

The Role of Small Airways in Childhood Asthma

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Over the last 10 to 15 years, the emerging role of distal or small-airway inflammation in the pathogenesis of asthma has been increasingly recognized. This review attempts to focus on the importance of small-airway dysfunction in asthma. Pathologic changes seen in the distal airways were highlighted using data obtained from biopsy studies, as well as changes seen in fatal asthma. Advances in the diagnostic evaluation of the distal airways were reviewed, specifically pulmonary function tests (including exhaled nitric oxide and impulse oscillometry), and newer imaging techniques. Finally, studies that have led to advances in therapeutic treatment of the small airways in childhood asthma were highlighted. The terms distal airways and small airways are used interchangeably throughout the article.

Introduction

OVER THE LAST 10 years, there have been many advances in the understanding of the small airways in both health and disease. Many review articles^{1–12} have focused on the importance of the small airways in obstructive lung diseases such as asthma and chronic obstructive pulmonary disease (COPD). Despite the understanding of the importance of the distal airways, many opportunities exist for a deeper appreciation of this important area of gas exchange and site of early pathological occurrence, as newer diagnostic tools become more widely available. As researchers further explore this often forgotten and largely misunderstood region of the human lung, newer therapeutic tools are becoming available, allowing better peripheral deposition of anti-inflammatory medications into the small airways.¹³ This article emphasizes the latest diagnostic and therapeutic advances over the last 10 years in the exploration of the small airways and their role in obstructive lung disease.

Physiology of Small-Airway Dysfunction

The tracheobronchial tree is conventionally divided into the conducting zone and the respiratory zone.¹⁴ The bronchial tree consists of approximately 23 levels of branching. The first 16 to 17 branches play no part in gas exchange, and they are referred to as the conducting zone. They simply serve to transport the inhaled air into the remaining 6 to 7 branches, known as the respiratory zone, where gas exchange takes place. The conducting zone includes the cartilaginous airways or bronchi, whereas the respiratory zone includes the respiratory bronchioles, alveolar ducts, and alveolar sacs. The airways in this respiratory zone consist of those airways that are <2-mm inner diameter and are known as the small airways or sometimes referred to as the

anatomic unit known as the acinus.¹⁴ A recent review by Hyde et al. highlights the importance of the small airways in the anatomy and physiology of the tracheobronchial tree.¹⁵

The velocity of airflow (and airway resistance) in the respiratory bronchioles or small airways drops dramatically, and gas exchange occurs mainly by diffusion.^{16,17} The combined cross-sectional area of the airways in the respiratory zone (generations 16 to 23) is enormous because of the large number of branching airways. In fact, the respiratory zone volume of 2.5 to 3 L makes up the majority of the normal lung volume, given that the adult lung volume is about 5 L.¹⁶ Because the total volume and combined surface area of the distal airways are much greater than the combined volume and surface area of the large airways, inflammatory changes in the distal airways in patients with asthma can have a dramatic effect and a large impact on lung function, disease progression, and physiologic disturbances.⁷

Studies performed in healthy animals over 30 years ago demonstrated that the small airways accounted for <10% of the total resistance to airflow.¹⁸ However, subsequent studies showed that small airways contributed a larger proportion (~80%) of total airway resistance than previously believed. Consequently, only a minor role was assigned to the small airways in the pathophysiology of asthma and other lung diseases. Advances were made when the dynamic effects of small airways were investigated by a new-found technique that measured the pressure gradient in the distal lung (tissue viscance: defined as a measure of the pressure gradient from one end of tube to other when flow occurs). The technique involved placing a capsule directly on the pleural surface while air was delivered to the airways through a catheter.¹⁹ When the animals were given histamine, tissue viscance accounted for 80% of the total lung resistance.

Understanding human lung mechanics in asthma was advanced when Wagner et al.²⁰ utilized an orthograde

collateral ventilation technique that employed a wedged bronchoscope to measure airway resistance. Compared to controls, patients with mild asthma demonstrated elevated resistance in the small airways, even when FEV₁ was normal. Shortly thereafter, in a landmark study, Yanai et al. compared distal airway resistance to total lung resistance in mildly sedated, awake human subjects.²¹ A catheter-tipped micromanometer sensing lateral pressure of the airway was wedged into the right lower-lobe distal bronchus. Small airway resistance contributed only 24% of resistance in the normal lungs, but in patients with long-standing obstructive lung disease, it contributed over 50% of the total airway resistance.²¹ Furthermore, the peripheral airways were the predominant site of obstruction, irrespective of the different pathogenesis of chronic airway disease.²¹ A decade later, Kraft et al.²² using the wedged bronchoscopic technique investigated small-airway dysfunction in nocturnal asthma. At 4 a.m., small airway resistance was increased in subjects with nocturnal asthma when compared to those asthmatics without nocturnal worsening and with normal control subjects. Given the previous findings that parenchymal inflammation, as seen on transbronchial biopsies, is increased in nocturnal asthma,^{22,23} it was concluded that the distal lung units were selectively altered by the cyclic inflammatory process observed in nocturnal asthma.

Pathology of Small-Airway Dysfunction

Understanding the pathology of the small airways in asthma has been limited because of the difficulty in sampling and studying the distal respiratory zone of the tracheobronchial tree. As the understanding of asthma evolves, it is clear that the small airways, as well as the large airways, are affected by the inflammatory process characteristic of this disease (Fig. 1). Previously, the inability to measure the function of small airways delayed awareness of their contribution to the overall obstructive disease. The availability of more sophisticated investigative techniques is opening a new

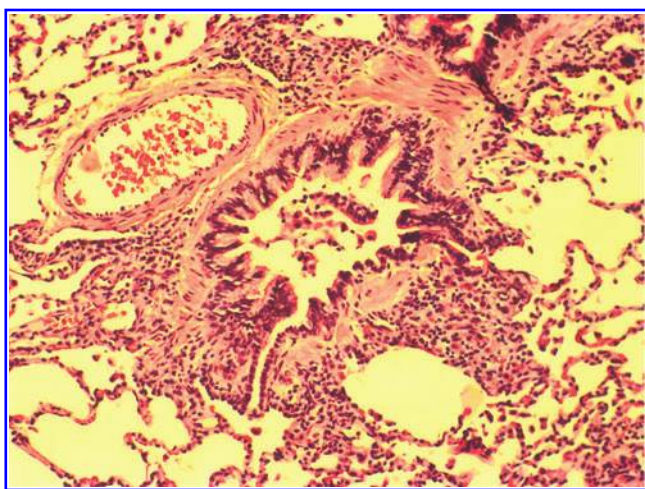


FIG. 1. Lung biopsy showing a bronchiole (small airway) (200× magnification; hematoxylin and eosin stain) from a 9-year-old child with severe persistent asthma demonstrating airway inflammation, smooth muscle hyperplasia, and epithelial sloughing characteristic of significant small-airway involvement. Photomicrograph picture courtesy of Dr. Susan Coventry, University of Louisville.

horizon in the knowledge of asthma pathophysiology with new possibilities for developing highly effective therapies.

Histological evidence of inflammation in the small airways in asthma is seen in autopsy studies, surgical specimens, and transbronchial biopsies. Increasing evidence suggests that inflammation occurs in the distal airways, as well as in the central airways. Compared with larger airways, more severe inflammation is apparent in the small airways in patients with severe asthma, and in patients with nocturnal asthmatic symptoms.^{23,24} Glucocorticoid receptors are distributed throughout the lung, with the highest concentration found in the small airways (i.e., alveolar walls and endothelium) and the smooth muscle of the bronchial and pulmonary vessels. Furthermore, the numbers of glucocorticoid receptor β -expressing cells,²⁵ high-affinity IgE receptor expression,²⁶ and basophils²⁷ are increased in fatal asthma, and are found equally in both the large and small airways. Although further clarification on the clinical effect of inflammation in the distal airways is needed, it is likely however that poorly controlled inflammation in the peripheral airways might exacerbate asthma, contributes to the accelerated decrease in lung function, and promotes airway remodeling.⁷ However, all of these studies were done in adult subjects, and there remains a paucity of direct biopsy data in pediatric subjects.

Structural changes (airway remodeling) have been demonstrated in airway walls in fatal asthma.^{28–30} One study²⁸ compared 24 adult patients with fatal asthma with non-asthmatic controls using immunohistochemical markers for collagen, fibronectin, and matrix metalloproteinases. An increased expression for all these markers in the outer wall of the distal (small) airways in fatal asthma compared to controls was found. This study demonstrated the airway wall remodeling and structural changes leading up to fatal asthma. The same investigators also showed abnormal alveolar attachments in the adventitial layers of small airways in fatal asthma.³⁰ These structural changes lead to airway–parenchymal uncoupling. Although parenchyma and airways are highly interdependent in most circumstances, their relationship may change with inflammation in the peripheral lung. Inflammation of the small airways results in a separation of these 2 compartments and adverse changes in lung mechanics that are typical of asthma.⁴ Theoretically, edema or inflammatory exudates in the peribronchial space reduce the negative peribronchial pressure, and the elastic load pulling the airway open will decrease.³¹ Thus, the protective effects of airway–parenchyma interdependence are lost, resulting in a widespread airway obstruction. Such uncoupling of airways and parenchyma has also been observed to follow a circadian pattern in subjects with nocturnal asthma.³² The availability of more sophisticated investigative tools is opening a new chapter in our understanding of the small airways in both health and disease. The basis of these methods measures ventilation inhomogeneity and/or increased airway closure.³³

Diagnostic Studies of Small Airways

Most commonly, the tools used to evaluate and follow small-airway dysfunction are accomplished in the pulmonary function laboratory. The ability of peak flow monitoring to detect accurately the presence of small airway obstruction is poor.³⁴ Lung volumes can be used to show the

hyperinflation and air trapping seen in small airways disease.³⁵ An elevation in residual volume/total lung capacity (RV/TLC) has been shown in asthmatics to correlate with small-airway obstruction.³⁶ In the diagnosis and management of asthma, spirometry remains the procedure of choice.³⁷ Forced expiratory volume in one second (FEV₁) and FEV₁/forced vital capacity (FVC) mainly represent the larger airways, whereas forced expiratory flow between 25% and 75% of forced vital capacity (FEF₂₅₋₇₅) is a reflection of small-airway function.¹⁷ FEF₂₅₋₇₅ is a relatively imprecise marker for peripheral lung function, but one that is readily available and used most frequently in clinical practice. Furthermore, the normal value range for this parameter is still disputed. However, recent studies by Ciprandi et al.³⁸ showed that FEF₂₅₋₇₅ was below 65% of predicted in 45% of pediatric patients with mild asthma, and elegant studies from the Childhood Asthma Research and Education Network found that by constructing a receiver-operating curve for FEF₂₅₋₇₅-versus-bronchodilator responsiveness (20% change in FEV₁), a cutoff value of 68% was able to predict bronchoreponsiveness³⁹ in patients with mild asthma and normal FEV₁. These findings suggest that FEF₂₅₋₇₅ is a more-sensitive measure of peripheral airflow obstruction than FEV₁ or FEV₁/FVC. In addition, de Lange et al.⁴⁰ showed in young asthmatic adults that the FEF₂₅₋₇₅ had a better correlation with air trapping measured by hyperpolarized Helium-3 MRI than FEV₁ or FEV₁/FVC.

Unfortunately, FEF₂₅₋₇₅ is hampered by its poor reproducibility and requirement of a forced expiratory maneuver.⁴¹ As such, the use of impulse oscillometry (IOS) shows promise in the evaluation of the small airways and is effort independent, with minimal patient cooperation needed. This technique provides useful clinical information that prominently includes functional assessment of small, peripheral airway behavior beyond what is available from commonly used pulmonary function tests. IOS utilizes external applied pressure signals and their resultant flows to determine lung mechanics. In IOS, low oscillation frequencies are transmitted to the distal lung. Hence, the resistance at 5 Hz (R5), which reflects both the proximal and distal airway, and the resistance at 20 Hz (R20), which reflects the proximal airway, can be subtracted to get a measure of the distal airway contribution to resistance (R5–R20). Other measures of the distal airways include resonance frequency (Fres), the frequency at which the total reactance is zero, and the area of reactance (AX), the total area between 5 Hz and Fres.⁴² IOS has been shown to be useful in the diagnosis of asthma and small-airway disease, assessment of control, and correlates with CalvNO.⁴³⁻⁴⁶ Currently, IOS typically is only available at large academic centers.

A recent study of adults with asthma showed significant correlations between CalvNO, R5–R20, FEV₁, and FEF₂₅₋₇₅.⁴⁴ A study in children showed a decrease in exhaled nitric oxide (eNO) after methacholine-induced bronchoconstriction.⁴⁵ This decrease correlated with small-airway resistance by R5–R20, but not with large-airway resistance or FEV₁. The eNO decrease was more pronounced in those that had a larger decrease in R5–R20 after methacholine, implying more small-airway dysfunction. A future study looking at CalvNO instead of total eNO would give this more credence. A recent study comparing conventional spirometry to IOS in children with asthma showed that the majority (95%) had normal FEV₁ percent predicted despite physician assessment of uncontrolled

asthma.⁴³ FEF₂₅₋₇₅ percent predicted (36%) and FEV₁/FVC (39%) fared better. Using IOS, R5, R5–R20, Fres, and AX were all statistically different in those with uncontrolled asthma. Both prebronchodilator AX and R5–R20 had a >80% positive and negative predictive value in classifying patients as having uncontrolled asthma. In this study, IOS had a better discriminatory value than spirometry,⁴⁷ despite spirometry being one of the parameters used to define control by the physicians.

With airway inflammation involving the large and small airways noted in asthma,²⁸ utilizing exhaled breath molecular markers is an attractive potential noninvasive measure. eNO, the most widely used of these biomarkers, can be shown to be a marker of small-airway disease. Keen et al.⁴⁸ showed in a cross-sectional pediatric study that asthmatics had elevated eNO levels that correlated with a positive isocapnic dry air hyperventilation challenge. While NO is generated from all levels of the respiratory tract by NO synthetase, the levels have been shown to correlate with a steeper slope of the single-breath nitrogen test phase III.⁴⁹ This correlates with the nonhomogeneous emptying of lung units as noted in those with small-airway pathology.⁵⁰ The Lung Clearance Index (LCI) is a measure of this ventilation heterogeneity derived from the multiple-breath inert gas washout (MBW) during tidal breathing. This measure has been shown to be more sensitive than FEV₁ at detecting airway disease in children with asthma and cystic fibrosis.^{48,51,52} Detailed information on ventilation homogeneity can be gathered from MBW by calculating the relative contribution of the conducting airways, S_{cond}, and the acinar airways, S_{acin}. Keen et al.⁵³ showed in pediatric asthma that elevated S_{cond} was the most common abnormality, and that it correlated with decreased asthma control test scores and elevated LCI, but not with FEV₁.

More recently, the use of mathematical modeling and multiple extraction flow rates can assess the small-airway contribution.^{54,55} Using either the 2 compartment (2CM) or the trumpet shape of the airway tree and axial diffusion (TMAD) model for NO dynamics, a measure of bronchial flux (J_{NO}, proximal contribution) and alveolar concentration (C_{alv}, peripheral contribution) can be obtained. In a study of steroid-naïve newly diagnosed asthmatics, both J_{NO} and C_{alv} were elevated in comparison to normal.⁵⁵ While in asthmatics, J_{NO} was correlated with FEV₁/FVC and not with FEF₂₅₋₇₅, C_{alv} was the opposite. After 12 weeks of ICS, J_{NO} levels decreased and were no longer significantly different than controls, while there was only a marginal decline in C_{alv}. Interestingly, C_{alv} was markedly decreased with hydrofluoroalkane-beclomethasone propionate (HFA-BDP) as opposed to fluticasone treatment. This same group has since postulated that C_{alv} via the TMAD model may be a more selective measure of small airways function than the 2CM.⁵⁴ While both models led to correlation with FEF₂₅₋₇₅, C_{alv} was not correlated with FEV₁/FVC and sputum eosinophils in the TMAD, as opposed to the 2CM, model. Based on the modeling, one might predict contamination by the larger airways in the 2CM model. Other biomarkers such as N8-(carboxymethyl) lysine (CML) have also been used to look at small airways in asthma. CML is located in the epithelial cells of the small airways. As seen with CalvNO, CML levels are elevated in asthmatics, correlate with FEF₂₅₋₇₅, and decline markedly with HFA-BDP compared to fluticasone.⁵⁵

Sputum induction is another potential modality of evaluating airway inflammation noninvasively in asthmatics.⁵⁶ The clinical utility of sputum analysis and the relationship to

small airways remain unclear. Lex et al.⁵⁷ evaluated pediatric patients with moderate-to-severe persistent asthma and showed that increased sputum eosinophil percentage is a reasonable predictor of the presence of airway eosinophils in BAL. However, a normal sputum eosinophil percentage has a 63% negative predictive value for ruling out the presence of BAL eosinophils. Snijders et al.⁵⁸ in a pediatric bronchoalveolar lavage study showed that eosinophils and associated proteins were increased in asthmatic children when compared to controls without atopy, but not when compared to atopic controls.

Previous work has shown that patients with fatal asthma or those with asthma undergoing pneumonectomy or lobectomy for unrelated reasons have changes in their small-airway pathology that separates them from nonasthmatics and those with COPD.^{28,59} While that is not a viable diagnostic modality, transbronchial biopsy can be used to assess the small airways. In severe steroid-dependent asthmatics, the small airways have an increase in the number of inflammatory cells when compared to the large airways.⁶⁰ Although the type of ICS used was not reported, perhaps if one of the newer smaller steroid molecule moieties were used, these changes could be ameliorated. No transbronchial biopsy data are available from asthmatic children due largely to ethics concerns.⁶¹

Radiologic Studies

While the central airways in asthma have been imaged with computerized tomography looking at airway wall thickening, the use of high-resolution computerized tomography (HRCT) allows better spatial resolution of the smaller airways. The HRCT findings of increased air trapping, as evidenced by decreased lung attenuation, and prominence of the centrilobular structures have been shown in adult asthmatics.^{62,63} The importance of obtaining both inspiratory and expiratory images on HRCT scanning to differentiate air trapping and ground-glass opacities is discussed in detail in a review by Brody.⁶⁴ Lee et al.⁶² in a study of HRCT findings in adult patients with near-fatal asthma showed a stepwise increase in centrilobular structures from none in controls to 36% of mild asthma cases, 70% with moderate-to-severe asthma, and 100% in those with near-fatal asthma. In a subset of patients treated with inhaled corticosteroids and asymptomatic at follow-up, repeat HRCT showed a significant reduction in these centrilobular structures. Of note, the HRCT prominence of centrilobular structures and air-

trapping did not correlate with FEV₁. This prominence of centrilobular structures may be the HRCT correlate of bronchiolar mucus impaction, peribronchiolar inflammation, and small-airway remodeling seen pathologically.

Quantitative HRCT measurements of lung density can be used to look at air trapping. The percentage of lung field occupied by low attenuation (LAA%), the mean lung density (MLD), and their respective ratios on inspiratory and expiratory scans have been shown to differ between those with and without asthma, controlled, and uncontrolled asthma, and be relatable to pulmonary function in adults.^{63,65,66} Unfortunately, a prospective 6-year study of mild-to-moderate adult asthmatics showed irreversible or progressive HRCT changes despite ICS therapy.⁶⁷ While no pediatric asthma studies are available, in other pediatric obstructive disease processes, HRCT correlates of small-airway disease are seen.^{68,69}

Partly due to the ionizing radiation hazards of repeated HRCT scanning, there is emerging interest in the use of hyperpolarized gases as contrast agents for MRI. When there is a ventilation defect, the helium-3 or xenon-129 does not fill the airspaces, leading to a dark area on an otherwise high signal throughout the lung. While there is general concordance with HRCT, discordance has been postulated to demonstrate the existence of functional versus structural differences in air trapping.⁷⁰

In conclusion, for most patients, the diagnosis of asthma can be made with clinical assessment and conventional spirometry. Assessment of small-airway dysfunction (using FeNO, IOS, or HRCT scanning) may reveal those with uncontrolled disease and allow fine-tuning of the clinical control.⁷¹ Until improved outcomes are noted by targeting the small airways, these tests will not be used in routine practice. However, they will remain useful to gain further appreciation of the role of the small airways in asthma.

Treatment of Small-Airway Disease in Asthma

Due to environmental concerns, asthma inhalers containing chlorofluorocarbons (CFCs) have been largely eliminated from the market. HFA is an alternative propellant that does not destroy the ozone layer.⁷² The aerosol inhalers containing HFA can be either in solution or in suspension. Suspension aerosols are heterogeneous mixtures of solid drug particles in a propellant, whereas solution aerosols are homogeneous mixtures of drug dissolved in a propellant. When HFA solutions are delivered from an MDI, extrafine

TABLE 1. PARTICLE SIZE OF VARIOUS INHALED CORTICOSTEROIDS AND THEIR TOTAL LUNG DEPOSITION

Parameter	BDP-HFA	CIC-HFA	BUD-HFA	MF-DPI	FLU-HFA	FP-HFA
Formulation	Solution	Solution	Suspension	Dry Powder inhaler	Solution	Suspension
Inhaled form	Inactive parent compound Active: BMP	Inactive parent compound Active:des-CIC	Active compound	Active compound	Active compound	Active compound
Particle size (MMAD) of respirable fraction (μ)	1.1	1.1	2.4–4	No data	1.2	2.6–2.8
Lung deposition (% of total dose (exactualtor)	58%	52%	28%	Unknown	68%	16%

BDP, beclomethasone (beclomethasone); BMP, beclomethasone-17-monopropionate; BUD, budesonide; CIC, ciclesonide; des-CIC, des-ciclesonide; FLU, flunisolide; FP, fluticasone propionate; HFA, hydrofluoroalkane; MF, mometasone; MMAD, mass median aerodynamic diameter; (adapted from references 74 and 76).

aerosol of particles around 1 μm is created as the propellant evaporates.

These HFA solutions like ciclesonide,⁷³ beclomethasone-dipropionate (BDP), and flunisolide have a large proportion of fine particles, and the size of the inhaled particles directly impacts their distribution in the lungs (Table 1⁷⁴). These small particles are swept down into the distal airways by laminar airflow.⁷³ Both HFA-BDP and ciclesonide demonstrate high peripheral lung deposition when administered via HFA-MDI,^{73–75} as measured using technetium-labeled scintigraphy. With proper on-time actuation of the device, lung deposition of HFA-BDP is 58% exactuator with 26% of the total dose depositing in the peripheral lung units.⁷⁵ A similar proportion of lung deposition has also been demonstrated for both ciclesonide⁷³ and flunisolide.⁷⁶ Lung deposition studies in children 5 to 17 years of age surprisingly showed similar results to adults when HFA-BDP extrafine formulation was delivered via an aerochamber device, and breathhold was performed at the end of inhalation.⁷⁷

Furthermore, the advent of a new technology⁷⁸ that is able to manipulate a number of device and formulation variables of metered dose inhalers, such as the addition of a nonvolatile component to the formulation and the geometry of the actuator orifice, along with minor variables like change in vapor pressure and the volume of the metering valve, has allowed the design of aerosols with a chosen particle size and plume speed for targeting drug delivery to different parts of the lung. Since the evidence points to the small or distal airways as a major site of airway inflammation and obstruction in asthma, using small particle size aerosols that can target the distal airways makes a rational therapeutic sense. Since these HFA solutions deposit throughout the lung, it would take much less drug to achieve similar clinical and physiologic effects.

To investigate this question, Busse et al.⁷⁹ in a 6-week clinical trial compared the efficacy of 2 different BDP formulations, one an HFA solution with a small particle size and one CFC formulation with large particles over a range of doses. Patients, who exhibited deterioration in asthma control during an inhaled corticosteroid washout period, were randomized to receive either formulation in a wide range of doses for 6 weeks. Based on the Finney bioassay method, the study found that it would take 2.6 (95% CI 1.1–11.6) times the dose of CFC-BDP to result in the same improvement in FEV₁ as that obtained with HFA-BDP.⁷⁹ Similarly, Corren et al.⁸⁰ compared the efficacy and safety of 2 HFA and CFC-flunisolide formulations. Outcome measures were changes from baseline in FEV₁, PEF, as-needed albuterol use, nocturnal awakenings, and asthma symptoms. HFA flunisolide provided comparable efficacy and safety at one-third the dose of CFC flunisolide.

In a more recent study, the effects of small-particle BDP-HFA on FeNO levels were compared to the large-particle BDP-HFA.⁸¹ In this study, patients received either small-particle extrafine BDP-HFA at 100 μg twice daily or large-particle nonextrafine BDP-HFA at 250 μg twice daily; thus, the nonextrafine BDP-HFA was administered at 2.5 times the dose of the extrafine BDP-HFA. The particle size of the nonextrafine BDP-HFA is 2.6 μm , compared with 1.1 μm for the extrafine BDP-HFA, with much lower lung deposition of the nonextrafine particles. Both the small- and large-particle BDP-HFA led to significant reductions in bronchial NO compared with baseline, but the bronchial NO values were

lower after treatment with small-particle BDP-HFA ($P < 0.05$). Only the small-particle BDP-HFA caused a significant reduction in alveolar NO compared with baseline, whereas large-particle BDP-HFA did not. This study comparing 2 HFA pMDI formulations of the same drug provides the first evidence of a different distribution of the anti-inflammatory effect in the central and peripheral airways. The small aerosol particles seem to provide a uniform and more complete anti-inflammatory effect.

Similarly, the efficacy of small-particle BDP-HFA on surrogate markers of airway inflammation was compared with large-particle FP.⁵⁵ Steroid-naïve patients with asthma were randomly assigned to receive inhaled FP 400 $\mu\text{g}/\text{day}$ ($n = 21$) or small-particle, extrafine BDP-HFA 400 $\mu\text{g}/\text{day}$ ($n = 16$) for 12 weeks. Pulmonary function testing, methacholine provocation testing, assessment of exhaled NO levels, and sputum induction were performed. After 12 weeks of treatment, both FP and BDP-HFA groups of patients had significantly lower N^c-[carboxymethyl]lysine (CML) levels in induced sputum and alveolar concentrations of nitric oxide (Calv) from pre- to post-therapy, but BDP-HFA patients had significantly lower between-group levels than did FP patients post-therapy.

While all of the above studies on BDP-HFA have focused on adult populations, several studies have evaluated BDP-HFA in the pediatric population, and found an equivalent asthma control to the same dose of fluticasone, and twice the daily dose of budesonide.^{77,82,83} Using a similar ratio, we studied changes in lung function in asthmatic children with abnormal small-airway function who had been treated with optimal doses of fluticasone and budesonide. After switching to BDP-HFA, FEF_{25%–75%} improved from 50.75% to 68.85% predicted ($P < 0.001$), and FEV₁ improved from 84.6% to 93.8% predicted ($P = 0.001$).⁷¹

Several studies^{13,73,84–89} have assessed the effects of ciclesonide, another approved aerosol solution with a small particle size. Hoshino compared ciclesonide (200 μg once daily) and fluticasone (100 μg twice daily) for 5 weeks in thirty mild adult asthmatics using IOS and induced sputum eosinophils.⁸⁴ He found that ciclesonide significantly improved IOS measures of small-airway function (R5–R20, distal reactance [X5], and AX) and late-phase sputum eosinophils compared to fluticasone. Two adult studies by Cohen and colleagues looked at the effects of ciclesonide on small-airway function and structure.^{13,85} Their first study evaluated the effects of ciclesonide (320 μg daily for 5 weeks) in 16 subjects with mild-to-moderate asthma.⁸⁵ They found that ciclesonide improved both alveolar eNO and air trapping on HRCT compared with placebo. The second elegant study investigated the effects of 2 different ICS, ciclesonide and fluticasone, on bronchial hyper-responsiveness (BHR) using 2 different particle sizes of adenosine monophosphate (AMP) as a challenge agent. They found that ciclesonide improved BHR to small particle size AMP, whereas fluticasone improved BHR to large particle size AMP. They suggest that when designing studies using BHR as an endpoint, it may be important to target the airway size.

Several studies have evaluated ciclesonide HFA in the pediatric population, and found it to be effective and well tolerated in children 4 to 11 years of age.^{85,90} However, it should be noted that ciclesonide is not approved for children < 12 years of age in the United States. Like HFA-BDP, ciclesonide was found to have equivalent asthma control to the

same dose of fluticasone,⁸⁸ and approximately twice the daily dose of budesonide.⁸⁷

The effects of antileukotriene receptor antagonists on small-airway function have been also studied. Oral montelukast is commonly used as an add-on therapy for mild-to-moderate asthma. One study compared the effect of montelukast with placebo in 16 adults with mild-to-moderate steroid-naïve asthma subjects over 4 weeks.⁹¹ They found that montelukast-treated subjects showed less air trapping on baseline HRCT compared to placebo. However, montelukast failed to show any effect on regional air trapping in response to the methacholine challenge. A second study by Kraft and colleagues evaluated the effect of montelukast in 19 adults with mild asthma subjects over a 4-week treatment.⁹² They showed significant improvement in FEV₁, specific conductance, and residual volume (RV) in the montelukast group compared to placebo, with improvement in RV correlating with improvement in symptoms.

Finally, the effects of combination therapy (ICS plus LABA) on small-airway function have been evaluated. Extrafine beclomethasone/formoterol (BDP/F) was compared with large-particle fluticasone/salmeterol (FP/S) in thirty subjects with asthma over a 12-week duration.⁹³ A trend toward improvement was observed in the BDP/F group in closing capacity. Bronchial hyper-reactivity also improved significantly in the BDP/F group compared to the FP/S group. Of note, this study was conducted in Italy, and the BDP/F combination inhaler is currently unavailable in the United States.

In a recent literature review of all published studies that have assessed whether fixed dose combinations achieve greater asthma control compared with the monocomponents administered as separate inhalers,⁹⁴ only one controlled study found a statistically significant improvement in asthma control.⁹⁵ This study compared the fixed combination of extrafine HFA beclomethasonedipropionate and formoterol given via a single pressurized metered-dose inhaler (pMDI) with beclomethasonedipropionate CFC pMDI and formoterol dry-powder inhaler (DPI) given via separate inhalers.⁹⁵ It should be noted that the beclomethasone- and formoterol-separate inhalers delivered larger particle sizes, and that the ICS dose was greater in the separate treatment compared with the fixed treatment (1000 µg versus 400 µg, respectively). A *post hoc* analysis showed that combination therapy resulted in a 50% increase in the percentage of days with asthma control, which rose from 15.4% with separate inhalers to 23% with combination therapy ($P < 0.005$).

Conclusion

There is now substantial evidence that small-airway inflammation contributes considerably to the clinical expression of asthma and that small-particle ICSs improve small-airway function and inflammation to a higher extent than large-particle ICSs.¹¹ This is due largely to the increased drug delivery of small particles to the distal airways compared with the larger particle size, and to the differential effects on airway inflammation, which seem to be pronounced when small-particle ICSs are used. Whether these differential effects may translate into clinical benefit for the patient remains to be determined. Furthermore, given the marked and rapid changes in respiratory tract development that occur in infants (aged 0–1 year) and young children

(aged 1–3 years), they represent a unique subpopulation with regard to therapeutic aerosols.^{81–83} A recent review⁹⁶ reports that smaller aerosol particles may be more appropriate for treating very young children with respiratory disease, and that based on currently available aerosol deposition data, extrapolation of studies in adults to children, especially those who are under 4 years of age, should be avoided. The authors conclude that the current recommendations for ICS therapy of asthma in infants and young children should be reconsidered and that better clinical outcomes may be achieved using smaller particles and more patient-friendly delivery systems. Additional long-term studies of the therapeutic efficacy of ICS with small particles designed simultaneously to look at functional and clinical outcomes in both adults and children will help to establish the role of small-particle ICSs in modifying disease progression and airway remodeling in asthma.

Author Disclosure Statement

Dr. Morton and Dr. O'Hagan report that no competing financial interests exist. Dr. Eid reports participating on the advisory board and the speaker bureau for Teva Pharmaceuticals.

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