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Therapeutic significance of distal airway inflammation in asthma

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Inflammation in asthma is not merely confined to the large central airways but also extends to the small peripheral airways. Distal lung inflammation can be observed even in patients with asthma with mild disease and normal spirometric readings. Subjects with asymptomatic asthma can exhibit significant increases in peripheral airway resistance, likely the result of distal lung inflammation. As determined from measurements of eosinophilic and other cellular infiltrates, the inflammatory response in the distal lung can exceed that in the large airways. Nocturnal asthma, a natural model of cyclic asthma worsening, is associated with an increase in nighttime distal lung inflammation, as evidenced by the accumulation of alveolar tissue eosinophils. Distal lung disease appears to increase the risk of recurrent asthma exacerbation, whereas disease-related anatomic changes in the small airways of the distal lung are prominent in fatal asthma. The clinical significance of distal lung disease makes this region an important therapeutic target. Chlorofluorocarbon (CFC)-based preparations of inhaled corticosteroids used to treat airway inflammation produce aerosols of relatively large particle size (~4 μm); such aerosols have poor access to the distal lung. New formulations of inhaled corticosteroids that use hydrofluoroalkane (HFA) propellants can have smaller particle sizes (~1 μm). Extrafine HFA aerosols have better access to the distal lung, with less oropharyngeal deposition. Imaging studies suggest that anti-inflammatory medication delivered as an extrafine

aerosol produces beneficial changes in distal lung function. In one study, an HFA formulation of an inhaled corticosteroid reduced air trapping to a greater degree than a CFC formulation of the same corticosteroid. By extending the delivery of anti-inflammatory medication to the distal lung, the new HFA-based corticosteroids have the potential to treat asthma more effectively and at reduced steroid doses. (*J Allergy Clin Immunol* 2002;109:S447-60.)

Key words: Asthma, distal airway inflammation, nocturnal asthma, inhaled corticosteroids, chlorofluorocarbon-based preparations, hydrofluoroalkane propellants

INTRODUCTION

Asthma is characterized by airway obstruction and hyperresponsiveness to constricting stimuli. This condition typically assumes a course of periodic or sporadic exacerbation that often occurs against a background of chronically impaired pulmonary function. In the past, before emphasis was placed on the inflammatory component of asthma, its clinical manifestations were viewed as the sole targets of pharmacologic intervention; treatment, primarily with bronchodilating agents, was aimed at alleviating acute attacks. The therapeutic approach to asthma underwent a fundamental change when it was treated as a disease of airway inflammation. Pulmonary obstruction and bronchial reactivity occurred secondary to an ongoing inflammatory process, one that was active even during quiescent periods when symptoms abated. Recognition of the underlying nature of the disease led to the introduction of antiinflammatory steroids as a controlling therapy in the maintenance and treatment of asthma. Inhaled corticosteroids rapidly gained acceptance as the mainstay of therapy in the treatment of persistent asthma.¹ This review examines (1) histologic evidence, (2) physiologic correlates, (3) imaging of mid-zone airways, and (4) targeted therapeutic sites relating to inhaled corticosteroid therapy of distal airway inflammation in asthma.

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Abbreviations used

BAL: Bronchoalveolar lavage
BDP: Beclomethasone dipropionate
CFC: Chlorofluorocarbon
CT: Computed tomography
DPI: Dry powder inhaler
HFA: Hydrofluoroalkane
HRCT: High-resolution computed tomography
IFR: Inspiratory flow rate
pMDI: Pressurized metered-dose inhaler

Although their success in ameliorating the symptoms of asthma and in preventing exacerbations is not disputed, inhaled corticosteroids do not appear to be a panacea. After more than 20 years' experience with their widespread use, it is apparent that a substantial number of patients with asthma receiving such therapy are steroid insensitive and continue to experience frequent exacerbations.² Furthermore, the natural age-related decline in pulmonary function, which occurs at a faster pace in patients with asthma, is not completely normalized with long-term corticosteroid therapy.^{3,4} These observations suggest that lingering regions of inflammation may remain beyond the reach of current inhaled steroid formulations.

Although questions continue to be raised concerning the adequacy of antiinflammatory therapy in asthma, our understanding of the extent of its inflammatory disease process continues to advance. Until recently, asthma was considered a disease primarily of the central airways, whereas the contribution of distal lung inflammation to its development and persistence had gone largely unexamined. The distal airways (also referred to as the *peripheral* or *small airways*) have been ignored primarily for 2 reasons: (1) they are, by nature, less available for observation than the larger proximal airways, and (2) commonly used physiologic measures of pulmonary function are weighted toward measuring the caliber of the large airways. In turn, histopathologic evidence of inflammatory disease in the central airways is more easily correlated with gross measures of lung performance.⁵ Therefore, characterization of asthma as a disease of the central airways has been motivated more by convenience than by scientific evidence.

With the introduction of sophisticated imaging⁶ and immunohistochemical⁷ techniques, it has become increasingly evident that small distal airways are indeed significant sites of inflammation in asthma. It has been proposed that distal airway inflammation contributes to a host of clinically significant processes in asthma. Distal inflammation may play a role in airway hyperresponsiveness, nocturnal asthma, spontaneous exacerbations of symptoms, asthma complicated by smoking and/or viral respiratory tract infections, and severe steroid-dependent asthma. The importance of distal inflammation in asthma has called attention to the fact that inhaled corticosteroids—the first line of therapy for asthma prophylaxis—are not efficiently delivered to the distal lung

by conventional formulations. This has led to suggestions that the effectiveness of inhaled antiinflammatory medications could improve if more drug is deposited in the small and large airways.⁸

This review presents evidence that distal lung inflammation plays a significant role in asthma and that inflammation at distal sites is currently undertreated. Recent improvements in the design and formulation of inhaled corticosteroids increase delivery of these drugs to the distal lung, which may address some of their current therapeutic limitations. The potential therapeutic and safety benefits of disseminated pulmonary antiinflammatory therapy are discussed.

HISTOLOGIC EVIDENCE OF DISTAL LUNG INFLAMMATION

Convincing evidence that distal airways and lung parenchyma are significant sites of inflammation in asthma comes from studies identifying cellular infiltrates in these areas. Fiberoptic bronchoscopic sampling and cellular staining techniques used to identify inflammatory infiltrates were first applied in studies of large airway inflammation.⁹ Such studies identified not only the composition of the cellular infiltrates but also their activation status. For example, using histochemical staining and monoclonal antibodies specific for cell surface activation markers, Azzawi et al⁷ found a significant increase in IL-2 receptor–positive cells in mucosal biopsy specimens taken from large airways by fiberoptic bronchoscopy. The presence of IL-2 receptors was an indication of lymphocyte activation. The investigators also found an increased number of eosinophils in specimens from patients with asthma compared with samples taken from nonasthmatic control subjects. In another study, eosinophil levels and their degree of activation, based on a marker of degranulation, correlated with the degree of asthma severity.⁵

The inflammatory process in the distal airways of patients with asthma shows similarities to, as well as differences from, that observed in the large airways. In a study conducted with postmortem specimens, lymphocytes were found in increased numbers in all airway size groups, including the distal airways, both in patients who died of asthma and in patients with asthma who died of nonrespiratory causes. The degree of eosinophilic infiltration appeared to correlate with asthma severity.¹⁰ Although this study indicates that the inflammatory process is qualitatively similar in distal and central airways, the nature of the infiltrating cells can differ significantly. For example, Hamid et al¹¹ observed that infiltrating cells were present in greater numbers in specimens from surgically resected lungs of patients with asthma than in specimens from patients without asthma; consistent with findings from other studies, the increases were observed in distal airways (Fig 1), as well as central airways. However, a greater number of activated (EG2+) eosinophils were present in the distal airways than in the central airways, suggesting a higher level of inflammatory activity in the distal airways.

Haley et al¹² performed a morphometric analysis of postmortem lung specimens from patients who died of asthma. They also found evidence that the inflammatory process in distal airways might be qualitatively different from that in large airways, because the distribution of infiltrates within the walls of large and small airways differed. In large airways, relatively more T cells and eosinophils were found in the inner region of the airway wall (between basement membrane and smooth muscle), compared with the outer region (between smooth muscle and alveolar attachments). In the small airways, the pattern was reversed, with CD45+ cells and eosinophils more abundant in the outer region.¹²

Large numbers of T cells and activated eosinophils were found in both proximal and distal lung tissue in subjects who died of asthma.¹³ In contrast to individuals with stable asthma, the infiltrate for those with fatal asthma contained large numbers of CD8+ T cells. Synek et al¹⁴ compared inflammatory cell infiltrates in patients who had fatal severe asthma with those of patients who had mild-to-moderate asthma and died of unrelated causes. They found a greater number of eosinophils infiltrating the airway wall of the larger airways in patients with fatal asthma than in patients with mild-to-moderate asthma. In the smaller airways, eosinophils were elevated in both asthma groups.¹⁴

It should be noted that although evidence from postmortem specimens taken from individuals with fatal asthma strongly suggests that inflammation in the distal airways is a significant factor in severe asthma, these conclusions are not indicative of mainstream asthma theories. Howarth⁹ has pointed out some of the dangers in using such postmortem samples, including the fact that cellular architecture and airway anatomy might be distorted as a result of acute asphyxia that is not the case in chronic clinical disease. Furthermore, there is the possibility that patients were not receiving adequate treatment or were not compliant with their treatment regimen.

Although studies of airway changes in tissue taken from individuals who died of severe asthma remain an important source of information, specimens recovered in vivo from patients with severe, potentially fatal, asthma are clearly preferred. Such studies are hindered by bronchoscopic procedures in individuals with highly reactive airways. Nevertheless, tissue specimens from the central and distal airways of patients with severe, steroid-dependent asthma have been successfully analyzed. Inflammatory infiltrates were still observed in the airways of these patients who were receiving intensive steroid treatment, but the inflammatory process appeared to differ somewhat in patients with mild-to-moderate asthma.¹⁵ In severe asthma, neutrophils rather than eosinophils appeared to predominate; this was observed in the distal, as well as central, airway biopsy specimens and in bronchoalveolar lavage (BAL).

Further evidence of distal lung inflammation comes from a study by Vignola et al¹⁶ who compared several markers of inflammation in mucosal biopsy specimens and BAL fluid from healthy control subjects, patients

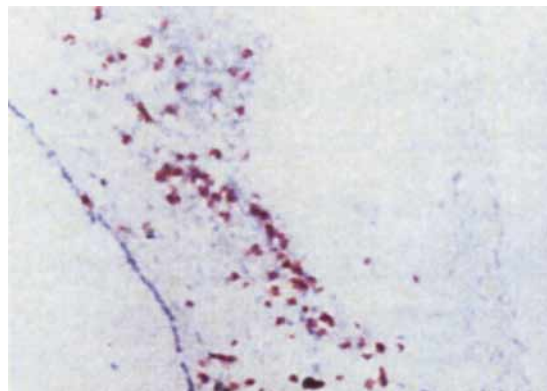


FIG 1. Inflammation in distal lung assessed by immunocytochemistry. Example of EG2-positive cells (activated eosinophils) in an airway less than 2 mm in diameter from a patient with asthma. A large number of activated eosinophils are present. (Adapted with permission from Hamid Q, Song Y, Kotsimbos TC, Minshall E, Bai TR, Hegele RG, et al. Inflammation of small airways in asthma. *J Allergy Clin Immunol* 1997;100:44-51.)

with intermittent asthma, and patients with mild-to-moderate persistent asthma. They found that alveolar macrophage activation was significantly increased in patients with asthma compared with control patients. Evidence of distal airway inflammation inferred from observations in BAL fluid must, however, be interpreted with caution, because BAL samples include both large and small airway luminal cell populations, in addition to recovering vascular exudates.⁹

Taken together, the data indicate that distal airways are significant and are active sites of inflammation in asthma, as indicated by inflammatory cell infiltration levels. Eosinophils appear to be commonly observed in distal airway infiltrates of patients with asthma; they have been observed in a degranulated state, indicating activation, and their numbers appear to correlate with asthma severity.

PHYSIOLOGIC CORRELATES OF DISTAL AIRWAY INFLAMMATION

For beneficial results to be derived from asthma treatment, some attempt at measuring the contribution of distal airway inflammation to diminished pulmonary function must be made. There is a possibility that even with ample histologic evidence of distal airway inflammation, the actual effect on lung function might be negligible compared with the effect on larger proximal airways. Numerous studies have attempted to correlate clinical measures of standard lung function with the presence and degree of distal airway involvement.

Changes in peripheral airway resistance in asthma

Wagner et al¹⁷ used the wedged bronchoscopic technique to measure airway resistance in the peripheral lung of patients with asymptomatic asthma who had near-

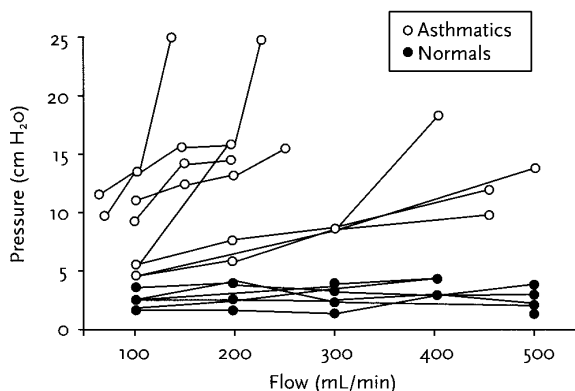


FIG 2. Peripheral airway resistance is increased in asthma. Pressure-flow relationships of 6 healthy subjects (filled circles) and 9 subjects with asymptomatic asthma (open circles). (Adapted with permission from Wagner EM, Liu MC, Weinmann GG, Permutt S, Bleecker ER. Peripheral lung resistance in normal and asthmatic subjects. *American Review of Respiratory Disease* 1990;141:584-8. Official Journal of the American Thoracic Society © American Lung Association.)

normal spirometric values. Using a double-lumen catheter inserted through the instrument channel of a bronchoscope, Wagner et al¹⁷ introduced a gas mixture of 5% carbon dioxide in air at increasing flow rates; they measured changes in pressure caused by the increasing flow through the other channel of the catheter. As the flow was increased in healthy subjects, there was little to no change in pressure, meaning that resistance was constant. However, in patients with asthma, marked pressure changes were measured. Despite the apparent lack of pulmonary impairment, patients with asthma had significantly increased peripheral airway resistance compared with control subjects; there was more than a 7-fold increase in peripheral lung resistance in the asthma group (Fig 2).¹⁷

In addition to increased peripheral resistance, patients with asthma exhibited a significantly lower forced expiratory flow rate at 25% to 75% of forced vital capacity (FEF_{25%-75%}) than control subjects. Although this measurement does reflect peripheral airway function, it is not very specific.¹⁷ Though they did not measure it, Wagner et al¹⁷ suggest that chronic distal inflammation, and its attendant mucus hypersecretion and mucosal edema, might serve to explain their findings. The demonstration of increased resistance in patients with mild asthma is important, because it suggests that even in the context of minimal impairment, there is significant disease activity that can be detected by measures of lung function more sensitive than those typically administered during a routine pulmonary examination.

In a model of the human tracheobronchial tree, application of various values for airway smooth muscle shortening and airway wall thickness simulated dynamic changes in airway resistance. Data from postmortem measurements of lung tissue from patients with asthma

and from healthy individuals with a wide range of airway sizes were used to establish a relationship between wall area and airway internal perimeter.¹⁸ The analysis revealed that increases in peripheral airway wall thickness, even in amounts too small to affect baseline airway resistance, were nevertheless capable of dramatically changing airway narrowing caused by smooth muscle shortening. Wiggs et al¹⁸ surmised that exaggerated airway narrowing in response to smooth muscle contraction could occur without influencing baseline resistance if the increase in wall thickening was primarily due to surrounding lung parenchyma, rather than invasion of airway lumen. Particularly revealing was that narrowing of the peripheral airways, instead of the large airways, had the most pronounced effect on maximal airway resistance.¹⁸ The increased effects of smooth muscle shortening might, therefore, account for the exaggerated airway narrowing that occurs in response to smooth muscle agonists, such as methacholine in patients with asthma (see below).¹⁸ The results are even more striking considering that the contribution of small airway resistance to total pulmonary resistance is relatively low, with estimates ranging from 10 to 29%.^{19,20}

Distal airway remodeling in asthma

The findings by Wiggs et al¹⁸ suggest that structural changes of a lasting nature (eg, remodeling) can occur in the distal airways of patients with asthma. Carroll et al²¹ found that in comparison with findings in nonasthmatic control subjects, the inner-wall area of distal airways was increased in individuals with asthma who died as a result of their disease and in patients with asthma who died of nonrespiratory causes. Of importance was the fact that most patients in the fatal asthma group were using corticosteroids, indicating that airway remodeling was not altered by corticosteroid therapy. Increased smooth muscle mass, as observed, was proposed to allow a greater shortening in response to bronchoconstricting stimulus. Interestingly, the structural changes implicated in airway hyperresponsiveness were predominantly found in the distal airways of nonfatal asthma cases but were also found in both large and small airways in fatal asthma cases. The observed anomalies might be the result of long-standing or undertreated airway inflammation.²¹

A number of studies have uncovered evidence of remodeling in the distal lung that might be the result of persistent inflammation. In a postmortem histologic study, lung specimens from patients who died of asthma revealed distorted anatomies in their peripheral airways. The lumen of the bronchioles appeared occluded, possibly with mucus; there was smooth muscle thickening; and inflammatory infiltrates comprising eosinophils and mononuclear cells were visible in the bronchiolar wall (Fig 3). These structural changes were not focal in their distribution but were observed throughout the distal lung.²²

In specimens from individuals who died of asthma, the adventitial, submucosal, and muscle areas of the distal airways were greater than those measured in patients with chronic obstructive pulmonary disease and control

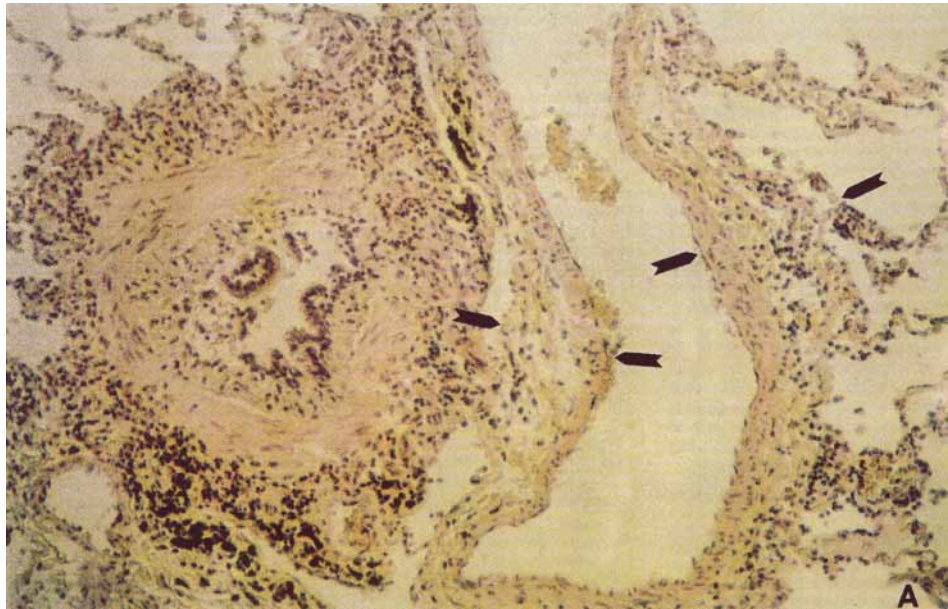


FIG 3. Peripheral airway appearance in a case of fatal asthma. Microphotograph showing an overview of a peripheral pulmonary artery and the adjacent airway. An inflammatory infiltrate is present in both the bronchiole and the artery. Arrows indicate areas of the vessel walls. (Adapted with permission from Saetta M, Di Stefano A, Rosina C, Thiene G, Fabbri LM. Quantitative structural analysis of peripheral airways and arteries in sudden fatal asthma. *American Review of Respiratory Disease* 1991;143:138-43. Official Journal of the American Thoracic Society © American Lung Association.)

subjects.²³ The smooth muscle layer in patients with asthma was 2 to 3 times thicker than that in control subjects and patients with chronic obstructive pulmonary disease, along with some indication of a relationship to disease severity. Muscle thickness was, in general, greater in patients with fatal asthma compared with those with nonfatal asthma.²³

Airway remodeling resulting from ongoing and persistent inflammation is not the only possible explanation for fixed expiratory airflow limitation found in some patients with chronic asthma. Loss of lung elasticity, a cardinal feature of emphysema, was observed in a large proportion of patients with asthma and severe lung obstruction who did not have other signs of emphysema, such as decreased total lung capacity or decreased diffusing capacity. Diminished lung elastic recoil is an overlooked, yet potentially significant, factor in the loss of lung function in asthma. Although the mechanism is unclear, the loss of elasticity is likely to reflect distal airway abnormalities, especially at the alveolar-lung parenchymal interface.^{24,25}

Distal airways and hyperresponsiveness

An increase in small airway muscle mass of the kind described previously does not necessarily contribute to an exaggerated shortening of smooth muscle in asthma.²³ However, it is likely to contribute to hyperresponsiveness by amplifying the effect of even slight amounts of muscle shortening. The ability of increased wall thickness to

exaggerate the response of muscle shortening has been demonstrated in large airways. A calculation of the amount of airway smooth muscle shortening required for occluding the lumen showed it to be less in asthmatic than nonasthmatic airways.²⁶

Because hyperresponsiveness to bronchoprovocation is a cardinal feature of asthma, researchers have tried to determine whether changes in distal airway function caused by inflammation might lead to an increase in airway sensitivity. One possibility is that increased airway wall thickness, commonly seen in distal airways of patients with asthma and attributed to chronic inflammation,¹² might intensify the response to smooth muscle shortening during induced bronchoconstriction.

Wagner et al²⁷ examined the hyperresponsiveness in small airways by measuring changes in peripheral resistance after a histamine challenge by using a wedged bronchoscopic technique. Peripheral resistance doubled at lower average concentrations of histamine in patients with asthma compared with healthy control subjects, indicating an increased sensitivity to the provoking agent. A striking result was that a small airway response to histamine in patients with asthma was correlated with whole-lung responsiveness. Meanwhile, inhaled isoproterenol completely reversed the histamine-associated increase in peripheral resistance of healthy subjects; the increase was only partly reversed in patients with asthma. This suggests that current inhaled β -agonist therapies might not be adequate for treating small airways con-

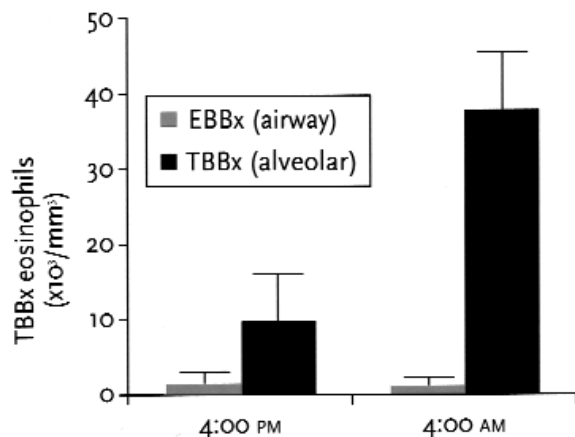


FIG 4. Changes in alveolar eosinophils in patients with nocturnal asthma and number of eosinophils per volume from a group of patients with nocturnal asthma. Counts are from endobronchial (airway tissue) and transbronchial (alveolar tissue) biopsy specimens obtained at 4:00 AM and 4:00 PM. Note the dramatic nighttime increase in eosinophilic infiltrates in alveolar tissue. All values are expressed as means and error bars indicate SEM (mean $\pm$ SEM). EBBx, Endobronchial; TBBx, transbronchial. (Adapted with permission from Kraft M, Djukanovic R, Wilson S, Holgate ST, Martin RJ. Alveolar tissue inflammation in asthma. *American Journal of Respiratory and Critical Care Medicine* 1996;154:1505-10. Official Journal of the American Thoracic Society © American Thoracic Society.)

striction.²⁷ In another study by Berman et al,²⁸ provocation of the peripheral airways with bradykinin, an endogenous bronchoconstrictor, introduced through a wedged bronchoscope produced a dose-dependent increase in peripheral airways resistance of patients with asthma. However, by measuring plasma exudation, Berman et al²⁸ were able to exclude distal airway edema as a cause of the hyperresponsiveness.

Taken together, evidence from morphometric and airway resistance studies indicates that distal airways of individuals with asthma undergo pronounced and, perhaps, permanent structural changes from long-standing inflammation that appears to affect coarse measures of lung performance. Structural changes, with wall thickening being the most pronounced, are likely to contribute to hyperresponsiveness. These structural changes in distal airways were observed even in patients receiving corticosteroid therapy, suggesting that this therapy did not completely control distal airway inflammation.

Distal airway involvement in nocturnal asthma

The study of nocturnal asthma has proven to be a productive avenue of research for correlating physiologic changes in pulmonary function with changes in distal airway inflammation. The cyclic worsening of nighttime symptoms that remit during the day makes nocturnal asthma a natural model for worsening asthma.

Preliminary evidence that an inflammatory process might be undergoing periodic changes in distal airways

that parallel changes in lung function was provided by an analysis of BAL fluid recovered from patients with nocturnal asthma. In comparison with findings in patients with asthma whose symptoms did not worsen overnight, a significantly greater number of inflammatory cells were observed in BAL samples from patients with nocturnal asthma. The numbers of neutrophils and eosinophils were increased in these subjects at 4:00 AM compared with patients without nocturnal asthma; however, cell counts were similar between groups in the afternoon.²⁹ Another study, reported by Jarjour et al, demonstrated increased superoxide content in BAL fluid at 4:00 AM in subjects with nocturnal asthma compared with those without nighttime symptoms.³⁰ Increased production of oxygen radicals is one indicator of inflammatory activity, especially of macrophage activity; and radical-induced airway injury can exacerbate bronchial obstruction.

Evidence that nocturnal asthma is indeed associated with inflammatory changes in the distal lung was provided by Kraft et al³¹ through examination of biopsy samples from distal and proximal lung tissue. The inflammatory changes that accompanied nocturnal asthma were more prominent in the alveolar tissue area, whereas the number of inflammatory cells found in the proximal airways was similar in patients with asthma who did or did not experience nocturnal worsening. The number of inflammatory cells, especially eosinophils and macrophages, increased at night in the alveolar tissue area of patients with nocturnal asthma (Fig 4). Of particular interest was the observation that alveolar tissue eosinophils, excluding eosinophils in the more central airways, could be correlated with nighttime decline in lung function, specifically the nighttime decline in FEV₁.³¹ Another study, by Martin et al,²⁹ showed that changes in alveolar eosinophilic infiltrates were not paralleled in patients with nocturnal asthma by similar increases in peripheral blood eosinophils. In other words, this was not part of a generalized inflammatory response but a specific accumulation of inflammatory cells in the alveolar tissue, as shown in Fig 5.³¹

Distal airway inflammation might contribute to changes in pulmonary mechanics associated with nocturnal asthma. There appears to be a physiologic uncoupling of distal lung units from their parenchymal attachments in nocturnal asthma.³² This phenomenon explains the loss of the airway resistance–lung volume relationship that results in no significant fall in airway resistance with increased lung volume. The fall in airway resistance that normally accompanies an increase in lung volume is an important compensatory mechanism observed in patients with asthma. During sleep, loss of the volume–resistance relationship suggests a physiologic uncoupling caused by distal inflammation (Fig 6).³²

It can reasonably be stated that studies of nocturnal asthma provide convincing evidence of a correlation between circadian changes in distal airway inflammatory activity and nighttime lung function. The findings suggest that therapeutic intervention aimed at treating distal airway disease might produce benefits that can be observed in measures of lung function and asthma symptoms.

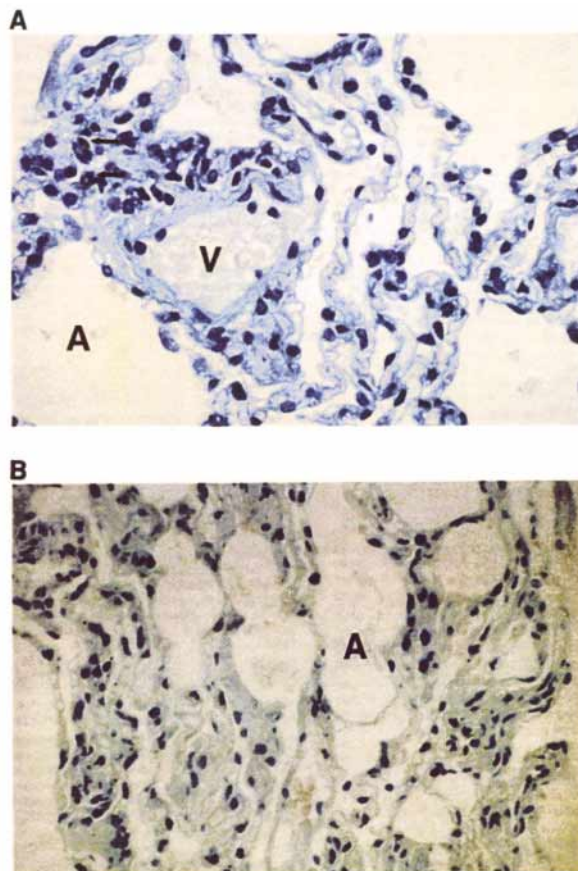


FIG 5. Peripheral airway inflammation in nocturnal asthma (A) and non-nocturnal asthma (B). Photomicrographs of trans-bronchial biopsy specimens showing an increase in eosinophilic infiltration at 4:00 AM in the alveolar tissue area of a patient with nocturnal asthma compared with a patient with non-nocturnal asthma. The biopsy specimens were stained with hematoxylin-eosin and azure. Arrows indicate eosinophils. A, Alveolar space; V, vessel. (Adapted with permission from Kraft M, Djukanovic R, Wilson S, Holgate ST, Martin RJ. Alveolar tissue inflammation in asthma. *American Journal of Respiratory and Critical Care Medicine* 1996;154:1505-10. Official Journal of the American Thoracic Society © American Thoracic Society.)

IMAGING OF THE MID-ZONE AIRWAYS

The entire branching network of distal airways cannot easily be visualized directly with current radiographic techniques. Thin-section computed tomography (CT) can reveal anatomic details of the lung only as small as 200 to 300 μm , corresponding to wall thickness in airways 2 mm in diameter or larger.³³ This CT is at the uppermost limit of small airway dimensions, making the method inadequate for visualizing smaller airways. High-resolution CT (HRCT) studies have attempted to view anatomic features of the small airways in the distal lung. One such study showed that the thickness of small airway walls was increased in patients with asthma compared with control subjects without asthma³⁴; furthermore, small airway wall thickness was correlated with

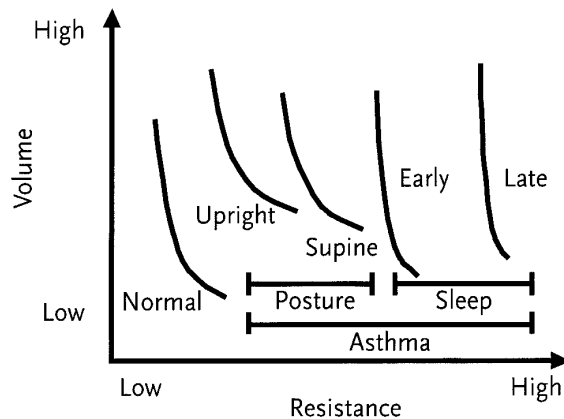


FIG 6. Uncoupling of volume-airway resistance relationship in nocturnal asthma. Volume-resistance curves for healthy subjects and individuals with asthma. Curves for patients with asthma were determined in awake state (upright and supine positions) and supine position during early and late stages of sleep. Note that in patients with nocturnal asthma, as lung volume was increased during sleep (by negative pressure applied to the chest wall), there was very little drop in airway resistance, suggesting airway-parenchyma uncoupling. The effect is especially pronounced during late sleep and does not result from assuming a supine posture during sleep. (Adapted with permission from Irvin CG, Pak J, Martin RJ. Airway-parenchyma uncoupling in nocturnal asthma. *American Journal of Respiratory and Critical Care Medicine* 2000;161:50-6. Official Journal of the American Thoracic Society © American Thoracic Society.)

the severity of asthma. Although these results are consistent with and confirm the extensive structural observations of postmortem studies, they do not supply new information on distal lung function in asthma.

HRCT has proved to be of unique value for its ability to detect functional changes in the small airways by indirectly monitoring air trapping at distal sites.³³ Air trapped in the mid-zone airways at residual lung volume after methacholine challenge can be indirectly detected by HRCT, appearing as regions of decreased signal attenuation.³³ A shift to greater attenuation implies a reduction in gas trapping. Patients with moderate asthma exhibit an aberrant “mosaic” pattern of pulmonary perfusion, which is correlated with small airways obstruction as indicated by gas trapping on HRCT.³⁵ The ability to visualize, albeit indirectly, gas trapping in the small airways is of potential diagnostic value. A study by in’t Veen et al² demonstrated that patients with mild persistent asthma who had frequent exacerbations had increased closing volumes and closing capacities, compared with patients with similar FEV₁ who did not experience frequent exacerbations (Fig 7). The results indicate that distal airways inflammation may be the cause of difficult-to-control asthma and that therapies targeted to that region may be of particular clinical benefit in such cases.

CT scanning has proved useful for observing the effects of constricting stimuli on small airways and of

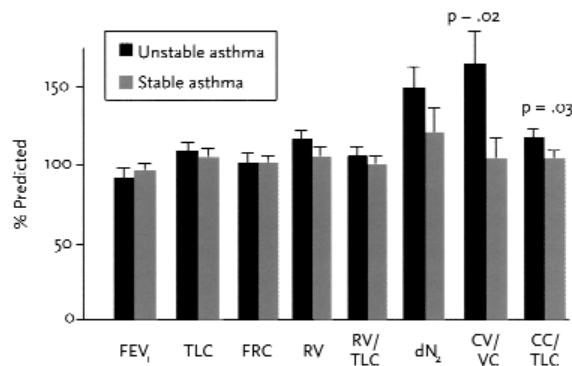


FIG 7. Results of lung volume measurements of patients with difficult-to-control asthma (black bars) and patients with stable asthma (gray bars). All parameters are expressed as percent predicted values (mean $\pm$ SEM). Note that increases in closing volume and closing capacity in patients with recurrent exacerbations are indicative of early airway closure, possibly caused by small airways disease. TLC, Total lung capacity; FRC, functional residual capacity; RV, residual volume; dN₂, slope of phase 3 of the nitrogen expiration curve; CV, closing volume; CC, closing capacity; VC, vital capacity. (Adapted with permission from van't Veer JCCM, Beekman AJ, Bel EH, Sterk PJ. Recurrent exacerbations in severe asthma are associated with enhanced airway closure during stable episodes. *American Journal of Respiratory and Critical Care Medicine* 2000;161:1902-6. Official Journal of the American Thoracic Society © American Thoracic Society.)

pharmacologic interventions aimed at ameliorating distal lung disease. The ability of HRCT to detect gas trapping was used by McNitt-Gray et al³⁶ to demonstrate that methacholine challenge resulted in an increase of gas trapping, confirming that the small airways of the distal lung are hyperresponsive to bronchoconstricting stimuli. In a study by Goldin et al,⁶ helical thin-section CT was performed before and after methacholine challenge in patients with asthma and control subjects. Control subjects showed a decrease of less than 10% in FEV₁, whereas patients with asthma showed a 20% to 36% decrease in FEV₁. Goldin et al⁶ also found that a decrease in pulmonary function was correlated with a decrease in the area of the smallest visible airways; a similar decrease was not observed in the areas of medium or large visible airways. Mean predicted FEV₁ decreased 24% after methacholine challenge; at the same time, a 95% decrease in the area of small airways was detected.⁶

In a study with potentially far-reaching consequences in asthma therapy, Laurent et al³⁵ found no change in air-trapping score after salbutamol inhalation in patients with moderate asthma, suggesting either that bronchodilation was not effective at peripheral sites or that such sites were inaccessible. However, antiinflammatory therapy might supply a more valuable means of therapeutic intervention in the distal lung, as evidenced by an HRCT study demonstrating that a small-particle-size (~1 μ m) hydrofluoroalkane (HFA) preparation of beclomethasone dipropionate (BDP) can diminish air trapping in patients

with mild-to-moderate asthma,³³ thereby increasing peripheral airways patency. In the study by Goldin et al,⁶ functional HRCT proved to be a sensitive means of monitoring pulmonary alterations, detecting changes in distal lung physiology that escaped conventional measures of pulmonary performance such as spirometry.

DISTAL LUNG TARGETING OF INHALED CORTICOSTEROIDS

At present, inhaled corticosteroids remain the mainstay of therapy for the long-term control of asthma.¹ Although their efficacy and safety are established, the therapeutic actions of inhaled corticosteroids at sites of small airway inflammation are still the subject of ongoing research. These studies are particularly challenging because of the relative anatomic inaccessibility of the distal lung and the difficulty of separating the distal lung and large airways physiologically.

Therapeutic adequacy of current inhaled corticosteroid formulations

Although inhaled corticosteroids are the gold standard of control therapy for asthma, the most commonly used formulations are deposited in relatively low amounts in the peripheral lung, a reflection of their unfavorable aerodynamic properties. Antiinflammatory treatment needs to be directed to both the large airways and the distal lung if maximal suppression of airway inflammation is to be achieved.⁹

Even aggressive treatment at a young age may not be sufficient to contain airway damage and prevent pulmonary deficits later on. A study of remissions in childhood asthma after long-term inhaled corticosteroid therapy demonstrated a high rate of residual obstruction resistant to treatment, manifested as a plateau in airway caliber improvement; although hyperresponsiveness did stabilize, it did so at subnormal levels of methacholine.³⁷ It is possible that poor access of inhaled medication to distal sites allows lingering regions of inflammation to continue even as the central airways receive adequate treatment.¹¹

The role of particle size

Aerosol particle size is a key element in determining lung deposition and the regional distribution of inhaled medication within the lung. In general, smaller aerosol particles are more likely to be deposited in the lung. The respirable fraction of particles emitted by a pressurized metered-dose inhaler (pMDI) is closely related to the proportion of drug availability for deposition in the lung; aerosol particles with a mass median of approximately 4.7 μ m are respirable.³⁸ In the lung, the smaller and less dense the particle, the more likely it is to reach the distal regions. However, particles between 0.6 and 0.3 μ m mass median aerodynamic diameter are often exhaled.³⁹

The mandated worldwide phase-out of ozone-depleting chlorofluorocarbons (CFCs) offered manufacturers an opportunity to enhance pMDI technology, a device system that has remained largely unchanged since

its introduction over 40 years ago.⁴⁰ Among the alternative propellants developed for use in pMDIs are HFAs, which produce aerosols that differ significantly in particle size from CFCs. For example, new HFA formulations of inhaled corticosteroids have an average particle size of 1.1 μm compared with up to 4.0 μm for CFC corticosteroid aerosols (Table I).⁸ The fact that the aerodynamic properties of corticosteroids in HFA aerosols differ so much from those of CFC aerosols has implications in terms of reaching into airways. With their relatively large particle size, the CFC pMDIs typically deliver about 90% of their particles to the oropharynx^{8,41}; in contrast, approximately 60% to 70% of drug particles enter the lungs with new HFA formulations. The shift toward greater pulmonary deposition on substitution of HFA propellant for CFCs is illustrated in Fig 8 for the inhaled corticosteroid fluticasone. Deposition studies in which scintigraphic techniques with technetium Tc 99m–radio-labeled HFA-BDP are used supply visual evidence of marked alterations in deposition compared with CFC-BDP. The increased solubility of BDP in HFA compared with CFC is likely the reason for reduction in particle size resulting in lung deposition increasing by 55% to 60% from 4% to 7%.³⁸ In addition to increasing lung deposition, the reduction in oropharyngeal deposition with HFA formulation can minimize local side effects.⁴² A scintigraphic study comparing fluticasone HFA with fluticasone CFC showed a similar shift in deposition patterns, with almost 70% of labeled fluticasone HFA deposited in the lung, compared with less than 20% of the CFC formulation (Fig 9).⁴³

The importance of corticosteroid solubility to lung deposition is illustrated in a scintigraphic study of the regional pulmonary distribution of ^{99m}Tc–radiolabeled HFA mometasone furoate.⁴⁴ Unlike BDP, mometasone furoate is not soluble in HFA and is delivered as an aerosol suspension in that propellant. Average whole-lung deposition of HFA–mometasone furoate was 13.9%, with the central, intermediate, and peripheral lung zones receiving 5.3, 4.7, and 4.0% of the dose, respectively. Although oropharyngeal deposition was lower with a CFC formulation, it was nevertheless significantly higher than with corticosteroids soluble in HFA, such as BDP or fluticasone, with an oropharyngeal deposition of 29% and 25%, respectively.³⁸

Goldin et al³³ used HRCT and regional air trapping to compare the efficacy of HFA- and CFC-corticosteroid formulations in corticosteroid-naïve patients with mild-to-moderate asthma. Pretreatment functional CT before and after a methacholine challenge was performed at baseline and after 4 weeks of treatment. Post-treatment scanning indicated significant improvement in air trapping for both groups. However, after challenge with equal constrictor stimuli, smaller increases in air trapping were observed for subjects treated with the HFA formulation.³³ Results are consistent with the hypothesis that the finer HFA aerosol has better access to the small airways of the distal lung and may provide more effective antiinflammatory therapy. There is no significant differ-

TABLE I. Comparative particle sizes of inhaled corticosteroid formulations

	Particle size (MMAD) (mm)	Lung deposition (%)
Fluticasone DPI*†	5.4	15.0
Triamcinolone acetonide†‡	4.5	22.0
Budesonide DPI†§	4.0	32.0
Flunisolide CFC¶	3.8	19.7
Beclomethasone CFC¶#	3.5	4.0
Fluticasone CFC†‡	2.4	26.0
Flunisolide HFA	1.2	68.3
Beclomethasone HFA	1.1	56.0

MMAD, Mass median aerodynamic diameter; DPI, dry powder inhaler; CFC, chlorofluorocarbon; HFA, hydrofluoroalkane.

*Asmus MJ. Respirable dose of fluticasone from a metered dose inhaler (MDI) and two dry powder inhalers (DPI) [poster]. Presented at the American Thoracic Society Annual Meeting, 2001 May 18–23; San Francisco, Calif.

†Sheth KK. Innovations in dry powder inhalers [supported by Glaxo-SmithKline], unpublished data, 2000.

‡Gabrio BJ. Particle size and dynamic plume characteristics of corticosteroid-containing metered dose inhalers [poster]. Presented at the 2000 American College of Asthma, Allergy, and Immunology Annual Meeting, November 3–8; Seattle, Wash.

§Mitchell JP, Nagel MW, Archer AD. Size analysis of a pressurized metered dose inhaler-delivered suspension formulation by the API Aerosizer time-of-flight aerodynamic particle size analyzer. *J Aerosol Med* 1999;12:255–64.

¶Richards J, Hirst P, Pitcairn G, Mahashabde S, Abramowitz W, Nolting A, et al. Deposition and pharmacokinetics of fluticasone delivered from pressurized inhalers containing non-CFC and CFC propellants. *J Aerosol Med* 2001;14:197–208.

||Leach CL. Improved delivery of inhaled steroids to the large and small airways. *Respir Med* 1998;92(suppl A):3–8.

#Barnes PJ, Pedersen S, Busse WW. Efficacy and safety of inhaled corticosteroids. New developments. *Am J Respir Crit Care Med* 1998;157:S1–S53.

ence between the two treatments with respect to symptoms, spirometry, or methacholine responsiveness as assessed by FEV₁, suggesting that the CT scanning technique was, perhaps, more sensitive than commonly used measures of pulmonary function.³³

Differences in deposition patterns are governed by a statistical model predicting that small particles have a greater likelihood of reaching the lung; as particle size increases, the balance shifts to one favoring deposition in the mouth and throat.³⁸ According to this model, HFA-based corticosteroids should be able to achieve efficacy equivalent to that of existing CFC-based formulations at lower doses and, consequently, with less adverse effects.⁸

Dry powder inhalers

In addition to a change to an HFA propellant, breath-actuated dry powder inhalers (DPIs) represent another alternative to CFC-pMDIs. However, data on regional lung deposition and distal lung access by DPI-delivered corticosteroids are scarce. Particle sizes can vary, with some formulations producing particles smaller than those in CFC-based formulations; in such cases, enhanced deposition in the distal lung area is likely. The major concern affecting deposition with DPIs is the relationship

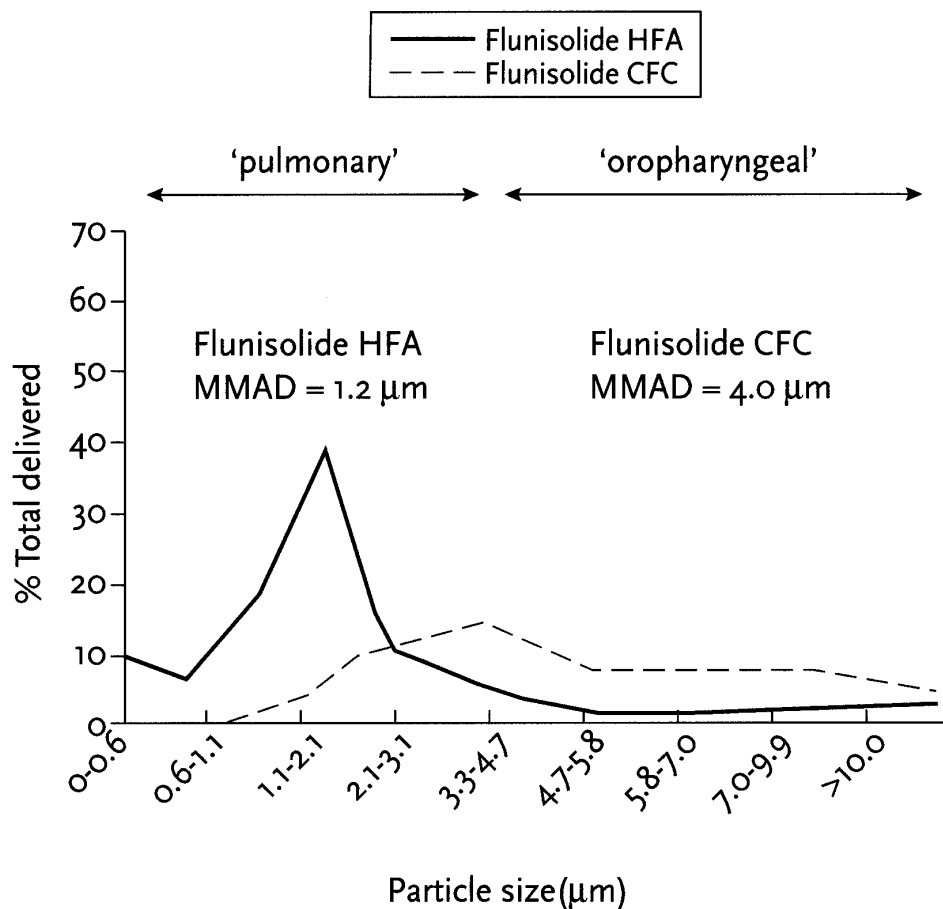


FIG 8. Particle size distribution and regional deposition of HFA and CFC flunisolide. A small average aerosol particle size is associated with relatively greater deposition in the lungs and relatively less deposition in the oropharynx. *MMAD*, Mass median aerodynamic diameter. (Adapted from Greos LS. Re-engineering asthma formulations to target the small airway. Presented at: CME symposium, "Advances in understanding the role of small airway inflammation: implications for optimizing asthma treatment," at the Fifty-seventh Annual Meeting of the American Academy of Allergy, Asthma & Immunology; March 18, 2001; New Orleans, La. With permission from Forest Laboratories, Inc.)

between deposition and inspiratory flow rates (IFRs), with faster flow rates seeming to increase lung deposition. For example, scintigraphic imaging of budesonide delivered by DPI in healthy volunteers showed an overall pulmonary deposition of 14.8% and 27.7% at slower and faster IFRs, respectively.⁴⁵ Regional distribution of the inhaled medication was also affected by IFRs, with 11.8% and 6.3% of the metered dose reaching the lung periphery at faster and slower IFRs, respectively.⁴⁶ With the delivery device contributing to the efficacy of a DPI, the amount of medication deposited in the central and peripheral airways can vary dramatically from one individual to the next because of differences in inspiratory flow and the mechanics of DPI use.

Particle size and efficacy

The relationship between aerosol particle size and clinical parameters of efficacy has been well studied for

bronchodilators. A study of patients with mild asthma who received monodisperse β -agonist aerosols of two different diameters—5 μ m and 2.5 μ m—showed marked improvements in $FEF_{25\%-75\%}$ and $FEF_{75\%-85\%}$ (variables thought to be indicators of small airway function in the distal lung) with the smaller particle. The results suggest additional clinical benefits for medications that can reach peripheral airways.⁴⁷

Another study, by Zanen et al,⁴⁸ examined FEV_1 in patients with stable asthma after administration of monodisperse ipratropium bromide aerosols in particle sizes of 1.5, 2.8, and 5 μ m. The two smaller particle sizes produced significantly better bronchodilation than the 5- μ m aerosol, leaving the investigators to conclude that optimal particle size for anticholinergic aerosols should be 2.8 μ m or less. Again, the increased efficacy of the smaller particles was attributed to extended reach into lower airways.⁴⁸

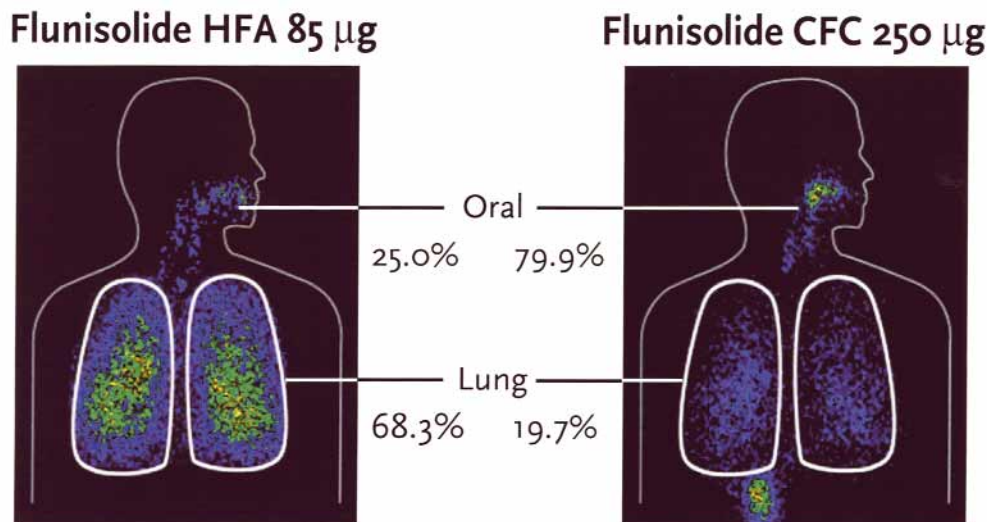


FIG 9. Flunisolide lung deposition. Scintigraphic studies of CFC flunisolide and HFA flunisolide at one third the dose. Flunisolide formulations were ^{99m}Tc -radiolabeled. (Adapted from Tashkin DP. Measuring asthma outcomes: Is FEV₁ still appropriate? Presented at: CME symposium, "Advances in understanding the role of small airway inflammation: implications for optimizing asthma treatment," at the Fifty-seventh Annual Meeting of the American Academy of Allergy, Asthma & Immunology; March 18, 2001; New Orleans, La. With permission from Forest Laboratories, Inc.)

Short-term studies with HFA-corticosteroid formulations have assessed the efficacy of reduced dosages in relation to extended pulmonary reach. Corren et al⁴⁹ showed comparable efficacy between flunisolide HFA at one third the dose of its CFC counterpart. However, trends favored flunisolide HFA on several parameters, including 40.4% fewer asthma exacerbations ($P = .077$). Similar efficacy at lower doses was reported for HFA-BDP compared with CFC-BDP in a 6-week study by Busse et al.⁵⁰ However, longer-term efficacy studies are still needed.

Oral anti-inflammatory agents: An alternative route to the distal lung?

Small-particle formulations of inhaled corticosteroids are not the only potential means of treating distal airway inflammation associated with asthma. Oral antiinflammatory agents would appear to have access to this area of the lung through the circulation. The leukotriene receptor antagonists (eg, montelukast and zafirlukast) are a new class of oral antiinflammatory agents that also possess bronchodilating activity.⁵¹ They are efficacious and safe for the treatment of asthma in adults and children,^{51,52} they appear to reduce the risk of asthma exacerbations, and they are steroid-sparing.⁵³ Leukotriene antagonists may be especially useful as add-on therapy in patients with difficult-to-control asthma.⁵⁴ Because they are newly introduced agents, their potential long-term effectiveness and safety need to be established.⁵⁵ There are only a few published studies on the regional airway

effects of these drugs. The leukotriene antagonist montelukast reduced circulating eosinophil counts,^{56,57} indicating a generalized antiinflammatory activity. Sputum eosinophils are also reduced after 4 weeks of montelukast therapy.⁵⁷ However, specific studies are needed to define the potential action of anti-leukotrienes on distal airway inflammation.

Their systemic availability would appear to give oral corticosteroids the potential to treat distal lung inflammation. However, there is little evidence to support the argument that oral corticosteroids, by virtue of their potential access to distal sites, have a therapeutic benefit over their inhaled equivalents in the long-term treatment of asthma, especially in light of the hazards associated with long-term use of these drugs. Patients with asthma receiving long-term prednisone therapy are at substantially increased risk for systemic adverse effects such as bone loss⁵⁸ and growth inhibition.⁵⁹ Inflammation can be observed in the central and distal airways of patients receiving intensive oral corticosteroid therapy for severe asthma,¹⁵ which suggests that those patients are relatively steroid insensitive.

Systemic and local adverse effects of extrafine corticosteroid aerosols

The enhanced peripheral airway deposition for new formulations of inhaled corticosteroids has implications regarding their adverse effects, as well as their clinical efficacy. This is particularly important for inhaled corticosteroids because of concerns about systemic availabil-

ity. Oropharyngeal deposition poses a potential problem, because the swallowed portion that escapes first-pass metabolism becomes systemically available⁶⁰; pulmonary deposition is of concern because of lack of significant lung metabolism, allowing medication to be absorbed unaltered into a patient's circulation.⁶¹ Most inhaled corticosteroids are absorbed unaltered into the pulmonary circulation, so that with increased deposition, a larger portion of the drug may become systemically available.⁶² Both low systemic availability and a high rate of first-pass metabolism reduce the potential for unwanted systemic effects.^{63,64}

The concern about adverse systemic effects from inhaled corticosteroids is clearly justified. Highly potent corticosteroids can suppress cortisol levels after a single dose,⁶⁵ and even an agent with low systemic availability can exert significant effects if its affinity for the glucocorticoid receptor is sufficiently high.⁶⁶ Thus, another potential advantage of fine aerosol corticosteroids is the dose reduction that is derived from efficiencies in pulmonary targeting. As a result, fewer local adverse events (eg, oral candidiasis, pharyngitis), as well as fewer systemic events, are likely. In a 1-year study, HFA flunisolide at a dose equal to one third the standard CFC flunisolide dose was compared with CFC-BDP in adults and adolescents with mild-to-moderate asthma. No significant between-treatment differences were observed for efficacy. Significant hypothalamo-pituitary-adrenocortical axis suppression was not observed in either group as determined by urinary cortisol measurements and response to cosyntropin stimulation. With regard to local effects, patients receiving HFA flunisolide had consistently fewer positive smears and cultures for *Candida albicans* and a lower incidence of candidiasis.⁶⁷

Given the enhanced lung deposition of a new HFA formulation, if it were administered at a milligram dose equal to that of the CFC formulation, a large amount of the drug would probably become available for absorption from the lung. Without being subject to first-pass metabolism, the systemic availability of corticosteroid absorbed from the lung is likely to be accompanied by a substantial increase in the risk of systemic adverse effects. Therefore, the favorable aerosol properties that allow equivalent efficacy of an HFA formulation at a reduced dose are also essential for maintaining its safety.

Systemic events with inhaled corticosteroids are of particular concern in the pediatric setting. A slowing of growth velocity was reported in children with asthma receiving inhaled CFC-BDP^{68,69}; the risk of growth suppression appeared lower for budesonide.⁷⁰ A recent study of children receiving reduced-dose flunisolide HFA delivered through a spacer, CFC-BDP, or cromolyn sodium for 1 year showed no significant growth effects. Mean changes from baseline height at week 52 were 6.2 cm for the flunisolide HFA and cromolyn sodium groups and 5.1 cm for the CFC-BDP group. In contrast, CFC-BDP was associated with a decline in linear height.⁷¹

CONCLUSIONS

Although the distal airways are significant and persistent sites of inflammation in asthma, inflammation in this lung compartment appears to be undertreated with most current inhaled medications. The weight of evidence from clinical and preclinical studies of inhaled bronchodilators and corticosteroids strongly supports the role of aerosol particle size, as well as corticosteroid potency, as important considerations for achieving optimum efficacy in patients with asthma. The fact that smaller particles have better access to peripheral airways suggests that this feature accounts, in large part, for the improved performance at lower doses of inhaled corticosteroid medications delivered as extrafine aerosols. It is likely that as the value of treating inflammation in the entire lung becomes more accepted, there will be further refinements in targeting antiinflammatory medications to distal airways. As extrafine-particle steroids with access to distal lung inflammation become increasingly available, long-term asthma outcome studies will determine the exact clinical efficacy of these agents.

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