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Original Research Article

A REVIEW ON THE ROLE OF OSCILLOMETRY AND CICLESONIDE IN SMALL AIRWAY DISEASE MANAGEMENT IN ASTHMA

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ABSTRACT

Asthma is a chronic inflammatory respiratory disease characterized by reversible airflow obstruction, airway hyperresponsiveness, and persistent inflammation. Small airway disease (SAD) has an important role in the pathophysiology of asthma, especially in cases of severe disease or poorly controlled asthma. Dysfunction of small airways (≤2 mm in diameter) leads to the events of exacerbation, gas trapping, and impaired lung function, while detection remains poor due to the limitations of conventional pulmonary function tests. Impulse oscillometry (IOS) provides a new avenue of small airway assessment through a sensitivity measurement of airway resistance and reactance at different frequencies without patient effort, particularly in small airways. Measurements such as R5-R20, X5, and AX correlate well with the degree of asthma receptors and provide greater accuracy in diagnoses over spirometry techniques. Among the inhaled corticosteroids (ICS) used for SAD, ciclesonide is recognized for its ultrafine particle size, which ensures deep lung penetration. Similar benefits have also been observed with other extra-fine ICS such as budesonide and fluticasone when delivered via HFA propellants. Preliminary evidence suggests that ciclesonide can have a favorable effect on small airway function, exacerbation prevention, and asthma control. The review outlines the pathophysiology of SAD, the oscillometry in diagnosis, and the therapeutic role of ciclesonide, ending with the need for further studies that could finalize the way for focused therapy for the small airway in asthma.

Keywords: Asthma, Ciclesonide, Impulse oscillometry, Inhaled corticosteroids, Pulmonary function, Small airway disease..

INTRODUCTION

"Breath is the bridge which connects life to consciousness."
Thich Nhat Hanh

Asthma represents a chronic inflammatory syndrome of the airways that affects millions of people in the world with considerable morbidity and healthcare costs.[1,2] As characterized by reversible airflow obstruction of transient nature, accompanied by airway hyperreactivity as well as persistent inflammation, asthma continues to be a public health danger. The management of asthma becoming increasingly sophisticated, small airway diseases (SADs) now affect many duly diagnosed and poorly treated patients.[3]

Small airway disease has a major role in the evolution of asthma, especially in the context of severe or poorly controlled asthma. Table 1 depicts estimates of the worldwide epidemiology of asthma and the relative proportion of cases where small airway diseases are determining severity and triggering exacerbation. Baraldo et al., (2012) stated that dysfunction of small airways (≤2 mm in diameter) increases resistance in peripheral airways, leading to progressive or episodic limitation of airflow with enhanced clinical features, increased exacerbation events, and progressive reductions in lung function.[4] SAD involves airway remodeling, inflammation, and gas exchange impairments, all of which justify the importance of SAD for the early diagnosis and

management of patients for the successful control of asthma.[5]

Presently, diagnosing and keeping track of SAD in asthma is an onerous task. The traditional pulmonary function tests (PFTs), namely, spirometry, are measuring large airway function and frequently do not show small airway-related subtle changes.[6] Among these, impulse oscillometry (IOS) is an advanced diagnostic technique that can evaluate small airway impairment by measuring airway resistance and reactance at multiple, varying frequencies. Oscillometry is the most comfortable noninvasive way to assess lung function with a nonenergy effort; it has its own set of advantages in pediatric and geriatric populations in which correct spirometry execution may be difficult.[7]

Beyond diagnostics, effective management of SAD in asthma is one critical research area. Williams et al., (2018) found Ciclesonide as an inhaled corticosteroid (ICS) with a favorable deposition in lungs and negligible systemic availability, has shown promising results targeting small airway inflammation and subsequent asthma outcomes.[8] In lung activation, there is less potential for conventional ICS side effects, allowing for more significant therapeutic benefit in controlling airway inflammation in the peripheral airway.[9] The diagnosis of SAD and the therapeutic use of ciclesonide in small airways inflammation that should enable the better provision of care for asthma.[10]

Table 1: Global prevalence of asthma and the burden of small airway disease.[11,12]

Region	Asthma Prevalence (%)	SAD Involvement in Asthma Cases (%)
North America	8.4	55
Europe	7.3	50
Asia	6.1	48
Africa	5.8	52
South America	6.9	53
Australia	9.2	57

Though increased SAD awareness provides an opportunity to alleviate burden through better diagnostics and targeted therapies, further explorations into oscillometry and ciclesonide as platforms to improve asthma management are warranted for maximizing patient advantages and minimizing costs to the health system globally.[13]

Role of Small Airway Disease in Asthma

In asthma, small airway disease (SAD) is an important, usually neglected, component of disease pathology.[14] Traditionally regarded as a disorder of large airways, mounting evidence suggests that small airway dysfunction plays an important role in the progression and control of the disease.[15] The small airways (bronchioles with a diameter <2 mm) are extremely prone to inflammation and structural changes, leading to airflow limitation, gas trapping, and increased airway resistance.[16]

Pathophysiology and Clinical Consequences of Small Airway Disease in Asthma: The initiation of small airway disease (SAD) in asthma arises from a mix of airway inflammation, remodeling, and obstruction. Inflammatory pathways involving eosinophils, neutrophils, and mast cells trigger airway wall thickening and mucus hypersecretion that led to luminal narrowing.[17] Chronic inflammation causes structural remodeling, characterized by subepithelial fibrosis, smooth muscle hypertrophy, and deposition of extracellular matrix changes that progressively diminish compliance in the airway and give rise to fixed airflow obstruction, especially in patients with severe or uncontrolled asthma.[18]

Lu et al., (2025) found that disrupted surfactant function and increased closure of the airways are other important microbial characteristics of SAD.[19] With the breakdown of surfactant integrity, small airways become more collapsible; hence, these are prematurely closed during expiration, leading to gas trapping [Table 2]. This leads to an increase in residual lung volume and dynamic hyperinflation, worsening respiratory symptoms and reduced exercise capacity.[20]

Table 2: Key Physiological Changes Observed in Small Airway Dysfunction in Asthma.[21,22]

Physiological Parameter	Small Airway Dysfunction in Asthma
Airway inflammation	Predominantly eosinophilic/neutrophilic
Airway remodeling	Fibrosis, smooth muscle hypertrophy, epithelial damage
Airway closure	Increased due to surfactant dysfunction
Gas trapping	Present, leading to hyperinflation and ventilation heterogeneity
Response to bronchodilators	Often reduced compared to large airways
Diagnostic tools	Impulse oscillometry, multiple breath washout, HRCT

Involvement of small airways in asthma has serious ramifications for disease management and exacerbation. Patients affected by SAD are often symptomatic most of the time, have nocturnal asthma, and complain of dyspnea upon exertion despite maximum inhaled therapy.[23] Associated small airway dysfunction may also lead to a poor response to bronchodilators and corticosteroids and may require alternative therapeutic considerations.[24] Barkas et al., (2015) studied that SAD has

additionally been shown to be associated with increased airway hyper-responsiveness and increased risk for severe exacerbations, indicating SAD's relevance in clinical decision-making regarding disease management.[25]

Differences Between Large and Small Airway Dysfunction: Asthma entails pathological changes in large and small airways, but their respective contributions to disease manifestation are disparate. Bronchospasm, mucus plugging, and reversible airflow obstruction, with the last one being commonly assessed by spirometry techniques,[26] typify the pathophysiological conditions associated with large airway involvement. On the contrary, small airway dysfunction pertains to more insidious alterations that involve gas trapping and an uneven clear-cutting of ventilation that are elusive to conventional pulmonary function tests. Rather, further assessment of small airway function can benefit from advanced diagnostic techniques, such as impulse oscillometry, multiple breath washouts, and high-resolution computed tomography (HRCT).[27]

SAD is a major challenge for asthma therapy because it begins insidiously and often remains unsuspected. Yii et al., (2018) investigated that therapeutic measures targeting small airway dysfunction could potentially improve symptom control or overall disease outcomes.[28] Thus, understanding its pathophysiology, clinical impact, and diagnostic problems is fundamental to providers optimizing their strategies for best asthma care.[29,30]

Role of Oscillometry in Small Airway Disease

Oscillometry as an Advanced Pulmonary Function Test and its Principles: Oscillometry, which is evolving as a sensitive indicator of small airway function while circumventing the drawbacks of conventional spirometry, cannot be categorized as a pulmonary function test as it stands. Oscillometry enhances spirometry by including passive breathing rather than requiring active patient effort, making it particularly beneficial for children, the elderly, and those with significant airway blockage.[31] According to Ziora et al., (2024) a significant interest in oscillometry has emerged among those focused on the increasing acknowledgment of small airway disease (SAD) in asthma, particularly for diagnosis and monitoring.[32]

Oscillometry is based on the Forced Oscillation Technique (FOT) which uses external pressure waves at varying frequencies applied to tidal breathing to measure respiratory impedance.[33] Impulse Oscillometry (IOS) is a refined version of FOT that uses brief pulses of sound waves to analyze airway resistance and reactance at different oscillatory frequencies. Both techniques provide information on airway mechanics, differentiating between large and small airway involvement.[34] Key parameters include resistance at 5 Hz (R5) and 20 Hz (R20), reactance at 5 Hz (X5), and area of reactance (AX), which are particularly useful for assessing peripheral airway dysfunction,[35] [Figure 1].

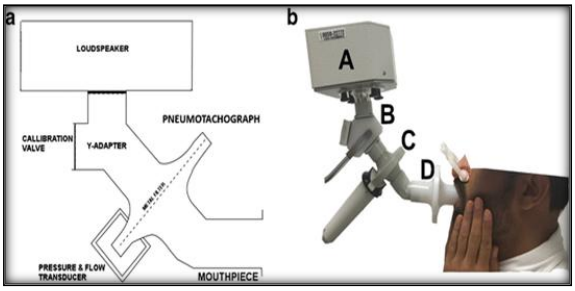

Figure 1: Schematic representation of an oscillometry test setup.[36]

Clinical Sensitivity and Evidence Supporting Oscillometry in Asthma Management: Oscillometry has demonstrated superior sensitivity in detecting early-stage SAD before spirometry reveals abnormalities. Traditional spirometry markers, such as forced expiratory volume in one second (FEV1), often remain within normal limits even in the presence of significant small airway involvement.[37] In contrast, increased R5-R20 (difference between total and proximal airway resistance) and more negative X5 values indicate peripheral airway impairment, highlighting the utility of oscillometry in early diagnosis and disease monitoring.[38]

Several studies have validated the clinical relevance of oscillometry in asthma. Research indicates that increased R5 and AX values correlate with worse asthma control, more frequent exacerbations, and greater symptom burden,[39] [Table 3]. Furthermore, oscillometry has been shown to detect lung function impairment in asymptomatic patients with a history of asthma, suggesting its role in proactive disease management.[40]

Table 3: Comparison of Oscillometry Parameters (R5, R20, X5, AX) with Spirometry Parameters.[41,42]

Parameter	Measurement	Physiological Significance	Role in Small Airway Disease
R5 (Resistance at 5 Hz)	Total airway resistance	Increased airway narrowing	Elevated in SAD,reflecting distal obstruction
R20 (Resistance at 20 Hz)	Proximal airway resistance	Represents central airway function	Usually unchanged in SAD, distinguishing large airway contribution
R5-R20	Difference between total and proximal resistance	Marker of small airway involvement	Higher values indicate significant SAD presence
X5 (Reactance at 5 Hz)	Lung elasticity and compliance	More negative values indicate airway closure and hyperinflation	Decreased in SAD due to increased small airway stiffness
AX (Area of Reactance)	Integrated reactance measure	Reflects overall lung impedance	Elevated in SAD, correlating with disease severity

FEV1 (Forced Expiratory Volume in 1 sec, Spirometry)	Volume exhaled in one second	Main parameters in spirometry	May remain normal despite SAD progression

Despite its advantages, oscillometry is not without limitations. The technique requires specialized equipment, and normative values are not yet universally standardized across populations.[43] Additionally, its interpretation is still evolving, necessitating further research to establish clear diagnostic thresholds. Future advancements may include integration with artificial intelligence for automated interpretation and its incorporation into routine asthma management guidelines.[44]

Ciclesonide as a Targeted Therapy for Small Airway Disease in Asthma

Effective management of small airway disease (SAD) in asthma requires deep-lung deposition of anti-inflammatory agents to counteract distal airway inflammation, remodeling, and obstruction.[45] Ciclesonide, an ultrafine-particle ICS, offers enhanced peripheral lung delivery and is one of several corticosteroids—including extra-fine budesonide and fluticasone—that have shown efficacy in managing small airway inflammation in asthma.[46]

Ciclesonide is a prodrug that undergoes pulmonary activation into its pharmacologically active metabolite, des-ciclesonide, upon inhalation. Peng et al, (2025) stated that Due to ultra-fine particle size (~1.1 µm) of Ciclesonide, it achieves superior small airway penetration compared to conventional ICS, which predominantly deposit in the central bronchi.[47] This enhanced lung deposition ensures a more uniform anti-inflammatory effect, reducing airway hyperresponsiveness and improving overall asthma control,[48] [Figure 2].

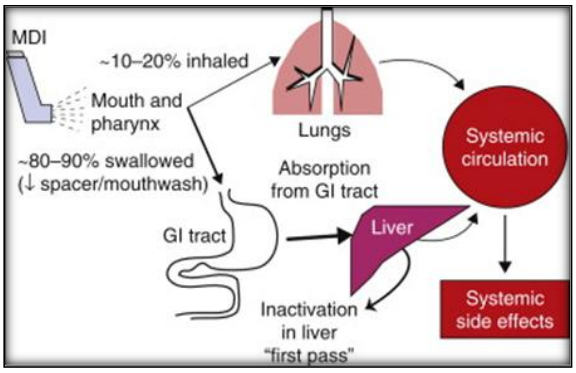

Figure 2: Activation and Distribution Pathway of Ciclesonide in the Lungs and Systemic Circulation.[49]

Clinical Efficacy and Comparative Benefits: Several inhaled corticosteroids (ICS) with extra-fine particle formulations have demonstrated therapeutic potential in managing small airway disease (SAD) in asthma. These include ciclesonide, fluticasone, budesonide, and beclomethasone, which vary in their physicochemical properties, pulmonary deposition, and systemic absorption profiles [Table 4]. When delivered via hydrofluoroalkane (HFA) propellants, these formulations can achieve improved deposition in the peripheral airways—an essential criterion for effective SAD control.[50–52]

Ciclesonide, a prodrug activated locally in the lungs, has been reported to provide enhanced penetration into the small airways due to its ultra-fine particle size (~1.1 µm) and favorable aerodynamic properties.[50,51,53] Clinical trials have shown that patients treated with ciclesonide experience significant reductions in small airway resistance (R5-R20), reactance (AX), and gas trapping, with improved asthma control and decreased exacerbation frequency.[50,55] As shown in comparative studies, ciclesonide is associated with a ~45% reduction in exacerbation rates, outperforming fluticasone (30%) and budesonide (35%) in some trials.[56]

However, these benefits are not exclusive to ciclesonide. Fluticasone and budesonide, when delivered as extra-fine formulations via HFA inhalers, have also shown moderate improvements in small airway function and clinical outcomes. Their particle sizes (~2.2–2.5 µm) allow partial penetration into distal bronchioles, with small airway deposition rates of approximately 40–45%.[52,54] Although beclomethasone shows lower small airway deposition (~30%), it still plays a therapeutic role depending on the formulation used.

In terms of safety, ciclesonide demonstrates low systemic bioavailability (<1%), reducing the risk of corticosteroid-related adverse effects such as adrenal suppression or osteoporosis.[56,53] Its low oropharyngeal deposition minimizes local side effects, including dysphonia and oral candidiasis. The convenience of once-daily dosing also enhances patient adherence, making it a practical option in long-term asthma care.[54]

While ciclesonide may provide pharmacokinetic advantages, all ICS listed have demonstrated efficacy when used with appropriate delivery techniques and formulations. Comparative evaluations (Table 4) underscore the importance of individualizing therapy based on disease phenotype, inhaler technique, and patient-specific factors.

Table 4: Comparative Efficacy of Ciclesonide vs. Other ICS in Small Airway Disease

Parameter	Ciclesonide	Fluticasone	Budesonide	Beclomethasone	References
Particle Size (µm)	1.1	2.5	2.2	3.0	[52]
Small Airway Deposition (%)	High (~60%)	Moderate (~40%)	Moderate (~45%)	Low (~30%)	[54]
Reduction in R5-R20 (Small Airway Resistance)	Significant	Moderate	Moderate	Mild	[55]
Reduction in Exacerbations (%)	45%	30%	35%	25%	[56]
Systemic Bioavailability (%)	Low (<1%)	Moderate	Moderate	High	[57]

Integrating Oscillometry and Ciclesonide for Optimized Small Airway Disease Management

Integrating oscillometry for diagnosis and ciclesonide as an agent for therapy, it provides a unique and excellent approach towards the management of SAD in asthma.[56] Meanwhile, older spirometry may fail at times to pick up any signs of early small airway dysfunction, but oscillometry helps detect the peripheral airways abnormalities easily. It makes it possible for clinical intervention to be at an earlier point by identifying subtle changes in the airway resistance and reactance upon application. Ciclesonide causing site-specific activation within the lungs complements this added detail in diagnostic precision through its targeting of inflammation in the small airways.[57] This may constitute proactive management, which may include reducing the number of exacerbations and improving long-term outcomes.[58]

Huang et al., (2022) studied that clinical evidence indicates that oscillometry markers, such as the difference from total to central airway resistance (R5-R20) and area reactance (AX), correlate with the extent of small airway impairment.[59] They also allow specialty almost tailored therapy. Ciclesonide has also been shown to be more efficacious in improving small airway function due to its high pulmonary deposition and low systemic bioavailability.[60] Given treatment response monitored using ciclesonide dosage under oscillometry, continuous dynamic modification would thus be possible ensuring disease control with less side effects. An evidence-based and individualized treatment strategy is a major improvement compared to the traditional asthma management strategy.[61]

Bringing this approach to practice will require integrating oscillometry into routine pulmonary function testing, as well as harmonizing ciclesonide therapy with results from oscillometry assessment.[62] Continuous monitoring of small airway function could lead to earlier treatment modifications as the disease deteriorates. Then, the efficacy profile of ciclesonide enhances adherence as the most important obstacle to inhaled corticosteroid use is solved.[63] However, as technology continues to improve the availability of oscillometry, even for home-based monitoring, the future of management for asthma is apparently shaping up to be more personalized and less dependent on actual data.[64]

Limitations and Challenges

Diagnostic Challenges: Existing diagnostic tools, including spirometry and oscillometry, lack universally accepted reference values and standardization for small airway disease (SAD) detection. The variability in cut-off values and interpretation criteria makes it difficult to implement these techniques uniformly across clinical settings.[65]

Limited Longitudinal Data: There is a scarcity of long-term studies comparing different inhaled corticosteroids (ICS), including ciclesonide, specifically targeting small airways. Most available studies focus on short-term outcomes, leaving gaps in understanding the sustained benefits and potential risks of prolonged therapy.[66]

Variability in Clinical Response: Patient responses to SAD-targeted therapies vary due to factors such as genetic predisposition, environmental influences, and differences in inhalation techniques. This variability necessitates the development of precision medicine approaches that are yet to be fully established.[67]

Integration in Clinical Practice: Despite its sensitivity, oscillometry is not widely integrated into routine clinical practice due to limited physician familiarity, lack of standardized training, and the absence of strong guideline recommendations supporting its routine use. This restricts its adoption as a first-line diagnostic tool for SAD.[68]

Lack of Real-World Evidence: Most studies on SAD and its management rely on controlled trials, with insufficient large-scale real-world data to validate findings across diverse populations. Damoiseaux et al., (2024) found that factors such as adherence, real-life inhalation techniques, and treatment adjustments over time remain inadequately studied.[69]

Future Perspectives

Improvement of diagnostics and therapeutics for asthma will be the focus of future development in the management of small airway disease (SAD), aiming to enhance its management. Technologies like functional respiratory imaging (FRI) and multiple-breath washout (MBW) are at an early stage of investigation in their ability to assess small airway dysfunction as part of therapy development. Artificial intelligence (AI)-driven analysis of oscillometry data is likely to improve diagnostic accuracy and early detection along with the advancements in methodologies in the management of asthma when it has been finally adopted for application in successful use. Ultra-fine particle inhaled corticosteroids (ICS) with favorable deposition in the small airways are gaining attention, along with biologic therapeutics specific against inflammatory pathways involved in SAD. Nanoparticle systems and lipid formulations for improved delivery within distal airways are also under study. Personalized medicine that incorporates biomarkers and genetic profiling will help tailor treatment strategies for individual patients. In the future, these approaches should be validated through large-scale, real-world studies, which will eventually integrate them into routine clinical practice to impact asthma control in the long run and improve patient outcomes.

CONCLUSION

This review underscores the critical role of small airway disease (SAD) in asthma pathophysiology and its impact on disease progression and control. Advances in oscillometry have provided a more sensitive and reliable means of detecting small airway dysfunction, offering an alternative to

traditional spirometry for early diagnosis and monitoring. The therapeutic potential of ciclesonide, with its targeted activation in the small airways, further reinforces the importance of precision medicine in asthma management. Integrating oscillometry-driven diagnostics with ciclesonide-based treatment strategies presents a promising approach to optimizing asthma control. However, addressing current research gaps, refining diagnostic methodologies, and exploring innovative therapeutic options remain crucial to improving patient outcomes. A multidisciplinary approach focusing on early detection, personalized treatment, and continued research is essential to advancing the management of SAD in asthma.

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