



Why We Should Target Small Airways Disease in Our Management of Chronic Obstructive Pulmonary Disease

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Abstract

For more than 50 years, small airways disease has been considered a key feature of chronic obstructive pulmonary disease (COPD) and a major cause of airway obstruction. Both preventable and treatable, small airways disease has important clinical consequences if left unchecked. Small airways disease is associated with poor spirometry results, increased lung hyperinflation, and poor health status, making the small airways an important treatment target in COPD. The early detection of small airways disease remains the key barrier; if detected early, treatments designed to target small airways may help reduce symptoms and allow patients to maintain their activities. Studies are needed to evaluate the possible role of new drugs and novel drug formulations, inhalers, and inhalation devices for treating small airways disease. These developments will help to improve our management of small airways disease in patients with COPD.

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For more than 50 years, small airways disease has been identified as a major cause of airway obstruction, particularly early in the course of chronic obstructive pulmonary disease (COPD).¹⁻⁴ Although somewhat underrecognized in daily clinical practice,⁵ small airways disease is reported in at least three-quarters of patients with COPD.⁶ Indeed, given the difficulties in assessing small airway abnormalities, which we describe later in this article, it is likely that small airways dysfunction is a common factor in all patients with COPD, coexisting in differing degrees with other phenotypic variations of this complex and heterogeneous disease.

Also known as *peripheral airways*, the small airways (<2 mm in diameter) include bronchioles, terminal bronchioles, respiratory bronchioles, alveolar ducts, and alveolar sacs (Figure 1A). The term “small airways disease” was first coined in 1968 and identified as the major cause of airway resistance in patients with obstructive lung disease.³ More recently,

the role of small airways disease in the pathogenesis of COPD has been recognized by the Global Initiative for Chronic Obstructive Lung Disease (GOLD)⁷ and Interasma/the World Allergy Organization.⁸

Notably, the documented prevalence of small airways disease (74%-83%^{6,9}) increases with rising GOLD classification, indicating that it is progressive and worsens with increasing severity of COPD.⁶ Small airways disease is particularly notable (~93%) in patients with a high effect of COPD on health status and daily life.⁶ The fact that small airways are involved in the development of airflow limitation in both predominant COPD phenotypes—emphysema and chronic bronchitis—indicates their prominent role in the pathogenesis of the condition.^{3,10,11}

METHODS

The aims of this focused review were to summarize key information on the pathophysiology of small airways disease, how it is assessed, and why it is an important

treatment target as well as to review available treatments and future directions in the management of the condition. Studies included in this article were identified by searching the PubMed (MEDLINE) database, using the search terms *COPD AND ("small airway disease" OR "small airways disease" OR "small airway dysfunction" OR "small airways dysfunction")* and by cross-referencing citations in identified studies that were available in print or online, including relevant studies in patients with asthma.

PATHOPHYSIOLOGY

Airway Remodeling, Mucus Plugging, and Immune Cell Infiltration

In COPD, small airways disease is characterized by airway remodeling, mucus plugging, and immune cell infiltration (Figure 1B).^{4,12-14} Injury caused by factors such as cigarette smoke or infection triggers the wound healing process, resulting in an increase in airway wall thickness and therefore a decrease in the airway lumen.⁴ Cigarette smoking also induces hypersecretion of mucus, leading to mucus plugging and physical blockage of airflow.⁴ This is compounded by the effect of smoking in reducing cilia length in the small airways, leading to decreased mucociliary clearance.⁴ Mucus may also harbor pathogenic microorganisms that promote inflammation and tissue destruction.⁴ Immune cell infiltration involves the recruitment of increased numbers of macrophages, neutrophils, CD20⁺ B cells, and CD4⁺ and CD8⁺ T cells to the small airways,⁴ with CD8⁺ T cells hypothesized to be the predominant inflammatory cells contributing to small airway obstruction and tissue damage.¹²

Evidence Early in the Course of COPD

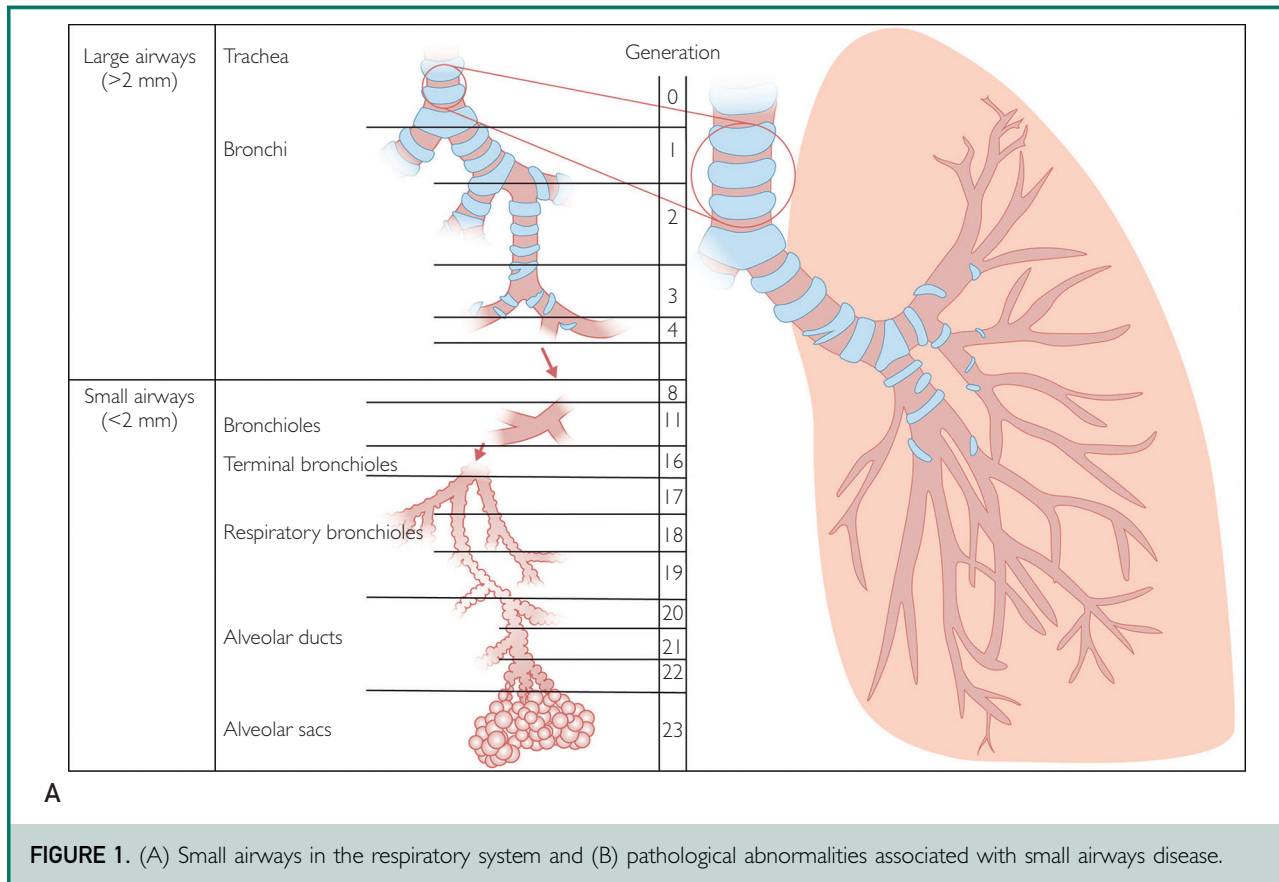
Small airways disease is often evident before the onset of symptoms or changes in spirometry or imaging findings in COPD.^{5,15} The small airways represent a "silent zone" in the normal lung in which defects can accumulate without being noticed; this finding has led to the development of specialized tests to detect early abnormalities in the

ARTICLE HIGHLIGHTS

- Small airways disease is a key feature of chronic obstructive pulmonary disease (COPD) and a major cause of airway obstruction.
- Patients with COPD and small airways disease have worse spirometry results, more severe lung hyperinflation, and poorer health status compared with those without small airways disease, making the small airways an important treatment target.
- In this article, we evaluate several new techniques that have the potential to achieve the early detection of small airways disease.
- We review therapy options designed to target the small airways that may help reduce symptoms and allow patients to maintain their activities.
- Advances in our ability to assess the extent of small airways involvement, as well as the use of novel drugs, formulations, and inhalers that target the small airways, will help to improve our management of small airways disease in patients with COPD.

hope of preventing or delaying disease progression.¹³ However, traditional imaging techniques may not be sufficiently sensitive to identify the early stages of small airways disease or to differentiate between the contribution of small airways disease and emphysema.¹³ Because extensive small airways damage and obliteration can occur before it is detectable with conventional spirometric tests, spirometry is also of limited use as a screening tool for early disease.⁵

Small airways disease may be a precursor to emphysema.^{4,16} Very severe COPD is associated with a marked reduction in both the number of terminal bronchioles and the minimal lumen caliber of those that remain.¹⁶ These changes can be present in regions of the lungs not yet affected by emphysema, suggesting that they may begin at very early stages in the natural history of COPD.¹⁶ Other studies have reported that both small airways disease and emphysema are associated with decline in forced expiratory volume in 1 second (FEV₁), but small airways disease has a greater role in the decline associated with mild-to-moderate airflow limitation, which indicates a role early in the disease course.^{17,18}



Effect of Small Airways Disease on Hyperinflation

Pulmonary hyperinflation is a common cause of dyspnea and functional limitation in patients with COPD.¹⁹ Small airways disease can lead to expiratory flow limitation, gas trapping within the lung and dynamic hyperinflation.^{14,20} This is characterized by flattening of the diaphragm, sternal bowing, chest kyphosis, and enlarged intercostal spaces, resulting in a barrel chest.²¹ Dynamic hyperinflation develops as a result of expiratory airflow limitation coupled with decreased exhalation time, for example, during exercise, and is associated with decreased inspiratory capacity and increased functional residual capacity (Figure 2).¹⁹

Hyperinflation affects clinical outcomes in COPD; for example, activity-related dyspnea associated with hyperinflation can lead to a vicious cycle of activity avoidance, physical deconditioning, and reduced

health-related quality of life.²⁰ Indeed, dynamic hyperinflation and exercise limitation are both independent predictors of mortality in patients with COPD.¹⁹ Hyperinflation also has implications for the early development of comorbidities such as cardiovascular disease.²⁰ Of particular concern, hyperinflation impairs the mechanical function of the respiratory muscles and has adverse effects on the cardiocirculatory system.²²

Role of Bacterial Colonization and Exacerbations

Bacterial colonization and exacerbations (or acute clinical deterioration) of COPD both have a role in the progression of small airways disease.⁴ Bacterial colonization is aggravated by reduced clearance and decreased antimicrobial activity of mucus in patients with COPD.⁴ This can lead to chronic low-grade inflammation, which at times can increase acutely,

leading to an exacerbation.⁴ Furthermore, acute exacerbations are often associated with new strains of colonizing bacteria, supporting a causative role of bacteria in the onset of exacerbations.²³ Exacerbations of COPD also appear to play a part in the airway remodeling process, by promoting rapid turnover of the extracellular matrix (including increases in degradation fragments of collagens I, IV, and VI and the pro-form of collagen V), increasing sputum neutrophils and neutrophil proteases, increasing expression and activity of matrix metalloproteinases, and dysregulating proteinase activity.²⁴⁻²⁷ These effects, in turn, lead to tissue destruction and reduced mobility of mucus.⁴

CLINICAL EFFECT

Small airways disease is associated with poor spirometry results, increased lung hyperinflation, and poor health status, making the small airways an important treatment target in COPD.⁹ There is also a significant correlation between small airways disease and quality of life (measured by the St. George's Respiratory Questionnaire) as well as between small airways disease and dyspnea (measured by the modified Medical Research Council Scale) (both $P < 0.01$).²⁸

Small airways disease and emphysema are associated with FEV₁ decline, particularly in mild-to-moderate COPD.¹⁷ Treatments targeting the small airways in COPD may reduce the rate of emphysema progression.⁴ In fact, because small airways disease appears to precede the onset of emphysema, the development of treatments that specifically target small airways disease has the potential to treat progression of both airway and parenchymal disease.¹⁴

ASSESSMENT

Small airways disease can be difficult to assess because of the small size and inaccessibility of the airways.¹⁵ Many methods are complex or invasive, and overall, there is no unanimously accepted approach. Different methods of assessment are described below and summarized in the [Supplemental Table](#) (available online at <http://www.mayoclinicproceedings.org>).

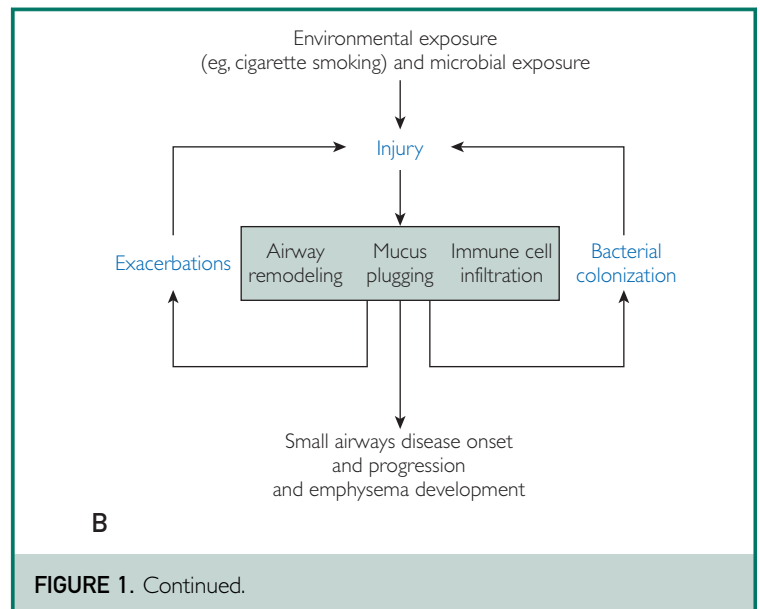


FIGURE 1. Continued.

org), with [Figure 3](#) providing an infographic overview of these techniques and their outputs.

With small airways disease, traditional lung function tests may only become abnormal once there is a significant burden of disease.^{5,12,13,15} Hence, although spirometry is the gold standard for diagnosing COPD, FEV₁ is not an adequate measure of small airways disease.^{5,12,14,15} Small airways disease is associated with bronchodilator responsiveness in terms of volume (forced vital capacity [FVC]) but not in terms of flow (FEV₁).⁹ Indeed, FVC has been used as an indirect measure of small airways disease in several clinical trials.²⁹ Forced expiratory flow between 25% and 75% of the FVC is another common measure of small airways abnormality, though there is conflicting evidence regarding its reliability.^{12,15} Other measures of expiratory flow include evaluation of maximal expiratory flow when 75%, 50%, or 25% of FVC remains.⁵ The ratio of forced expiratory volume in 3 and 6 seconds (FEV₃/FEV₆) has also emerged as an earlier and more sensitive marker of small airways disease compared with other spirometric measures, with low FEV₃/FEV₆ found to be associated with impaired computed tomography (CT) scanning measures of small airways disease in patients with normal FEV₁/FVC.³⁰ Furthermore, the Genetic Epidemiology of

COPD (COPDGene) Study reported that patients with a reduced FEV_3/FEV_6 had a higher degree of gas trapping, worse symptoms (according to both the St. George's Respiratory Questionnaire and the modified Medical Research Council Scale), and worse functional indices (6-minute walk distance) than patients with FEV_3/FEV_6 greater than the lower limit of normal.^{30,31}

Body plethysmography—which provides a sensitive measure of gas trapping and lung hyperinflation—can be used to assess lung volumes, providing measures such as total lung capacity (TLC), functional residual capacity, inspiratory capacity, and residual volume (RV).^{12,15} As TLC is commonly elevated in COPD, the

ratio of RV/TLC may provide a more robust marker of gas trapping and small airways disease than RV alone.¹⁵ Airways resistance—which provides a measure of airway obstruction—may also be assessed by body plethysmography by measuring the pressure required to drive airflow during tidal ventilation.⁵ Diffusing capacity for carbon monoxide (also known as transfer factor of the lung for carbon monoxide), which indirectly measures the degree of gas transfer from alveoli to pulmonary capillary blood, has also been found to correlate with small airways disease.³² Data from ever-smokers in the COPDGene cohort indicated that functional small airways disease correlates significantly with

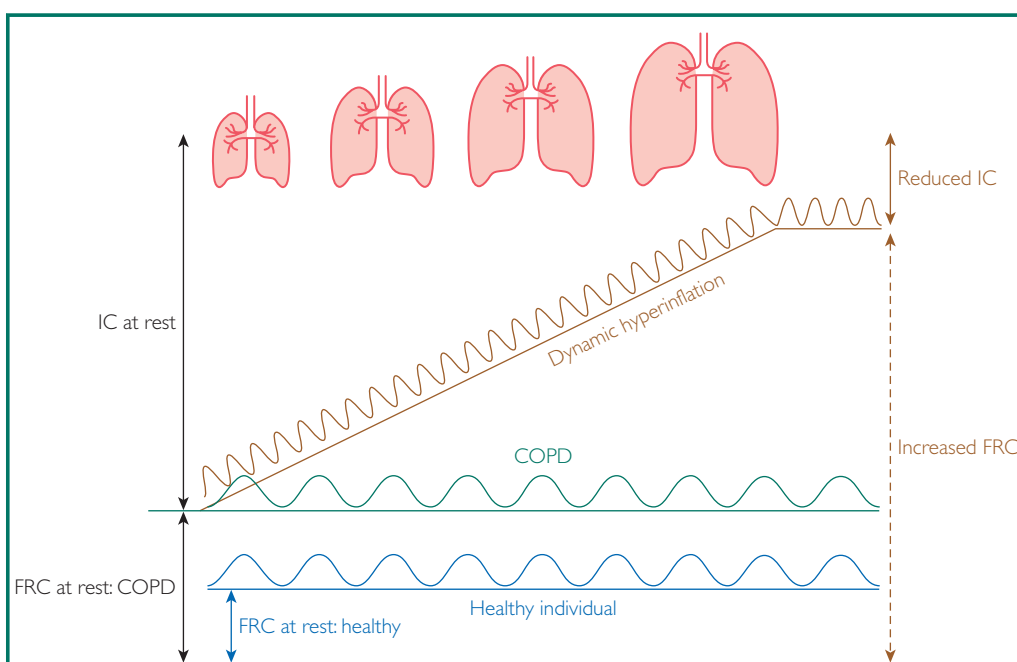


FIGURE 2. Dynamic hyperinflation in COPD. This figure shows the effects of dynamic hyperinflation on lung volumes. In COPD, if the small airways are narrowed or obstructed and there is expiratory airflow limitation, the inhaled volume of air is greater than the exhaled volume and air is retained in the lung. Accordingly, individuals with COPD often have some degree of hyperinflation in their lungs, even at rest. During resting breathing (COPD: green line; healthy individual: blue line), a breath is inhaled to tidal volume and an equal volume is exhaled so that the FRC remains stable but is still increased in patients with COPD. During exertion, agitation, or anxiety, the tidal volume and breathing frequency increase (red line) with a reduction in expiratory time. Because the inspiratory volume is greater than the expiratory volume, the end-expiratory volume increases with each breath, leading to a progressive increase in FRC and reduction in IC. This results in an increasing sensation of dyspnea and consequent limitation of physical activity in COPD. COPD, chronic obstructive pulmonary disease; FRC, functional residual capacity; IC, inspiratory capacity.

lower diffusing capacity for carbon monoxide among nonobstructed and GOLD stage 1-2 individuals ($P < 0.001$ and $P = 0.004$, respectively).³²

The forced oscillation technique and impulse oscillometry are techniques that can be used to determine the mechanical properties of the lung.^{5,13-15,33,34} The forced oscillation technique and impulse oscillometry work by applying oscillating pressure variations of varying frequencies to the lung during normal tidal breathing, with the resulting pressure and flow changes measured at the mouth.¹⁵ Higher-frequency signals reflect the contribution of larger airways, whereas low frequencies reflect the whole lung; as such, the contribution of the small airways can be found by comparing the two.¹⁵

Inert gas washout techniques such as the single-breath nitrogen washout test and multiple-breath nitrogen washout test may also be used to assess small airways disease.¹³ These techniques work by measuring the efficiency of gas mixing in the lungs, which varies according to the structure of the large and small airways and can therefore give an indication of small airways disease.^{5,12,13,15} The sensitivity of the multiple-breath washout test has been found in smokers, with evidence of small airways disease detected from more than 10 pack-years onward, compared with more than 20 pack-years onward when assessed using spirometry.³⁵ An analysis of the slope of phase III, which forms part of the characteristic trace that is recorded during the single-breath nitrogen washout test (Figure 3), can provide further information on the differences in ventilation in different parts of the lung.¹⁵ Measurement of novel exhaled biomarkers, including exhaled nitric oxide, can give an indication of inflammation (particularly eosinophilic inflammation) in the lung, including its location within central or peripheral airways.^{12,15}

Lung imaging techniques for visualizing the small airways (Supplemental Table and Figure 4) include high-resolution CT, which is increasingly being supplemented by parametric image response mapping.^{5,12-15,36,37}

Hyperpolarized helium magnetic resonance imaging is another useful technique for evaluating regional lung function, including assessment of the distribution of ventilation and morphometry of the distal airways and lung parenchyma.¹⁵ Other imaging techniques include nuclear medicine (scintigraphy, single photon emission CT, and positron emission tomography)¹⁵ and functional respiratory imaging, which uses airway imaging techniques such as CT combined with computational fluid dynamic simulations to determine patterns of airflow and inhaled drug deposition.³⁸⁻⁴⁰ Another recent method uses CT imaging techniques to identify and assess the relative contributions of emphysematous and nonemphysematous gas trapping, thus helping to assess different COPD phenotypes.⁴¹

Other techniques to assess small airways are more invasive and typically only used for research purposes, for example, sputum induction after inhalation of hypertonic saline, bronchoalveolar lavage, and endobronchial and transbronchial biopsies.¹²

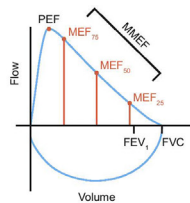
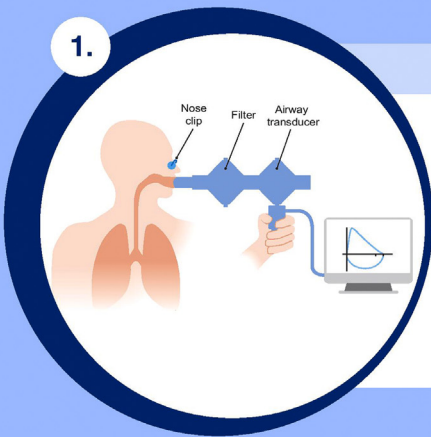
For the assessment of dynamic hyperinflation and ventilatory limitation, exercise testing is a commonly used clinical tool that is easy to implement. Measurement of tidal exercise flow volume loops can provide sensitive data on the extent of expiratory flow limitation, inspiratory flow reserve, and alterations in dynamic hyperinflation and tidal volume/inspiratory capacity and may enable earlier detection of abnormalities than other approaches.^{42,43} Constant work rate endurance protocols are also an effective patient-centered method to assess the response to therapeutic interventions in patients with COPD.⁴⁴

PREVENTION

Although it is not the primary focus of this article, it is important to note that prevention is the best means to tackle the global burden of small airways disease and COPD. This can be achieved by implementing effective smoking cessation programs and reducing environmental exposure to biomass fuels and air pollution; however, this is difficult to achieve in practice.⁴⁵

1.

Spirometry/expiratory flow



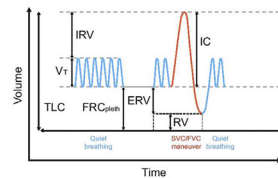
Spirometry, the most commonly used pulmonary function test, measures the volume and/or flow of air that can be inhaled/exhaled.

Spirometric measures such as FEV₁ and FVC and measures based on maximal expiratory flow (when 75%, 50%, or 25% of FVC remains) may not be reliable markers of early small airways disease, and the ratio of FEV₁/FEV_{0.5} may be preferred.

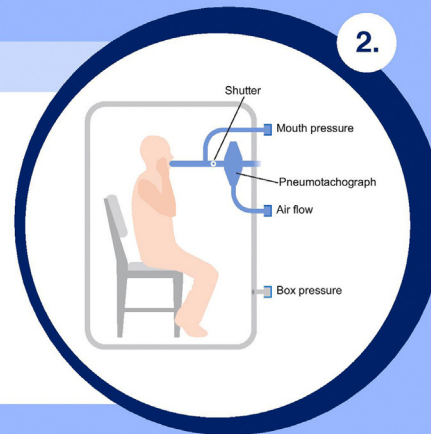
Body plethysmography

Body plethysmography provides data on patients' breathing at rest by recording respiratory flow rate under defined breathing conditions.

Body plethysmography allows the determination of static lung volumes and airflow resistance. In particular, the ratio of residual volume: total lung capacity (RV/TLC) may act as a marker of gas trapping and small airways dysfunction.

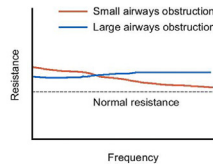
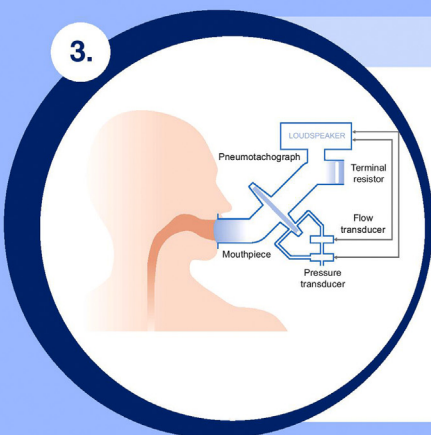


2.



3.

Impulse oscillometry/forced oscillation technique



Impulses of multiple frequency sound waves (impulse oscillometry system) or forced oscillations of single frequency sound waves (forced oscillation technique) are pushed into the lungs as pressure waves to measure respiratory resistance.

When either central or small airway obstruction occurs, the resistance increases above normal values compared with healthy individuals. Central airway obstruction elevates resistance evenly independent of oscillation frequency, whereas small airway obstruction increases resistance at low frequencies, an effect that diminishes with increasing frequency. Frequency-dependent resistance is considered a characteristic feature of small airways obstruction.

FIGURE 3. Measurement of small airways disease: physiological techniques. COPD, chronic obstructive pulmonary disease; CV, closing volume; ERV, expiratory reserve volume; FE_{NO}, fractional exhaled nitric oxide; FEV_{1/3/6}, forced expiratory volume in 1/3/6 second(s); FRC_{pleth}, functional residual capacity measured using plethysmography; FVC, forced vital capacity; IC, inspiratory capacity; IRV, inspiratory reserve volume; MEF_{25/50/75}, maximal expiratory flow when 25%/50%/75% of forced vital capacity remains; MMEF, maximal mid-expiratory flow; NO, nitric oxide; PEF, peak expiratory flow; RV, residual volume; SVC, slow vital capacity; TLC, total lung capacity; V_T, tidal volume.

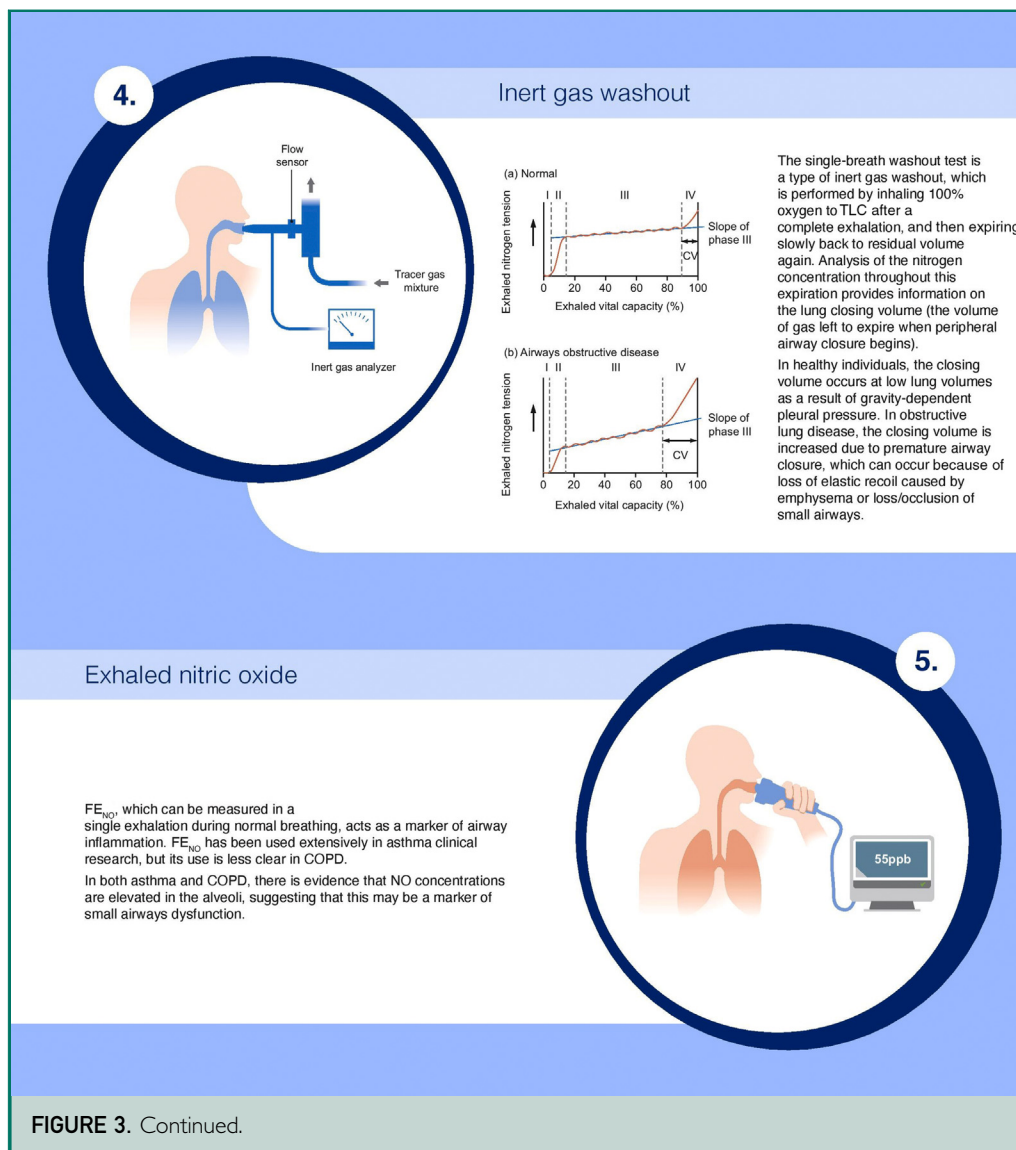


FIGURE 3. Continued.

TREATMENT

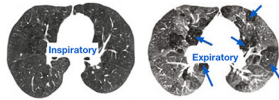
What Treatments Are Available to Target the Small Airways?

Directing drugs to the small airways via the inhaled route has a number of advantages compared with oral or intravenous routes. For example, smaller drug doses can be used, the onset of action is more rapid, and the incidence of adverse effects—particularly those of corticosteroids—is reduced.^{46,47}

The choice of both the drug molecule and the inhaler device is critical, particularly

when considering how best to enhance drug deposition at the site of disease. As well as the total dose of drug delivered to the lungs, the regional deposition pattern within the lungs is an important factor.^{47,48} As most inhaled therapies do not sufficiently reach the small airways, it is necessary to improve the precision of drug deposition to increase the efficiency and effectiveness of inhaled drug delivery.^{49,50} Different therapeutic options with the potential to target the small airways are described below and are summarized in the Table.^{14,57-81}

1. High-resolution computed tomography



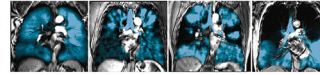
High-resolution computed tomography (HRCT) is a noninvasive imaging technique that can quantify certain features of small airways disease, such as air trapping and ventilation heterogeneity (e.g. during expiration, as observed in the accompanying image).

However, as HRCT can estimate the wall thickness of only those bronchi that are ≥ 2 mm in diameter the technique does not allow direct assessment of small airway abnormalities, such as airway wall thickening.^a

2. Hyperpolarized helium magnetic resonance imaging

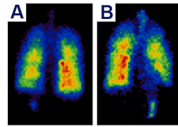
Magnetic resonance imaging (MRI) after the inhalation of hyperpolarized helium or xenon allows the estimation of alveolar size and emphysema and can therefore provide further insight into small airway involvement in COPD.

For example, the accompanying hyperpolarized helium MRI images show progressively poorer ventilation (black areas) with increasing emphysematous destruction of the lungs.^b



3. Nuclear medicine

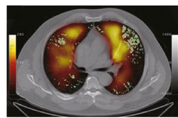
Scintigraphy



Scintigraphy uses radioactive tracers to obtain images of organs and/or record their functioning. It is a powerful tool that has been widely used to visualize and characterize intrapulmonary drug delivery in airways diseases such as asthma and COPD. It allows the measurement of overall lung deposition, and, to some extent, regional deposition (such as the lung periphery).

The accompanying scintigraphic images from a patient with asthma show aerosol deposition of radioactively labeled albuterol particles in the (a) posterior thorax and (b) anterior thorax, which were recorded sequentially, with the patient repositioned between views. Red areas indicate regions of highest radioactivity and black of least radioactivity.^c

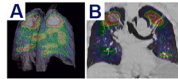
Single-photon emission computed tomography



Single-photon emission computed tomography (SPECT) is a 3-dimensional nuclear imaging technique involving use of radioactive tracers to highlight certain features of organs/tissues, such as the patchy distribution of small airways disease. Single-photon emission computed tomography images are sometimes combined with traditional computed tomography images to correlate functional and structural features.

The accompanying Technegas ventilation SPECT/computed tomography (CT) fusion image shows the axial dimension of a 68-year-old man with moderately severe COPD. It highlights well-ventilated areas of the lung (bright yellow), less-ventilated areas (red), and nonventilated areas (black). Green indicates emphysema. It is apparent that poorly ventilated areas tend to correspond with areas of emphysema.^d

Positron emission tomography



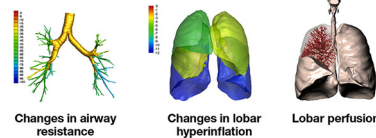
Positron emission tomography (PET), which may also be combined with CT, is another three-dimensional nuclear imaging technique that allows visualization of the regional deposition of radiolabeled tracers. The major difference compared with SPECT is a higher radiation exposure, leading to higher-resolution images.

The accompanying PET images show (a) 3-dimensional and (b) coronal views illustrating the distribution of an inflammatory biomarker, ¹⁸F-fluorodeoxyglucose, predominantly in the upper lungs of a patient with COPD. The range of colors indicate uptake of biomarker, with maximum uptake represented by white and minimum uptake by black.^e

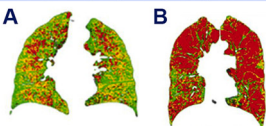
4. Functional respiratory imaging

Functional respiratory imaging combines 3-dimensional computational modeling with imaging techniques to create patient-specific models of lung function.

This can include patient-specific 3-dimensional imaging of airway and lung geometry, defining regional airway resistance as well as patient-specific aerosol deposition patterns. The technique can provide measures of internal airflow distribution, lung volume, lobe volume, airway volume, airway resistance, or lobar perfusion. It can also provide information on aerosol deposition and response to treatment.^f



5. Inspiratory/expiratory computed tomography scanning



Inspiratory/expiratory CT scanning is an automated technique providing a quantitative analysis of both large and small airways to help phenotype patients with COPD.

The accompanying images highlight relative volume of normal parenchyma (green), persistent airway disease (red), and functional airway disease (yellow). Case (a) is a patient with predominant conductive airway disease (47% functional and 14% persistent), whereas case (b) is a case with predominant emphysema (25% functional and 55% persistent).^g

FIGURE 4. Measurement of small airways disease: imaging techniques. COPD, chronic obstructive pulmonary disease. ^aReprinted from Contoli M, et al. *Allergy*. 2010;65(2):141-151. <https://doi.org/10.1111/j.1398-9995.2009.02242.x>. © 2009 John Wiley & Sons *AVS*.⁵¹ ^bReprinted with permission from *Chronic Obstructive Pulmonary Diseases: Journal of the COPD Foundation*. Kirby M, et al. *J COPD F*. 2014;1(2):200-211. <http://doi.org/10.15326/jcopdf.1.2.2014.0136>.⁵² ^cAdapted with permission of the American Thoracic Society. Copyright © 2020 American Thoracic Society. All rights reserved. Usmani OS, Biddiscombe MF, Barnes PJ. Regional lung deposition and bronchodilator response as a function of β_2 -agonist particle size. *Am J Respir Crit Care Med*. 2005;172(12):1497-1504. *The American Journal of Respiratory and Critical Care Medicine* is an official journal of the American Thoracic Society. Readers are encouraged to read the entire article for the correct context at <https://doi.org/10.1164/rccm.200410-1414OC>. The authors, editors, and the American Thoracic Society are not responsible for errors or omissions in adaptations.⁴⁸ ^dReproduced with permission from Milne M, King GG. *J Thorac Dis*. 2014;6(11):1570-1585. <https://doi.org/10.3978/j.issn.2072-1439.2014.11.30>. Copyright © 2020 AME Publishing Company.⁵³ ^eAdapted with permission of the American Thoracic Society. Copyright © 2020 American Thoracic Society. All rights reserved. Subramanian DR, et al. 2012. Assessment of pulmonary neutrophilic inflammation in emphysema by quantitative positron emission tomography. *Am J Respir Crit Care Med*. 2012;186:1125-1132. *The American Journal of Respiratory and Critical Care Medicine* is an official journal of the American Thoracic Society. Readers are encouraged to read the entire article for the correct context at <https://doi.org/10.1164/rccm.201201-0051OC>. The authors, editors, and the American Thoracic Society are not responsible for errors or omissions in adaptations.⁵⁴ ^fImages from Burrowes KS, et al. *J Transl Med*. 2014;12:S5. Published by BioMed Central Ltd. This work is licensed under a Creative Commons Attribution (CC BY) 4.0 License.⁵⁵ ^gImages from Occhipinti M, et al. *Aging Dis*. 2017;8(4):471-485. Published by Aging and Disease. This work is licensed under a Creative Commons Attribution (CC BY) License.⁵⁶

TABLE. Therapeutic Options to Target Small Airways Disease

Novel formulations	Mechanism of action
Extrafine particle ICS/LABA formulations ^{14,57-65} <ul style="list-style-type: none"> ● Beclomethasone dipropionate + formoterol fumarate ● Beclomethasone dipropionate + formoterol fumarate + glycopyrronium bromide 	<ul style="list-style-type: none"> ● Extrafine particle size enhances delivery to small (as well as large) airways
Co-suspension LAMA/LABA formulation (Bevespi Aerosphere) ^{66,67} <ul style="list-style-type: none"> ● Glycopyrrolate/formoterol fumarate, formulated using a novel co-suspension delivery technology for administration via MDI 	<ul style="list-style-type: none"> ● Co-suspension delivery technology used to formulate glycopyrronium and formoterol fumarate dihydrate together in MDI enables the uniform delivery of both treatments
Extrafine particle ICS ⁶⁸ <ul style="list-style-type: none"> ● Extrafine beclomethasone 	<ul style="list-style-type: none"> ● Extrafine particle size enhances delivery to small (as well as large) airways
Novel inhalers/inhalation systems	Mechanism of action
Respimat [®] Soft Mist [™] inhaler ⁶⁹⁻⁷³	<ul style="list-style-type: none"> ● Respimat droplets deposit more uniformly in the different lung regions compared with particles from dry powder inhalers ● Respimat exhibited a higher proportion of particles reaching all parts of the lung than did DPIs
Adaptive Aerosol Delivery (AAD [®]) system ⁷⁴	<ul style="list-style-type: none"> ● Adapts to changes in patient's breathing pattern and pulses aerosol during the inspiratory part of the breathing cycle
AKITA [®] inhalation system ⁷⁵	<ul style="list-style-type: none"> ● Uses individualized controlled inhalation to optimize the inhalation maneuver of the patient
Other agents in development	Mechanism of action
Inhaled antibiotics ⁷⁶	<ul style="list-style-type: none"> ● Combined antimicrobial and anti-inflammatory effects
Alpha-1 antiprotease ^{77,78}	<ul style="list-style-type: none"> ● Inhibition of proteases involved in the progression of disease
Anti-inflammatory compounds, eg, monoclonal antibodies ^{79,80}	<ul style="list-style-type: none"> ● Target molecules involved in the inflammatory cascade such as cytokines
Mucolytic agents ⁸¹	<ul style="list-style-type: none"> ● Reduce viscosity of the sputum; antioxidant effects

DPI, dry powder inhaler; ICS, inhaled corticosteroid; LABA, long-acting β_2 -agonist; LAMA, long-acting muscarinic antagonist; MDI, metered-dose inhaler.

Drug Formulations Optimized to Reach the Small Airways

Recent advances in inhaled drug delivery have improved delivery of aerosolized medicine to the small airways.⁴⁶ Many factors can influence the deposition of medical aerosols in the lung, including characteristics such as size, density, and charge of drug particles (with smaller particles being preferable), lipophilicity/hygroscopicity of formulation, and speed and duration of aerosol spray (with slower inhalation flow being preferable).^{46,82} Patient-specific factors are also important, including the patient's breathing pattern and inhalation

technique (inspiratory flow, inhaled volume, and breath-hold pause), severity of disease, and device acceptance and adherence.⁴⁶ In particular, particle size plays a key role in determining the fate of the aerosolized medicine within the respiratory tract, with larger particles being deposited in the oropharynx, trachea, and upper bronchial tree and smaller particles able to reach the distal airways.^{14,46} To ease differentiation, particle size can be classified as extrafine, fine, or coarse according to whether the mass median aerodynamic diameter is less than 2.1, 2.1 to 5, or greater than 5 μm , respectively.⁸²

Recently developed inhaled formulations that optimize delivery to the small airways include extrafine inhaled corticosteroid (ICS), ICS/long-acting β_2 -agonist (LABA) formulations (eg, ciclesonide and beclomethasone dipropionate/formoterol fumarate), and ICS/LABA/long-acting muscarinic antagonist (LAMA) formulations (eg, beclomethasone dipropionate/formoterol fumarate/glycopyrronium bromide). These agents have been evaluated for use in small airways disease both in COPD^{14,57,58,65} and in asthma.^{59-64,83} A novel fixed-dose LAMA/LABA combination of glycopyrrolate/formoterol fumarate has also been formulated using co-suspension delivery technology for administration via a pressurized metered-dose inhaler (pMDI; Bevespi Aerosphere; AstraZeneca, Cambridge, UK).^{66,67} Clinical findings from a scintigraphy study reported that doses of glycopyrrolate/formoterol fumarate pMDI were deposited in both central and peripheral lung regions,⁸⁴ revealing that this approach can successfully target the small airways and provide a further treatment option for patients who prefer to use a pMDI, such as those who may be unable to achieve the minimum inspiratory flow rate necessary to use a dry powder inhaler (DPI).⁶⁷

For patients who require ICS in addition to bronchodilator therapy, it may be beneficial to target the small airways with extrafine particle formulations.⁶⁸ The FOsteR 48-Week trial to reduce exAcErbations in COPD (FORWARD) study reported that compared with formoterol alone, extrafine beclomethasone/formoterol significantly reduced the exacerbation rate and improved lung function in patients with severe COPD and a history of exacerbations.⁸⁵ In another study by Tzani et al,⁸⁶ extrafine beclomethasone/formoterol significantly reduced air trapping and dyspnea in patients with COPD and lung hyperinflation when compared with fluticasone/salmeterol. Furthermore, findings from the randomized controlled trial TRILOGY suggest that triple therapy with extrafine beclomethasone dipropionate/formoterol/glycopyrronium bromide fixed-dose combination can reduce moderate and severe exacerbations more effectively than ICS/LABA combination

therapy.⁸⁷ There is also evidence that extrafine beclomethasone at lower doses is equivalent to fluticasone at higher doses in terms of reducing exacerbations, with improved treatment stability over a 2-year period, suggesting greater lung deposition of extrafine beclomethasone to the small airways.⁶⁸ This is supported by a recent study, which used a model approach based on functional respiratory imaging computer simulations.⁸⁸ This revealed that extrafine beclomethasone dipropionate/formoterol fumarate/glycopyrronium bromide had higher peripheral deposition of all three components (ICS, LABA, and LAMA) compared with a non-extrafine formulation of fluticasone furoate/vilanterol/umeclidinium on the basis of profiles from patients with moderate-to-very severe COPD.⁸⁸ It must be noted, however, that research supporting the benefits of enhanced drug delivery to the small airways on patient-centered outcomes is limited.

Using lower doses of ICS is also likely to be associated with a reduced risk of adverse events. Findings from a real-life COPD study suggest that patients taking extrafine particle ICS have a lower risk of pneumonia than those taking fine-particle ICS.⁸⁹ In addition, data from patients with asthma suggest that extrafine particle ICS is associated with an improved chance of asthma control and lower exacerbation rates at significantly lower ICS doses as compared with fine particle ICS.⁹⁰

Inhalers Optimized to Reach the Small Airways

Conventional pMDIs and most DPIs emit drug particles that are too large to effectively target the small airways.⁴⁹ However, some newer DPIs such as the NEXThaler (Chiesi, Manchester, UK) have been developed to deliver extrafine particles that can reach them.⁹¹ Inhaler technique also has an important role in ensuring efficient delivery of drug.⁹²

Inhaler delivery efficiency is another important factor affecting the level of deposition in the small airways.⁶⁹ For example, the Respimat[®] Soft Mist[™] inhaler (Boehringer Ingelheim, Ingelheim, Germany) produces aerosol droplets with a diameter of 1 to

5.8 μm to ensure efficient lung deposition while avoiding loss of small droplets during exhalation.⁷⁰ The fine particle fraction is approximately 75% for Respimat with most formulations (range, 65%-80%), representing nearly double the value reported for aerosols generated by conventional pMDIs and DPIs.^{70,93} Coupled with the low velocity and long generation time of the aerosol, this means that more of the emitted dose is deposited in the lungs and less in the oropharynx compared with aerosols from other inhalers.^{70-73,94} This is supported by a combined *in vitro/in silico* model of COPD, in which Respimat exhibited the lowest throat deposition and the highest deposition in the whole lung and in different lung generations, compared with the tested DPIs.⁶⁹ Further support has been provided by an *in vivo* scintigraphy study, which revealed similar Respimat deposition data to the *in vitro* analyses.⁹⁵

Novel aerosol delivery systems such as the Adaptive Aerosol Delivery (AAD[®]; Philips Respironics, Murrysville, PA) system may also be of use in small airways disease. These are designed to continuously adapt to changes in the patient's breathing pattern so that they pulse aerosol only during the inspiratory part of the breathing cycle, thus eliminating waste and ensuring precise aerosol delivery.⁷⁴ Another aerosol delivery system that actively controls the entire inhalation maneuver of the patient is the AKITA[®] inhalation system (Activaero, Gemünden, Germany).⁷⁵ This uses information delivered by a computer-controlled compressor programmed from the patient's own individual lung function data.⁷⁵

Drugs Aimed at Improving Small Airway Function

In addition, there is significant ongoing interest in the development and application of both existing and novel drugs to target the small airways, including inhaled antibiotics, anti-inflammatory compounds, monoclonal antibodies, antiprotease therapy, and mucolytic agents.^{76-81,96}

Macrolide antibiotics, which are commonly used in cystic fibrosis and other

forms of bronchiectasis, may be of use in patients with small airways disease caused by underlying infection and inflammation.⁹⁶ Efforts are underway to develop inhaled formulations of these drugs, which may have a lower risk of systemic toxicity, for example, QT prolongation and ototoxicity.⁷⁶

Mucolytic agents are associated with modest reductions in exacerbations and improvements in quality of life in some studies^{81,97} and could have a role in long-term management of COPD. In a study comparing the mucolytic agent *N*-acetyl cysteine with placebo, *N*-acetyl cysteine was found to provide significantly greater improvements in measures of small airways function, forced expiratory flow at 25% to 50%, and forced oscillation technique.⁸¹

FUTURE DIRECTIONS

Despite growing insight into small airways disease, a number of questions have so far remained unanswered in our understanding of the area. Early detection remains the key barrier, although we have outlined several new approaches that have the potential to achieve this goal. Critically, if detected early, treatment with therapy options designed to target small airways should help slow disease progression, reduce symptoms, and help patients maintain their activities. It may therefore be beneficial to further investigate whether the ability to target treatments to the lung periphery and increase lung deposition could slow disease progression in patients with COPD and thereby become a viable treatment option for patients who have small airway involvement and early signs of COPD.

Recent increases in understanding concerning the inflammatory pathways underlying COPD are also giving rise to the development of targeted therapies, such as biologics and small molecules.⁷⁹ As small airways are the major site of obstruction, caused by airway remodeling and accumulation of inflammatory exudates,⁷⁹ treatments targeted to the small airways may be particularly beneficial. However, despite significant

interest in cytokines and chemokines as a therapeutic target in COPD, there is a need for novel targets that are more specific and have a reduced adverse effect profile.⁸⁰

Another possible target in COPD is to address protease-antiprotease imbalance, which may be involved in the pathology of small airways disease. Recent evidence suggests that enhanced protease activity is associated with small airway remodeling and that serine protease inhibitors may be a potential therapeutic target for small airways disease.

Studies are needed that compare outcomes obtained by traditional management of COPD (ie, according to GOLD recommendations) with those based on small airway-directed management. Moreover, evidence is required to find the possible role of new drugs in the development for treating small airways disease, as well as novel drug formulations, inhalers, and inhalation devices. It will be of particular interest to discern whether the progression of COPD can be slowed in some patients after they stop smoking by targeting the inflammation in the small airways.

It is important to recognize that the characterization and targeted treatment of small airways is just one component of a broader strategy to evaluate the phenotypic variations of patients with COPD to provide them with the most effective and appropriate targeted therapy. This comprehensive diagnostic and management strategy includes many different modalities, including immunizations, oxygen therapy, lung volume reduction surgery, bronchoscopic lung volume reduction, pulmonary rehabilitation, mindfulness, and breathing techniques, in addition to pharmacological therapy. These are discussed in more detail elsewhere.⁷

Finally, we have concentrated here on treating disease, but it is also important to consider prevention of COPD by reducing environmental exposure to biomass fuels in third world countries and reducing particulate and gaseous air pollution in major metropolitan areas.

CONCLUSION

Both preventable and treatable, small airways disease has important clinical consequences

if left unchecked. Small airways disease is associated with poor spirometry results, increased lung hyperinflation, and poor health status, making the small airways an important treatment target in COPD. Further advances in our ability to assess the extent of small airways involvement, as well as the use of novel drugs, formulations, and inhalers that target the small airways, will help improve our management of small airways disease in patients with COPD.

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SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at: <http://www.mayoclinicproceedings.org>. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

Abbreviations and Acronyms: COPD = chronic obstructive pulmonary disease; CT = computed tomography; DPI = dry powder inhaler; FEV₁ = forced expiratory volume in 1 second; FEV₃ = forced expiratory volume in 3 seconds; FEV₆ = forced expiratory volume in 6 seconds; FVC = forced vital capacity; GOLD = Global Initiative for Chronic Obstructive Lung Disease; ICS = inhaled corticosteroid; LABA = long-acting β_2 -agonist; LAMA = long-acting muscarinic antagonist; pMDI = pressurized metered-dose inhaler; RV = residual volume; TLC = total lung capacity

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