CHEST

Seven Pillars of Small Airways Disease in Asthma and COPD

Supporting Opportunities for Novel Therapies

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Identification of pathologic changes in early and mild obstructive lung disease has shown the importance of the small airways and their contribution to symptoms. Indeed, significant small airways dysfunction has been found prior to any overt airway obstruction being detectable by conventional spirometry techniques. However, most therapies for the treatment of obstructive lung disease target the physiological changes and associated symptoms that result from chronic lung disease, rather than directly targeting the specific underlying causes of airflow disruption or the drivers of disease progression. In addition, although spirometry is the current standard for diagnosis and monitoring of response to therapy, the most widely used measure, FEV_1 , does not align with the pathologic changes in early or mild disease and may not align with symptoms or exacerbation frequency in the individual patient. Newer functional and imaging techniques allow more effective assessment of small airways dysfunction; however, significant gaps in our understanding remain. Improving our knowledge of the role of small airways dysfunction in early disease in the airways, along with the identification of novel end points to measure subclinical changes in this region (ie, those not captured as symptoms or identified through standard FEV_1), may lead to the development of novel therapies that directly combat early airways disease processes with a view to slowing disease progression and reversing damage. This expert opinion paper discusses small airways disease in the context of asthma and COPD and highlights gaps in current knowledge that impede earlier identification of obstructive lung disease and the development and standardization of novel small airways-specific end points for use in clinical trials.

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KEY WORDS: asthma; COPD; MRI; oscillometry; respiratory function tests

ABBREVIATIONS: FOT = forced oscillation technique; HP-MRI = hyperpolarized gas MRI; ICS = inhaled corticosteroids; IOS = impulse oscillometry; MBW = multiple-breath washout; PRM = parametric response mapping

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Obstructive lung diseases such as asthma and COPD often remain undiagnosed until progression to at least moderate severity has occurred.[1] Consequently, most therapies target the physiological changes and associated symptoms that result from chronic lung disease by improving smooth muscle tone and reducing inflammation.[1] Limited success in attempts to develop therapies that prevent long-term lung disease progression and reverse pathogenesis indicates that existing therapies do not sufficiently address the underlying disease mechanisms in obstructive lung disease.[2-4] It is possible that this may be due to an incomplete understanding of the pathophysiology of the early disease stages and a lack of end points capable of measuring subclinical changes in the small airways.[5]

Spirometry is the current standard for the diagnosis and monitoring of therapeutic response in obstructive lung disease.[6,7] Although forced expiratory flow between 25% and 75% of the FVC is associated with changes in small airways,[8] the measure is highly variable and not considered sufficiently specific.[9] FEV_1 is the approved regulatory end point for obstructive lung disease; however, despite guiding clinical therapy and decision-making, changes in FEV_1 do not align with the pathologic changes observed in either early or mild disease, and they may not correlate with symptoms or exacerbation frequency at an individual level.[10,11] Indeed, by the time significant changes in FEV_1 (or other spirometry end points) are observed, it is likely that there has already been substantial disease progression and airway remodeling, leaving limited capacity for reversal and recovery.[12]

Investigation of early pathologic changes in obstructive lung disease has identified significant small airways dysfunction prior to any overt airway obstruction being detectable by conventional spirometry techniques.[12-15] Imaging techniques that now allow regional assessment of the small airways dysfunction include hyperpolarized gas MRI (HP-MRI)[16] and registration-based mapping of paired chest CT imaging.[17,18] Physiological techniques such as oscillometry[19] and multiple-breath washout (MBW)[20] provide whole lung assessment. However, significant gaps in our understanding of the function of the small airways remain.[21] By building a better understanding of small airways dysfunction in early disease/disease progression, along with the identification of novel end points to measure subclinical changes, it should be possible to not only measure disease status but also provide enhanced sensitivity for predicting and measuring disease progression in asymptomatic or mildly symptomatic obstructive lung disease. This action, in turn, may lead to the development of novel therapies that directly combat early airways disease processes with a view to slowing disease progression and even reversing damage.

The current expert opinion paper discusses small airways disease in the context of asthma and COPD across seven pillars (Fig 1). In addition, we specifically highlight gaps in current knowledge that impede earlier identification of obstructive lung disease and the development and standardization of small airways-specific novel end points that could enable discovery of treatments targeting early disease and prevent progression.

Pillar 1: Pathogenesis of Small Airways Disease

The small airways are defined as those < 2 mm in diameter, based on the size of the catheter used to measure resistance in the early studies of peripheral airways,[13,22] and they incorporate the final eight divisions of the airways, comprising the respiratory bronchioles, alveolar ducts, and alveolar sacs (Fig 2).[23-27] They have been described as the "quiet zone," in which disease can accumulate without being detected by conventional tests,[28] and small airways pathology is now known to be a key feature of COPD that precedes emphysema.[14,15,29,30] Moreover, small airways disease is detectable across all severities of asthma and has been associated with asthma instability, severity, quality of life, exacerbation frequency, and increased health care resource use.[31] Although the small airways account for between 10% and 25% of the total resistance to airflow in the normal human lung, in patients with emphysema, there is an increase in the total resistance between fourfold and 40-fold.[13,22] Reduced function in small airways results in increased residual volume and decreased vital capacity due to loss of elastic recoil and airways closure.[32]

Examination of lung biopsy specimens and postmortem lung tissue has identified numerous structural differences in the small airways of patients with asthma and COPD compared with those of healthy individuals. In COPD, these include: increased airway wall thickness and fibrosis caused by expansion of epithelial, lamina propria, smooth muscle, and adventitial compartments[33]; remodeling and tertiary lymphoid follicle formation following infection of the lower airways[33]; obstruction of small airways lumina by inflammatory mucus exudates following malfunction of the mucociliary clearance apparatus[33]; and terminal

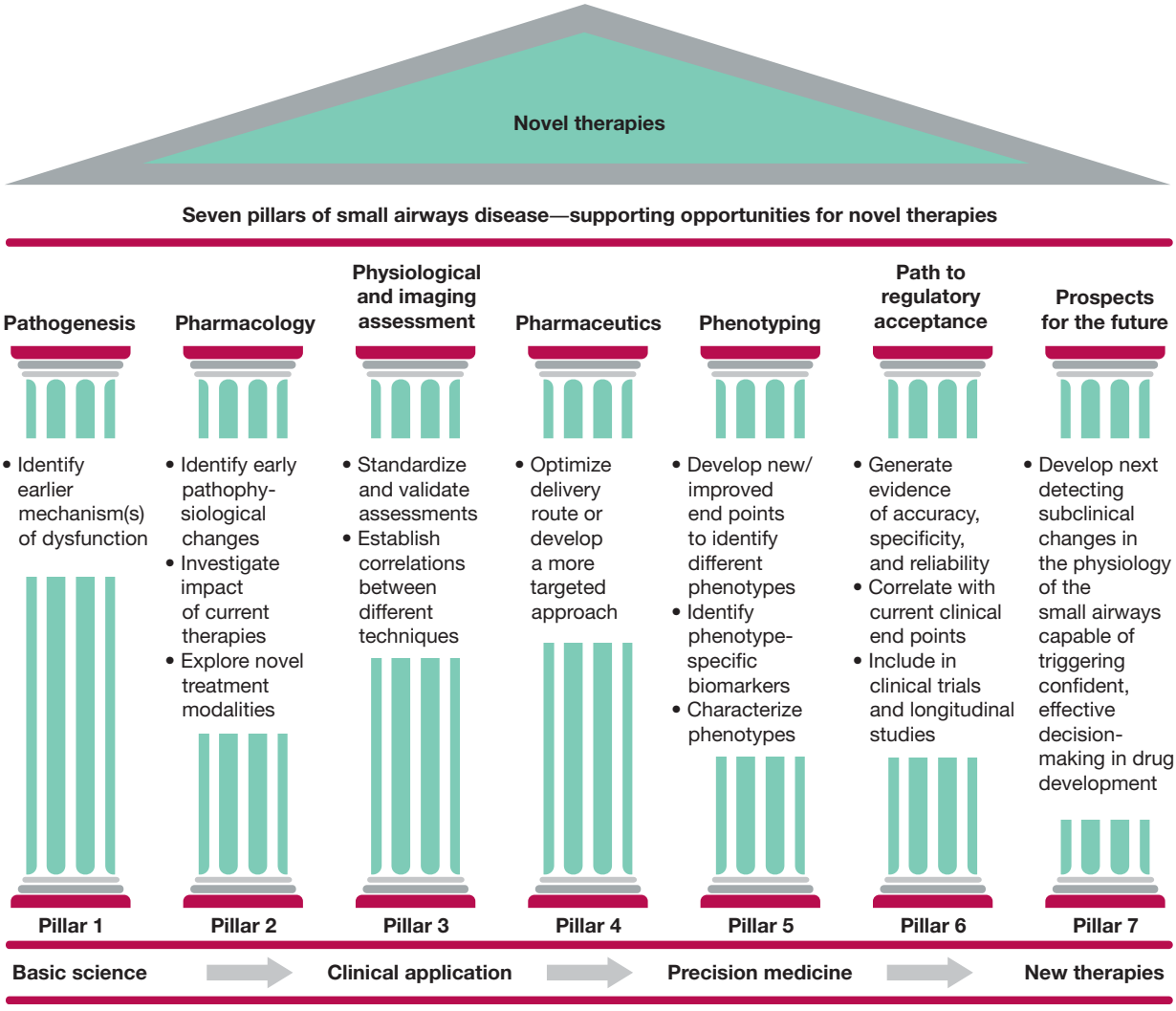


Figure 1 – *Seven pillars of small airways disease in asthma and COPD—supporting opportunities for novel therapies.*

bronchiole loss.[29] In asthma, patients with ≥ 2 exacerbations during the previous 12 months have increased closing capacity and volume compared with patients with asthma and the same disease severity but ≤ 1 exacerbation during the previous 12 months, even after bronchodilation during well-controlled episodes, which may be indicative of small airways pathology.[34] However, because the mechanism of small airways disease is poorly understood, it is not clear exactly how each of these abnormalities contributes to airflow limitation, what the events are that lead to the abnormalities, or if and how these findings are related to abnormalities of the large airways and parenchyma in chronic airways disease. Indeed, different forms of remodeling of airway smooth muscle may account for differences in the severity of asthma, with greater changes observed in the larger airways compared with the small airways in fatal asthma.[35]

Knowledge Gap

Identification of the mechanism(s) of dysfunction in the small airways to uncover a modifiable target for novel therapies that affects disease progression.

Pillar 2: Pharmacology of Therapies With Potential to Improve Small Airways Disease

At present, core asthma and COPD therapies, such as bronchodilators and corticosteroids, primarily treat symptoms. Table 1[25,36-44] summarizes these and newer targeted treatments. Of these, a study of mepolizumab using MBW with nitrogen found an early improvement in small airways function that was associated with asthma control, suggesting that systemic administration of medication can influence small airways pathology, which may be a significant contributor to successful clinical outcomes.[45]

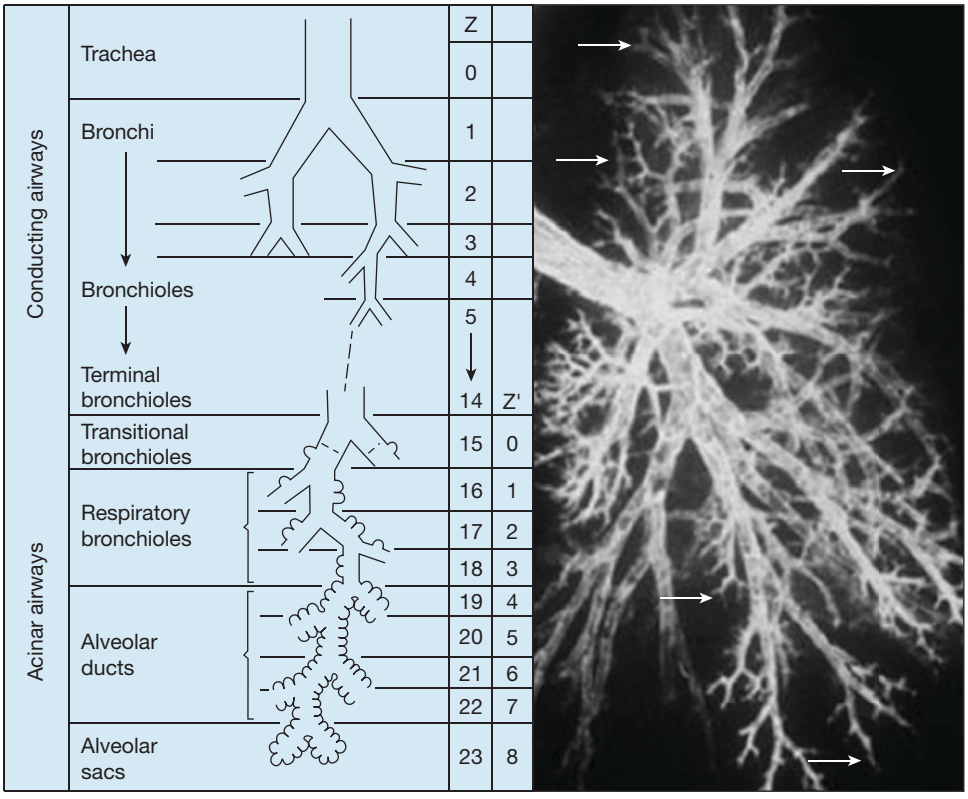


Figure 2 – *Airway branching of the human lung alongside a bronchogram showing the first division of the trachea (generation Z = 0) into bronchi, through to the alveolar sacs (generation Z = 23). As the airway generations increase, they narrow, and the particle size required for effective deposition decreases. Older inhalers typically had a mass median aerodynamic diameter (MMAD) > 5 μm, whereas most current devices produce fine (MMAD 2-5 μm) or extra-fine (MMAD < 2 μm) particles, resulting in increased peripheral deposition. White arrows indicate small airways. Note that the airway branching diagram is representative of the branching only; branching extends in all directions from the bronchi as indicated in the bronchogram. (Adapted with permission from Hogg et al.*[24] *Physiol Rev. 2017;97(2):529-552, Copyright © 2017 the American Physiological Society; and Weibel ER,*[23] *Swiss Med Wkly. 2009;139(27-28):375-386 [https://creativecommons.org/licenses/by-nc-nd/4.0/].)*

Several drugs or combinations targeting long-term outcomes, such as lung function decline and survival, have met with failure.[2-4,46] This failure is likely due to inclusion of patients with disease types that were not accessible by the drugs being tested; for example, due to particle distribution issues, heterogeneity of the asthma and COPD patient populations being studied, and/or the end points evaluated were not sensitive enough to detect treatment response.

A number of other new asthma and COPD therapies are in development and include novel inhibitors of specific inflammatory mediators, such as phosphodiesterase inhibitors, broad-spectrum antiinflammatories, and kinase inhibitors; new modalities are also under investigation, including peptides, proteins, and oligonucleotides.[47]

As we enter the era of precision medicine, it will be important to identify patients with a small airways component to their obstructive lung disease that is susceptible to advanced precision therapy. This approach will likely require novel, fully validated, and simple methods of identifying early changes in the small airways that would predict a clinically meaningful improvement. In addition, by specifically recruiting these patients into clinical trials, the development of novel therapeutic drugs may be facilitated, potentially leading to earlier and more effective disease management.

> *Knowledge Gap*
>
> Investigation of how current therapies affect the small airways and correlate changes with clinically meaningful outcomes, potentially in long-term studies.

Pillar 3: Physiological and Imaging Assessment of the Small Airways

Currently available techniques for the assessment of the small airways are summarized in Figure 3,[48-58] with details of advantages and disadvantages of the different techniques included in Table 2.[12,14,16-20,32,48,51,54,55,57-123] Imaging techniques provide spatial information and can identify disease regional heterogeneity, extent, and progression.[21] CT imaging is the technique most

TABLE 1] Current Medications for Obstructive Lung Disease

Drug/Drug Class	Mode of Action
Inhaled short- and long-acting muscarinic antagonists, short- and long-acting β_2-agonists	Interact with receptors on the smooth muscle to relax and dilate the airways
Corticosteroids	Cornerstone treatment for controlling asthma and preventing exacerbations in both asthma and COPD. Suppress many aspects of the inflammatory process through signal transduction pathways
Targeted biologics	
Montelukast	Cysteinyl leukotriene receptor-1 antagonist; reduces inflammation and relaxes smooth muscle
Zafirlukast	Cysteinyl leukotriene receptor-1 antagonist; reduces inflammation and relaxes smooth muscle
Pranlukast	Cysteinyl leukotriene receptor-1 antagonist; reduces inflammation and relaxes smooth muscle
Zileuton	5-lipoxygenase inhibitor; reduces inflammation and relaxes smooth muscle
Benralizumab	Monoclonal antibody directed against IL-5 receptor; reduces eosinophilic inflammation
Mepolizumab	Monoclonal antibody directed against circulating IL-5; reduces eosinophilic inflammation
Reslizumab	Monoclonal antibody directed against circulating IL-5; reduces eosinophilic inflammation
Dupilumab	Monoclonal antibody directed against IL-4 and IL-13 signaling; reduces inflammation
Omalizumab	Monoclonal antibody directed against IgE; reduces allergic inflammation

extensively studied and typically the easiest to use in clinical trials; however, even at high resolution, CT imaging does not permit direct visualization of small airways.[32] Nevertheless, abnormalities in small airways, such as small centrilobular nodules and linear branching opacities, can be identified both directly or indirectly by the recognition of mosaic perfusion and air trapping, which are reflective of bronchiole obstruction.[124,125] Recently developed image-matching techniques include voxel-based registration methods that match the inspiratory and expiratory CT scans: parametric response mapping (PRM) uses voxel classification based on cutoff values[17]; and disease probability measures use voxel classification based on probabilities.[18] These techniques have enabled the discrimination of non-emphysematous air trapping from the low-attenuation areas on paired CT imaging, to allow more specific quantification of this small airways disease surrogate. These quantitative assessments have been further validated in parallel investigations of their ability to predict clinical outcomes[126] and their correlation with human lung airway pathology,[59] as well as other small airways disease metrics.[127] Furthermore, longitudinal studies suggest that localized PRM small airways abnormality precedes the development of emphysema.[128] However, there are few long-term investigations assessing the impact of treatments on small airways[32] because of the challenges of nonstandardized, specialized software and ionizing radiation.

An alternative imaging technique that does not require ionizing radiation is HP-MRI, using either helium-3 or xenon-129. Quantification of the distribution of the gas in the lungs can be used to assess regional ventilation defects,[129] and the gas diffusion coefficient can be used to assess changes in airway caliber.[60] HP-MRI has been shown to have high reproducibility and sensitivity and has successfully detected changes following treatment.[130-134] Furthermore, helium-3 MRI has been used to calculate ventilation defect percent, which provides a more sensitive tool to measure treatment response in both the large and the small airways.[135] Efforts are being made to relate imaging metrics to functional measures specific to small airways,[134] including total airway count, which has been associated with changes in FEV_1 in patients with COPD[136] and asthma.[137]

The forced oscillation technique (FOT, or "oscillometry")[19,57,61-63,138] and other physiological measurements, such as inert gas washout, provide a more global assessment of airway function, with potentially increased sensitivity and more quantitative measurements compared with imaging techniques

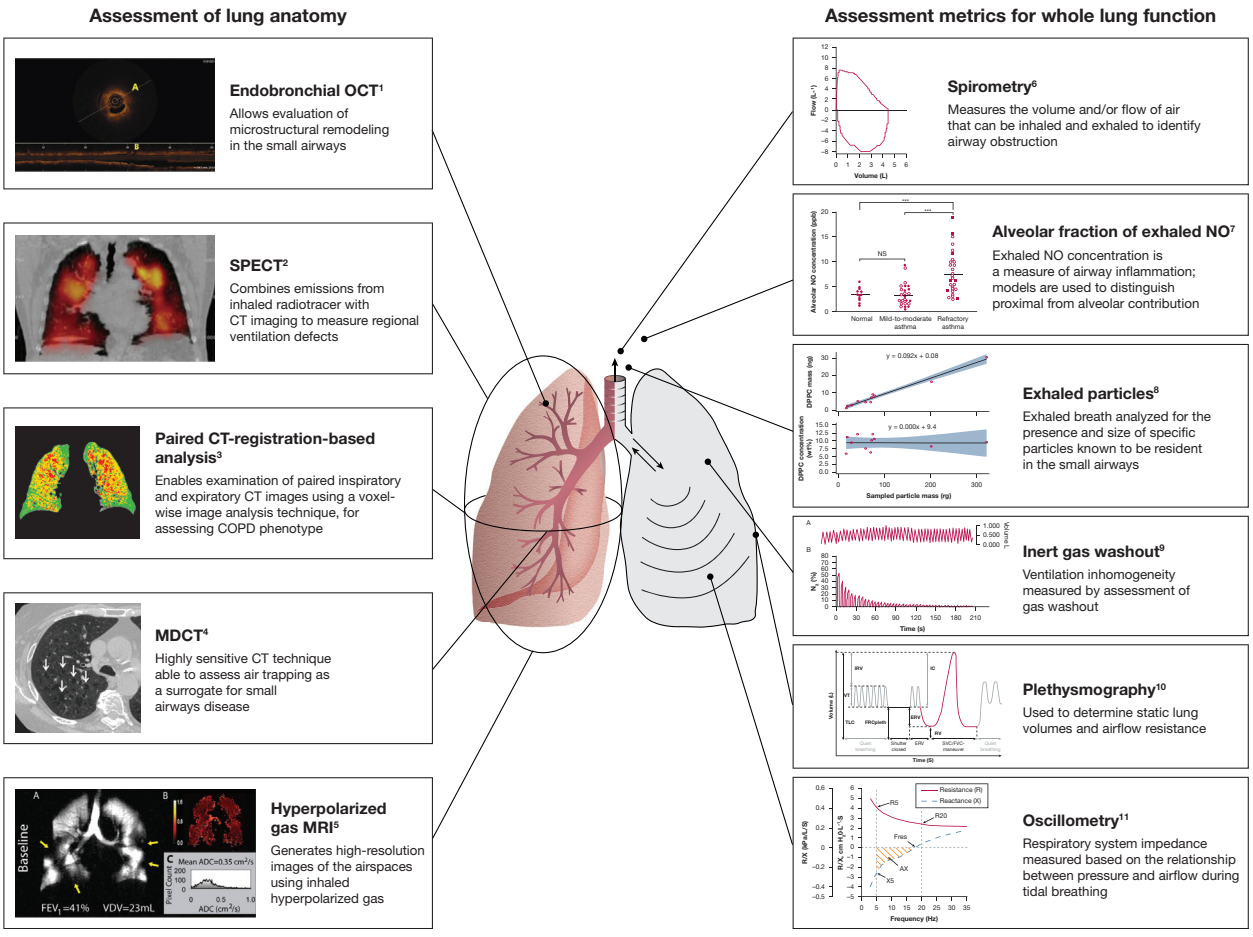


Figure 3 – *Current techniques for assessment of the small airways. MDCT = multi-detector CT; NO = nitric oxide; OCT = optical coherence tomography; SPECT = single-photon emission CT. (The sections in the graphics were adapted from the sources as noted in the following list. 1, Reprinted from* Respiratory Medicine*. Chen Y, Ding M, Guan W-J, Wang W, Luo W-Z, Zhong C-H, Jiang M, Jiang J-H, Gu Y-Y, Li S-Y, Zhong N-S. Validation of human small airway measurements using endobronchial optical coherence tomography.* Respir Med. *2015;109(11):1446-1453. Copyright © 2015 with permission from Elsevier.*[48] *2, Reproduced with permission from Milne S and King GG.* J Thorac Dis. *2014;6(11):1570-1585.*[49] *3, Reproduced with permission from Imbio, LLC – Minneapolis, Minnesota, USA (www.imbio.com).*[50] *4, Reprinted from* Radiologic Clinics of North America. *Litmanovich DE, Hartwick K, Silva M, Bankier AA. Multidetector computed tomographic imaging in chronic obstructive pulmonary disease: emphysema and airways assessment.* Radiol Clin North Am. *2014;52(1):137-154. Copyright © 2014 with permission from Elsevier.*[51] *5, Kirby M, Lindsay M, Wheatley A, Santyr GE, McCormack DG, Parraga G.* Radiology. *Copyright © 2010;256(1):280-289 with permission from the Radiological Society of North America.*[52] *6, Reproduced with permission of the © ERS 2021.* Breathe *Mar 2012, 8(3):232-240; DOI: 10.1183/20734735.0021711.*[53] *7, Reproduced from Bake B et al.* Respir Res. *2019;20(1):8.*[54] *8, Reproduced with permission of the © ERS 2021.* Eur Respir J. *41(3):507-522; DOI: 10.1183/09031936.00069712 Published 28 February 2013.*[55] *9, Reprinted from* Respiratory Medicine *105. Criée CP, Sorichter S, Smith HJ, Kardos P, Merget R, Heise D, Berdel D, Köhler D, Magnussen H, Marek W, Mitfessel H, Rasche K, Rolke M, Worth H, Jörres RA, Working Group for Body Plethysmography of the German Society for Pneumology and Respiratory Care. Body plethysmography - Its principles and clinical use, 959-971. Copyright © 2011 with permission from Elsevier.*[56] *10, Reprinted from* Respiratory Medicine *106. Frantz S, Nihlén U, Dencker M, Engström G, Löfdahl CG, Wollmer P. Impulse oscillometry may be of value in detecting early manifestations of COPD, 1116-1123. Copyright © 2012 with permission from Elsevier.*[57] *11, Reproduced with permission of the © ERS 2021.* Eur Respir J. *2005;25(6):986-991; DOI: 10.1183/09031936.05.00132404 Published 1 June 2005.*[58])

(Fig 3, Table 2). In the research setting, alveolar nitric oxide has been used as a marker of distal airways inflammation.[58] In addition, it has been suggested that elastance, measured using oscillometry, may represent the small airways, but resistance reflects both the large and small airways.[139] MBW can identify physiological changes in patients who have only 10-pack years smoking history and normal spirometry,[140] with improvements detected as soon as 1 week following smoking cessation.[141] Of note, the lung clearance index, a global index of abnormality in gas mixing in the lungs calculated from MBW, is also an indirect measure of small airways disease[20] and is gaining acceptance as an end point in trials of cystic fibrosis therapies.[142]

Some smokers with normal spirometry have abnormal MBW and normal impulse oscillometry (IOS), whereas others have normal MBW and abnormal IOS,[143] suggesting that different functional techniques measure different aspects of damage to the small airways. Thus, in practice, a composite of oscillometry, imaging, and spirometry,[31] or oscillometry, imaging, and modeling,[134]

TABLE 2] Current Techniques for the Functional Assessment of the Small Airways

Small Airways Assessment	Description (What/How Measured)	Correlation(s) With Clinical End Point(s)	Advantages/Disadvantages
Imaging techniques: provide regional anatomic detail throughout the lung			
Hyperpolarized gas MRI	Uses hyperpolarized helium-3 or xenon-129 gas to generate images of ventilated air spaces	In asthma, the estimated MCID for helium-3 MRI ventilation defect volume is 110-200 mL, equating to an MCID ventilation defect of 2-4%	**Advantages** Does not require ionizing radiation, allowing safe longitudinal evaluation. The persistence of a reduced ventilation defect or regional improvement may be a means to assess disease modification. Sensitive to the small airways
	Apparent diffusion coefficient, regional ventilation defects, and anisotropic assessment of respiratory bronchioles can be measured. Whole lung, high-resolution technique		**Disadvantages** Currently limited to research applications and requires highly trained operators. Expensive to operate; not widely available. Specificity to small airways is still to be shown
	Knowledge Gaps: Automation to develop standardized approaches of measurement and quantification is required and currently ongoing. An MCID needs to be established for COPD. Validation of whether regional improvement reflects disease modification is required		
Multi-detector CT imaging	Highly sensitive CT technique used to generate three-dimensional images to identify expiratory air trapping as a surrogate for small airways disease. Whole lung, high-resolution, low-dose technique	Not established	**Advantages** Excellent general availability and cost-effectiveness. Easy to implement. Total airway count using multi-detector CT imaging and micro CT imaging has been used to show the extent of small airways destruction in patients with COPD. May be useful for quantifying mucus plugging in larger airways **Disadvantages** Lacks sufficient resolution to reach the small airways, and therefore any measurements are indirect only. Specialized software is required to quantify airway thickening. Requires ionizing radiation
	Knowledge Gaps: Need for standardized analysis software across many platforms. Validation of methods of quantification and correlation with clinical end points are required		
Paired CT-registration-based analysis	PRM or DPM of paired inspiratory and expiratory CT images analyzed by using a voxel-wise image analysis technique to assess COPD phenotype. Whole lung, low-resolution technique	Not established	**Advantages** Allows differentiation between emphysematous and non-emphysematous air trapping, permitting a more realistic estimate of small airways disease. The PRM metric for small airways abnormality has been validated with human lung tissue in severe COPD **Disadvantages** Lacks sufficient resolution to reach the small airways, and therefore any measurements are indirect only. Requires additional ionizing radiation for inspiratory and expiratory scans. Specialized software is required
	Knowledge Gaps: Methods of quantifying topographical distributions, validated with longitudinal data, and correlation with clinical end points in interventional studies are required		

(Continued)

TABLE 2] *(Continued)*

Small Airways Assessment	Description (What/How Measured)	Correlation(s) With Clinical End Point(s)	Advantages/Disadvantages
SPECT	Detects emissions from inhaled radiotracer combined with CT imaging to measure regional ventilation defects. Whole lung, low-resolution technique	Not established	**Advantages** Ultra-fine (< 1 μm) carbon particles in the radiotracer (Technegas [Cyclomedica Asia Pacific]) adhere to the lung structures without appreciable movement for ≥ 20 min, allowing upright inhalation followed by supine or prone imaging. SPECT hardware and radiotracer are widely available **Disadvantages** Requires ionizing radiation. Poor spatial resolution
	Knowledge Gaps: Currently limited to research applications and requires highly trained operators. Methods of quantifying topographical distributions need to be developed and validated. Correlation with clinical end points is required		
FRI	Proprietary, highly sensitive CT technique that converts CT images into patient-specific reconstructions of the lung lobes and the airway tree. By segmenting lung lobes at the functional residual capacity and total lung capacity, the internal airflow distribution can be derived from the relative volume change. Can identify expiratory air trapping as a surrogate for small airways disease. Whole lung, low-dose technique	Not established	**Advantages** Potential ability to assess the pharmacodynamic effect of a novel compound in a limited set of patients due to the enhanced sensitivity of the FRI outcome parameters. Requires less radiation than typical CT scans, permitting use in clinical studies and follow-up. Technique cleared by the US FDA's Center for Devices and Radiological Health under the 510(k) process (FDA, K073468) and has received a CE mark in Europe (Conformité Européenne certificate, BE 05/1191. CE.01) **Disadvantages** Currently limited to research applications and requires highly trained operators. Expensive to operate; not widely available
	Knowledge Gaps: Additional studies are required to further confirm the potential for use in measuring changes in the small airways. Establishing MCIDs is required		

(Continued)

TABLE 2] *(Continued)*

Small Airways Assessment	Description (What/How Measured)	Correlation(s) With Clinical End Point(s)	Advantages/Disadvantages
Endobronchial OCT	Enables evaluation of microstructural remodeling that occurs as a result of damage to the small airways. Regional, high-resolution technique	Not established	**Advantages** Compares favorably with CT imaging in larger airways and histology. Provides direct visualization of the small airways **Disadvantages** Requires bronchoscopy. Currently limited to research applications
	Knowledge Gaps: Studies are required to further confirm the potential for use in measuring changes in the small airways and to develop MCIDs and gain validation. Correlation with clinical end points is required		
Physiological techniques: provide metrics for function of whole lung			
Spirometry (FEV_1, FEF_{25-75}, FEV_1/FVC, FEV_1/FEV_6, FEV_3/FEV_6, FEV_1/SVC)	Measures whole lung airflow obstruction by assessing the flow rate and volume of exhaled air during a forced expiratory maneuver	Several spirometry measures are well-established clinical end points	**Advantages** Established technique, widely available, reproducible, and standardized. Easy to perform; inexpensive **Disadvantages** Requires coordinated and forced maneuver. Not well correlated with other clinical end points such as exacerbations. Unable to detect early disease and subtle clinical changes. Not specific to small airways changes
	Knowledge Gaps: Identification of how changes in other small airways-specific end points and their relation to changes in spirometry in the longer term		
Plethysmography (RV, RV/TLC, airways resistance)	Measures changes in whole lung volume and airway resistance	Readily correlates with changes in lung capacity	**Advantages** Widely available, reproducible, relatively easy to perform, sensitive to early changes **Disadvantages** Requires specific breathing maneuvers. Relatively time-consuming. Not specific for small airways disease
	Knowledge Gaps: Identification of how changes in other small airways-specific end points and their relation to changes in plethysmography in the longer term		

(Continued)

TABLE 2] *(Continued)*

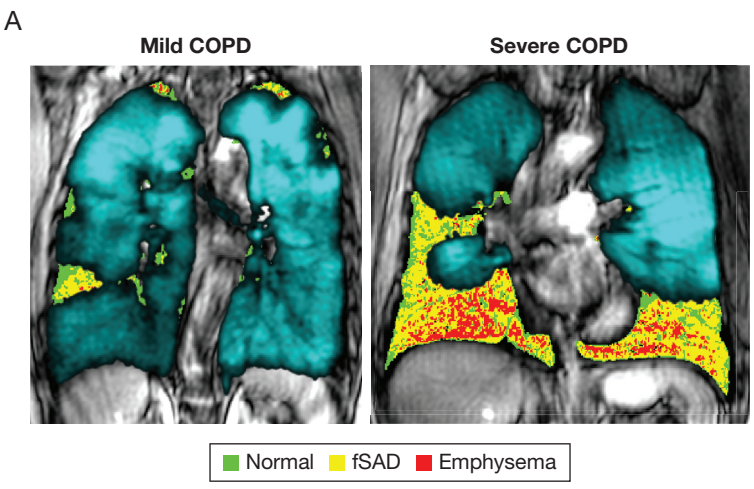
Small Airways Assessment	Description (What/How Measured)	Correlation(s) With Clinical End Point(s)	Advantages/Disadvantages
Oscillometry (FOT, IOS, AOS)	An oscillating pressure signal is propagated through the airways to measure impedance (a combination of resistance and reactance) of the entire respiratory system based on the relationship between pressure and airflow during tidal breathing	Computer modeling has implicated anatomic narrowing of small airways in asthma and COPD. Further correlations found vs physical activity in severe asthma, asthma control, and SGRQ scores. FOT reactance (but not resistance) correlates with recovery following an acute COPD exacerbation	**Advantages** Easy to implement, noninvasive, and reliable. Modern systems use a relatively small device, and no forced respiratory maneuvers are required **Disadvantages** Interference from swallowing and upper airway artifacts is common; coaching and repetition may be required to overcome this. Oscillometry indices may be influenced by large airways abnormalities; the interpretation of measurements and meaning of results is not straightforward
	Knowledge Gaps: Alignment required between different devices and systems. Further improvement is required for modeling systems and links to disease progression and other outcomes. Better understanding of natural variation over time and differences due to age, BMI, height, race, sex, and weight. Establishment of MCIDs required		
Inert gas washout (LCI, Phase III slope, S_{acin}, S_{cond})	Measurement of gas washout of entire lung using nitrogen, helium, argon, methane, or sulfur hexafluoride to assess ventilation inhomogeneity, closing capacity, and closing volume. Functional residual capacity, clearance index, and mixing ratio can be calculated	S_{acin} and S_{cond} correlate with various asthma outcomes	**Advantages** Commercial systems are now available. Sensitive to small airways and early changes. Inexpensive. ERS/ATS consensus statement available **Disadvantages** Requires specialist equipment. Currently restricted to research settings. Can be time-consuming depending on technique used. Variations remain between systems and techniques. Confounded by changes in the proximal airways and the presence of emphysema; to date, the contribution of the small airways alone is based largely on computer simulation rather than direct measurement. Not specific for small airways
	Knowledge Gaps: An understanding of how to differentiate between structural damage, such as bronchiectasis, and airway narrowing due to mucus secretion. Overcome variations due to gas used, equipment set-up, method of analysis, software used, and patient age. Validation required for detection of early abnormalities in peripheral or parenchymal sites. Establishment of MCIDs is required		

(Continued)

TABLE 2] *(Continued)*

Small Airways Assessment	Description (What/How Measured)	Correlation(s) With Clinical End Point(s)	Advantages/Disadvantages
Alveolar fraction of exhaled nitric oxide	F_{ENO} is a marker of eosinophilic airway inflammation; modeling can be used to distinguish the alveolar fraction of nitric oxide from proximal airway inflammation	Not established	**Advantages** Sensitive to small airways and therapy changes in asthma in the presence of eosinophilic inflammation. Associated with lack of asthma control in patients with mild untreated asthma; reflects eosinophilic inflammation in the small airways **Disadvantages** Conflicting data for F_{ENO} in COPD affects interpretation of alveolar fraction of exhaled nitric oxide. Affected by smoking status. Technique is currently in an exploratory research phase
	Knowledge Gaps: Clarification of the role in the inflammation of the small airways. Validation with longitudinal data and correlation with clinical end points is required for both asthma and COPD. Understanding how to adjust for smoking status. Standardization of protocols and establishing of MCIDs required		
Exhaled particle analysis	Exhaled breath is analyzed for the presence and size of specific particles. Particles are generated by different mechanisms, and the sites of origin differ depending on the breathing maneuver used (eg, the process of reopening small airways has been confirmed as a particle-generating mechanism)	Not established	**Advantages** An ERS technical standard is available that includes exhaled particle analysis **Disadvantages** This technique is currently at the very earliest stages of development and requires highly trained operators; it is not widely available and is expensive to perform
	Knowledge Gaps: Correlation with clinical end points is required. A better understanding of the mechanisms and sites involved could enable the generation of a fingerprint of clinically important biomarkers from exhaled breath. Establishment of exact relationship to the small airways is required		

Almost all methods require a better understanding of natural variation over time and differences due to age, BMI, height, race, sex, and weight. AOS = airwave oscillometry; ATS = American Thoracic Society; DPM = disease probability measure; ERS = European Respiratory Society; FDA = US Food and Drug Administration; FEF_{25-75} = forced expiratory flow between 25% and 75% of the FVC; F_{ENO} = fraction of exhaled nitric oxide; FOT = forced oscillation technique; FRI = functional respiratory imaging; IOS = impulse oscillation; LCI = lung clearance index; MCID = minimal clinically important difference; OCT = optical coherence tomography; PRM = parametric response mapping; RV = residual volume; S_{acin} = slope of acinar ventilation; S_{cond} = slope of conductive ventilation; SGRQ = St. George's Respiratory Questionnaire; SPECT = single-photon emission CT; SVC = slow expiratory vital capacity; TLC = total lung capacity.



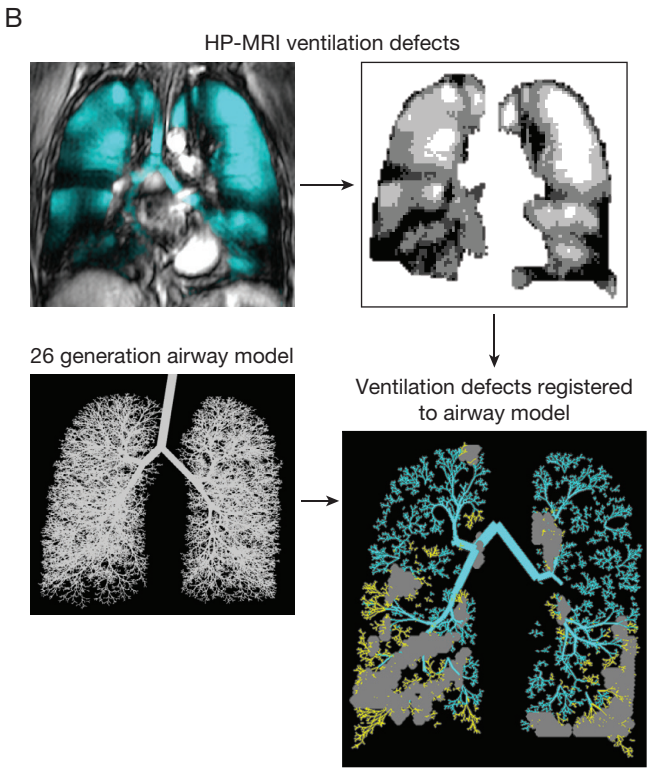


Figure 4 – *Combining structural and functional small airways assessments may provide better disease characterization. A, Helium-3 MRI co-registered with helium-1 MRI and CT imaging. Blue coloring indicates helium-3 MRI ventilation; green indicates parametric response mapping-determined healthy tissue; yellow indicates gas trapping indicative of small airways disease; and red indicates emphysema. B, Co-registration of HP-MRI and airway mesh model with plethysmography. Blue indicates ventilated areas of the lung; yellow indicates areas of defective lung ventilation. fSAD = functional small airways disease; HP-MRI = hyperpolarized gas MRI. Images in panel A taken from Capaldi DPI, Zha N, Guo F, Pike D, McCormack DG, Kirby M, Parraga G.* Radiology. *2016;279:597-608.*[144] *Copyright © 2016 with permission from the Radiological Society of North America. Images in panel B reproduced with kind permission from Dr Grace Parraga, Robarts Research Institute, Western University, Ontario, Canada.)*

may prove to be a more accurate means to assess an individual's disease state. Indeed, combining HP-MRI with PRM, plethysmography, or FOT has previously shown potential (Figs 4, 5).[134,144] Analysis of regional changes in airflow obstruction in longitudinal studies can be useful to monitor airway improvement or response to global or regional treatments.[132] Indeed, correlation between regional ventilation changes following treatment and change in whole lung defect percentage indicates that ventilation imaging may be a sensitive biomarker of the physiological and clinical responses observed in patients.[145]

Imaging and physiological measures of the small airways may offer valuable insight into the clinical status of

Knowledge Gaps

Standardization of the approach to the functional assessment of the small airways (validated across different patient populations) and identification of clinically meaningful changes. Establishment of whether there are correlations between different functional assessment techniques. Longitudinal studies, including multiple small airways assessments, are required to understand the progression of small airways measurements in relation to changes in other clinical end points.

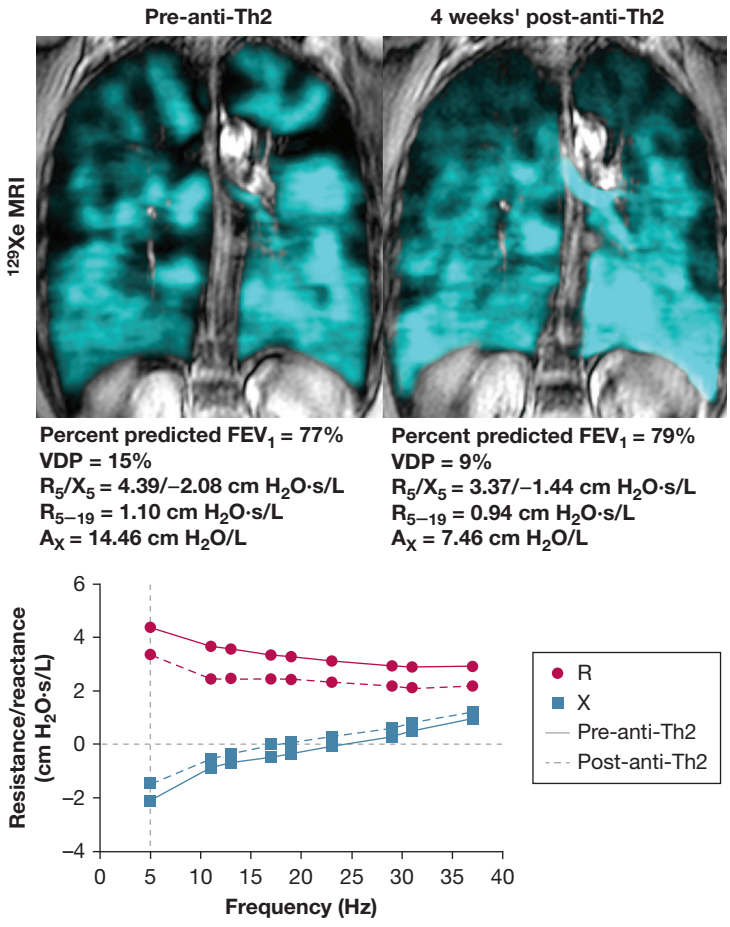


Figure 5 – *Xenon-129 ventilation MRI and oscillometry in a patient with asthma prior to and 4 weeks following anti-type 2 biologic therapy. A_x = reactance area; R_X = resistance at given frequency; Th2 = type 2; VDP = ventilation defect percent; X_x = reactance at given frequency. (Reproduced with kind permission from Dr Grace Parraga, Robarts Research Institute, Western University, ON, Canada.)*

obstructive lung disease; however, due to a lack of standardization and specificity in many of these methods and their interpretation,[64] along with other drawbacks, such as cost, accessibility, and technical expertise associated with imaging techniques, they are currently largely reserved for research purposes. Because the techniques discussed measure different aspects of small airways functionality, it is likely that no single test in isolation would be sufficient to accurately determine disease severity. In addition, a better understanding of natural variation over time and differences due to age, BMI, height, race, sex, and weight are required for almost all of these techniques.

Pillar 4: Pharmaceutics of Current Therapies

The majority of current treatments for obstructive lung disease are administered via inhalation. Conventional inhaler devices predominantly aerosolize large drug particles using a pressurized metered dose inhaler,[146] dry powder inhaler,[146] or nebulizer.[147] For corticosteroids, this approach avoids systemic administration and the associated risk of adverse events.[148-150] There are a number of different devices within each category and not all classes of inhaled drugs are available from all types of device. A combination of the physics of the device mechanism and the chemistry of the formulation leads to drug particles of different sizes, which in turn affects the amount and site of drug deposition. Older inhalers typically produced particles with a mass median aerodynamic diameter $>$ 5 μm, resulting in a large proportion of particles being deposited in the oropharynx; however, most current devices produce fine particles with a mass median aerodynamic diameter of 2 to 5 μm, with some producing extra-fine particles $<$ 2 μm, resulting in increased peripheral deposition.[26] Subtle changes to inhaler formulation characteristics can have a considerable impact on the airway deposition pattern within this particle size range.[151] Slow inhalation has also been shown to enhance delivery to the small airways.[152] However, correct handling and inhalation technique also remain significant barriers to adequate treatment, despite training.[153]

As previously discussed, a proportion of patients with asthma have uncontrolled inflammation, despite therapy with inhaled corticosteroids (ICS), and may experience a higher frequency of exacerbations.[146,154] This may reflect the inability of conventional inhalers to effectively deliver drugs to the small airways (Fig 2).[155] Indeed, production of smaller particle aerosol solutions of hydrofluoroalkane-beclomethasone using a pressurized metered dose inhaler has been found to improve drug distribution in the lung periphery, enabling reduced dosing without loss of efficacy and reduced potential for local adverse events.[156] A recent pilot study provided proof of concept for choosing asthma therapy based on a patient-driven, phenotypic approach: patients with uncontrolled asthma with/without air trapping were treated with extra-fine beclomethasone dipropionate/formoterol fumarate.[157] Patients with air trapping exhibited superior improvements in forced expiratory flow between 25% and 75% of the FVC , FVC, and residual volume compared with patients without air trapping. Ciclesonide was specifically developed to be a small-particle treatment and has been shown to improve alveolar exhaled nitric oxide and methacholine-induced air trapping, indirectly suggesting reduced small airways inflammation.[158] Extra-fine ICS has been associated with greater treatment stability and improved asthma control, with lower rates of exacerbations at significantly lower prescribed doses than larger-particle ICS, again suggestive of enhanced deposition in the small airways.[159,160]

To provide a consistent drug distribution, it may ultimately prove more practical to develop novel systemic alternatives to inhaled therapies, such as biologic therapies, with the caveat that systemic therapies may be associated with increased risk of adverse events compared with targeted delivery.[148] However, until there is an effective, validated, and standardized technique to measure changes in the small airways, it will not be possible to demonstrate efficacy in this target region, regardless of the route of treatment administration.

Knowledge Gaps

Establishment of whether drug delivery to the small airways results in clinically meaningful changes compared with full airway delivery or systemic delivery. Ascertainment of whether a specific formulation, device, or delivery route can contribute to a precision medicine strategy.

Pillar 5: Phenotyping—How Small Airways Function Can Differentiate Specific Phenotypes of Asthma and COPD

Currently, there is considerable variation in the end points used to define the presence of small airways disease.[161] Positive correlations between small airways disease (defined using combinations of spirometry, body plethysmography, IOS, or MBW rather than individual variables) and increased asthma severity and exacerbation history have been found.[31] This may be reflective of either a distinct asthma phenotype with structural lung changes that are not responsive to the use of corticosteroids, or an inability of most conventional inhalers to effectively deliver ICS to the small airways.[155] Treatment step-up to high-dose combination therapy in patients with uncontrolled asthma has been associated with improved peripheral airway function; moreover, baseline MBW and FOT parameters have been found to correlate with improvements in symptoms and may predict treatment response.[162]

Measurement of respiratory system impedance (a combination of resistance and reactance) using FOT is believed to reflect abnormalities of lung function.[19,162] Lower frequency impedance likely reflects peripheral airway function, including the small airways, with resistance at 5 Hz, reactance at 5 Hz, and area of reactance being the most common outputs.[163,164] A progressive increase in impedance has been associated with increased COPD severity.[96] The difference in reactance between 5 and 20 Hz is also believed to reflect peripheral airway function, but this parameter is not specific and may also reflect ventilation heterogeneity and upper airways shunting.[164]

Of note, when analyzed according to the presence or absence of small airways disease, the number of patients with small airways disease in Global Initiative for Chronic Obstructive Lung Disease Group B ($\leq$ 1 previous exacerbations/high symptom severity) was significantly higher than the number of patients with small airways disease in Global Initiative for Chronic Obstructive Lung Disease Group C ($\geq$ 2 exacerbations or $\geq$ 1 exacerbation leading to hospitalization/low symptom severity),[14] potentially indicating a physiological basis for highly symptomatic, but otherwise mild, cases. The mechanisms underlying this observation are likely multifactorial given that large and small airways dysfunction both contribute and are interrelated in their effects on symptoms. Moreover,

although a close correlation between the presence of small airways disease and COPD Assessment Test score has been observed,[14] some patients have normal oscillometry findings,[14] and there is some disconnect between large airways measurements (spirometry) and symptoms,[10,11] further showing the heterogeneity of COPD and highlighting the potential importance of composite end points for accurately defining an individual's disease.[31] In addition, the perception of symptoms is complex; it relates to a patient's treatment and multiple pathophysiological parameters, including the degree of lung and ventilation abnormalities, lung perfusion, dead space, and mechanical impedance due to both the large and small airways compartments.

It is likely that there are multiple drivers of obstructive lung disease that represent distinct phenotypes. Novel small airways end points may provide an opportunity to advance precision medicine approaches to therapy by capturing subtle physiological changes in early disease.[165]

Knowledge Gaps

Development of new/improved end points/ biomarkers (blood/airway) for measuring pathophysiological changes in the small airways to distinguish phenotypes and identify new disease targets. Collection and analysis of relevant patient data for subjective health, respiratory health, quality of life, pulmonary function testing, and any other assessments that may enable further identification of distinct disease phenotypes.

Pillar 6: Pathway to Regulatory Acceptance of a Novel End Point to Assess the Small Airways

Evidence suggests that the small airways are key for the development and progression of obstructive lung disease; therefore, the pathologic mechanisms involved in small airways disease represent an appealing target for therapeutic intervention. In addition, there is a need to establish whether affecting small airways dysfunction can be correlated with an important clinical outcome such as mortality, exacerbation rate, long-term lung function, or quality of life. However, it is vital to first develop and validate novel end points capable of reliably measuring disease progression in the small airways.

Newer imaging and physiological techniques for assessing the small airways, both alone and in combination with physiological techniques (Fig 5), show promise and may prove more effective than using spirometry. Indeed, the lung clearance index is already a well-established technique for assessing patients with cystic fibrosis and has been found to be more sensitive than both FEV_1 and forced expiratory flow when 75% FVC has been exhaled for detecting structural lung disease in these patients.[166] However, to develop a novel end point that is acceptable to patients and ultimately regulators, more extensive evidence of its accuracy and specificity would be required. In particular, small airways disease measurements need to be included in therapeutic clinical trials, at least initially, as exploratory end points. Longitudinal studies would be required to assess the usefulness of the end point in detecting progression of small airways disease over time.

Once small airways assessments are identified that reflect clinically meaningful changes in the end points that are drivers of health care value (eg, quality of life, morbidity, mortality), validation will be required to show acceptable reproducibility. Furthermore, normal ranges for healthy individuals and minimal clinically important differences will need to be established. These advances will ultimately provide confidence in making go/no-go decisions concerning novel drugs in the early stages of development and may lead to expedited patient access to new therapies.[167,168] In addition, novel tests could be used for early detection or early treatment trials and for screening of high-risk patients.

From a regulatory perspective, the US Food and Drug Administration and the European Medicines Agency have biomarker qualification processes that require evidence to support the relationship between the biomarker and clinical outcome of interest, the biological rationale, and analytical performance.[167,169] If a novel small airways assessment yielded a larger effect size than that seen with FEV_1, a study could then be specifically powered to detect the change, using fewer patients, reducing recruitment time and cost, and potentially accelerating the drug development process.

Knowledge Gaps

Development of novel end points and generation of extensive evidence of their accuracy, specificity, and reliability, and establishment of correlation with current clinical end points of interest. Inclusion of novel end points in therapeutic clinical trials and longitudinal studies.

Figure 6 – *Key questions to advance our understanding of the small airways.*

Pillar 7: Prospects for the Future: A Call for Action

New therapies to treat obstructive lung disease are desperately needed; however, it is not currently possible to adequately evaluate new therapies by using established clinical end points. A shift in emphasis is needed from treating late-stage obstructive lung disease to early-stage identification and prevention. This cannot be achieved until a better understanding of the pathogenesis of early-stage, subclinical disease is established and end points to measure changes in small airways move beyond "exploratory" to gain regulatory approval.[170] More sensitive measurements of small airways function may show changes that could be assessed over shorter periods,[30] potentially accelerating the development of novel therapies.

Earlier diagnosis brings opportunities for earlier treatment and greater chances of slowing disease progression and potential for physiological recovery before small airways damage becomes irreversible. However, as outlined, gaps in our understanding of the significance of the small airways in obstructive lung disease are an ongoing clinical challenge. Nevertheless, the capability to assess small airways in both a research and a clinical setting now exists. This opens up the potential for novel interventions that could be selective for specific types of obstructive lung disease,[171] and may be particularly important as we move toward more personalized precision medicine.[165]

Our call to action to the respiratory community is to develop end points that are capable of detecting subclinical changes in small airways lung physiology, facilitating effective decision-making in the drug

development process. These end points should be reliable, reproducible, easily and safely assessed, cost-effective, and must be associated with clinically meaningful outcomes. A collaborative effort between academia, industry, and health authorities will be key to achieving these goals.

Through discussion of the seven pillars of small airways disease presented here, a number of knowledge gaps have been identified. Figure 6 summarizes the key questions to be answered to advance our understanding of the small airways and novel techniques capable of measuring changes in the small airways, and to support novel therapies for the management of small airways disease.

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