



Small Airways: The “Silent Zone” of 2021 GINA Report?

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Asthma is a chronic disease, affecting approximately 350 million people worldwide. Inflammation and remodeling in asthma involve the large airways, and it is now widely accepted that the small airways (those with an internal diameter <2 mm) are involved in the pathogenesis of asthma and are the major determinant of airflow obstruction in this disease. From a clinical perspective, small airways dysfunction (SAD) is associated with more severe bronchial hyperresponsiveness, worse asthma control and more exacerbations. Unlike the GOLD guidelines which, in their definition, identify COPD as a disease of the small airways, the Global Initiative for Asthma (GINA) guidelines do not refer to the prevalence and role of SAD in asthmatic patients. This decision seems surprising, given the growing body of compelling evidence accumulating pointing out the high prevalence of SAD in asthmatic patients and the importance of SAD in poor asthma control. Furthermore, and remarkably, SAD appears to possess the characteristics of a treatable pulmonary trait, making it certainly appealing for asthma control optimization and exacerbation rate reduction. In this mini-review article, we address the most recent evidence on the role of SAD on asthma control and critically review the possible inclusion of SAD among treatable pulmonary traits in international guidelines on asthma.

Keywords: small airways dysfunction, GINA report, bronchial asthma, asthma control, recommendations

INTRODUCTION

Asthma is a chronic condition affecting the airways, characterized by inflammatory infiltration and remodeling of the bronchial tree (1). Recently, small airways have been recognized as a major site of airflow limitation in both asthma and chronic obstructive pulmonary disease (2–5). According to the current Global Initiative for Asthma (GINA) guidelines, spirometry remains the method of choice in evaluating the respiratory function (6). However, conventional spirometry reflects mostly the variability and/or the reversibility of airway obstruction and is unable to sensitively evaluate small airways, becoming abnormal only when approximately 75% of small airways are obstructed (7). In recent years more specialized tests have been developed, which may better assess small-airways dysfunction (SAD). These tests are now moving from clinical research laboratories

TABLE 1 | Available techniques for the assessment of bronchial airways by size (small vs. large airways).

Method	Small airway function	Large airway function
Spirometry	FEF25–75%, FVC, FVC/SVC	FEV1, FEV1/FVC
Impulse oscillometry (IOS)	R5–R20, X5, $\Delta X5$ in-esp, AX, Fres	R20
Single breath nitrogen washout (SBNW) or Multiple breath nitrogen washout (MBNW) test	Slope phase III, CV, CC, Sacin, Sccond, LCI	
Body plethysmography	RV, RV/TLC	
High resolution computerized tomography (HRCT)	Air trapping, airway wall thickness	Airway wall thickness
Nuclear medicine (Scintigraphy, SPECT, PET)	Regional ventilation defects	
^3He -MRI	Non-ventilated lung volume	
Bronchoscopy	Transbronchial biopsy, BAL	Endobronchial biopsy
Sputum induction	Late phase sputum	Early phase sputum

AX, reactance area; Fres, resonant frequency; LCI, Lung Clearance Index; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; R5, resistance at 5 Hz; R20, resistance at 20 Hz; RV, residual volume; Sacin and Sccond, acinar and conductive airways ventilation heterogeneity; TLC, total lung capacity.

TABLE 2 | Prevalence data of Impulse Oscillometry-defined small airways dysfunction (SAD) in recent studies.

References	Tool of assessment	Measure	Prevalence of SAD
Anderson et al. (24)	Impulse oscillometry	R5-R20	BTS 2 65% BTS 3 64% BTS4 70%
Postma et al. (18)	Impulse oscillometry	R5-R20	42%
Cottini et al. (19, 22)	Impulse oscillometry	R5-R20	62% GINA 2 58% GINA 3 61% GINA 4 63% GINA 5 78%
Abdo et al. (20)	Impulse oscillometry	R5-R20	63% GINA 2–3 53% GINA 4–5 75%
Alfieri et al. (25)	Impulse oscillometry	R5-R20	48%
Manoharan et al. (26)	Impulse oscillometry	R5-R20	42%
Berti et al. (23)	Impulse oscillometry	R5-R20	84% (Elderly asthmatic patients)

R5, resistance at 5 Hz; R20, resistance at 20 Hz; R5-R20, the difference between R5 and R20.

into routine clinical practice (8). **Table 1** summarizes the techniques available for the assessment of small airways disease.

In particular, impulse oscillometry (IOS) is an effort-independent modality based on the well-described forced oscillation technique (FOT) (9, 10) and has emerged as a method to measure pulmonary function in both children and adults (11, 12).

We previously reviewed the prevalence and negative impact of SAD on asthma control, without addressing the position of current international guidelines on the role of SAD in asthma (13). In recent years, several original studies and systematic reviews confirmed that SAD is associated with, among others, greater bronchial hyper-responsiveness, worse asthma control and severity, more nocturnal and exercise-induced symptoms, and a higher number of exacerbations (14–16). Nevertheless, unlike the GOLD guidelines (17) which, in their definition, identify COPD as a disease of the small airways, the Global Initiative for Asthma (GINA) guidelines do not refer to the prevalence and role of SAD in asthmatic patients (6). This

decision seems surprising, given the growing body of compelling evidence accumulating pointing out the high prevalence of SAD in asthmatic patients and the importance of SAD in poor asthma control. Furthermore, and remarkably, SAD appears to possess the characteristics of a treatable pulmonary trait, making it certainly appealing for asthma control optimization and exacerbation rate reduction.

In this mini-review article, we address the most recent evidence on the role of SAD on asthma control and critically review the possible inclusion of SAD among treatable lung traits in international guidelines on asthma.

PREVALENCE OF SAD IN ASTHMATIC PATIENTS

Overall, the prevalence of SAD in patients with asthma is around 50–60% (18–21). In the ATLANTIS study, the largest multinational study showing the contribution of SAD to asthma

severity, 91% of asthmatics was found to have SAD, defined as any abnormal physiological variable, and SAD was strongly present across all GINA severity stages (18). Several other cohort studies showed the prevalence of SAD as defined by impulse oscillometry (IOS) (19, 20, 22, 23). We found (19, 22) in a cohort of 400 community-managed patients with physician-diagnosed asthma an overall prevalence of SAD of 62% in all the GINA step classes (step 2 58.3%; step 3 60.9%; step 4 63.3%; step 5 78.6%). Abdo et al. (20) confirmed these data, finding an IOS-defined prevalence of SAD of 63% in 268 asthma patients, with a higher prevalence of SAD in higher severity GINA stages, i.e., steps 4–5. **Table 2** shows the prevalence data of IOS-defined SAD in studies from recent years.

ASSOCIATION OF SAD WITH SPECIFIC ASTHMA PHENOTYPES AND POOR ASTHMA CONTROL

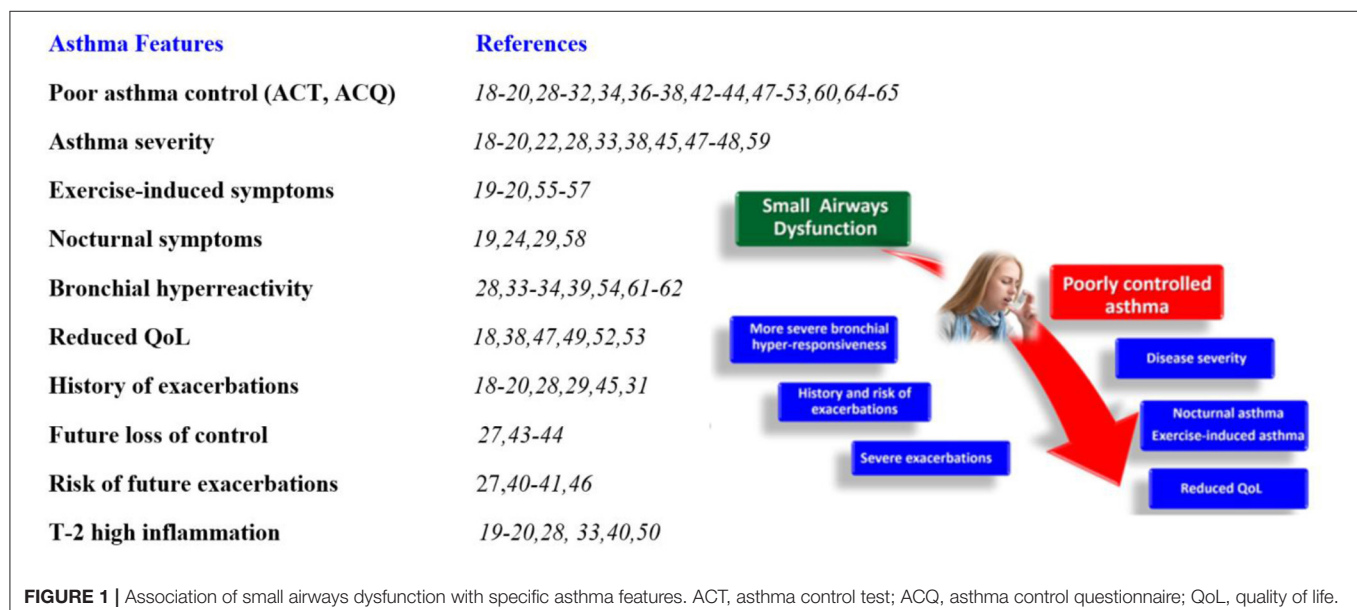
Regardless of its prevalence in asthma, identifying SAD is of particular importance since it is clearly associated with specific clinical features and worse asthma control (19). Ignoring these key aspects would reduce the chances of maintaining asthma control.

SAD was previously linked to some clinical phenotypes of patients, i.e., active smokers, elderly patients with long duration of asthma and presence of fixed airflow obstruction, patients with nocturnal and exercise-induced symptoms, severe/uncontrolled asthma (13–16). The limit of most of the available studies is that they analyze the association of single features with SAD, instead of comprehensively address multiple asthma features associated with SAD. In more recent studies, multivariable analyses, classification tree analysis and structural equation modeling indicated that exercise-induced symptoms, overweight/obesity, asthma-related nocturnal symptoms, older age, smoking, and T2 inflammation are strong independent predictors of SAD

in patients with community-managed asthma (19, 20, 27). Furthermore, emerging evidence shows that small conducting airways are an important site of disease also in pediatric asthma and are affected from an early stage of the disease (28). These associations may be of help in distinguishing subjects with SAD among patients with asthma, especially when IOS cannot be performed.

Spirometry is the most commonly used procedure to assess pulmonary function and GINA Guidelines and the Expert Panel Report-3 Guidelines for the Diagnosis and Management of Asthma both stated that pulmonary function measures are weakly correlated with asthma symptoms (6, 29). This statement refers to the “standard” pulmonary function test, unable to sensitively evaluate small airways, despite a growing body of literature supporting the correlation of SAD with asthma features (19). For instance, IOS-measured SAD has been shown to be present in virtually all patients with uncontrolled asthma vs. one third with well-controlled asthma, and to correlate (i.e., as assessed by the value of the difference in the resistance at 5 and 20 Hz [R5-R20], the IOS physiological marker that most strongly correlates with SAD) with worst asthma control and higher GINA step categories (19). Of note, a very weak inverse correlation between the spirometry value FEF25-75 and R5-R20 has been observed (19).

Similarly, Abdo et al. (20) recently showed that small airway dysfunction is strongly associated with poor control of the disease. In the ATLANTIS study (17), a SAD score (by both impulse oscillometry and spirometry) was significantly associated with asthma control, history of exacerbation, and disease severity. Kraft and colleagues very recently published the longitudinal one-year follow-up data of the ATLANTIS study, which showed that SAD (as measured by IOS, lung volumes, MBNW, and FEF25-75) was longitudinally associated with asthma control, exacerbations, and quality of life (30). In all of these studies, asthma control was



intimately related to SAD and clinical phenotypes associated with SAD, and notably the IOS has better associations than spirometry, supporting the importance of using IOS and more modern tools in addition to spirometry. Studies supporting the relationship between asthma control and severity, asthma features, and SAD (18–28, 30–63) are summarized in **Figure 1**.

SAD IS A TREATABLE PULMONARY TRAIT

The term “precision medicine” usually refers to an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person (64). A new personalized approach, termed the “treatable traits” approach, has been suggested to address the limitations of the existing treatment strategies. IOS may be of great help to better characterize SAD as a “pulmonary treatable trait,” leading to a more targeted asthma management and more individualized patient care (64, 65). The importance of the peripheral airways in the pathophysiology and clinical manifestations of asthma makes them the intuitive target for long-term pharmacologic approaches (66, 67), i.e., for extra-fine formulations of bronchodilators and inhaled steroids (the mainstay treatment for COPD and asthma) and biologicals. Technological progress has allowed the development of new delivery systems and drug formulations designed to increase drug deposition and improve therapeutic efficiency, effectiveness, and drug safety (68–71). In real-life studies (72–75), extra-fine formulations (ICS and ICS/LABA) have shown significantly higher odds of achieving asthma control, even in small airway clinical phenotypes (76–78). Several real-life studies found an association between inhaled extra-fine ICS and ICS/LABA vs. standard particles size ICS or ICS/LABA and a reduction in airway resistance (18, 24).

Very intriguing, SAD may be modified by biologics; indeed, biologic therapies result not only in improvements in asthma

control, OCS use, and exacerbation frequency but also in small airways function (54, 79–85).

CONCLUSIONS

Despite the availability of effective therapies, a substantial proportion of asthmatics remain poorly controlled in real life. Given the clinical impact of SAD on asthma control, we believe that SAD should be actively searched as part of the daily management of patients with asthma. Since asthma control has been extensively proved to be linked with SAD, and SAD to be better assessed with IOS than conventional spirometry, we truly believe that IOS should complement spirometry as part of the routine diagnostic work-up of asthma patients in a *real-life* clinic setting. IOS-defined SAD can assist the clinician in understanding the risk of an asthma exacerbation in their patients along with routinely collected information on treatment intensity and asthma control. In clinical routine practice, the identification of SAD during the diagnostic work-up should influence clinicians on the treatment choice. Therefore, IOS may be of great help to better characterize SAD as a “pulmonary treatable trait,” leading to a more targeted asthma management and individualized patient care. Based on the above arguments, there appears to be an urgent need to implement the GINA recommendations with SAD, which is shown to be present in the majority of asthmatic patients and associated with worse disease control, helping to guide the therapeutic approach.

AUTHOR CONTRIBUTIONS

MC, CL, and GP contributed to conception and design of the study. AB organized the database. MC, CL, GP, PC, and ML wrote the first draft of the manuscript. EH wrote sections of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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