# Anatomy, pathology, and physiology of the tracheobronchial tree: Emphasis on the distal airways

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**This article covers the airway tree with respect to anatomy, pathology, and physiology. The anatomic portion discusses various primate groups so as to help investigators understand similarities and differences between animal models. An emphasis is on distal airway findings. The pathology section focuses on the inflammatory responses that occur in proximal and distal airways. The physiologic review brings together the anatomic and pathologic components to the functional state and proposes ways to evaluate the small airways in patients with asthma. (J Allergy Clin Immunol 2009;124:S72-7.)**

***Key words:*** *Anatomy, pathology, histology, physiology, airways, small airways*

*Abbreviations used*
FVC: Forced vital capacity
GR: Glucocorticoid receptor
NA: Nocturnal asthma
NNA: Nonnocturnal asthma
RV: Residual volume

## ANATOMY OF THE TRACHEOBRONCHIAL TREE WITH EMPHASIS ON THE DISTAL AIRWAYS: CONSEQUENCES OF DISTAL AIRWAY ABNORMALITIES

The tracheobronchial conducting airways form a complex series of branching tubes that culminate in the gas exchange area, with the average number of branches approximately the same for most mammalian species (Table I).[1-4] The more proximal of these branches, the bronchi, are usually characterized by their unique histologic composition, including the presence of mucus and basal cells in the epithelium, mucosal glands in the interstitium, and a significant amount of cartilage in the interstitial spaces. More distally, the bronchioles have a thinner wall, the complex nature of the airway epithelial population is reduced, and the preponderance of the wall is composed of smooth muscle with little to no cartilage. The tracheobronchial airways occupy approximately 1%, 2%, or 11% of the lung volume in human subjects, rhesus monkeys, and rodents, respectively. The remainder of the lung is comprised of large vessels and parenchyma (small vessels and bronchioles, interalveolar septa, and alveolar airspaces). In human subjects and nonhuman primates, cartilage is found in the walls of the tracheobronchial airways, from the trachea distally to the smallest bronchioles. In the distal bronchioles of human subjects and rhesus monkeys, cartilage is restricted to a small zone in the bifurcation area. By contrast, cartilage ends at the lobar bronchus in mice and rats. All species have a significant number of generations of intrapulmonary airways that are very thin walled and with minimal cartilage (nonrespiratory bronchioles). The organization of the zone of transition between conducting airways and the gas exchange area separates the lungs of primates and carnivores from those of other mammalian species. In primates and carnivores there is an extensive transition zone, with the walls of the distal airways having a mixture of bronchiolar epithelial cells mixed among alveolar outpockets.

The walls of tracheobronchial airways are highly complex cellular structures. All the airway wall compartments (epithelium and interstitium) making up the wall are present to varying degrees in all species. In all species the interstitium of the tracheal wall contains C-shaped cartilage, and there is a band of smooth muscle that joins the open end of the cartilage. The trachea and proximal airways have extensive submucosal glands beneath the epithelium in rhesus monkeys and human subjects. These glands are present to a variable extent in smaller laboratory species. There is a substantial difference among species in the amount of epithelium that lines the luminal surface in the trachea. The thickness of the epithelium in the trachea of rhesus monkeys is approximately twice that of mice and rats and one half to one third that of human subjects. Other major differences between species are the composition of the epithelium, the density of cells lining the surface, and the proportion of cell phenotypes in the epithelium. Mucus cells are a substantial percentage of the airway in primates but generally not to a substantial extent in the tracheas of healthy, pathogen-free mice and rats. The proportion of ciliated cells in the epithelium is relatively similar in all species, yet the proportion of basal cells found in the epithelial surface varies by species. As would be expected with the differences in secretory cell populations that line the trachea of different species, there is considerable variation in the carbohydrate content of the secretory product. Primates in general have a more heavily sulfated secretory product that is not usually found in laboratory mammals. The difference in secretory product composition is also reflected, to some degree, in the composition of the carbohydrates in tracheal submucosal glands.

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**TABLE I.** Comparison of species differences in tracheobronchial airway organization[1-4]

| Parameter | Human | Monkey | Mouse |
|---|---|---|---|
| Lung % | 1 | 1.8 | 11 |
| Cartilage in wall | Trachea to distal bronchiole | Trachea to distal bronchiole | Trachea to lobar bronchi |
| Nonrespiratory bronchiole | Several generations | Several generations | Several generations |
| Respiratory bronchioles | Several generations | Several generations | None or 1 |
| Generations to respiratory bronchiole (axial path) | 17-21 | 13-17 | 13-17 |
| Branching pattern | Dichotomous | Dichotomous/ trichotomous | Monopodial |

The organization of the tracheobronchial airways varies by airway generation within the airway tree. The largest, most proximal intrapulmonary bronchi show considerable organizational variation between species. Although smooth muscle is present in the walls of all mammalian species, there is a substantial difference in the extent of cartilage found in the lobar bronchus in laboratory mammals and in the distribution of submucosal glands. Epithelium is reduced in thickness in more distal airways compared with that seen in the trachea. There are also major differences in the organization of the surface epithelial population, with mucus and basal cells predominating in primates and Clara cells being the principal nonciliated cell population in other laboratory animals. In the most distal conducting airways, the bronchioles, the major differences between species are related primarily to the epithelial surface lining. In laboratory mammals the Clara cell is the primary secretory cell phenotype, and there are no mucous cells. The extent of basal cells in the epithelium varies by the extent of alveolarization. The bronchioles of rhesus monkeys have an extensive smooth muscle portion, which is arranged in large bundles and is interspersed with extensive connective tissue not generally observed in smaller laboratory mammals.

Alterations of the distal airways in rhesus monkeys, including decreased diameter, smooth muscle hyperplasia and hypertrophy, inflammatory cell accumulation ($CD4^+$ cells, $IgE^+$ cells, dendritic cells, eosinophils, and mast cells), basement membrane thickening/thinning, mucous cell metaplasia, and increased airway production of cytokines (IL-4, IL-5, macrophage chemoattractant protein 3, IL-12p40, IL-17, and eotaxin 2 and 3) and growth factors (fibroblast growth factor 2; vascular endothelial growth factor 121, 165; and TGF-β), were observed after house dust mite and ozone inhalation.[5-8] The same changes are observed in the distal airways of human subjects with asthma.[9-13]

Histologic examples of proximal to distal airways are shown in Fig 1.

## PATHOLOGY OF DISTAL AIRWAYS IN PATIENTS WITH ASTHMA

Pathologic evidence has emerged in the last few years suggesting that the airway inflammation and remodeling that characterize asthma occur not only in the central airways but extend to the distal lung and the lung parenchyma. The correlation between pathologic features and physiologic responses has been suggested by many studies. However, it is still unclear whether treating the inflammation in the distal airways is associated with better control of asthma and whether deposition of anti-inflammatory drugs to the distal region of the lung can lead to the prevention of remodeling in this area.

### Pathology of the large and small airways

Asthma is characterized by inflammatory cell infiltration into the airways, an upregulation of $T_H2$ cytokines, and structural changes, including epithelial detachment, subepithelial fibrosis, and increased smooth muscle mass. The majority of these observations have been obtained from studies that sampled central airways because bronchoscopic sampling was largely limited to proximal airway sites. A role of the distal airways and lung parenchyma in patients with asthma has been suggested by studies conducted in the early 1970s.[9,10] However, investigation of the pathology of the distal airways lagged because of the difficulties in obtaining adequate tissue from the peripheral structures.

Early studies looking at the pathology of distal airway disease originated from autopsy specimens[11,12] and have demonstrated that the entire length of the airway is involved in asthma. Carroll et al[12] have examined the distribution of inflammatory cells throughout the bronchial trees of patients who experienced both fatal and nonfatal asthma and have shown increased numbers of lymphocytes and eosinophils to be uniformly distributed throughout the large and distal airways of both patients with mild and those with severe asthma when compared with those seen in control subjects. Similarly, Hamid et al[13] have demonstrated, using resected lung specimens from asthmatic and nonasthmatic patients, that the inflammatory response in asthma is not restricted to the proximal airways. They reported increased numbers of T cells (CD3 cells), total eosinophils (major basic protein–staining cells), and activated eosinophils ($EG2^+$ cells) in both the large and distal airways of asthmatic patients when compared with those seen in control subjects. Comparing the large and distal airways directly, a greater number of activated eosinophils (EG2) was seen in airways with an internal diameter of less than 2 mm compared with larger airways. In these patients Minshall et al[14] have also shown increased numbers of IL-5 and IL-4 mRNA–positive cells in the distal airways of asthmatic patients compared with those seen in nonasthmatic control subjects, and more importantly, the expression of IL-5 mRNA was increased in the distal airways compared with that seen in the large airways.[14] The increased expression of eotaxin and monocyte chemotactic protein 4 mRNA also has been reported to be present in the epithelial cell layer and in the airway wall of the distal airways of asthmatic patients compared with that seen in nonasthmatic control subjects.[15] In this study the number of chemokine-positive cells in the distal airways correlated with the number of major basic protein–positive eosinophils at the same site. Chemokines were also demonstrated in the smooth muscle of the distal airways, and inflammation was detected outside the smooth muscle area. These observations have been confirmed by Haley et al,[16] who showed that inflammation extends beyond the airway smooth muscle of the distal lung in patients who died of asthma and suggested a significant role of this inflammation to the pathophysiology of asthma.

Using endobronchial and transbronchial biopsies, Kraft et al[17,18] have shown alveolar inflammation in patients with nocturnal asthma (NA), which is not present in those with

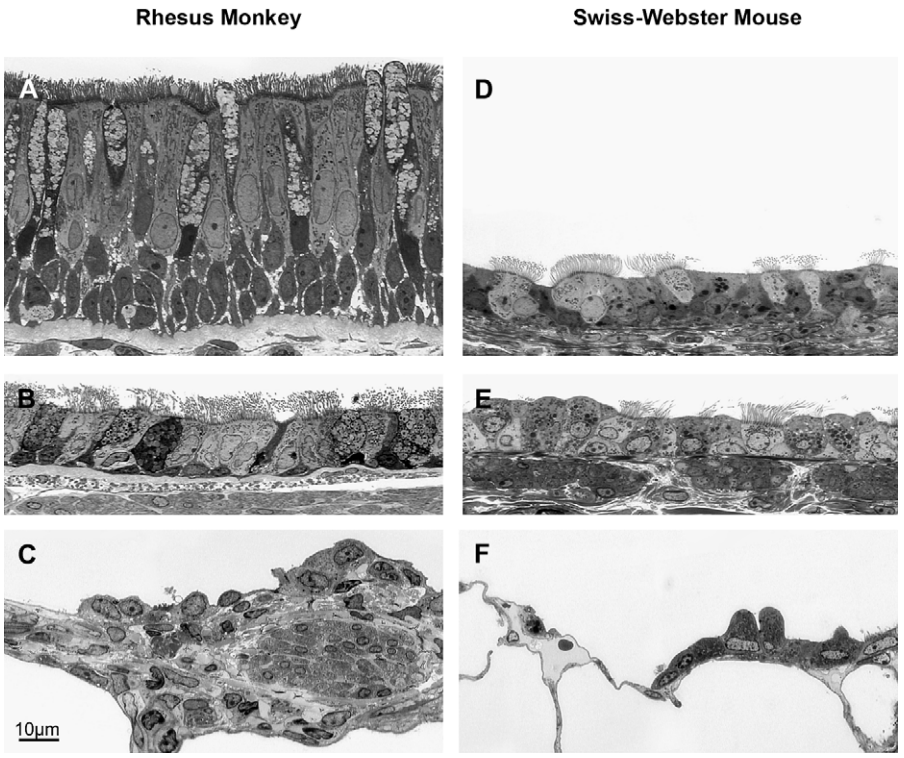


**FIG 1.** Histologic comparison of the airspace walls in the same airway generations (**A** and **D** are from tracheas, **B** and **E** are from proximal bronchi, and **C** and **F** are from bronchioles) of an adult male rhesus monkey (Fig 1, *A–C*) and an adult male Swiss Webster mouse (Fig 1, *D–F*). The luminal airspace *(top)* and the epithelium are set so that the basal lamina matches for both species. The epithelium is more complex and taller in the proximal airways of monkeys than at the same site in mice. Smooth muscle occupies a larger portion of the interstitium in monkeys than in mice at all airway levels. All micrographs are at the same magnification, with the magnification bar indicating 10 μm. Toluidine blue staining was used.

nonnocturnal asthma (NNA). Patients with NA had increased numbers of eosinophils per lung volume in their lung parenchyma at 4 AM compared with patients without NA, and the patients with NA had a greater number of eosinophils and macrophages in their alveolar tissue at 4 AM than at 4 PM. In addition, in the patients with NA, only alveolar (and not central airway) eosinophilia correlated with an overnight reduction in lung function. Those same investigators have shown increased numbers of CD4 cells in the alveolar tissue of patients with NA at 4 AM compared with those found in patients with NNA. Although the number of CD4 cells in the endobronchial lamina propria was higher than that in the alveolar tissue, once again, only the alveolar tissue CD4 lymphocytes correlated with the predicted lung function (ie, $FEV_1$) at 4 AM ($r = 0.68$) and with the number of activated alveolar eosinophils ($r = 0.66$). In this same patient cohort, NA was associated with reduced glucocorticoid receptor (GR)–binding affinity, reduced proliferation of blood mononuclear cells, and decreased responsiveness to steroids at 4 AM compared with that seen in patients with NNA.[19] These findings have suggested that the increased numbers of CD4 cells in the alveolar tissue of patients with NA, the reduced GR-binding affinity, and the reduced steroid responsiveness might be responsible for promoting eosinophil influx and exacerbations of symptoms in patients with NA. One of the mechanisms that might be responsible for this phenomenon is an upregulation of GRβ, which has been reported previously[20] in the peripheral airways of steroid-insensitive subjects with severe asthma. The main cells expressing GRβ are CD3 T lymphocytes and, to a lesser extent, eosinophils, neutrophils, and macrophages. These results suggested that the increased number of $GR\beta^+$ cells in the distal airways of patients with fatal asthma might be associated with steroid resistance, contributing to asthma mortality.

Similar distal airway inflammation has been reported in symptomatic, steroid-dependent asthmatic patients with severe disease. Using endobronchial and transbronchial biopsies, Wenzel et al[21] reported persistent proximal and distal airway inflammation. Although the number of eosinophils was similar between patients with severe asthma and healthy control subjects, asthmatic patients with severe disease had high numbers and percentages of neutrophils in their bronchoalveolar lavage fluid and endobronchial and transbronchial biopsy specimens when compared with asthmatic patients with mild-to-moderate disease, despite receiving aggressive treatment with steroids. It has been speculated that the inflammatory cell density in the distal airways in patients with severe asthma might relate to the peripheral airway obstruction that is characteristic of this disease. The distal airway inflammation might cause an uncoupling of the parenchyma and airways because of the mechanical interdependence between these 2 compartments, leading to changes in the overall accumulated lung mechanics in asthmatic patients. Recently, evidence has been accumulated in the central[22] and peripheral (unpublished data) airways of patients with severe asthma that another subset of T cells is present ($T_H17$ cells). This might explain the steroid hyporesponsiveness and neutrophilia seen in this subtype of the disease.

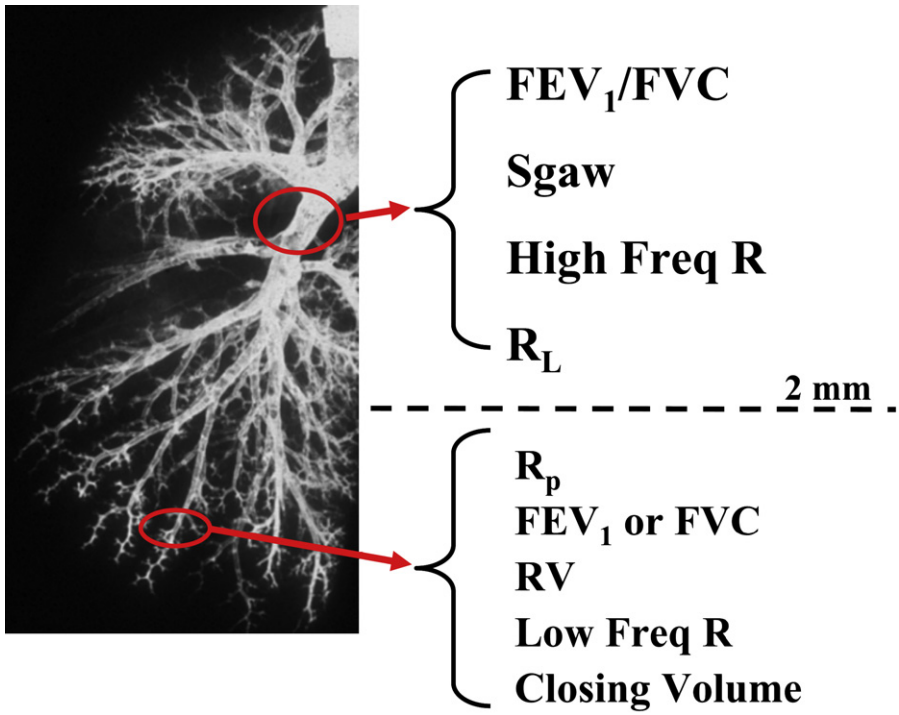


**FIG 2.** Function of the tracheobronchial tree is reflected by the physiologic lung function measures as indicated. *Freq R*, Resistance at low or high frequencies; $R_L$, lung resistance; $R_p$, peripheral resistance; *Sgaw*, specific airway conductance.

The nature of airway wall remodeling has been reasonably well described in the large airways; however, relatively little is known about structural remodeling of the distal airways. Subepithelial fibrosis and thickening have been reported as a result of excess deposition of collagen, laminin, fibronectin, and proteoglycans in the airway walls of asthmatic patients, and changes in these structural proteins have been positively correlated with airway responsiveness to methacholine. In a modeling study, Wiggs et al[23] have shown that a moderate increase in distal airway wall thickness, which has little effect on baseline resistance, can profoundly affect the airway narrowing caused by airway smooth muscle shortening. The combination of peripheral airway wall thickening and a loss of lung recoil are additive in their effect on enhanced airway responsiveness. In that study the investigators concluded that the contribution of the distal airways to total lung resistance has been thus far grossly underestimated and that the physiologic outcome is largely dependent on the frequency used to measure the peripheral lung mechanics. Bergeron et al[24] have demonstrated a considerable amount of subepithelial fibrosis and increase in smooth muscle mass in the distal airways of asthmatic patients but could not find any evidence of epithelial detachment. They have also shown that smooth muscle mass in the distal airways could be reduced in response to treatment.

## Conclusion

A large body of literature has suggested that airway inflammation occurs throughout the airway. Although the clinical significance of the distal airways and the lung parenchyma in asthma is not yet known, it is possible that poorly controlled inflammation in peripheral airways, which are not reached by conventional inhaled steroids, might contribute to an accelerated decrease in lung function and airway remodeling.

## PHYSIOLOGY OF THE TRACHEOBRONCHIAL TREE AND PHYSIOLOGIC TECHNIQUES TO EVALUATE THE DISTAL LUNG

In 1967, Malcolm Green[25] wrote a provocative essay that debunked the then commonly held notion that most of the resistance to airflow was attributed to the smallest airways.[26,27] Using the recently published morphometric measurements of Weibel for airway size, length, and number[28] and the simple laminar flow equation, Green's model suggested that the major source of resistance to breathing was in the central or large airways and not the smaller airways. Moreover, airways less than 2 mm in diameter or beyond 13 generations of airway branching contributed virtually nothing to total resistance. Two years later, Macklem and Mead[29] proved that Green's predictions were correct with direct measurements of small (<2 mm) airway resistance using the retrograde catheter. Hogg et al[30] then showed the same was true for the airways of human subjects. Both of these studies demonstrated that small (<2 mm) airways account for less that 10% of the total airflow resistance, and the term the "quiet zone" of the lung was born.[31] Since these pioneering studies, we have learned a great deal about those factors and methods that effect airway caliber as a function of axial position (ie, large [>2 mm] vs small [<2 mm]).

The large conducting airways have several important mechanisms that alter airway patency. These include neural influences (parasympathetic, nonadrenergic, and adrenergic), structural

support (eg, cartilage), smooth muscle tone, and, perhaps most importantly, the profound effects of lung volume.[32] On the other hand, we know that small airways have almost none of these protective mechanisms; nerves generally do not penetrate that deep into the small airways, small airways do not have cartilaginous support, and surfactant is important to their patency.[33] Smooth muscle does exist in smaller airways, but without parenchymal airway independence, the activation of small-airway smooth muscle leads to uninhibited small-airway narrowing.[34] As was shown years ago, the ability to increase airway diameter as a function of increasing lung volume is not a feature of airways less than 2 mm in diameter.[29,30] It has been calculated and supported by experimental evidence that airway resistance could increase 10-fold without a significant increase in overall pulmonary resistance because these airways contribute minimally to total resistance.[29-31] Because there are estimated to be 24,000 small airways and bronchioles,[28] thousands could be narrowed or totally obstructed without a significant loss of lung function. There is also a potential functional difference between events that narrow peripheral (<2 mm) airways and complete obstruction. A homogenous narrowing by half results in an increase in resistance of 16-fold when using Pouiselle's law, whereas complete obstruction of 75% of these same airways only results in a quadrupling of resistance, assuming that resistance of those parallel airways is determined as follows:

$$\frac{1}{Rtotal} = \frac{1}{R_1} + \frac{1}{R_2} = \frac{1}{RN}$$

where $N$ is defined as the total number of parallel airways. The most important mechanism to preserve airway function in these small airways appears to be their sheer number.

Clearly the complete removal of the lungs and insertion of airway catheters is not very practical. An alternative approach to directly partition airways resistance in human subjects is to use an intra-airway pressure sensor[35] or the wedged bronchoscope.[36,37] In this latter technique, pressure is measured at the end of the bronchoscope in response to a constant airflow rate that is injected into the subtended segment. Studies with either technique have shown that peripheral resistance was about 10-fold higher in patients with mild asthma, even though the spirometric results were within normal limits.[34-36] This increase in peripheral resistance could be explained as being due, in part, to occlusion of the small peripheral airways.[37] This decruitment of airway units increases as a function of asthma severity.[38] It was also shown that peripheral resistance was correlated to the residual volume (RV) and that RV is correlated to airways hyperresponsiveness.[38] Thus airway closure could be the sole cause of airway hyperresponsiveness, as demonstrated in an animal model and with computational modeling.[39]

There are several diseases and situations that have a specific effect on the small airways. These include the symptomatic smoker,[40,41] viral infections, exposure to gas and fumes, or mild asthma.[42] Small-airways constriction can also be selectively affected by the infusion of histamine.[43] The indirect measurement of small-airways function in living human subjects, however, is not straightforward. Woolcock et al[44] first suggested that the dysfunction that involves only the small airways can be defined as a situation when (1) static lung compliance is unaltered, (2) resistance is not significantly increased or marginally so, and 3) frequency dependence of compliance or resistance is present. This has lead to a number of investigations that have shown that frequency-dependent behavior of lung mechanics can be used to assess distal lung function.[43,45] Perhaps the most direct validation of the forced oscillation technique was a study by Bhansali et al[43] that showed a histamine infusion caused subsequent frequency-dependent behavior.

Measurement of distal airway function that is more acceptable to clinical practice has progressed. Since the 1970s, a number of techniques were developed or proposed, including closing volume,[46] frequency dependence of compliance or resistance,[43-46] forced expiratory flow at 25% to 75% of forced vital capacity (FVC), $FEV_1$/FVC ratio,[41] and other measurements, some of which are still used today to measure the function of the distal lung. The most common measurement of lung function is $FEV_1$, which is commonly taken as a function of airway resistance. However, it has been shown recently that $FEV_1$ is highly related to FVC in patients with asthma, the latter because of an increase in RV caused by airway closure, whereas the $FEV_1$/FVC ratio appears to measure central airway remodeling.[47,48] In the general population the correlation between $FEV_1$ and FVC is high at 0.9.[49] More recently, the increase in RV can be shown to be reduced when a systemic mediation, such as a leukotriene mediation, is used, resulting in improved systems.[50] Hence in a patient with an increased RV, decreased FVC, and normal $FEV_1$/FVC ratio, the most likely cause is disease of the small airways.[47,48] Accordingly this measure provides future investigations a relatively simple approach to assess disease and the response of the distal lung to therapeutic interventions.

Fig 2 demonstrates the level of the bronchial tree where certain airway function measurements are reflected.

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