice daily) would lead to greater improvement in small airways patency in patients with mild-to-moderate persistent asthma (FEV_1 , $\geq 60\%$ predicted; PC_{20} , ≤ 4 mg/mL) after a 1-month course of treatment. Because serial changes in small airways function are difficult to measure physiologically and to distinguish from concomitant changes in larger airways¹², we assessed changes in small airways patency indirectly using a validated thoracic HRCT technique for quantitating changes in regional hyperinflation.^{9,10}

MATERIAL AND METHODS

Subjects

Thirty-four subjects who were 19 to 56 years of age (50% male) with a clinical history of asthma were studied. Inclusion criteria at screening (visit 1) included a FEV_1 between 60% and 90% of predicted,¹³ a positive methacholine challenge test (PC_{20} , ≤ 4 mg/mL), use of an inhaled β -agonist bronchodilator for asthma symptom relief as needed, nonuse of tobacco for 1 year, a less than 10 pack-per-year lifetime smoking history, and a willingness to complete the study. Additional inclusion criteria included a positive methacholine challenge test (PC_{20} , ≤ 4 mg/mL) at the second visit (day of randomization), symptomatic asthma as documented by the use of at least 15 puffs of a short-acting inhaled β -agonist bronchodilator during a 2-week run-in period and a baseline FEV_1 at the second visit that was within 10% of the screening FEV_1 . Exclusion criteria included the following: a recent (within 4 weeks) respiratory tract infection or asthma exacerbation requiring an emergency department visit or hospitalization; use of systemic corticosteroids within 3 months before screening; use of inhaled corticosteroids, cromolyn or nedocromil, salmeterol, or oral theophylline within 4 weeks of screening; use of an anticholinergic drug, an oral β -agonist or an antihistamine within 24 hours before the screening visit or each clinic visit; use of a short-acting inhaled β -agonist, methylxanthine, or alcohol-containing foods or beverages within 6 hours of the screening visit and each clinic visit. Pregnant or lactating female patients were not studied; women of child-bearing potential were required to use an acceptable method of birth control.

All subjects were fully informed of the nature and potential risks of the study and signed an informed consent form approved by the University of California, Los Angeles, Human Subjects Protection Committee before screening.

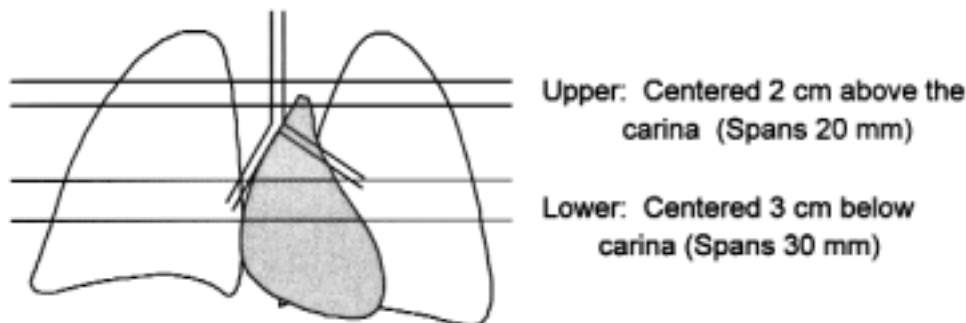


FIG 1 Schematic representation of image location protocol. Upper and lower sections centered 2 cm above and 3 cm below carina, respectively.

Study design

The study was a double-blind, double-dummy, parallel-group, randomized comparison study of HFA-134a BDP and CFC-BDP in 34 patients with a known history of asthma. The study duration was approximately 6 weeks and included a 2-week run-in period and a 4-week double-blind treatment period. During the double-blind treatment period, patients were randomly assigned to receive either 200 g daily of HFA-134a BDP or 200 g daily of CFC-BDP delivered from 50 g/actuation press-and-breathe metered dose inhalers. Patients received 2 puffs twice daily of active treatment from 1 inhaler and 2 puffs twice daily of placebo treatment from another inhaler to maintain the treatment blind. Subjects were carefully instructed in proper press-and-breathe inhaler technique at the screening and baseline visits. A closed-mouth technique was used without an add-on spacer or holding chamber. At screening (visit 1), all patients underwent a methacholine inhalation challenge to determine the presence and degree of nonspecific airways hyperresponsiveness. On visits 2 (baseline) and 4 (end-of-treatment visit), the subjects underwent HRCT imaging before and after a methacholine challenge. The study design is summarized in Table I.

Screen-eligible subjects were issued a daily diary card at visit 1 and at each subsequent visit. The diary card was used for recording use of daily β -agonist medication, daytime and asthma symptoms (wheeze, shortness of breath, chest tightness, and cough) on a scale of 0 (none) to 5 (symptoms very severe and interfering with normal daily activities) and sleep disturbances caused by asthma on a scale of 0 (none) to 4 (asthma preventing sleep). A mini-Wright peak flow meter was also dispensed at visit 1. Patients were instructed to perform 3 peak flow maneuvers twice daily (immediately on arising in the morning and before bedtime before the evening dose of medication), preferably 4 hours after any dose of concomitant medication, recording the highest measurement on the diary card.

Pulmonary function and methacholine inhalation challenge testing

At visits 1, 2, and 4, spirometry was performed at least in triplicate with a Pulmoscreen spirometer (S&M Instrument Company, Doylestown, Pa) with calculation of forced vital capacity and FEV₁. All maneuvers and equipment conformed to American Thoracic Society recommendations.¹⁴ The FEV₁ at visit 2 had to be within 10% of the FEV₁ measured at visit 1 (screening) before methacholine challenge.

At these visits, spirometry was followed by methacholine inhalation challenge testing. For visits 2 and 4, these challenges were performed within 1 hour of the challenge performed at the screening visit. Challenges were performed with a modification of the technique

of Chai et al.¹⁵ Methacholine solutions were nebulized with a nebulizer (DeVilbiss 646; Pharmaceutical service of the University of Iowa, College of Pharmacy, Iowa City) filled with a 3-mL solution, driven by compressed air at 20 PSI and breath-activated through a dosimeter (Rosenthal-French; Johns Hopkins University, Baltimore, Md) with a solenoid device timed to hold the valve open for 0.6 seconds. Methacholine was administered in the following concentrations: 0.075, 0.15, 0.30, 0.60, 1.25, 2.5, 5.0, 10.0, and 25 mg/mL. Subjects inhaled first nebulized 0.9% saline solution (diluent), followed by solutions of methacholine in incremental concentrations to a maximum concentration of 4 mg/mL (on the screening and baseline visits) and of 25 mg/mL (on visit 4). Spirometry was performed after administration of saline solution and each concentration of methacholine. The test was stopped after inhalation of the lowest concentration that produced a 20% decline in baseline FEV₁ from the postsaline solution baseline value (ie, the PC₂₀), up to a maximum methacholine concentration of 4 mg/mL (visits 1 and 2) or 25 mg/mL (on visit 4). Methacholine-induced bronchoconstriction was reversed by an aerosolized bronchodilator administered as 3 inhalations from a β_2 -agonist metered-dose inhaler (albuterol, 100 μ g per inhalation).

At visit 2 (baseline), after pre-methacholine HRCT images were obtained, a methacholine challenge test was performed as already described, except that, after inhalation of the saline solution diluent, the lowest concentration of methacholine administered was a 2-fold concentration lower than the methacholine PC₂₀ determined during the initial screening (visit 1) challenge test. Immediately after the methacholine challenge, image sequences were performed at suspended functional residual capacity (FRC) and RV at the same 2 anatomic regions of interest. The same protocol was repeated at visit 4, except that HRCT imaging was repeated after inhalation of the highest concentration of methacholine administered at visit 2, if possible. At visit 4, in some patients, the methacholine challenge test was resumed after the second HRCT until the FEV₁ declined by 20% from the postdiluent control value, if it had not already done so.

Functional imaging

Helical thin-section HRCT imaging was performed immediately before and immediately after methacholine challenge at visits 2 (baseline) and 4 (end-of-treatment) with a previously validated protocol.¹² Scanning was performed on the same scanner (GE HiSpeed Advantage; General Electric, Milwaukee, Wis) with a technique of a 120 kVp, 300 mA, beam collimation of 1 mm, and table incrementation of 3 mm/sec (pitch, 3.0). Image sequences were performed at 2 levels of breathhold corresponding to FRC and RV. These levels were chosen to enable bronchial measurements made at the resting end-expired volume (FRC) at which the elastic forces of the lung and

TABLE II. Numbers of participants* and mean baseline patient characteristics

	CFC group	HFA group
Gender (male/female)	7/8	7/9
Age, yrs (range)	30.5 ± 8.0 (19-46)	30.3 ± 11.3 (19-56)
FEV ₁ , % predicted (range)	82.7 ± 5.6 (72.1-91.5)	79.5 ± 11.8 (62.0-97.0)
Wheeze (0-5)	0.73	1.00
Shortness of breath (0-5)	0.78	1.25
Sleep disturbance (0-4)	0.23	0.47
Inhaler puffs/d	3.2	4.2
PEFR AM, (L/min)	423	381
PEFR variability (%)	4.8	6.3

PEFR, Peak expiratory flow rate.

*Evaluable participants completing at least premethacholine imaging.

chest wall are physiologically balanced and at the most optimal volume for demonstrating air trapping (RV). Images were acquired in single volume data sets of 6 to 10 seconds through each of 2 anatomic regions of interest (Fig 1). Digital scout views obtained at both FRC and RV were used to localize 2 anatomic regions of interest centered 2 cm above and 3 cm below the carina, respectively.

Image analysis

From the volumetric data sets, original projection data were used to reconstruct images at 2-mm intervals to optimize visual registration of like anatomic regions between sequences. Images were reconstructed with the high spatial frequency (bone) algorithm with the smallest field of view (FOV) possible for subject size at a matrix of 512 × 512. In addition, targeted reconstructions of the right lung only were obtained (to avoid the effects of cardiac motion), consisting of 15-cm FOV centered on the central airways and 20- to 25-cm FOV to encompass the entire cross-section of the right lung. All original and reconstructed image data were electronically archived. Imaging was completed only in subjects able to reproduce spirometric maneuvers to within 10% or 100 mL of their best effort, as measured during baseline pulmonary function tests. Subjects remained attached to the spirometer during imaging for the detection of leakage or loss of suspended breathhold.

Quantitative measures of internal airway dimensions and lung attenuation were made with semiautomated image-processing routines on a custom-developed thoracic radiology image analysis and display (TRIAD) workstation.^{11,16} Comparisons of data from images obtained before and after methacholine and before and after treatment were performed with like anatomic regions on the basis of visual registration of bronchi and vessels. Bronchial measurements were performed on 15-cm FOV targeted reconstructions of the right lung; lung attenuation measurements were performed on 20- to 25-cm FOV targeted reconstructions.

Measures of internal bronchial area were limited to airways that, on the premethacholine sequences, had a roughly circular cross-section (the ratio of greatest to least internal diameters, 1.25). Measurements were recorded for each individual airway. In addition, mean dimensions ± SD were calculated for specific airway generations (lobar, segmental, subsegmental, or higher) and for 3 categories of macroscopic airway area corresponding to large (>20 mm²), medium (6-20 mm²), and small (2-5 mm²).

Variations in lung attenuation as an indirect measure of air trapping were characterized in 2 ways: median lung attenuation and the lowest 10th percentile of the frequency distribution.¹² Lung attenuation was assessed on these parameters for the regions of interest in the right upper and lower lobes at the different mea-

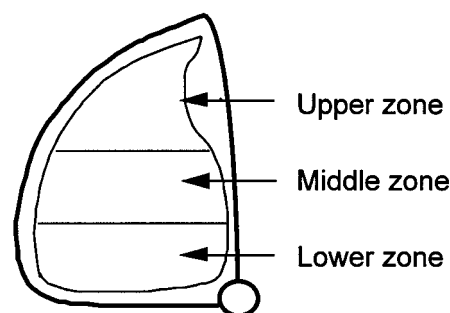


FIG 2. Lung contouring isolates the right lung and automatically divides the lung into 3 area-equivalent zones (anterior-nondependent, middle, and lower-dependent zones analogous to West's zones) for lung attenuation analysis.

surement times. Automated routines divided axial right lung sections into 3 area-equivalent gravitational zones (anterior [nondependent], middle, and posterior [dependent]), intended to correspond roughly to West's 3 physiologic zones¹⁷ (Fig 2). At any axial level, whole lung and regional (gravitational zone) measurements were obtained.

Data analysis

Statistical analysis was performed with the S-PLUS software package (StatSci; Seattle, Wash). Univariate analysis was performed to describe the dataset and individual subgroups to assess the distribution and validity of the data. For continuous variables, group means of changes from baseline to posttreatment were compared with the Student *t* test for paired and unpaired data. Because the frequency distributions of lung attenuation were characterized by median values, lung attenuation distributions were analyzed with the Wilcoxon rank sum test.¹⁸ Analysis was performed between the 2 groups for both the entire group of 31 evaluable patients who completed both the baseline (visit 1) and posttreatment (visit 4) procedures and for groups defined by undergoing the HRCT imaging procedures at visit 4 after inhalation of the same concentration of methacholine administered at the baseline visit. Fisher's Exact Test was used to compare the directional changes in lung attenuation on the posttreatment versus baseline premethacholine computed tomography scan between the HFA and CFC groups across all lung zones in both the upper and lower lobes with both the median and 10th percentile LAC measures. Fisher's Exact Test was also used to compare the relative post- to premethacholine shift in the LAC on the posttreatment versus the baseline pairs of computed tomography images between the HFA and CFC groups. *P* values of less than .05 were considered statistically significant.

RESULTS

Thirty-one of the 34 enrolled participants completed visits 1 through 4; the other 3 subjects withdrew from the study or failed to complete the visit 4 procedures satisfactorily for reasons unrelated to the study drug. Baseline characteristics of these evaluable subjects are shown in Table II. No significant differences in gender, age, or baseline spirometry (FEV₁) were present between the 2 groups, nor were significant differences found between the 2 groups with respect to baseline diary data.

Calculated values for the internal bronchial area of macroscopic airways of roughly circular cross-section visualized on matched baseline and posttreatment images

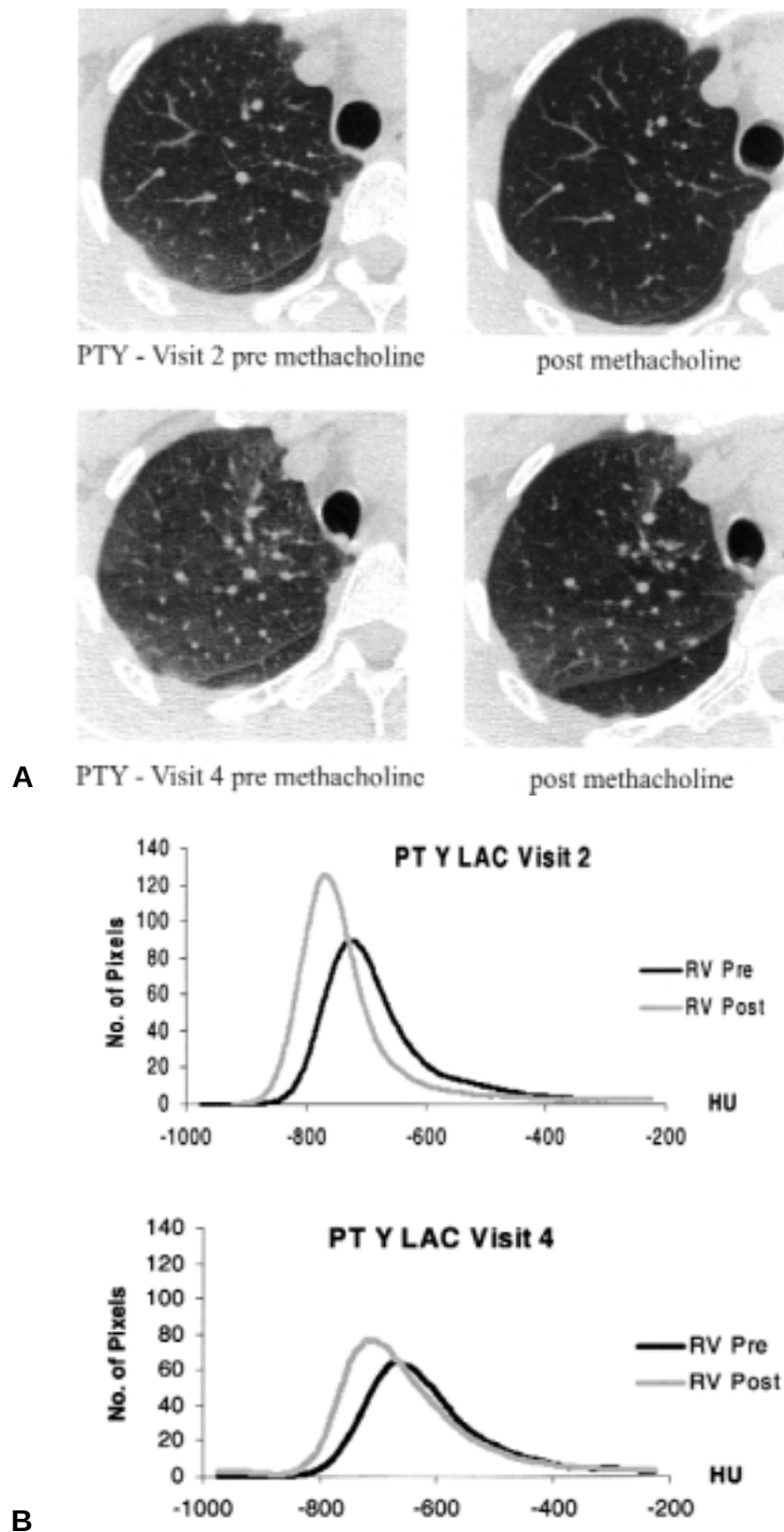


FIG 3. A, Images demonstrate right upper lobe matched pairs before and after methacholine challenge at visits 2 (baseline) and 4 (posttreatment) in a patient representative of the CFC cohort. *PTY*, Patient Y. B, The resultant LAC curve analysis (in the mid zone) demonstrates no significant change in distribution (and therefore no change in air trapping) either before or after the methacholine challenge on visit 4 compared with visit 2.

showed no significant differences on comparison of the posttreatment with the pretreatment values for airways more than 20 mm², 6 to 20 mm², or 2 to 5 mm² either before or after methacholine for either the HFA or CFC treatment groups (data not shown).

For assessment of regional air trapping as an indirect measure of possible changes in small airways calibre, LACs were computer generated from matched pairs of images obtained from the right upper lobe at RV before and after methacholine administration. Representative matched pairs of images are shown in Fig 3, A, from 1 subject (patient Y) both at the pretreatment baseline visit (visit 2) and at the posttreatment visit (visit 4) after 4 weeks of treatment with CFC-BDP. These images demonstrate regional areas of low attenuation that are similar in extent and magnitude at both visits before methacholine; moreover, areas of low attenuation become equally more prominent after methacholine-induced bronchoconstriction at both visits. The resultant LACs constructed from the gravity-dependent mid-lung zone of these images are shown in Fig 3, B. These demonstrate similar shifts of the LACs to the left (ie, in the direction of lower attenuation) at visits 2 and 4, indicating similar degrees of worsening regional air trapping after methacholine before and after treatment with the CFC corticosteroid aerosol.

Matched pairs of images obtained at RV from the same region (right upper lobe) before and after treatment with methacholine from a representative subject (patient H) at visit 2 and visit 4 after 4 weeks of treatment with HFA-BDP are shown in Fig 4, A. Comparison of the images obtained at both visits tends to show fewer and less prominent regional areas of low attenuation on the visit after treatment compared with the visit before treatment. The resultant LACs (Fig 4, B) show a similar shift in the LAC in the direction of lower attenuation after methacholine at the baseline visit as demonstrated by patient Y, but a significantly less methacholine-induced shift (almost none in this case) at the posttreatment visit, indicating less regional methacholine hyperreactivity after 4 weeks of treatment with HFA-BDP.

The average (± 1 SD) median values of lung attenuation (in Hounsfield Units [HUs]) determined from LACs constructed from matched pairs of premethacholine images obtained in the mid zone of the right lower lobe at the baseline and posttreatment visits are shown in Table III for all subjects undergoing premethacholine imaging at both visits ($n = 31$ patients). In this region, the average median premethacholine lung attenuation increased by 39 Hounsfield units in the HFA group between the 2 visits (indicating less regional air trapping) but remained essentially unchanged in the CFC group. The difference in the changes in lung attenuation on the premethacholine images before and after treatment between the 2 treatment groups (measured as either the median or 10th percentile determined from the LAC) did not reach statistical significance in either the entire region of interest or in any single gravity-dependent lung zone in either the right upper or lower lobe. However,

lung attenuation increased (improved) significantly more often after treatment with HFA-BDP than CFC-BDP across all conditions (all gravity-dependent zones in the regions of interest of both the right upper lobe and the right lower lobe with both the median and 10th percentile values from the LACs; $P < .05$; Fisher's exact test).

The average (± 1 SD) median values of lung attenuation determined from LACs from matched pairs of both before and after methacholine images obtained in the mid zone of the region of interest in the right lower lobe at the baseline and posttreatment visits are shown in Table IV. Included in this table are data for all subjects who underwent imaging at both visits both before methacholine and after inhaling the same concentration of methacholine (ie, same constrictor stimulus) at both visits ($n = 19$ patients). At the baseline visit, the reduction in lung attenuation after methacholine (indicating worsening regional air trapping in response to methacholine) is similar for the HFA and CFC groups (-29 vs -27 , respectively; $P = .90$). In contrast, at the posttreatment visit, the magnitude of the decrease in lung attenuation in response to methacholine is reduced in the HFA group compared with the baseline response in the same subjects (-17 vs -29), although the magnitude of the decrease in lung attenuation after methacholine compared with the baseline response is augmented in the CFC group. The difference in the effects of the 2 treatments (HFA vs CFC) on response to methacholine is statistically significant ($P = .04$), implying a relatively more favorable effect on regional hyperreactivity after treatment with HFA-BDP than with CFC-BDP. Moreover, the lung attenuation response to methacholine improved (ie, lung attenuation decreased less, implying less increase in regional air trapping induced by methacholine) significantly more often after treatment with HFA-BDP than CFC-BDP across all conditions (all gravity-dependent zones in the regions of interests of both the right upper and right lower lobes with both the median and 10th percentile values from the LACs; $P < .001$; Fisher's exact test).

Spirometry and methacholine response data for the 31 evaluable patients are presented in Table V. Premethacholine FEV₁ improved modestly but not significantly after 4 weeks of treatment in both the HFA and CFC groups. The percent decline in FEV₁ for the same concentration of methacholine at both visits was significantly less marked after treatment with both HFA-BDP and CFC-BDP ($P < .05$), but the difference between the 2 treatment groups was not significant. The PC₂₀ and log PC₂₀ also improved after both forms of treatment, but the changes did not reach statistical significance.

Changes in respiratory symptoms, β -agonist use, and peak flow rates after the treatment compared with baseline are shown in Table VI. Changes in symptom scores with both forms of treatment were modest, but the decline in shortness of breath in the HFA group was significantly greater than the change in breathlessness in the CFC group. Morning peak flow increased significantly in both groups, but peak flow variability did not change.

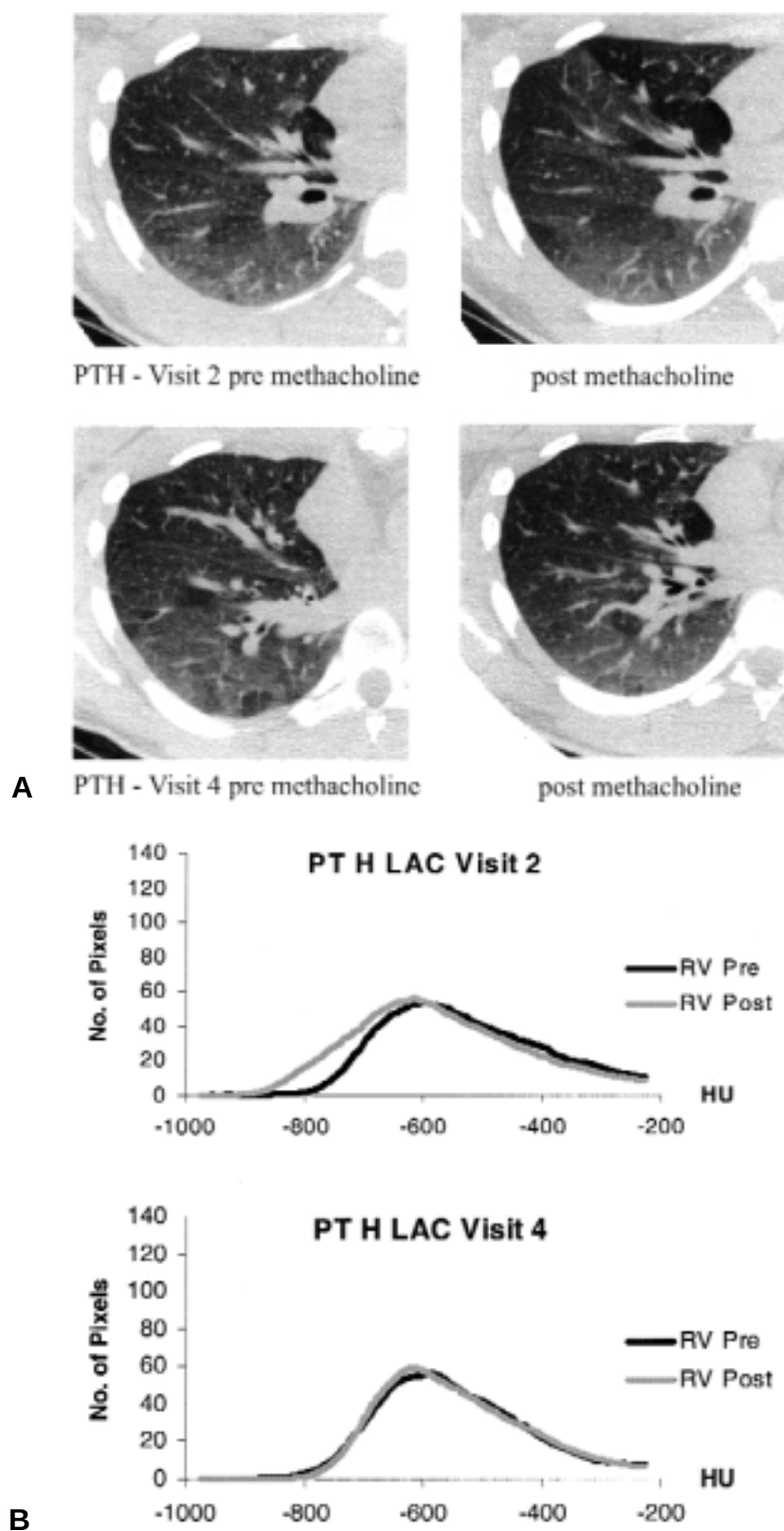


FIG 4. A, Images demonstrate right upper lobe matched pairs before and after methacholine challenge at visits 2 (baseline) and 4 (post-treatment) in a patient representative of the HFA cohort. PTH, Patient H. B, The matched premethacholine images (in the mid zone) shows an apparent decrease in prominence of low attenuation areas (and therefore air trapping) at baseline, and the resultant LAC curve analysis shows significantly less shift (almost none in this case) after methacholine at visit 4 compared with visit 2.

TABLE III. Premethacholine median lung attenuation values (Hounsfield units) at RV in the mid-lung zone of the right lower lobe at baseline and after 4 weeks of treatment with HFA-BDP or CFC-BDP (n = 31 patients)

Group	Baseline (HU)	Posttreatment (HU)	Change (HU)
CFC (n = 15 patients)	-695 ± 72*	-692 ± 61	3
HFA (n = 16 patients)	-674 ± 89	-635 ± 77	39

*Mean ± 1 SD.

TABLE IV. Median lung attenuation values (Hounsfield units [HU]) at RV in the mid-lung zone of the right lower lobe before and after the same concentration of methacholine at baseline and after 4 weeks of treatment with HFA-BDP or CFC-BDP (n = 20 patients)

Group	Baseline (HU)			Posttreatment (HU)			ΔΔ†
	Premethacholine	Postmethacholine	Change	Premethacholine	Postmethacholine	Change	
CFC (n = 9 patients)	-690* ± 93	-716 ± 84	-26	-680 ± 75	-740 ± 80	-60	-34
HFA (n = 11 patients)	-692 ± 68	-721 ± 70	-29	-646 ± 57	-663 ± 80	-17	12

*Mean ± 1 SD.

†Difference between baseline and posttreatment pre-post methacholine change.

TABLE V. Spirometry and methacholine results (n = 31 patients)

	CFC group			HFA group		
	Baseline	Posttreatment	Change	Baseline	Posttreatment	Change
FEV ₁ before methacholine (L)	3.26	3.37	0.11	3.09	3.29	0.20
FEV ₁ at baseline (% ↓)	28.2	19.7	8.5	23.0	13.6	9.6*
PC ₂₀	0.43	1.13	—	0.56	2.62	—
Log PC ₂₀	-1.24	-0.68	0.42	-1.13	-0.41	0.43

*P < .05, change from baseline.

DISCUSSION

The present study demonstrates a greater efficacy of HFA-BDP compared with CFC-BDP in reducing regional air trapping, as assessed by changes in the regional distribution of lung attenuation. In addition, greater efficacy of HFA-BDP is also shown in reducing regional airways hyperreactivity, as determined by changes in regional air trapping after bronchoprovocation with methacholine, again assessed by analyzing changes in the distribution of lung attenuation. These differences between the effects of the 1 formulations of BDP on regional air trapping and regional hyperreactivity are consistent with the greater penetration of the smaller airways by the extra-fine HFA, compared with the coarser CFC, corticosteroid aerosol previously demonstrated by radiolabeled aerosol deposition studies.⁴ We hypothesized that the greater access of the extra-fine corticosteroid aerosol to the small airways would lead to more effective suppression of inflammation at these sites and consequently greater peripheral airways patency, less gas trapping behind prematurely closed airways at RV, and less responsiveness of these airways to a constrictor agonist. The results of the present study are consistent with this hypothesis. With customized image processing routines, alterations in the size of visible airways were directly observed, although bronchiolar obstruction and distal air trapping were indirectly assessed on the basis of alterations of lung attenuation. The absence of significant differences

TABLE VI. Change from baseline symptom scores, inhaler use, and peak expiratory flow rates

	CFC group	HFA group
Wheeze (0-5)	-0.22	0.03
Shortness of breath (0-5)	0.09	-0.48*†
Sleep disturbance (0-4)	-0.08	-0.16‡
Inhaler use (puffs/d)	-0.68	-0.69
PEFR AM (L/min)	25‡	29‡
PEFR variability (%)	-1.1	0.5

PEFR, Peak expiratory flow rate.

*Change from baseline, P < .01.

†Difference from CFC group, P < .05.

‡Change from baseline, P < .05.

in the macroscopic airways between the 2 groups at each visit supports the conclusion that the differences observed in the LAC distributions reflect the efficacy of HFA-BDP on the small airways, which are the predominant site of obstruction in mild asthma.⁵ The absence of any differential effect of the 2 treatments on FEV₁, peak flow, peak flow variability, and overall methacholine responsiveness (as assessed by FEV₁ responses; Table V) is also consistent with this conclusion. On the other hand, it is possible that the modest, but significantly greater, effect of HFA-BDP than CFC-BDP on breathlessness (Table VI) might be a clinical expression of the superior efficacy of the extra-fine corticosteroid aerosol on the

peripheral airways, even in the absence of any demonstrable differences in the function of the larger airways.

Quantitative measures of air trapping have been shown to provide important information about the status of the lung parenchyma and airway behavior. The distribution of Hounsfield Unit values within an image can be represented in the form of a frequency distribution of lung attenuation (Figs 3, B, and 4, B). Previous investigators have used thin-section computed tomograph in vivo to characterize patients with asthma.¹⁹⁻²⁵ In a prospective study of asymptomatic patients with asthma and non-smoking normal subjects, Newman et al²³ compared lung attenuation on computed tomography and HRCT images obtained through the lung bases and found that the expiratory mean pixel index (percentage of pixels, <-900 HU) was significantly higher in patients with asthma. The mean pixel index correlated significantly with pulmonary function measures of airflow obstruction and air trapping, including FEV₁, RV, and FRC. Further changes in air trapping within regions of the lung can be assessed under different physiologic conditions (eg, before and after a bronchodilator or a bronchoconstrictor, such as methacholine).¹²

The attenuation of the lung represents a composite of the individual components of air, soft tissue, and blood and will be affected by changes in any 1 or more of these components.²⁶ In the interpretation of lung attenuation measurements, the confounding variables of the phase of respiration and lung volume, pulmonary blood volume, and the influence of gravity must be considered.^{26,27} In the present study, we addressed a number of technical considerations designed to maximize spatial resolution, achieve valid coregistration of anatomy between sequences, and ensure accuracy of the suspended breathhold conditions.^{11,12} A number of potential factors can introduce measurement error in studies of this type. Variations in anatomic registration between different physiologic conditions would be expected to bias results by influencing the calculations of percent change in airway areas or lung attenuation. However, unless anatomic misregistration occurs systematically, such as comparison of lung or bronchial anatomy under a given physiologic condition at a consistently higher (or lower) level, variations might be expected to cancel out one another. In the present study, visual registration was used to localize identical axial planes on the different sequences of images (before and after methacholine and before and after treatment).^{11,28} All cross-sectional imaging was registered with simultaneous flow-volume loops to ensure that the image data was a true reflection of the specific breathhold. Imaging at RV was performed only if subjects were able to reproduce their best expiratory effort to within 5%, as defined by the American Thoracic Society for the standardization of lung function tests.¹⁴

In conclusion, functional imaging provides a sensitive new tool for assessing the long-term effect of corticosteroid aerosols on small airways function. The present study used previously validated functional imaging to

detect changes in regional air trapping as an indirect measure of changes in small airways function and to assess changes in regional hyperreactivity, reflected by regional changes in small airways responses to methacholine before and after a 4-week course of treatment with either HFA-BDP or CFC-BDP. Using this new assessment tool, we have shown that the extra-fine HFA-BDP aerosol appears to have greater efficacy than the same dose of the coarser CFC-BDP aerosol on small airways function, most likely because of the more effective delivery of the extra-fine corticosteroid aerosol to the lung periphery. Additional studies are needed in larger numbers of patients with asthma of varying severity over longer periods of time to assess further the impact of targeting the small airways for treatment with anti-inflammatory agents on lung function and other clinical outcomes.

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