

Small Airway Dysfunction in Chronic Obstructive Pulmonary Disease Pathology: Assessment and Clinical Implications

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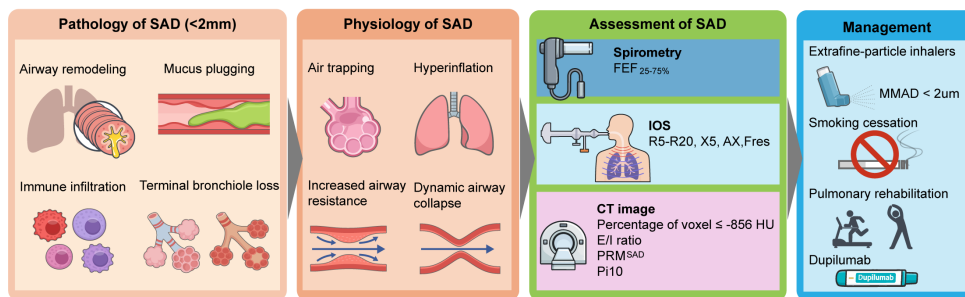
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Small airway dysfunction in COPD



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Abstract

Chronic obstructive pulmonary disease (COPD) is a progressive lung disease characterized by airflow limitation and persistent respiratory symptoms. A key factor in the progression of COPD is small airway dysfunction (SAD), which originates in airways smaller than 2 mm in diameter. Chronic exposure to smoke and toxins leads to inflammatory remodeling and luminal obstruction, detectable through micro-computed tomography (CT) studies before spirometric airflow limitations become evident. SAD exacerbates COPD by increasing airway resistance and promoting dynamic airway collapse during exhalation. Clinically, SAD presents as gas trapping, hyperinflation, and exercise intolerance, which are associated with a rapid decline in lung function. Recent evidence indicates that SAD may be a modifiable and clinically significant trait in COPD, with management strategies including extrafine-particle inhalers, smoking cessation, pulmonary rehabilitation, and emerging biologic therapies. Various assessment methods, such as pulmonary function tests and CT imaging, are used to assess SAD. This review focuses on the role of SAD in the pathophysiology of COPD and the clinical implications of easily applicable measurements, including forced expiratory flow between 25% and 75% of forced vital capacity, impulse oscillometry, Pi10, and parametric response mapping, as well as potential treatment modalities for SAD in COPD.

Keywords: Chronic Obstructive Pulmonary Disease; Diagnosis; Lung Mechanics; Pathology; Small Airway Disease; Treatment



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Introduction

Chronic obstructive pulmonary disease (COPD) is a progressive lung disease characterized by airflow limitation and persistent respiratory symptoms. Small airway dysfunction (SAD) has emerged as a key pathological driver of disease progression^{1,2}. SAD originates in airways <2 mm in diameter, where chronic exposure to smoke and toxins triggers inflammatory remodeling (mucosal thickening, fibrosis) and luminal obstruction (mucus plugs, immune cell infiltration)^{3,4}. These changes begin subclinically, as micro-computed tomography (CT) studies reveal a 40%–50% reduction in terminal bronchioles and disrupted alveolar attachments in early COPD, occurring years before spirometric airflow limitation becomes apparent^{4,5}.

The pathophysiology follows Poiseuille's law ($R \propto 1/r^4$), where minor lumen narrowing exponentially increases resistance, while parallel airway loss amplifies regional airflow heterogeneity⁴. Concurrent emphysema exacerbates SAD by decreasing elastic recoil, which promotes dynamic airway collapse during exhalation⁴. Clinically, SAD manifests as gas trapping, hyperinflation, and exercise intolerance, with its progression correlating to an accelerated decline in lung function^{1,6}.

Although numerous measurement methods have been suggested, clinically, pulmonary function measurement (e.g., forced expiratory flow [FEF] between 25% and 75% of forced vital capacity [FVC] [FEF_{25–75%}], impulse oscillometry [IOS] measures, etc.) and/or CT imaging (e.g., Pi10, parametric response mapping [PRM], etc.) are most frequently used. Accordingly, this review aimed to focus on the role of SAD in the pathophysiology of COPD and the clinical implications of clinically relevant and easily applicable measurements of SAD as follows: (1) pulmonary measurements (FEF_{25–75%} and IOS measures) and (2) CT measurement parameters (Pi10 and PRM).

Regarding the treatment of SAD, traditional strategies have primarily focused on extrafine-particle inhalers to alleviate symptoms in patients with COPD⁷. However, recent emerging evidence highlights SAD as a treatable trait that can potentially be managed through various approaches, including smoking cessation⁸, pulmonary rehabilitation⁹, and biologics¹⁰.

Pathology of COPD and the Role of SAD

Small airways are defined as conducting airways with a diameter of less than 2 mm, typically located from approximately the eighth generation of bronchi¹. Small airways include the terminal bronchioles, respiratory

bronchioles, and the gas-exchange apparatus, which consists of the alveolar ducts and alveolar sacs¹¹. Although they contribute less than 10% of total airway resistance in healthy lungs, they become the primary site of resistance in COPD due to structural narrowing and obliteration¹².

The critical elements of SAD underlying inflammation in COPD include airway remodeling, mucus plugging, immune cell infiltration, loss of small airways, and emphysematous destruction¹³. Remodeling is an inappropriate and extensive wound healing response to inflammation caused by factors such as cigarette smoke, air pollution, bacteria, and viruses. Historically, various immune cells have been associated with SAD in COPD, including macrophages, neutrophils, eosinophils, and both CD4⁺ helper and CD8⁺ cytotoxic T lymphocytes, with lymphoid follicles also reported in some cases¹⁴. The number of T lymphocytes and cytotoxic CD8⁺ lymphocytes is associated with COPD severity¹⁵.

Increased mucus production and impaired clearance, which lead to extensive mucus plugging, are key pathological features of the small airways in patients with COPD¹. Cigarette smoking is linked to goblet cell hyperplasia and metaplasia in the small airways, which reduces mucus clearance by shortening the length of the cilia. Similarly, patients exposed to biomass smoke show pathological changes, including bronchial wall thickening, squamous cell metaplasia, goblet cell hyperplasia, peribronchial fibrosis, and bronchiectasis.

Emphysematous destruction, marked by the loss of alveolar walls and elastic fibers, is a key feature of COPD pathology and is closely associated with SAD. The loss of alveolar attachments to the small airways diminishes lung elastic recoil and promotes dynamic airway collapse during expiration, further exacerbating airflow limitation¹⁶. Vascular alterations, such as endothelial dysfunction and intimal thickening of pulmonary vessels, contribute to disease progression and impair gas exchange. Notably, the loss of alveolar attachments compromises mechanical support for the small airways and correlates with more severe airflow limitation and hyperinflation.

SAD is now recognized as an early and critical event in the pathogenesis of COPD, often occurring before the onset of emphysema. High-resolution imaging and histopathologic studies have demonstrated that the loss and remodeling of terminal and transitional bronchioles happen prior to any visible emphysematous destruction in many patients. The destruction of alveolar attachments, which tethers small airways open, may contribute centrilobular emphysema by destabilizing the distal airway and promoting parenchymal destruc-

tion. However, recent evidence indicates that the relationship between SAD and emphysema is not strictly linear or sequential. Instead, SAD and emphysema are closely interconnected and often coexist, with SAD typically occurring first and contributing to emphysematous destruction. While both conditions can develop simultaneously, SAD often represents the initial site of injury and dysfunction, paving the way for subsequent emphysematous changes. As COPD progresses, the interactions between small airway remodeling, airway loss, and parenchymal destruction lead to worsening airflow limitation and clinical decline.

Small airway loss serves not only as an early indicator of the disease but also as a structural driver of COPD progression, with emphysema representing a later and often more advanced stage of pathological change. This evolving understanding underscores the significance of early detection and intervention targeting SAD

to potentially prevent or delay the onset of emphysematous destruction in patients with COPD.

Measurement and Clinical Implications of Small Airway Disease in COPD

1. CT imaging

Small airways with an internal diameter of less than 2 mm cannot be directly visualized on CT due to the resolution limitations of current clinical CT imaging. To address this technical challenge, methods such as CT densitometry, PRM, and bronchial wall thickening measured by Pi10 have been employed to assess SAD (Table 1).

1) CT densitometry

SAD leads to airflow obstruction, resulting in air trapping. CT densitometry quantifies air trapping on expira-

Table 1. Summary of measurement methods for small airway dysfunction in chronic obstructive pulmonary disease

Modality	Measures	Change indicating SAD	Advantages	Disadvantage
CT imaging				Radiation exposure; relatively expensive
	≤ -856 HU on expiratory CT	Reflects air trapping	Widely used; Quantifies extent of air trapping	Limited ability to differentiate SAD from emphysema
	E/I ratio	Increased E/I ratio reflects air trapping	E/I ratio is sensitive in non-emphysematous regions	Influenced by lung volume, respiratory effort, and image registration
	PRM ^{SAD}	Inspiratory attenuation > -950 HU and expiratory ≤ -856 HU Increased PRM ^{SAD} voxels	Differentiates functional SAD from emphysema using voxel-to-voxel registration	Requires paired inspiratory/expiratory CT and specialized software Increased radiation exposure Limited clinical availability
	Pi10	Increased Pi10 indicates thicker airway walls	Quantitative marker of airway remodeling	Primarily represents medium-sized airways (theoretical 10-mm perimeter)
Spirometry	FEF _{25-75%}	Decrease ($< 65\%$ predicted)	Widely available Simple to perform Frequently used in early airflow obstruction detection	Highly variable Dependent on FVC Not specific to SAD Lacks standardized reference values
	R5-R20	R5-R20 increase (> 0.07 kPa·s·L ⁻¹)	Effort-independent (tidal breathing)	Requires specialized equipment
	X5	X5 decrease (< -0.12 kPa·s·L ⁻¹)	Useful when spirometry is difficult (children, elderly, individuals with cognitive impairment)	Cutoffs and reference values vary
	Ax	Ax increase (> 0.44 kPa·s·L ⁻¹)		
	F _{res}	F _{res} increase (> 14.14 Hz)	Sensitive and specific to SAD	

SAD: small airway dysfunction; CT: computed tomography; HU: Hounsfield unit; E/I: expiratory-to-inspiratory; PRM: parametric response mapping; PRM^{SAD}: parametric response mapping-defined small airway disease; FEF: forced expiratory flow; FVC: forced vital capacity; IOS: impulse oscillometry system; R5: resistance at 5 Hz; R20: resistance at 20 Hz; X5: reactance at 5 Hz; AX: area of reactance; F_{res}: resonant frequency.

tory CT scans, typically using attenuation thresholds of approximately -856 Hounsfield units (HU)¹⁷. However, the -856 HU threshold has limitations in differentiating air trapping caused by true SAD from emphysematous changes. To address this issue, additional methods have been developed, including the expiratory-to-inspiratory mean lung density ratio (E/I ratio)¹⁸. Under normal physiological conditions, lung density increases significantly during expiration as air exits the lungs. In patients with SAD, narrowed or obstructed distal airways prevent complete exhalation, leading to air trapping and a relatively smaller increase in lung density, which is reflected by a higher E/I ratio. Conversely, in emphysema, lung density is significantly reduced on inspiratory CT scans due to alveolar destruction, resulting in minimal density changes during expiration and a lower E/I ratio. Therefore, the E/I ratio is especially sensitive to SAD in non-emphysematous regions. Another method calculates the relative volume change between voxels with attenuation values ranging from -856 to -950 HU¹⁹. By excluding voxels below -950 HU, which indicate emphysematous changes²⁰, this approach more accurately identifies gas trapping regions caused by SAD, providing a precise measure of SAD severity, particularly in early-stage COPD.

2) PRM

PRM is an advanced CT imaging technique that combines matched inspiratory and expiratory images through image registration, aligning two or more images taken at different times or from different imaging modalities²¹. By spatially aligning two-phase CT scans, PRM facilitates direct voxel-to-voxel comparisons and

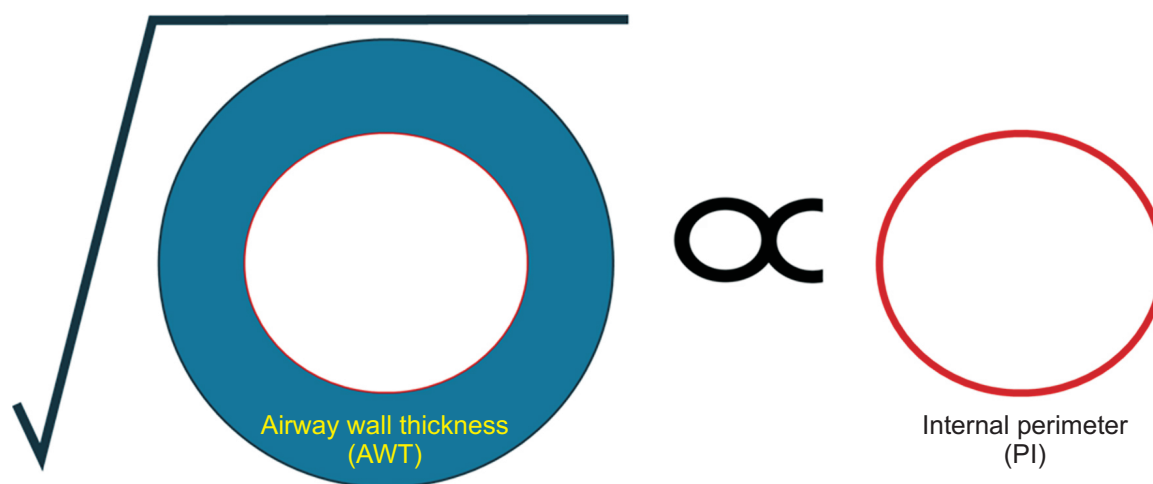
classifies lung parenchyma into three categories. This classification is based on thresholds that define emphysema (-950 HU during inspiration) and gas trapping (-856 HU during expiration)²⁰.

Normal, expiratory voxel density >-856 HU and inspiratory voxel density between -950 and -810 HU; SAD (PRM-defined SAD [PRM^{SAD}]), expiratory voxel density <-856 HU and inspiratory voxel density between -950 and -810 HU; Emphysema (PRM-defined emphysema [PRM^{emph}]), expiratory voxel density <-856 HU and inspiratory voxel density <-950 HU. PRM effectively distinguishes COPD phenotypes (emphysema and SAD), which conventional CT cannot differentiate. PRM^{SAD} specifically identifies lung areas with gas trapping during expiration but normal density during inspiration, representing pure functional SAD distinct from emphysema²². PRM^{SAD} correlates with Global Initiative for Chronic Obstructive Lung Disease (GOLD) severity, total lung capacity, alveolar volume, residual volume, and the decline in forced expiratory volume in 1 second (FEV₁)^{20,23}. PRM also enables the early detection of smoking-related changes and COPD²⁴. However, a notable concern regarding advanced CT techniques is increased radiation exposure due to additional expiratory CT imaging, increasing radiation exposure by approximately 1.5-fold²⁵.

3) Pi10

Pi10 is a quantitative imaging biomarker that represents the standardized airway wall thickness derived from chest CT scans. Specifically, Pi10 is defined as the average airway wall thickness normalized to a theoretical airway with an internal perimeter of 10 mm. When cal-

Figure 1. The square root of the airway wall area (blue area) is assumed to be correlated with internal diameter of the airway wall when measuring Pi10.



culating Pi10, it is assumed that the square root of the airway wall area is correlated with the internal diameter of the airway wall (Figure 1). Consequently, Pi10 can be calculated using regression analysis, where the square root of the airway wall area is plotted against the internal perimeter of the airway for all measured segments.

A linear regression line is fitted to these data points. Although Pi10 primarily represents medium-sized airways, it correlates with smaller airways (internal perimeter of 4 mm)²⁶ and air trapping (elevated residual volume/total lung capacity)²⁷. Increased levels of Pi10 are associated with smoking-related airway injury, exacerbation, and mortality in patients with COPD^{8,27}.

2. Pulmonary function tests

Spirometry is essential for COPD diagnosis and assessing airflow limitation. However, FEV₁ mainly indicates airflow obstruction in large and medium-sized airways and is less sensitive for detecting SAD. Alternative spirometric parameters have been utilized to assess SAD, including FEF_{25–75%}, FEF_{50%}, FEF_{75%}, various ratios (slow vital capacity/FVC, FEV₁/FEV₆, and FEV₃/FVC)^{28–30}.

SAD, as defined by these spirometric parameters, was well correlated with airway morphological changes observed on inspiratory-expiratory CT scans³¹. Among these, FEF_{25–75%} is the most commonly used parameter for detecting SAD and early airflow obstruction^{29,32}.

Despite its relevance, FEF_{25–75%} is highly variable and dependent on FVC^{33,34}. Although SAD was defined as FEF_{25–75%} less than 65% predicted in previous studies^{35,36}, a standardized reference value for FEF_{25–75%} is lacking. These limitations restrict its clinical utility as a robust marker for SAD assessment.

IOS is a non-invasive, effort-independent pulmonary function test that measures respiratory system impedance^{37,38}. Unlike spirometry, IOS does not require forceful expiration, making it particularly useful for children, elderly patients, and individuals with physical or cognitive impairments. IOS employs pressure impulses (sound waves) generated by a loudspeaker, which are delivered to the lungs through a mouthpiece at frequencies ranging from 5 to 40 Hz. High-frequency waves travel shorter distances and predominantly assess the central airways (e.g., throat or trachea), while low-frequency waves, which travel longer distances, reach the peripheral airways^{38,39}.

IOS calculates respiratory impedance, which comprises resistance and reactance^{39,40}. Resistance is the opposing force to airflow. Resistance at 5 Hz (R5) reflects total airway resistance, while resistance at 20 Hz (R20) indicates resistance in large airways. Therefore, the difference between R5 and R20 (R5–R20) rep-

resents small airway resistance. Reactance represents the combined effects of the lung's elastic and inertial properties. Capacitance reflects the elasticity of the airway, particularly influenced by small airways, while inductance denotes the pressure opposing flow acceleration in the airway column, generally influenced by large airways. The inertial component is represented by a positive value, whereas the elastic (capacitive) component is represented by a negative value³⁹. Reactance at 5 Hz (X5) indicates peripheral airway obstruction, where more negative values signify greater elasticity or increased airway stiffness³⁸. Resonant frequency (F_{res}) is the frequency at which reactance equals zero, reflecting lung stiffness. Values above the normal range of 8–12 Hz indicate increased stiffness^{39,40}.

The area of reactance (AX) represents the integrated AX between 5 Hz and F_{res} , reflecting the total area of capacitance. An increase in AX indicates a loss of lung elasticity due to SAD. The IOS can be utilized for diagnosing COPD and assessing its severity⁴¹.

In COPD, IOS parameters, including R5, R5–R20, F_{res} , and AX, typically increase, whereas X5 decreases⁴². These IOS parameters correlate well with lung function (FEV₁ and FEV₁/FVC), quality of life, and the risk of exacerbations^{42,43}. Among the IOS parameters reflecting airway resistance, R5 shows a greater increase compared to R20 or R5–R20 in patients with COPD. Additionally, X5 demonstrates a strong correlation with FEV₁, suggesting that X5 may better reflect the severity of airflow limitation^{42,44,45}. H.J. Smith proposed a clinically applicable classification scheme for assessing the severity of airway obstruction based on R5 and X5 values⁴⁶.

Although IOS cannot fully substitute for spirometry in the diagnosis and assessment of COPD, it is especially valuable for patients who are unable to perform spirometry. Furthermore, IOS provides important insights into the assessment of SAD. One study evaluated IOS-defined SAD using specific cutoff values (R5–R20 >0.07 kPa·s·L⁻¹, X5 <0.12 kPa·s·L⁻¹, F_{res} >14.14 Hz, AX >0.44 kPa·s·L⁻¹) in individuals with respiratory symptoms but preserved pulmonary function⁴⁷. These IOS parameters were correlated with decreased FEF_{25–75%} and a higher incidence of wheeze or other respiratory symptoms. Notably, F_{res} demonstrated greater sensitivity in detecting SAD compared to FEF_{25–75%}. Lu et al.⁴⁸ also reported that patients with abnormal IOS parameters had a higher risk of acute exacerbation of COPD in previous years than those with normal IOS results.

Clinical Implications of Small Airway Dysfunction on COPD

SAD represents an early pathological process of COPD, often occurring before the onset of symptoms, spirometric abnormalities, or the development of emphysema^{1,49}. Recent micro-CT analyses of lungs from patients with emphysematous pre-COPD revealed small airway loss and remodeling, even in the absence of airflow obstruction⁵. Thus, identifying SAD early, before the onset of COPD, could play a key role in preventing or delaying disease progression.

SAD significantly impacts clinical manifestations. In a cohort of 100 patients with COPD, distal airway obstruction, defined as $R5-R20 > 0.03 \text{ kPa}\cdot\text{s}\cdot\text{L}^{-1}$, was present in 80% of participants. This condition was associated with worse lung function, increased hyperinflation, and poorer health status⁵⁰. Bhatt et al.²⁰ also reported that PRM^{SAD} was a strong predictor of FEV_1 decline in both COPD patients and smokers without airflow obstruction, with SAD contributing more significantly to FEV_1 decline than emphysema.

IOS parameters indicative of SAD, including X5, AX, and F_{res} , were significantly associated with annual FEV_1 decline, with AX abnormality showing the greatest decline in lung function at 55.54 mL/year ⁵¹. Moreover, one study found a significant association between increased $R5-R20$ and the COPD Assessment Test (CAT) score. Notably, patients with $R5-R20 > 0.07 \text{ kPa}\cdot\text{s}\cdot\text{L}^{-1}$ had approximately a 12-fold increased odds ratio for reporting a CAT score ≥ 10 ²². $R5-R20$ and X5 were also associated with poorer quality of life and increased dyspnea⁵².

SAD also impacts clinical outcomes, such as acute exacerbations and mortality, in patients with COPD. A reduced $\text{FEF}_{25-75\%}$ is associated with a higher frequency of exacerbations⁵³. Furthermore, PRM^{SAD} from the COPDGene study showed a significantly increased risk of both moderate exacerbations (relative risk, 1.89) and severe exacerbations (relative risk, 2.02)⁵⁴.

Park et al. developed an IOS severity index comprising seven items ($R5$, $R5-R20$, AX, F_{res} , X5, smoking status, and sex), demonstrating that an IOS severity index score ≥ 4 was associated with a higher risk of SAD and a higher risk of moderate-to-severe exacerbations in patients with COPD.

Park et al.³⁶ developed an IOS severity index consisting of seven items ($R5$, $R5-R20$, AX, F_{res} , X5, smoking status, and sex). Their findings showed that an IOS severity index score ≥ 4 was linked to an increased risk of SAD and a higher likelihood of moderate-to-severe exacerbations in patients with COPD³⁶. A recent study

defined SAD using IOS parameters Z-score (AX and $F_{\text{res}} > 1.645$, X5 < -1.645) and classified patients as having consistent SAD (all parameters abnormal) and inconsistent SAD (one or more parameters abnormal, but not all)⁵¹.

Among 833 COPD patients followed over 2 years, the study found that both consistent and inconsistent SAD were significantly associated with a higher risk of moderate-to-severe exacerbations compared to patients with normal IOS results, with hazard ratios of 2.19 and 1.91, respectively⁵¹. SAD contributes to COPD exacerbations by causing mucus plugging in the small airways, leading to dynamic airway collapses due to the loss of alveolar attachments, and increasing susceptibility to infections as a result of impaired mucociliary clearance⁵⁵. Hogg et al.⁴⁹ also investigated the relationship between SAD and mortality in patients with severe COPD undergoing lung volume reduction surgery. They demonstrated that greater SAD, indicated by luminal occlusion, was independently associated with earlier mortality, regardless of baseline lung function.

Given that SAD can precede a COPD diagnosis and is associated with worsened symptoms, reduced quality of life, accelerated lung function decline, frequent exacerbations, and increased mortality, there is a need for active efforts to detect SAD early in individuals with or without COPD. Additionally, further research is necessary to identify effective treatment strategies.

SAD Management

1. Extrafine-particle inhalers

Extrafine-particle inhalers have traditionally been used to alleviate SAD in patients with COPD. These inhalers deliver medication in the form of very fine particles that can penetrate deeper into the small airways, where SAD originates. The extrafine-particles ensure a more uniform distribution of the drug throughout the bronchial tree, enhancing its therapeutic effects on the small airways. This targeted delivery helps mitigate inflammation, reduce mucus hypersecretion, and prevent airway remodeling, which are critical pathological features of SAD.

When comparing the lung deposition of two single-inhaler triple therapy combinations—extrafine beclomethasone dipropionate/formoterol fumarate/glycopyrronium bromide (BDP/FF/GB) versus non-extrafine fluticasone furoate/vilanterol/umeclidinium (FF/VI/UMEC)—using functional respiratory imaging, extrafine BDP/FF/GB demonstrated higher intrathoracic and peripheral deposition than non-extrafine FF/VI/UMEC. This suggests a potential advantage of the extrafine

formulation of BDP/FF/GB in the treatment of SAD⁷.

2. Smoking cessation

Smoking cessation is a critical intervention in managing COPD. Quitting smoking stops the ongoing exposure to harmful toxins and irritants that contribute to airway inflammation, mucus hypersecretion, and structural remodeling of the small airways. Furthermore, evidence suggests that smoking cessation may reverse SAD. In the COPDGene study, participants who quit smoking exhibited a significant decrease in Pi10 ($\Delta\text{Pi10} = -0.18$ mm, $p < 0.001$) at their 5-year follow-up visit. Therefore, smoking cessation should be recommended not only to slow the progression of COPD but also to improve SAD⁸. Another study evaluated the effect of smoking cessation on lung function parameters using spirometry and SAD, measured by conductive ventilation heterogeneity through the N2 multiple breath washout. In this study, while spirometric lung function parameters (e.g., FEV₁% predicted, FEF_{25–75%}) remained unchanged, there was a significant improvement in SAD parameters⁵⁶.

3. Pulmonary rehabilitation

Pulmonary rehabilitation for COPD is a comprehensive intervention that includes exercise training, education, and behavioral changes. It is associated with improvements in symptoms, exercise tolerance, and quality of life, as well as reductions in exacerbations and mortality⁹.

The exact mechanism by which pulmonary rehabilitation improves outcomes in COPD has not been fully elucidated. One potential benefit of pulmonary rehabilitation is its positive impact on SAD. It may help mitigate these effects by improving lung function, reducing gas trapping, and enhancing exercise tolerance. An observational study evaluating IOS parameters before and after pulmonary rehabilitation in 15 COPD patients revealed a significant improvement in reactance during inspiration (X_{insp}) with rehabilitation, measured as a change from a mean $\pm$ standard deviation of -2.35 ± 1.02 to -2.04 ± 0.85 cmH₂O $\cdot$ s $\cdot$ L⁻¹ ($p = 0.008$). Other IOS parameters did not change. Furthermore, baseline X_{mean} and the change in respiratory system reactance correlated with changes in 6-minute walk distance (6MWD) between the completion of rehabilitation and 3 months thereafter ($r_s = 0.62$, $p = 0.03$; $r_s = -0.65$, $p = 0.02$, respectively), indicating that worse ventilatory impairment predicts a loss of 6MWD⁹.

4. Dupilumab

Dupilumab, a monoclonal antibody that targets the interleukin-4 receptor alpha (IL-4R α), has shown promise

in improving SAD in patients with type 2 inflammatory airway diseases, particularly asthma⁵⁷.

By inhibiting the signaling pathways of IL-4 and IL-13, key cytokines involved in the inflammatory response, dupilumab helps reduce airway inflammation and remodeling, which are critical components of SAD. However, the evidence for potential improvements in SAD-related outcomes primarily comes from asthma studies, leaving its direct applicability to COPD uncertain. The VESTIGE study, a phase 4 trial, evaluated the impact of dupilumab on airway inflammation in moderate-to-severe asthma using spirometry, airway oscillometry, and functional respiratory imaging¹⁰. In this study, dupilumab treatment was associated with an improvement in mucus plugging and a numerical increase in the percentage change from baseline to week 24 in airway volumes (specific regional airway volumes corrected for lung volume, [s]iV_{aw}) at total lung capacity.

Although the difference was not statistically significant (least squares [LS] mean percentage change: 19.7% [standard error, 8.1] for dupilumab and -2.0% [standard error, 11.5] for placebo; $p = 0.14$), these results suggest that dupilumab may reduce regional SAD in the involved airways of asthma patients. In another study⁵⁷, the VESTIGE study group also reported that at week 24, dupilumab nominally significantly improved pre-bronchodilator FEF_{25–75%} (LS mean difference, 0.51 L/s; 95% confidence interval [CI], 0.21 to 0.80) and post-bronchodilator FEF_{25–75%} (0.50 L/s; 95% CI, 0.19 to 0.80) compared to controls. Besides, dupilumab reduced the frequency dependence of airway resistance and improved reactance area compared to placebo. Additionally, airway wall thickness, airway wall area, and air trapping decreased compared to placebo, with LS mean difference of -0.04 mm (95% CI, -0.07 to -0.01). Although these findings come from asthma studies, they suggest a potential mechanism by which targeting type 2 inflammation could affect small airway remodeling. While this data provides a strong rationale for this therapeutic approach, dedicated clinical trials are needed to determine whether the benefits observed in asthma translate to improved SAD outcomes in COPD.

Conclusion

SAD plays a crucial role in the progression of COPD. While various measurement methods—such as pulmonary function tests, IOS measures, and CT imaging parameters—are used to assess SAD, there are currently no definitive criteria for defining its presence in COPD,

highlighting the need for further research. Recent evidence suggests that extrafine-particle inhalers, smoking cessation, pulmonary rehabilitation, and biologics may help reduce SAD in COPD. Given the significant impact of SAD on the pathogenesis and prognosis of COPD, more in-depth studies are essential.

Author's Contributions

Conceptualization: Lee H. Writing - original draft preparation: all authors. Writing - review and editing: Lee H. Approval of final manuscript: all authors.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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