

The Small Airways in Chronic Obstructive Pulmonary Disease



Pathology and Effects on Disease Progression and Survival

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Abstract and Introduction

Abstract

Purpose of review Chronic obstructive pulmonary disease (COPD) is caused by a mixture of small airway disease (obstructive bronchitis) and parenchymal lung tissue destruction (emphysema). The relative contributions of these two pathologic states vary from person to person. Having the ability to phenotype patients into predominately small airways disease or emphysema may affect the clinical management.

Recent findings Pathologic studies have shown that the progression of COPD from Global Initiative for Chronic Obstructive Lung Disease stages 0 to 4 is most strongly associated with small airway wall thickening as a result of lung repair or remodeling. The narrowing and loss of small airways occurs prior to emphysematous destruction. There is an increase in the amount of neutrophils and CD8⁺ T lymphocytes (cells that induce apoptosis and necrosis) in the small airways in COPD. Small airways disease can be identified on pulmonary function testing, using multiple nitrogen breath washout testing, indirectly through high-resolution chest computed tomography (CT) imaging or MRI, or directly by using microCT of resected lung tissue. There may be increased mortality in advanced COPD and concomitant small airway disease. There are newer methods to deliver respiratory therapies to reach the small airways.

Summary The current techniques utilized to assess patients for small airway disease need to be improved, so clinicians can more effectively phenotype patients with COPD and small airways disease. This will allow new therapies that target the small airways to be developed and tested, and positively impact on the natural progression of COPD.

Introduction

Chronic obstructive pulmonary disease (COPD) is a disease state characterized by chronic airflow limitation caused by a mixture of small airways disease (obstructive bronchitis) and lung tissue parenchymal destruction (emphysema). The relative contributions of these two pathologic states vary from person to person.^[1,2] Small airways are usually defined as airways less than 2 mm in internal diameter, which includes airways from the fourth to fourteenth generation of branching. Unlike large airways, these airways lack cartilage, and have a greater proportion of smooth muscles and fewer goblet cells in the epithelial layer.^[3,4] While small airways contribute little to airway resistance in the normal lungs, studies have shown the small airways to be the major site of resistance in obstructive lung disease, including asthma and COPD.^[5,6]

Pathophysiology of the Small Airways in Chronic Obstructive Pulmonary Disease

In the landmark study by Hogg *et al.*^[5] in 1968, the investigators characterized the small airway abnormalities in COPD by the presence of inflammation, fibrosis, and mucous plugging, all of which correlated with the severity of airflow obstruction. The increase in airflow obstruction in emphysematous parenchyma is a result of early airway closure because of reduced lung tissue elastic recoil. Why some patients manifest airflow obstruction in the form of airway narrowing and others because of reduced elastic recoil remains unclear.

In 2004, Hogg *et al.*^[7] examined small airways from 159 COPD patients and correlated pathologic findings with their Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage. The results indicated that the progression of COPD from GOLD stages 0 to 4 most strongly correlated with airway wall thickening as a repair response to airway wall injury. The degree of luminal occlusion and the extent of inflammatory response, as reflected by the number and magnitude of airways containing acute inflammatory cells and lymphocytes organized into follicles, were weakly associated with disease progression.

More recently, McDonough *et al.*^[8] reviewed multidetector computed tomography (MDCT) images from 78 COPD patients who underwent imaging as part of a lung-cancer screening study. Volumetric MDCT allowed for a skeletonized visualization of the bronchial tree without overlapping obscuration of the view by lung parenchyma. The investigators also collected control data in four deceased patients without obvious lung diseases. Furthermore, the investigators collected data in four patients with centrilobular emphysema who each donated a lung, and eight patients with panlobular emphysema who donated 10 lungs. Portions of the lung tissues were examined on microCT as well as histologically. Although microCT allows direct visualization of the bronchiolar and alveolar structures, its use is limited to ex-vivo tissue samples because the level of radiation induces tissue damage. The investigators showed that the number of small airways (2.0–2.5 mm in diameter) per lung pair was reduced in patients with GOLD stage I COPD compared with control samples and was further reduced in patients with GOLD stages 3 or 4. A comparison of the number of terminal bronchioles and dimensions at different magnitudes of emphysema showed that the narrowing and loss of terminal bronchioles occurs prior to emphysematous destruction. The investigators could not determine whether the airways measuring 2.0–2.5 mm in diameter disappeared or narrowed to the point that they were no longer visible. Regardless, they were able to explain, using advanced imaging techniques, the significant increase in small airway resistance in COPD. Although this study suggests that the loss of terminal bronchioles occurs before the loss of the acini, further work is needed to confirm this hypothesis.

Small airways inflammatory reaction that results from exposure to cigarette smoking occurs prior to the development of tissue destruction and fibrosis, and clinically detectable airflow obstruction.^[9,10] The inflammatory reaction in various compartments of the lung in smokers and nonsmokers with and without COPD has been examined. The CD8⁺ T lymphocytes are the predominant cell in large airways, small airways, and the COPD lung parenchyma, and the number of cells correlates with the degree of airflow obstruction. These CD8⁺ T lymphocytes induce an apoptosis and necrosis of epithelial and endothelial cells, which likely contribute to the lung destruction found in COPD. Although inflammatory cell infiltration of the small airways is initiated by smoke exposure, it is independent of the intensity of smoking and may be perpetuated long after smoking ceases.^[11,12]

The patterns of inflammatory responses in the small airways compared to large airways may be important in elucidating the pathogenesis of COPD. Battaglia *et al.*^[13] examined the lung tissue from 15 smokers and found an increased neutrophil density in the lamina propria of small airways compared with the large airways. The CD4⁺ T lymphocyte count was higher in the lamina propria of large airways compared with the small airways, and the difference in CD8⁺ T lymphocytes was not statistically significant. More recently, Isajevs *et al.*^[14] examined tissue from 19 nonsmokers, 20 smokers with normal lung function, and 20 smokers with moderate COPD undergoing lung resection. The investigators identified nuclear factor (NF)- κ B p65 and histone deacetylase 2 (HDAC2) expression as well as the make-up of inflammatory cells in the airways. Cigarette smoke induces proinflammatory cytokine release by activating NF- κ B (a transcription factor). Furthermore, cigarette smoke inhibits HDAC2 (by posttranslational modifications) that is associated with increased inflammation in alveolar macrophages and leukocytes. The investigators discovered that COPD patients had more macrophages in large airways compared with small airways, and more CD8⁺ T lymphocytes and neutrophils in small airways compared with large airways. When compared to nonsmoking persons, COPD patients exhibited a greater intensity of inflammatory pattern with more neutrophils, CD8⁺ T lymphocyte involvement, increased NF- κ B p65 expression, and decreased HDAC2 expression. The NF- κ B p65 expression is greater in large airways compared with small airways, which correlates with increased numbers of macrophages. The HDAC2 expression was decreased in small airways compared with large airways, which suggests that HDAC2 may be involved in the development of bronchiolitis that is characteristic in COPD. The

nonuniform distribution of inflammatory cells could be explained by anatomic or immune differences, and further studies need to be done to clarify these differences.

Measurement of Small Airways Function

Pulmonary function tests (PFTs) are the gold standard for the diagnosis and management of COPD. However, it is often difficult to assess small airways function using PFTs, and there is little agreement on the most useful PFT parameters to evaluate the small airways. In small airway disease, there is regional heterogeneity of flow time constants, progressive increases of resistance as the lung deflates, and premature airway closure. This creates an upper concavity of the flow–volume curve relative to its normal contour, although this is a subjective measure that is difficult to quantify. Residual volume (RV) is elevated when there is premature airway closure and air trapping. At the same time, total lung capacity (TLC) is commonly elevated in obstructive lung disease. Therefore, the RV/TLC ratio is the best measure of an elevation in residual volume. As the RV/TLC varies with age and sex, the raw data should be compared to the predicted RV/TLC ratio. The forced expiratory flow at 25–75% (FEF_{25–75%}) of forced vital capacity (FVC) is the spirometric variable most commonly used to indicate small airways disease. This variable excludes the initial peak of expiratory flow and averages the flow rate over the mid-quartile range of FVC. The difficulty in relying on the FEF_{25–75%} as a tool to evaluate small airways function is that it is significantly limited by the variability in its measurement.^[11] Data from the Severe Asthma Research Program of the National Heart Lung and Blood Institute showed a poor correlation of FEF_{25–75%} with other measures of air trapping (FVC and RV/TLC).^[15]

It has been hypothesized that bronchodilator reversibility (BDR) is primarily due to airway disease. Despite this, many patients with advanced COPD, a group not classically associated with small airway disease, do demonstrate BDR.^[16] In a study by Kim *et al.*,^[17] the investigators analyzed 67 patients with advanced upper-lobe predominant emphysema who underwent lung volume reduction surgery (LVRS). The investigators divided the individuals into two groups based on whether they exhibited BDR or not using the American Thoracic Society definition [$>12\%$ and >200 ml increase in forced expiratory volume in 1 s (FEV₁) or FVC]. They also histologically examined the small airways of the resected lung tissue. The individuals with positive BDR demonstrated increased smooth-muscle mass compared with those without BDR responsiveness. These data suggest that small airway smooth muscle hypertrophy contributes to BDR in advanced COPD and that BDR can be used as a noninvasive way to assess for the presence of small airways disease.

It is clear that other testing is necessary to more accurately assess small airways function. Although there are invasive techniques that include wedging a bronchoscope to obtain direct measurement of peripheral airway resistance, noninvasive techniques are necessary. Single-breath nitrogen washout has been performed for a number of years, which involves measuring nitrogen concentration following a single inhalation of pure oxygen. The slope of the nitrogen alveolar plateau against the expired volume is calculated through phase 3 of the expiratory volume–concentration curve. Increasing values are indicative of increasing ventilation heterogeneity, which is indicative of abnormal small airways function.^[18] A newer technique, the multiple nitrogen breath washout, has been developed to more accurately assess airway function at specific locations of the bronchial tree. This technique was used in a study by Verbanck *et al.*^[19] to detect small airway changes in smokers from as little as 10 pack-years onward. Furthermore, ventilation heterogeneity was observed in those with emphysema compared to those without emphysema. Use of this technique is currently limited to experienced centers for research purposes.

Exhaled nitric oxide (FE_{NO}) and impulse oscillometry (IOS) have also been developed to evaluate small airways inflammation and small airways physiology/dynamics, respectively. FENO correlates to eosinophilic inflammation and bronchial hyperreactivity. It is possible to calculate the relative contributions of nitric oxide from the alveolar compartment (surrogate for small airways) and the conducting airways. IOS involves oscillations of sound at multiple frequencies that are sent throughout the respiratory tree during normal tidal breathing. The reflected signals produce characteristic traces from which values are derived to represent airway parameters. Williamson *et al.*^[20] studied 24 healthy volunteers, 15 mild-to-moderate asthmatics, 21 severe asthmatics, and 24 COPD patients with a mean

FEV₁ of 55.6%. The FE_{NO} level from the alveolar compartment was elevated in COPD compared with severe asthma, mild-to-moderate asthma, and healthy volunteers without any difference between groups. The IOS parameters that measure peripheral resistance were higher in those with severe asthma and COPD compared with healthy individuals and those with mild-to-moderate asthma. There was significant correlation observed between peripheral resistance as measured by IOS and FEF_{25-75%} ($r = 0.71$, $P < 0.01$). These techniques may provide clinicians with alternative methods to assess patients for small airways disease.

Imaging the Small Airways

The current diagnosis, classification of severity, and follow-up of patients with COPD involves PFTs.^[2] However, PFTs are limited in that they provide only a global assessment of lung function and do not give any information about regional heterogeneity nor quantification of emphysema versus small airways disease. Furthermore, they can be difficult to interpret when there are coexisting disease states that cause variable and at times conflicting pathophysiologic effects, such as emphysema and interstitial lung disease. Despite the recent advances in high-resolution computed tomography (HRCT), it remains difficult to directly evaluate the small airways in patients with COPD. Generally, small airways only become visible when there is inflammation of the bronchiolar wall with accompanying exudates. More commonly, small airways disease can be indirectly seen by the presence of air trapping in the absence of visually obvious emphysema or bronchiectasis. Fixed obstruction of the small airways leads to patchy differences in density as a result of distal hypoventilation, air trapping, and oligemia (because of reflex hypoxic vasoconstriction). During normal expiration, the cross-sectional area of the lung decreases with a concomitant increase in lung attenuation values. Air trapping is defined as a loss of reduction of the cross-sectional lung area and an increase in lung attenuation^[1] (Fig. 1).

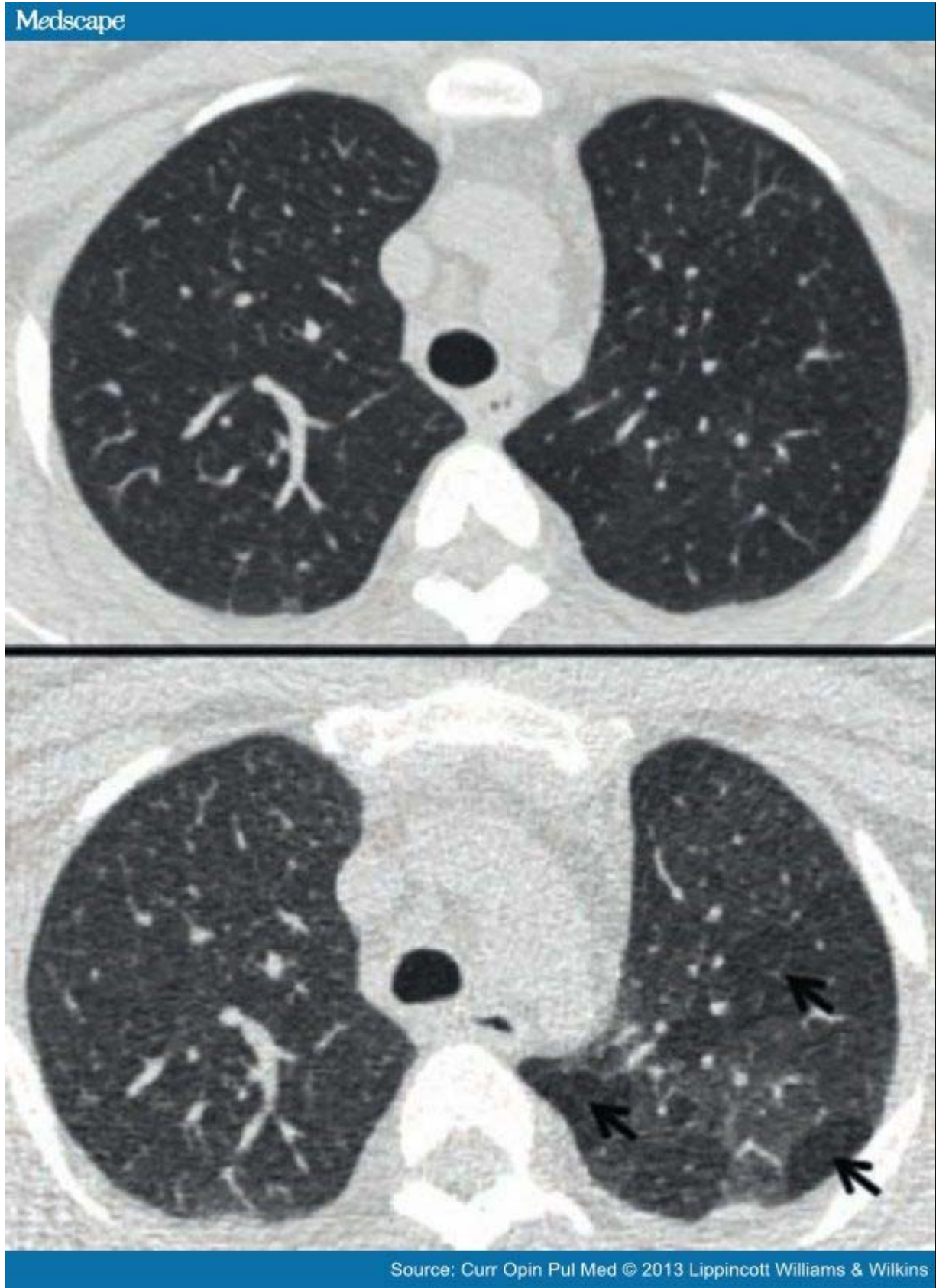


Figure 1.

High-resolution computed tomography (HRCT) inspiratory (above) and expiratory (below) images from a patient with chronic obstructive pulmonary disease (COPD). The presence of air trapping is evident by the increase in attenuation on expiratory images (arrows).

In clinical practice, the assessment of small airways disease is determined through visual detection of the lung densities obtained during expiratory and inspiratory HRCT images. However, there is no established method to objectively quantify the amount of air trapping. Mortani Barbosa *et al.*^[21] evaluated the use of an open-source imaging software to extract quantitative data about emphysema and air trapping between paired inspiratory and expiratory HRCT image datasets in an effort to improve quantification of small airways disease in obstructive lung disease. There was a strong correlation between air trapping volume and residual volume that was more pronounced in a subgroup of patients who had negligible emphysema, compared with those with moderate-to-severe emphysema. The investigators also quantified total segmented lung volume in inspiration and expiration as well as emphysema volume, all of which correlated with their corresponding PFT parameters. This study suggests that computer software can be used to quickly quantify the degree of air trapping from HRCT scans in patients with obstructive lung disease.

There is interest in using MRI following inhalation of hyperpolarized helium and xenon to provide further insight into small airway disease. This imaging technique offers additional functional information compared to HRCT without the use of ionizing radiation. However, HRCT gives better morphological information. Currently, the use of MRI is mostly limited to research studies.^[22]

Impact of Small Airways Disease on Chronic Obstructive Pulmonary Disease Progression and Survival

It is difficult to determine the effect of small airways disease on COPD progression and survival because of the still limited understanding of the role small airways play in COPD. Hogg *et al.*^[23] examined 101 individuals who underwent LVRS for advanced COPD (GOLD 3 or 4). The severity of luminal occlusion, wall thickening, and presence of small airways containing lymphoid follicles were determined in the resected tissue. The effect of corticosteroids on this pathology was assessed, as well as the survival at 72 months after LVRS. The investigators showed that the quartile of individuals with the greatest luminal occlusion died earlier than those who had the least occlusion. This association remains after adjustment for covariates (LVRS procedure, age, level of respiratory symptoms, and FEV₁). They also showed treatment with corticosteroids was associated with a lowering of the percentage of the airways containing lymphoid follicles. As this study only involved individuals with advanced COPD, it is difficult to generalize whether all patients with significant small airways disease have decreased survival.

In another study using tissue from LVRS, Kim *et al.*^[24] examined 25 patients with severe COPD and correlated their small airways pathologic findings to a change in FEV₁ at 6 months after LVRS. They classified patients as responders if they had a greater than 12% or a 200-ml change in FEV₁. The investigators showed that the small airways of nonresponders had a greater epithelial height, greater epithelial area, more mucous metaplasia, and less bullous disease in comparison to responders. Whether those with COPD and significant small airway pathology who have not undergone LVRS will experience a slower decline in FEV₁ is unknown and studies are required to elucidate this.

Verbanck *et al.*^[25] studied the impact of small airway disease in 87 asymptomatic smokers with greater than 10 pack-year history of smoking who had an absence of spirometric airflow obstruction at baseline and who successfully stopped smoking for variable times and compared their results to a control group of 16 persistent smokers. PFTs were performed, as well as the multiple breath washout tests (described earlier). While lung function parameters were relatively unaffected by smoking cessation, ventilation heterogeneity in the conductive airway compartments (indicative of small airways disease) improved by 30% at 1 week and 42% at 1 year. These data suggest that those with small airways disease who quit smoking show significant improvements in conductive airway malfunction.

Whether this can be generalized to smokers who have airflow obstruction is unknown. However, it is possible that a group of patients with small airways disease and airflow obstruction would experience an increase in pulmonary function parameters and an improvement in their symptoms with smoking cessation alone.

Treatments Targeting the Small Airways in Chronic Obstructive Pulmonary Disease

Pharmacologic therapies for COPD include the use of inhaled corticosteroids (ICS), long-acting beta-agonists (LABAs), and long-acting muscarinic antagonists. These therapies have been shown to reduce symptoms, improve health-related quality of life, and prevent exacerbations as well as hospitalizations. Although ICS is a highly effective therapy in almost all patients with asthma, the role of ICS in patients with stable COPD remains controversial.^[2,26] This might be the result of a difference in the type of inflammation in asthma versus COPD, the effect of cigarette smoke, or the loss of lung tissue in COPD. Alternatively, the difference in the effect of ICS could be explained by drug delivery. The traditional ICS is a large particle ICS which does not easily reach the peripheral airways, the site of a majority of the inflammation. Beclomethasone dipropionate (BDP) has been reformulated using hydrofluoroalkane-134a (HFA) as a propellant. This combination forms a solution that on evaporation forms an extra-fine aerosol of small droplets. Although there have been a number of studies evaluating the efficacy of extra-fine drug delivery in asthma, there are limited studies in patients with COPD.

Three studies have examined the use of HFA-BDP in COPD in relation to either placebo or large particle ICS (fluticasone or budesonide). Van Beurden *et al.*^[27] showed that ICS did reduce the concentration of exhaled H₂O₂ (surrogate for levels of oxidative stress), but there was no difference depending on the delivery of the ICS (small versus large particle). This is either because of the carry-over effect during the washout period or indicates that homogenous deposition of drug is achieved regardless of the size of the particles. John *et al.*^[28] observed a 13% reduction in RV/TLC and a 6.4-point improvement in St. Georges Respiratory Questionnaire (SGRQ) with HFA-BDP compared with placebo, but no effect on FEV₁ or cytokine levels. Tatis *et al.*^[29] showed that after 8 weeks of therapy, the individuals switched to HFA-BDP demonstrated a greater improvement in spirometric values and respiratory symptoms, and a decrease in β_2 -agonist use compared with those who remained on large particle ICS. The investigators also showed that low-dose HFA-BDP was more effective than medium-dose use of a traditional inhalant.

These studies support the improved efficacy of extra-fine aerosol respiratory treatments for COPD that have a deeper penetration into the lungs, and therefore the small airways. More studies are required to determine the clinical impact of these therapies on the long-term outcome of patients with COPD, and whether combination therapy with extra-fine BDP and long-acting β_2 -agonists would benefit patients as well.

Conclusion

Despite a considerable amount of interest in small airways disease since the 1960s, these airways remain a difficult area to study because of their relative inaccessibility and lack of a readily available, reproducible, and noninvasive technique to assess their function. A better understanding of the pathophysiology of small airway disease as well as the physiologic assessment of patients with this disease phenotype have the potential to pave the way for the development of new pharmacological therapies that target the small airways specifically. This in turn may impact the natural progression of COPD.

Sidebar

Key Points

- Small airways contribute little to airway resistance in normal lungs, yet are the major site of resistance in obstructive lung disease.

- Small airways disease is present in smokers without clinical evidence of airflow obstruction. Pathologically, there is progression to narrowing and loss of terminal bronchioles prior to the development of emphysematous destruction.
- It is difficult to assess for the presence of small airways disease on PFTs. New techniques are in development including computer analysis of HRCT, IOS, FENNO, and multiple nitrogen breath washouts.
- There may be an increased mortality in individuals with advanced COPD and concomitant small airway disease.
- Patients with small airway disease might benefit from respiratory drugs delivered via extra-fine particles.

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* This article retrospectively studied 16 patients with an obstructive pattern on PFTs who had concomitant HRCT (inspiratory and expiratory). This study used the open-source software Advanced Normalization Tools to extract quantitative data about emphysema and air trapping between paired inspiratory and expiratory HRCT image datasets. They then correlated these values with PFT parameters. This study suggests that

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* of special interest

** of outstanding interest

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