Small Airways Disease in Asthma

Jonathan Corren, MD

Corresponding author
Jonathan Corren, MD
Allergy Research Foundation, University of California, Los Angeles, 11620 Wilshire Boulevard #200, Los Angeles, CA 90025, USA.
E-mail: jcorren@ucla.edu

Current Allergy and Asthma Reports 2008, **8:**533–539
Current Medicine Group LLC ISSN 1529-7322
Copyright © 2008 by Current Medicine Group LLC

A mounting body of physiologic and pathologic evidence indicates that asthma involves the central and the more distal airways. In patients with asthma, the peripheral lung accounts for a significant portion of airway resistance and, similar to the large airways, the small airways have been shown to be hyperresponsive to nonspecific stimuli, such as methacholine. Cellular inflammation, consisting of an infiltrate rich with lymphocytes and eosinophils, is present in the small airways of patients with asthma and may be more intense than that observed in the large airways. Clinical assessment of the peripheral airways continues to be a challenge, and new techniques, such as quantitative analysis of chest CT images, have proven to be useful research tools. The recognition of small airways involvement in asthma has clinical relevance, as new formulations of inhaled corticosteroids with smaller particle aerosols may be more effective in addressing this component of asthma.

Introduction

Asthma is a chronic inflammatory disease of the lung characterized physiologically by airway obstruction and bronchial hyperresponsiveness. Pathologic studies of the central airways in patients with asthma have revealed several key features, including infiltration of the bronchial wall with inflammatory cells, smooth muscle hypertrophy, and mucus gland hyperplasia [1]. Dating back to the 1920s, investigators recognized that these findings were not limited to the large and medium airways and made similar pathologic observations in the small, peripheral airways [2]. Historically, our understanding of the small airways' role in asthma has been limited by difficulty in gaining access to this remote area of the lung. However, with the introduction of new methods for assessing the physiology, anatomy, and histopathology of the peripheral lung, there has been a wave of renewed interest in defining the importance of the small airways in asthma. In this review, we explore the key characteristics that distinguish the large and small airways, as well as implications regarding asthma treatment.

Physiology of Small Airways in Asthma

The small airways, which consist of the membranous, terminal, and respiratory bronchioli, begin at the seventh generation of airways and have internal diameters of 0.5 to 2.0 mm [3]. These airways contain the same structural elements as larger airways but have fewer ciliated epithelial cells. The nonciliated epithelia, which are found in the small airways, are referred to as Clara cells.

Based on morphometric studies that have determined that the volume and surface area of the lungs increase with increasing airway generations, it was speculated that the peripheral airways contributed minimally to total lung resistance [4]. These presumptions were supported by animal research conducted during the 1960s that demonstrated that the most distal airways contributed less than 10% of the total airway resistance [4]. Yanai et al. [5] challenged this assertion by assessing total, central, and peripheral pulmonary resistance in normal individuals and patients suffering from asthma or chronic obstructive pulmonary disease. Patients with bronchial asthma but without airflow obstruction showed values of central and peripheral resistance similar to those of normal individuals. In asthmatics with airflow obstruction, however, peripheral resistance increased significantly compared with central resistance, suggesting that the peripheral airways are the predominant site of airflow obstruction in asthma.

Differences in hyperresponsiveness between the large and small airways also have been investigated in many experimental models. Mitchell et al. [6] used an in situ model of acetylcholine-induced bronchial smooth muscle contraction and observed that maximum muscle shortening was 30% in small and 19% in large bronchi; lumen narrowing was 49% and 39% in small and large bronchi, respectively; high doses of acetylcholine stopped flow in small bronchi but produced a plateau in large bronchi; and small airways were 250 times more sensitive to acetylcholine than large airways [6]. These changes led the authors to conclude that alterations in airway wall shape or dimensions significantly influence airflow, particularly in the small airways.

Wagner et al. [7] conducted an in vivo study of small airways hyperresponsiveness in humans, using a wedged bronchoscope technique for measuring peripheral resistance after the local instillation of histamine. In normal individuals, peripheral resistance increased by 200% after the highest dose of histamine was administered, whereas in patients with asthma, the maximal increase was 320%. These results support the presence of greater nonspecific responsiveness to bronchoconstrictor agents such as histamine.

Ellis and colleagues [8] used an in situ model to determine whether these differences in large and small airway responsiveness also pertained to allergen exposure. After passive sensitization of human lung tissue with antiragweed IgE, ragweed allergen was selectively administered to large and small airways, and contractile responses were measured. They noted that the peripheral airways contracted at significantly lower doses of allergen; contracted at a faster rate; and released larger amounts of proinflammatory mediators, including histamine and leukotrienes, than the central airways on a per-weight basis. These data indicate that the small airways may be more immunologically reactive than the large airways, resulting in more mediator release and subsequent smooth muscle contraction, and suggest the possibility of increased nonspecific responsiveness.

Histopathology of the Small Airways in Asthma

Until recently, most of our knowledge regarding inflammatory changes in the airways in asthma was based on histopathologic studies of the large airways. Studies primarily relying on bronchoalveolar lavage and endobronchial biopsy revealed many distinct abnormalities, including infiltration of airway walls by inflammatory cells (eg, T lymphocytes and eosinophils), epithelial sloughing, smooth muscle hyperplasia, mucus cell hyperplasia, and basement membrane thickening [1]. Along with these pathologic changes, there is an increase in T-helper type 2 cytokines, particularly interleukin (IL)-4, IL-5, IL-9, and IL-13 [9]. However, pathologic analyses of specimens obtained from tissue samples during autopsy or surgery or via transbronchial biopsy have dramatically increased our knowledge of inflammation in the small airways in asthma.

Many of the data regarding inflammation in the distal airways have been derived from autopsy studies of patients with severe asthma [2,10–16]. These studies universally indicate that the small airways are heavily infiltrated with inflammatory cells, particularly lymphocytes and eosinophils. Haley and coworkers [16] recently sought to determine whether airway size (large vs small) or airway wall region ("inner" wall region, between the basement membrane and smooth muscle, vs "outer" wall region, between smooth muscle and alveolar attachments) were related to the intensity of inflammatory cell infiltration. They demonstrated that the inner area of the large airways had a higher density of $CD45^+$ cells and eosinophils than the inner area of the small airways. They also noted that in the small airways, $CD45^+$ cells and eosinophils accumulated to a greater degree in the outer compared with the inner wall region. Similar findings regarding this regional variation in inflammation were not observed in the airways of patients with cystic fibrosis. The authors concluded that regional differences in inflammatory cell distribution exist within the airway wall according to airway size in patients with fatal asthma that are not part of a generalized inflammatory response.

Two of the previously described studies included patients with fatal and nonfatal asthma, giving the investigators an opportunity to make histologic comparisons between asthmatics of varying severity. Using autopsy specimens, Carroll et al. [13] demonstrated that lymphocytes were significantly increased in the large and small airways in fatal and nonfatal cases of asthma compared with control patients. In addition, eosinophils were increased in both airway size groups in patients with fatal asthma compared with the nonfatal asthma and control groups, which were similar. Carroll et al.'s [13] findings suggest that increased numbers of lymphocytes are distributed in the large and small airways in asthma independently of asthma severity and that eosinophil infiltration throughout the airway may be related to asthma severity.

Synek et al. [15] performed a similar analysis of autopsy tissue from patients with fatal and nonfatal asthma. These authors noted that the numbers of intraepithelial $CD3^+$ T cells were significantly lower in fatal asthma than in mild to moderate asthma, primarily in the larger airways, whereas the numbers of activated eosinophils infiltrating the airway wall of the larger airways were greater in fatal asthma than in mild to moderate asthma. No significant differences were found between the groups in the smaller airways. These investigators concluded that in patients with fatal asthma, $CD3^+$ T cells are redistributed away from the epithelium and the eosinophil infiltrate is enhanced, most significantly in the proximal airways.

More recent studies by Hamid et al. [17] and Balzar et al. [18] sought to compare the inflammatory infiltrates in the large and small airways in patients with mild and severe but nonfatal asthma, respectively. Hamid and coworkers [17] used surgically resected lung tissue to assess cellular histology and noted an increased number of $CD3^+$ T cells and $EG2^+$ eosinophils in the large and peripheral airways of asthmatics compared with those of healthy controls. Moreover, they observed that the small airways had a larger number of activated eosinophils than the large airways.

Balzar et al. [18] used transbronchial biopsy to evaluate airway histology in patients with severe, steroid-dependent asthma; there was no control group in this study. They confirmed the findings of Hamid et al. [17],

demonstrating that the small airways had significantly more inflammatory cells than the large airways, although the differential counts did not differ between the two groups. Together, these studies suggest that inflammatory cells infiltrate into the small airways to an even greater extent than the more proximal airways, irrespective of asthma severity.

The above data in patients with more severe asthma prompted Kraft et al. [19] to examine the role of peripheral lung inflammation in patients with nocturnal worsening of asthma. They evaluated patients with nocturnal and nonnocturnal asthma by performing histocytochemical stains on proximal airway endobronchial and distal alveolar tissue transbronchial biopsies during the day (4 PM) and at night (4 AM). They noted that the nocturnal asthma group had a significantly greater number of $CD4^+$ cells in the alveolar tissue than the nonnocturnal asthma group. In patients with nocturnal asthma, there were significantly greater numbers of $CD4^+$ and $CD8^+$ lymphocytes and activated eosinophils in the proximal airways than in the distal airway during the day and at night. Only alveolar $CD4^+$ cells correlated inversely with the percentage predicted forced expiratory volume in 1 second (FEV_1) (r = -0.68) and positively with the number of activated eosinophils in the alveoli (r = 0.66) at 4 AM. These findings suggested the importance of $CD4^+$ lymphocytes in the distal airways in directing other effector cells and in modulating nocturnal changes in pulmonary function.

In addition to inflammatory cell infiltration, other components of the airway wall, such as smooth muscle and basement membrane, have been important areas of study in patients with asthma. Bergeron et al. [20•] used specimens from transbronchial and endobronchial biopsies to compare constituents of the airway wall (total collagen deposition, collagen type III, transforming growth factor-β [TGF-β], and α-smooth muscle actin) in patients with mild to moderate asthma; there was no control group. They noted that total collagen occupied significantly more of the central airway wall area (55%) compared with the small airways (38%). However, there were no significant differences in collagen type III, TGF-β^+ cells in the submucosa, or α-smooth muscle actin comparing the central and small airways. In a study using autopsy specimens from patients with fatal and nonfatal asthma and a control group, Carroll et al. [13] determined that the total, outer, and inner wall areas were greatest in patients with fatal asthma and that these differences predominated in the large airways. Large airway smooth muscle and other components of the airway wall therefore may be factors in severe, fatal asthma.

As glucocorticoid responsiveness has proven to be an important therapeutic consideration in treating airway inflammation in asthma, there has been some investigation of glucocorticoid receptor (GR) expression in the small airways. In a pathologic study of patients with fatal asthma, mild asthma, chronic obstructive pulmonary disease, and normal controls, a significantly greater number of cells expressed the GR-β in fatal asthma compared with the other three groups [21]. The expression of GR-β in patients with severe asthma was similar in the large and small airways. These data suggest that possible cellular resistance to glucocorticoids may be an important factor in peripheral airway inflammation in severe asthmatics.

The presence of intense cellular inflammation in the small airways can be traced to the same proinflammatory mediators that are linked to inflammatory cell influx in the larger airways. Minshall et al. [22] provided evidence that cells staining for T-helper type 2 cytokines IL-4 and IL-5 from the distal airways of mild asthmatics are higher than in nonasthmatics [22]. Again, this aspect of the inflammatory response may be greater in the lung periphery, as the number of IL-5–positive cells was greater in these airways than in the central airways of asthmatics. Chemokines, including eotaxin and monocyte chemotactic protein 4, also have been shown to be increased in the large and small airways of mild asthmatics [23].

A mechanism that may be unique to inflammatory events in the small airways may relate to a new family of factors produced by Clara cells (nonciliated cells) that are present in the epithelium of the small airways. Clara cell 10 (CC10, or CC16) is a 10-kD protein that is a potent inhibitor of phospholipase A2 and interferon-γ and has been suggested as a potential regulator of T-helper type 1 and T-helper type 2 immune function in several pulmonary diseases [24]. Shijubo et al. [25] demonstrated that the serum protein concentration of CC10 and the number of $CC10^+$ cells in the peripheral airways were significantly lower than in healthy controls [25]. These results indicate CC10's potential role as an endogenous immunomodulatory factor in asthmatic inflammation and that the absence or depression of this protein may contribute to small airways disease in asthma.

Clinical Assessments of Small Airways Dysfunction

Many techniques have been used to assess small airways function and inflammation in patients with asthma (Table 1). Spirometry is widely available and easily performed. Maximal midexpiratory flow rates (forced expiratory flow rate, 25% to 75%) have been suggested as a measure of small airways function [26]. However, forced expiratory flow rates at middle to low volumes are highly variable and affected by large airway obstruction and volume changes. Sutherland et al. [27] found no relationship between maximal midexpiratory flow rates and small airway inflammation determined by transbronchial biopsy.

Lung volumes, including forced vital capacity, residual volume, total lung capacity, and functional residual capacity (thoracic gas volume), also have been used to characterize air trapping and, hence, small airways function. The Sutherland et al. [27] study did demonstrate a

Table 1. Methods for assessing the small airways

Maximal midexpiratory flow rates
Lung volumes (total lung capacity, thoracic gas volume)
Closing volume and closing capacity
Impulse oscillometry
Alveolar nitric oxide
Multiple breath washout of nitrogen
Quantitative analysis of high-resolution CT images of chest

significant correlation between total lung capacity and thoracic gas volume and the degree of alveolar eosinophilic inflammation derived from biopsy.

Assessment of airway closure by measuring closing volume and closing capacity is another method for estimating small airways narrowing in asthma. Many studies have determined that these tests of airway closure are sensitive and specific indicators of small airways disease [28,29]. In't Veen and colleagues [30] evaluated the utility of closing volume and capacity in two groups of asthmatics, one completely stable and the other with recurrent exacerbations. They determined that neither spirometric nor lung volume values differentiated these two groups, whereas closing volume and capacity were significantly higher in the patients with unstable disease. These data would suggest that tests of airway closure are useful in determining which patients are at highest risk of an asthma exacerbation and that this risk is predicated upon the presence of measurable small airways dysfunction. Unfortunately, the test is time-consuming and technically difficult, relegating its use to specialized pulmonary function centers.

Impulse oscillometry is a passive technique of measuring airway resistance that relies on forced oscillations [31]. This method has been widely used in children and has proven to be a more sensitive indicator of reversible bronchospasm than spirometric indices [32]. It has the capacity for measuring total and proximal airway resistance, thereby allowing for the calculation of peripheral airway resistance. This technique has been suggested as a tool for measuring small airways disease; to date, no studies have validated it against other acceptable techniques, such as closing volume and capacity.

Measurement of fractional exhaled nitric oxide (NO) is a simple and noninvasive test that has been useful for assessing eosinophilic inflammation in patients with asthma. Recently, several investigators have sought to develop newer techniques that discriminate NO originating in the airway and alveolar compartments [33]. Van Veen and colleagues [34] compared alveolar NO in patients with severe (on and off oral corticosteroids) and mild to moderate asthma. They determined that in severe but not in mild to moderate patients, strong correlations existed between alveolar NO and other measures of peripheral lung function, including closing capacity/total lung capacity ratio. They also found that patients with oral corticosteroid–dependent asthma had higher alveolar NO levels compared with severe patients not taking oral corticosteroids and compared with mild to moderate patients.

The newest pulmonary function assessment of the small airways uses an analysis of nitrogen washout via a multiple breath technique [35•]. The phase 3 slope analysis of the washout generates indices of acinar ventilation heterogeneity (a measure of small airway disease) and conductive ventilation heterogeneity (a measure of more central airway disease). The method's theory implies that ventilation heterogeneity is attributable to different lung depths, with more superficial levels corresponding to the conductive zones, and deeper levels representing the acinar zones. Verbanck et al. [35•] demonstrated that only patients with acinar lung function abnormalities at baseline received functional benefits from an extra-fine inhaled corticosteroid (ICS) aerosol.

Computerized assessment of high-resolution CT images of the chest has shown promise as a measure of small airways function [36,37•]. As the CT is performed at end-expiration, areas of relatively low attenuation are thought to represent air trapping due to small airways obstruction. Studies in adult asthmatics have shown that the results of computed-derived quantitative image analysis of chest CTs correlate significantly with asthma severity and peripheral airway obstruction [37•]. Moreover, some studies have suggested that high-resolution CT scans are more sensitive than lung function tests for assessing small airways disease [38].

Implications for Treatment

ICS is the most effective treatment for chronic asthma. However, recent work has demonstrated that most ICS preparations do not reach all sites of airway inflammation, particularly in the peripheral airways. Deposition studies have shown that many of the commonly used ICS administered by metered-dose inhalers have low total lung deposition and predominant deposition in the central airways [39]. Poor distal airway delivery by metered-dose inhalers has been attributed to particle sizes being too large (mass median aerodynamic diameter ~ 3.5–4.0 μm) to achieve substantial penetration into the small airways [40]. Due to the recent global ban on chlorofluorocarbon propellants, over the past decade, several ICS agents have been formulated in hydrofluoroalkane vehicles, including beclomethasone dipropionate (BDP), flunisolide, fluticasone propionate, and ciclesonide. Some of these compounds, including BDP, flunisolide, and ciclesonide, exist as solutions rather than suspensions when placed into a hydrofluoroalkane (HFA) vehicle and are delivered as an extra-fine aerosol (mass median aerodynamic diameter ~ 1.0–2.0 μm). These new, small-particle aerosols offer the poten-

tial opportunity to treat asthmatic inflammation in the small airways more effectively.

Lung deposition experiments have been shown to provide relevant information regarding the site of inhaled drug deposition. Radionuclide imaging studies have been conducted with HFA formulations of BDP, flunisolide, and ciclesonide and have been compared in some cases with chlorofluorocarbon (CFC) formulations of these same drugs. Inhaled HFA-BDP was deposited in the central, intermediate, and small airways, whereas CFC-BDP was mainly deposited in the oral cavity and central airways [39]. With respect to the small airways, HFA-BDP had 60% distal lung penetration, compared with 10% for CFC-BDP. Similar work has been done with flunisolide, which demonstrated that HFA-flunisolide had 68% total lung deposition, compared with 20% for CFC-flunisolide, and that more of the HFA formulation was deposited in the distal airways [41]. HFA-ciclesonide was shown to have 52% lung deposition, with highest distribution to the small airways [42].

Clinically, the differences in the regional distribution of these drugs have translated into differences in the doses of these agents required to effectively treat asthma. Busse and coworkers [43] compared HFA-BDP and CFC-BDP in symptomatic asthmatics and calculated that 2.6 times as much CFC-BDP would be required to achieve the same improvement in FEV_1 percent predicted as HFA-BDP. Corren et al. [44] observed similar results in a later study comparing HFA-flunisolide and CFC-flunisolide, with three times as much of the CFC formulation required to achieve the same improvement in FEV_1 percent predicted as HFA-flunisolide. Moreover, many of the outcomes tended to be better in patients receiving the HFA formulation, including 40% fewer asthma exacerbations; however, none of these secondary end points reached statistical significance.

Clinical trial data such as these cannot determine whether the superior efficacy of HFA-BDP and flunisolide are due strictly to the increases in total pulmonary deposition or whether enhanced peripheral lung deposition also plays a role. Toward this end, it is thus important to demonstrate that increased distribution to the small airways results in improvements in peripheral inflammation and/or function. Hauber et al. [45] treated a group of asthmatics for 6 weeks with HFA-flunisolide, 680 μg daily, and demonstrated significant reductions in eosinophils, neutrophils, and cells positive for IL-5 and eotaxin that were comparable in the central and peripheral airways. In a separate analysis of these same patients, the effects of HFA-flunisolide on multiple markers of airway remodeling (total collagen deposition, collagen type III, TGF-β, and α-smooth muscle actin) were assessed [20•]. In this analysis, the only significant effect of the small-particle ICS was a reduction in α-smooth muscle actin in the small airways. The data from these two publications suggest that small-particle ICS agents exert clinically important anti-inflammatory effects on the small airways but have only a partial effect on airway remodeling.

Goldin and colleagues [46] sought to determine whether HFA-BDP was more effective than CFC-BDP in reducing small airways dysfunction as measured by quantitative image assessment of chest CT scans. Patients underwent CT scanning (before and after inhaled methacholine challenge) at the beginning and end of a 4-week trial of HFA-BDP or CFC-BDP. Patients receiving the extra-fine HFA formulation but not the CFC-BDP demonstrated reduced methacholine-induced air trapping, indicating a reduction in small airways hyperresponsiveness. No differences were noted in spirometry- or methacholine-induced changes in FEV_1, indicating that the quantitative assessment of chest CT was more sensitive than these conventional measures in detecting small airways changes.

In a placebo-controlled study of ciclesonide, 320 μg daily for 5 weeks, significant improvements were seen in air trapping measured by chest CT, whereas other measures of small airway function, such as forced expiratory flow rate 25% to 75% and closing volume, did not change with treatment [47•]. Alveolar-exhaled NO also decreased significantly in the ciclesonide-treated patients, again affirming the peripheral anti-inflammatory effects of small-particle delivery systems.

In addition to the benefits of extra-fine aerosols to the peripheral lung, oral medications also may be useful. Zeidler and colleagues [48] demonstrated that montelukast, 10 mg once daily for 4 weeks, was significantly more effective than placebo in reducing regional air trapping as measured by quantitative image analysis of chest CT. These data suggest that oral drugs may play an important role in treating the inflammatory and bronchospastic changes in the small airways of asthmatics.

Conclusions

The past decade has brought new technologies for assessing the small airways and innovative therapies that more effectively target this portion of the respiratory tract. The growing body of data regarding small airways inflammation and dysfunction in asthma, particularly in patients with unstable disease, should help to guide the investigation and applications of future treatments for asthma.

Disclosure

Dr. Corren has served as a consultant for AstraZeneca Pharmaceuticals, Schering-Plough, GlaxoSmithKline, Amgen, Genentech, and Abbott Laboratories; as a speaker for AstraZeneca Pharmaceuticals, Schering-Plough, and GlaxoSmithKline; and has received research funding from AstraZeneca Pharmaceuticals, Schering-Plough, GlaxoSmithKline, Meda, Genentech, Novartis, and Sky Pharma.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Hogg JC: **The pathology of asthma.** In *Asthma: Physiology, Immunopharmacology, and Treatment*. Edited by Holgate ST, Austen KF, Lichtenstein LM, Kay AB. London: Academic Press; 1993:110–135.
2. Huber HL, Loessler K: **The pathology of bronchial asthma.** *Arch Intern Med* 1922, **30:**689–760.
3. Weibel ER: **Geometry and dimensions of airways conductive and transitory zone.** In *Morphometry of the Human Lung.* New York: Springer-Verlag; 1963:110–135.
4. Tashkin DP: **The role of small airway inflammation in asthma.** *Allergy Asthma Proc* 2002, **23:**233–242.
5. Yanai M, Sekizawa K, Ohrui T, et al.: **Site of airway obstruction in pulmonary disease: direct measurement of intrabronchial pressure.** *J Appl Physiol* 1991, **72:**1016–1023.
6. Mitchell HW, Cvetkowski R, Sparrow MP, et al.: **Concurrent measurement of smooth muscle shortening, lumen narrowing, and flow to acetylcholine in large and small porcine bronchi.** *Eur Respir J* 1998, **12:**1053–1061.
7. Wagner EM, Bleecker ER, Permut S, Liu MC: **Direct assessment of small airways reactivity in human subjects.** *Am J Respir Crit Care Med* 1998, **157:**447–452.
8. Ellis JL, Hubbard WC, Meeker S, Unden BJ: **Ragweed antigen E and anti-IgE in human central versus peripheral isolated bronchi.** *Am J Respir Crit Care Med* 1994, **150:**717–723.
9. Bentley AM, Meng Q, Robinson DS, et al.: **Increases in activated T lymphocytes, eosinophils, and cytokine mRNA expression for granulocyte/macrophage colony-stimulating factor in bronchial biopsies after allergen inhalation in atopic asthmatics.** *Am J Respir Cell Mol Biol* 1993, **8:**35–42.
10. Houston JC, de Navaquez S, Trounce JR: **A clinical and pathological study of fatal cases of status asthmaticus.** *Thorax* 1953, **8:**207–213.
11. Dunnill MS: **The pathology of asthma, with special reference to changes in the bronchial mucosa.** *J Clin Pathol* 1960, **13:**27–33.
12. Saetta M, DiStafano A, Rosina C, et al.: **Quantitative structural analysis of peripheral airways and arteries in sudden fatal asthma.** *Am Rev Respir Dis* 1991, **143:**138–143.
13. Carroll N, Carello S, James A: **The distribution of eosinophils and lymphocytes in the large and small airways of asthmatics.** *Eur Respir J* 1997, **10:**292–300.
14. Faul JL, Tormey VJ, Leonard C, et al.: **Lung immunopathology in cases of sudden asthma death.** *Eur Respir J* 1997, **10:**301–307.
15. Synek M, Beasley R, Frew AJ, et al.: **Cellular infiltration of the airways in asthma of varying severity.** *Am J Respir Crit Care Med* 1996, **154:**224–230.
16. Haley KJ, Sunday ME, Wiggs BR, et al.: **Inflammatory cell distribution within and along asthmatic airways.** *Am J Respir Crit Care Med* 1998, **158:**565–572.
17. Hamid Q, Song Y, Kotsimbos C, et al.: **Inflammation of small airways in asthma.** *J Allergy Clin Immunol* 1997, **100:**44–51.
18. Balzar S, Wenzel SE, Chu HW: **Transbronchial biopsy as a tool to evaluate small airways in asthma.** *Eur Respir J* 2002, **303:**254–259.
19. Kraft M, Martin RJ, Wilson S, et al.: **Lymphocyte and eosinophil influx into alveolar tissue in nocturnal asthma.** *Am J Respir Crit Care Med* 1999, **159:**228–234.
20. • Bergeron C, Hauber HP, Gotfried M, et al.: **Evidence of remodeling in peripheral airways of patients with mild to moderate asthma: effect of hydrofluoralkane-flunisolide.** *J Allergy Clin Immunol* 2005, **116:**983–989.

Important study showing that remodeling of airway tissues is present in the small airways and that extra-fine corticosteroid aerosols have only minimal effects on this process.

21. Christodoulopoulos P, Leung DY, Elliott MW, et al.: **Increased number of glucocorticoid receptor-beta expressing cells in the airways in fatal asthma.** *J Allergy Clin Immunol* 2000, **106:**479–484.
22. Minshall EM, Hogg JC, Hamid QA: **Cytokine mRNA expression in asthma is not restricted to the large airways.** *J Allergy Clin Immunol* 1998, **101:**386–390.
23. Taha RA, Minshall EM, Miotto D, et al.: **Eotaxin and monocyte chemotactic proten-4 mRNA expression in small airways of asthmatic and nonasthmatic individuals.** *J Allergy Clin Immunol* 1999, **102:**476–483.
24. Hung CH, Chen LC, Zhang Z, et al.: **Regulation of Th2 responses by the pulmonary Clara cell secretory 10-kD protein.** *J Allergy Clin Immunol* 2004, **114:**664–670.
25. Shijubo N, Itoh Y, Yamaguchi T, et al.: **Clara cell protein-positive epithelial cells are reduced in small airways of asthmatics.** *Am J Respir Crit Care Med* 1999, **160:**930–933.
26. McFadden ER, Linden DA: **A reduction in maximum mid-expiratory flow rate: a spirographic manifestation of small airways disease.** *Am J Med* 1972, **52:**725–737.
27. Sutherland ER, Martin RJ, Bowler RP, et al.: **Physiologic correlates of distal lung inflammation in asthma.** *J Allergy Clin Immunol* 2004, **113:**1046–1050.
28. McCarthy DS, Spencer R, Greene R, Milic-Emili J: **Measurement of "closing volume" as a single and sensitive test for early detection of small airway disease.** *Am J Med* 1972, **52:**747–753.
29. Cosio M, Ghezzo Hogg JC, Corbin R, et al.: **The relations between structural changes in small airways and pulmonary function tests.** *N Engl J Med* 1978, **122:**1277–1281.
30. In't Veen JC, Beekman AJ, Bel EH, Sterk PJ: **Recurrent exacerbations in severe asthma are associated with enhanced airway closure during stable episodes.** *Am J Respir Crit Care Med* 2000, **161:**1902–1906.
31. Aronsson D, Tufvesson E, Ankerst J, Bjermer L: **Allergic rhinitis with hyper-responsiveness differ from asthma in degree of peripheral obstruction during methacholine challenge test.** *Clin Physiol Funct Imaging* 2008, **28:**81–85.
32. Song TW, Kim KW, Kim ES, et al.: **Utility of impulse oscillometry in young children with asthma.** *Pediatr Allergy Immunol* 2008 Mar 7 (Epub ahead of print).
33. Berry M, Hargadon B, Morgan A, et al.: **Alveolar nitric oxide in adults with asthma: evidence of distal lung inflammation in refractory asthma.** *Eur Respir J* 2005, **25:**986–991.
34. Van Veen IH, Sterk PJ, Schot R, et al.: **Alveolar nitric oxide versus measures of peripheral airway dysfunction in severe asthma.** *Eur Respir J* 2006, **27:**951–956.
35. • Verbanck S, Schuermans D, Paiva M, Vincken W: **The functional benefit of anti-inflammatory aerosols in the lung periphery.** *J Allergy Clin Immunol* 2006, **118:**340–346.

Important paper proposing a new pulmonary function method for determining which patients will benefit most from extra-fine aerosol administration.

36. de Blic J, Scheinmann P: **The use of imaging techniques for assessing severe childhood asthma.** *J Allergy Clin Immunol* 2007, **119:**808–810.

37.• Ueda T, Niimi A, Matsumoto H, et al.: **Role of small airways in asthma: investigation using high-resolution computed tomography.** *J Allergy Clin Immunol* 2006, **118:**1019–1025.
Good analysis of CT technology in assessing the small airways in asthma.
38. Zeidler MR, Goldin JG, Kleerup EC, et al.: **Small airways response to naturalistic cat allergen exposure in subjects with asthma.** *J Allergy Clin Immunol* 2006, **118:**1075–1081.
39. Leach CL, Davidson PJ, Hasselquist BE: **Lung deposition of hydrofluoroalkane-134a beclomethasone is greater than that of chlorofluorocarbon fluticasone and chlorofluorocarbon beclomethasone: a cross-over study in healthy volunteers.** *Chest* 2002, **122:**510–516.
40. Zeidler M, Corren J: **Hydrofluoroalkane formulations of inhaled corticosteroids for the treatment of asthma.** *Treat Respir Med* 2004, **3:**35–44.
41. Richards J, Hirst P, Pitcairn G, et al.: **Deposition and pharmacokinetics of flunisolide delivered from pressurized inhalers containing non-CFC and CFC propellants.** *J Aerosol Med* 2001, **14:**197–220.
42. Newman S, Salmon A, Nave R, Drollmann A: **High lung deposition of 99mTc-labeled ciclesonide administered via HFA-MDI to patients with asthma.** *Respir Med* 2006, **100:**375–384.
43. Busse WW, Branzinsky S, Jacobson K, et al.: **Efficacy response of inhaled beclomethasone dipropionate in asthma is proportional to dose and is improved by formulation with a new propellant.** *J Allergy Clin Immunol* 1999, **104:**1215–1222.
44. Corren J, Nelson H, Greos L, et al.: **Effective control of asthma with hydrofluoroalkane (HFA) flunisolide delivered as an extra-fine aerosol in asthma patients.** *Ann Allergy Asthma Immunol* 2001, **87:**405–411.
45. Hauber HP, Gotfried M, Newman K, et al.: **Effect of HFA-flunisolide on peripheral lung inflammation in asthma.** *J Allergy Clin Immunol* 2003, **112:**58–63.
46. Goldin JG, Tashkin DP, Kleerup EC, et al.: **Comparative effects of hydrofluoroalkane and chlorofluorocarbon beclomethasone dipropionate inhalation on small airways: assessment with functional helical thin-section computed tomography.** *J Allergy Clin Immunol* 1999, **104:**S258–S267.
47.• Cohen J, Douma WR, ten Hacken NH, et al.: **Ciclesonide improves measures of small airway involvement in asthma.** *Eur Respir J* 2008, **31:**1213–1220.
This study clearly demonstrates that the extra-fine aerosol of ciclesonide does have functional effects on the small airways.
48. Zeidler MR, Kleerup EC, Goldin JG, et al.: **Montelukast improves regional air-trapping due to small airways obstruction in asthma.** *Eur Respir J* 2006, **27:**307–315.