



Small-airway dysfunction in paediatric asthma

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Purpose of review

Asthma is a chronic inflammatory airway disorder that can involve the entire bronchial tree. Increasing evidence shows that ventilation heterogeneity and small airway dysfunction are relevant factors in the pathogenesis of asthma and represent a hallmark in adults with persistent asthma. Little is known about the contribution of peripheral airway impairment in paediatric asthma, mainly due to the inaccessibility to evaluation by noninvasive techniques, which have only been widely available in recent years.

Recent findings

Emerging evidence suggests that small airways are affected from the early stages of the disease in childhood-onset asthma. Conventional lung function measurement, using spirometry, is unable to sensitively evaluate small airway function and may become abnormal only once there is a significant burden of disease. Recent studies suggest that chronic inflammation and dysfunction in the small airways, as detected with new advanced techniques, are risk factors for asthma persistence, asthma severity, worse asthma control and loss of pulmonary function with age, both in adults and children. Knowing the extent of central and peripheral airway involvement is clinically relevant to achieve asthma control, reduce bronchial hyper-responsiveness and monitor response to asthma treatment.

Summary

This review outlines the recent evidence on the role of small airway dysfunction in paediatric asthma development and control, and addresses how the use of new diagnostic techniques available in outpatient clinical settings, namely impulse oscillometry and multiple breath washout, could help in the early detection of small airway impairment in children with preschool wheezing and school-age asthma and potentially guide asthma treatment.

Keywords

asthma, children, impulse oscillometry, multiple breath washout, small airway dysfunction, small airways

INTRODUCTION

Asthma is the most common chronic disease in children and one of the most frequent chronic conditions throughout all ages [1,2]. Even if asthma affects the entire bronchial tree, peripheral airways have been recognized as the major site of airflow limitation in obstructive pulmonary diseases [3,4].

Disease severity in asthma is commonly assessed using spirometry in conjunction with symptom control and exacerbation frequency. Spirometry parameters routinely used to classify asthma status, the forced expiratory volume in 1 s (FEV₁) and the FEV₁/forced vital capacity (FEV₁/FVC) ratio, generally correlate poorly with asthma severity in children [5]. Most children with asthma have normal or near-normal FEV₁ ($\geq 80\%$ of predicted), irrespective of disease severity [6,7]. In addition, FEV₁ and FEV₁/FVC, which mainly reflect large airway function, are unable to sensitively evaluate small airways and may become abnormal only once there is a significant burden of disease [8].

Emerging evidence suggests that small airway dysfunction (SAD) can occur early, before clinical signs and spirometric abnormalities are evident, particularly the reduction in FEV₁ [9]. In recent years, new advanced techniques have been available in clinical practice, which can be more sensitive at

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KEY POINTS

- Small airway dysfunction (SAD) in asthma has been largely unrecognized due to the rather low sensitivity of conventional measures of lung function, such as spirometry.
- SAD can occur early, before symptoms and spirometric abnormalities (FEV₁) are detected, and can influence asthma control.
- New lung function tests, such as impulse oscillometry and multiple breath washout, offer in-office diagnostic tools that can detect SAD even in preschool children, predict loss of asthma control and help guide asthma treatment.
- Impulse oscillometry should complement spirometry as part of the diagnostic workup and management of children with asthma in real-life outpatient settings.
- Implementing access to noninvasive, practical techniques sensitive to small airway function and inflammation is of high priority to personalize asthma treatment strategies.

identifying SAD in asthmatic adults and children than spirometry.

Herein, we review the recent evidence supporting the influence of SAD in asthma development and control in children. We also highlight how the identification of SAD by new techniques different from spirometry and currently available in outpatient settings, namely impulse oscillometry (IOS) and multiple breath washout (MBW), could potentially be useful to guide asthma treatment in children.

SMALL AIRWAY DYSFUNCTION

Small airways are defined as those with an internal diameter of less than 2 mm, which do not contain cartilage in their walls and extend from the eighth generation airways to the periphery of the bronchial tree [10]. Small airways have long been considered the lung’s ‘quiet zone’, because under normal conditions, their contribution to airway resistance is minimal [11].

Most of the characteristic structural changes in asthma have been detected in the large airways, but

the role of SAD in asthma is increasingly being recognized [12]. Small airway involvement has been described in lung tissues of asthmatic individuals following surgical resection, biopsy and autopsy [13]. Some data suggest more extensive inflammation and remodelling in small airways than in large airways [14]. In adults, SAD correlates with greater bronchial hyper-responsiveness (BHR), worse asthma control and more exacerbations [15²²,16²²]. Similarly, in children, SAD is associated with airway inflammation and BHR [17–19], the risk for asthma development [20,21], exacerbation [22], loss of control [23,24,25²²], severity [26], steroid-resistant disease [27²²], exercise-induced bronchoconstriction [28] and loss of pulmonary function with age [29].

Despite the clinical relevance of SAD in asthma, it has been largely unrecognized until recent years, because of the rather inaccessibility to evaluation by conventional measures of lung function, such as spirometry and plethysmography [30]. New specialized tests that are currently available in-office can better differentiate SAD from large airway obstruction with respect to spirometry (Table 1). However, none of these tests is universally and directly representative of small airway function [30].

SMALL AIRWAY DYSFUNCTION ASSESSMENT IN CHILDREN

Conventional spirometry

According to the international asthma guidelines, spirometry remains the method of choice in evaluating lung function [31]. However, spirometry mostly reflects the variability of large airway obstruction and does not sensitively evaluate small airways [8,32,33]. It is estimated that ~75% of the small airways need to be obstructed before these changes can be detected by conventional spirometry parameters (FEV₁ and FEV₁/FVC) [8]. In addition, spirometry cannot be reliably performed before school-age years in most cases, due to the child’s limited ability to provide reproducible forced expiratory manoeuvres.

The mean forced expiratory flow between 25 and 75% of FVC (FEF_{25–75%}) is the traditional index of spirometry to assess peripheral airway obstruction,

Table 1. Noninvasive in-office available techniques for the assessment of large vs. small airway function

Technique	Large airway function	Small airway function
Spirometry	FEV ₁ , FEV ₁ /FVC	FEF _{25–75%} , FVC
Impulse oscillometry	R20	R5–R20, X5, AX, Fres
Multiple breath washout		LCI, S _{cond} , S _{acin}

Table 2. How to interpret impulse oscillometry results when suspecting a small airway dysfunction [38,39,41**]

Commercially available reference values in IOS are based principally on height, whereas most studies suggest that sex, age and ethnicity have no effect.

Baseline values for R5, R20 and X5 that are greater than 150% of predicted should be considered abnormal.

There is still a need to establish baseline reference values for R5–R20 and AX.

R5–R20 baseline value is considered elevated and suggestive of peripheral airway obstruction, if it is greater than 30% in children.

Current recommended thresholds for defining a positive bronchodilator response (BDR), for both adults and children, are a 40% decrease in R5, 50% increase in X5 and 80% decrease in AX.

There is still a need to establish reference values for positive bronchodilator response for R5–R20 and AX. Previous studies have reported great variability in defining the BDR in AX able to identify asthma, ranging from 29.1% in children to over 40% in adults.

which has been described as less effort-dependent than FEV₁ [34,35]. A low FEF_{25–75%} is associated with increased asthma severity and may represent a risk factor for the persistence of symptoms in children with asthma [26].

Although FEF_{25–75%} may be a more sensitive marker of small and medium airway obstruction than FEV₁, it is not specific to identify airflow limitation in small airways [36] and its higher coefficient of variability may limit its ability to detect poor asthma control [37]. In addition, the relationship between FEF_{25–75%} and asthma symptoms, as well as the risk of exacerbations, is not independent of the association with FEV₁. Indeed, FEF_{25–75%} seems more likely to represent the status of both central and peripheral airways, and its utility independently of FEV₁ or FEV₁/FVC is still debated [24,38].

Impulse oscillometry

IOS is a rapid, noninvasive lung function test that uses the forced oscillation technique to measure airway resistance (R), which detects central and peripheral airflow limitations, and reactance (X), which reflects the elastic recoil of peripheral airways [39,40]. IOS measurements are performed during normal tidal breathing, requiring only passive cooperation, which makes this technique of great utility for all individuals who are unable to perform spirometry, including young children from 3 years of age.

IOS measures R and X to differing frequencies, with low-frequency signals (5 Hz) penetrating the small airways, whereas high-frequency signals (20 Hz) only reach the proximal airways. Peripheral airway obstruction results in greater R at 5 Hz (R5) than at 20 Hz (R20), also expressed as an increase in the differential change R5–R20; reduction of X at 5 Hz (X5) due to the hyperinflation and loss of elastic recoil, which is normally greatest in the small airways; and increase of the ‘area of reactance’ (AX), due to lower (more negative) values for X5 and higher resonant frequency (Fres; corresponding to the frequency at which, in normal conditions, the

elastic forces are equal to the inertial properties of the small airways) (Table 2).

The recommended technical standards for oscillometry measurement have recently been published [41**] to guide the manufacturers of the different commercially available oscillometry devices, the comparability of which remains unclear [42].

Multiple breath washout

The MBW technique assesses ventilation distribution inhomogeneity by measuring inert gas clearance over a series of normal tidal breaths [43*]. Similar to IOS, the MBW is an effort-independent technique making it feasible also in early childhood. In contrast to IOS, MBW is a time-consuming test, which takes around 20 min in healthy children.

The tracer gases used include sulphur hexafluoride or helium, which must first be inhaled. A common alternative in children is the MBW delivering oxygen and recording the washout of nitrogen, which is normally present in the lungs. Currently, washout is considered complete when the concentration of the tracer gas has dropped to 1/40 of the starting concentration. After complete washout, different indices of ventilation inhomogeneity can be detected. The lung clearance index (LCI) is considered the most robust and represents a measure of global ventilation unevenness that also reflects SAD. The other two indices of distal airway function are S_{cond} and S_{acin}, which assess ventilation inhomogeneity in the conducting and acinar airways, respectively [43*].

The results obtained using different inert gases are not comparable, nor are those recorded using different available commercial devices. The recommended acceptability criteria for MBW testing have been detailed in an international consensus document [44].

SMALL AIRWAY DYSFUNCTION AND THE RISK OF DEVELOPING ASTHMA

A recent prospective birth cohort study with a 26-year follow-up showed that asthma was associated

with lung function impairment measured with spirometry between ages 10 and 18 years. $FEF_{25-75\%}$ was highly sensitive in detecting signals of airflow limitation before any abnormality was observed in FEV_1 or FVC in children at 10 years of age [45[¶]].

To *et al.* [46[¶]] showed that adults with persistent asthma from childhood were more atopic, had a higher incidence of severe asthma, had poorer lung function and greater evidence of SAD, as measured by $FEF_{75\%}$, compared with adults with adult-onset asthma, suggesting that the small airways of children might be more sensitive to airway inflammation.

A prospective birth cohort study showed that evidence of SAD at 16 years of age, as measured by IOS index R5–R20, was associated with persistent asthma in adolescence, but not with a history of childhood transient wheezing [47].

In a longitudinal study involving children with a history of hospitalization for bronchiolitis in infancy, IOS parameters measured at preschool-age predicted spirometry results in early adolescence, showing significant correlation especially between the reduction in X5 and FEV_1 or FVC in both baseline and post-bronchodilation measurements [48].

In another longitudinal study, both positive asthma-predictive index and abnormal lung function, as measured with IOS and an exercise challenge test, at preschool age successfully predicted asthma symptoms and the need for asthma medication in adolescence. However, only IOS (mainly as abnormal baseline R5) was able to predict the persistence of abnormal lung function at teenage, providing a comprehensive and objective diagnostic method of preschool asthma to combine to symptom-based clinical indexes [20].

Skylogianni *et al.* [21] recently showed that SAD, as identified by significant postbronchodilation changes in IOS index R5 and X5, precedes and predates the development of asthma in school-age children with intermittent moderate-to-severe allergic rhinitis. Significantly, the presence of SAD during allergic rhinitis exacerbation was the single most efficient predictor of asthma occurrence in the subsequent 5-year follow-up and proved to be superior to all spirometric measures.

PREVALENCE OF SMALL AIRWAY DYSFUNCTION IN PAEDIATRIC ASTHMA

SAD is a characteristic feature in adults with persistent asthma, with a prevalence ranging from 50 to over 90% depending on the physiological measure used to assess it [15^{¶¶}].

Emerging evidence shows that small conducting airways are an important site of disease also in paediatric asthma and are affected from an early stage of the

disease. In a recent cross-sectional analysis on children and adolescents with moderate-to-severe asthma, those with noncontrolled disease had evidence of SAD in 69–73% across age groups, when using the IOS X5 age-specific threshold, compared with 35–50% when using spirometry $FEF_{25-75\%}$ ($P < 0.05$). Significantly, in the group of well controlled asthmatic individuals, IOS identified SAD in 20% of children less than 12 years and in 45% of adolescents, compared with 0–10%, respectively, when using $FEF_{25-75\%}$ ($P < 0.05$). These results suggest that IOS is more sensitive at identifying SAD and the related risk for loss of asthma control than $FEF_{25-75\%}$ [49].

In the BAMSE birth cohort study, signs of SAD, as measured by IOS index R5–R20 and AX, and increased levels of fraction exhaled nitric oxide (FENO) and blood eosinophils were detected in adolescents with allergic asthma, compared with their healthy peers. Despite having a reduced FEV_1 /FVC, the group of nonallergic asthmatic individuals had no evidence of SAD, suggesting that peripheral airway impairment could be related to eosinophilic inflammation in adolescents with allergic asthma [50[¶]].

Regarding MBW, available evidence shows that LCI is within the normal range in most preschool and school-aged children with mild-to-moderate asthma [51[¶]], while is more likely to be abnormal in children with uncontrolled asthma [17] and severe asthma irrespective of symptom control [52]. Both LCI and S_{cond} seem to be associated with BHR [53], and some evidence suggests that S_{cond} could also detect the early disease of small conducting airways in young children with asthma. Sonnappa *et al.* [54] showed that S_{cond} was increased in 68% of preschool children with a wheezing phenotype at higher risk of school-age asthma, compared with healthy controls. Also, S_{cond} resulted to be the most sensitive MBW marker that distinguished preschool asthmatics from healthy controls [55]. An increased S_{cond} indicative of SAD was documented in 66% of school-age children with allergic asthma compared with their healthy peers, and correlated with airway inflammation, as measured with FeNO, and BHR. This suggests that allergic airway inflammation is an important determinant of SAD in asthmatic children and provides further evidence of the pathogenic role of SAD. Significantly, spirometry did not correlate with either asthma control or S_{cond} or FeNO, with 50% of asthmatic individuals with normal FEV_1 showing elevated S_{cond} [17].

HOW SMALL AIRWAY DYSFUNCTION CAN INFLUENCE ASTHMA CONTROL IN CHILDREN

Persistent inflammation in the peripheral small airways has recently emerged as an important

contributor to poor asthma control in both adults [56] and children [49].

An air-trapping obstruction pattern, a phenomenon closely associated with SAD, can be detected by using conventional spirometry and bronchodilator response in a subgroup of children and adolescents with asthma. This subgroup shows increased asthma severity and instability and requires a greater level of therapy compared with those with normal spirometry or airflow limitation without air-trapping during a stable period [57].

Preschool children with uncontrolled asthma show greater evidence of SAD, as detected by IOS parameters X5, AX, R5–R20 and higher FeNO levels than their peers with controlled asthma [58]. In preschools with mild-to-moderate asthma treated with inhaled corticosteroids (ICS), IOS proved to be clinically useful in identifying children at risk for loss of control in the 8–12 weeks after the initial visit. In this population, the AX value of 37.435 cmH₂O/l was the optimal cut-off point to predict future loss of asthma control [25^{***}].

Shi *et al.* [24] found that also school-age children with mild-to-moderate controlled asthma were at a high risk for loss of control at the 8 to 12-week follow-up visit if there was evidence of SAD at baseline, as measured by IOS (AX, R5–R20). Recently, Galant *et al.* [59^{*}] showed that SAD, defined by all available standardized IOS reference values (particularly for X5), is consistently associated with the risk of uncontrolled asthma in children, even in those on step 3 or higher of ICS therapy and across ethnicity.

Significantly, in young children with intermittent asthma during a symptom and medication-free period, IOS index R5 was a superior predictor of future asthma exacerbations than FEV₁ and methacholine bronchoprovocation testing, suggesting that unrecognized SAD increases the risk of exacerbation [22]. A previous report by Shi *et al.* [23] showed that neither FEV₁ nor FEF_{25–75%} was as effective as small airway IOS indexes in detecting poorly controlled asthma in children. Recent evidence confirms that IOS parameters of SAD (R5, X5 and AX), both baseline values and postbronchodilator response, are better predictors of future loss of asthma control than spirometric measures [60^{***}, 61]. However, the combination of these two techniques increases the prognostic accuracy in detecting poor asthma control [60^{***}].

Regarding MBW, among children with mild-to-moderate asthma symptoms, the index S_{cond} and the alveolar component of FeNO were significantly associated with the number of asthma exacerbations in the previous year, independently of the asthma-control test score and reliever medication use [28].

HOW SMALL AIRWAY DYSFUNCTION CAN INFLUENCE ASTHMA TREATMENT

Current guidelines recommend the use of symptom control and spirometry to guide asthma treatment [31]. However, accumulating evidence in adults and children shows that spirometry measures poorly correlate with both validated asthma control metrics [62,63] and disease severity [6^{***}]. SAD constitutes a phenotype that is often unrecognized by conventional spirometry, which could influence asthma control and severity. Thus, early recognition and targeted treatment of SAD may reduce the number of children with uncontrolled asthma and frequently associated exacerbations.

Most inhaled treatments do not sufficiently reach the small airways, and this inability may significantly contribute to the lack of efficacy of ICS in the subset of patients with refractory asthma. A different therapeutic approach, such as extra-fine particle ICS, may be required to treat those asthmatics with predominant SAD. Extra-fine ICS formulations with a mass median aerodynamic diameter (MMAD) of nearly 1–1.5 µm have a higher pulmonary deposition (50–60%) than coarse particle formulations with an MMAD of 3–4 µm (10–20%) and can better penetrate the small airways than traditional ICS. Randomized clinical trials are needed to determine whether asthmatic children with SAD would benefit from the use of extra-fine ICS, which have been shown to reduce exacerbations and improve asthma control in observational studies [64].

Assessing SAD could also be relevant in monitoring response to current asthma treatments. It has been shown that FEF_{25–75%} may be a more sensitive measure to detect bronchodilator responsiveness to tiotropium than FEV₁ in children with nonsevere asthma [65^{*}].

Children with severe therapy-resistant asthma (STRA) could particularly benefit from a multidomain lung function assessment which includes new diagnostic tests for SAD [27^{***}, 66^{*}]. In a recent cross-sectional study including children with STRA, LCI and FeNO showed significant improvements 4 weeks after treatment with intramuscular corticosteroid, whereas no changes were seen for any spirometry parameters. Improvements in LCI were concordant with FeNO, suggesting that the distal airway inflammation not responsive to ICS may be a driver of ventilation inhomogeneity in children with STRA [27^{***}]. Of great interest would be the application of new diagnostic tests for SAD in documenting and monitoring the effect of new biologicals in children with severe asthma, as already shown in adults treated with the anti-IL-5 mAb mepolizumab [67,68].

CONCLUSION

Despite the availability of effective therapies, a substantial proportion of asthmatics remain poorly controlled in real life. Given the impact of SAD on asthma control, routine assessment of SAD should be part of the management of children with asthma.

IOS can be used to detect airway obstruction in both adults and children [39[■],69[■]] and BHR during bronchoprovocation testing [22,70[■]] with comparable results to those of spirometry.

In asthmatic children, IOS can be more sensitive than spirometry at identifying impairment in the peripheral airways and at predicting loss of control and exacerbations [39[■]]. Available reference values for R5 and X5 seem appropriate, but further evidence is needed to define R5–R20 and AX baseline reference values and positive bronchodilator responses. For the time being, MBW seems to have potential in monitoring response to therapy in children with severe or therapy-resistant asthma [43[■]].

Implementing access to children-friendly, non-invasive investigations that are sensitive to both large and small airway function and inflammation is of high priority to complement spirometry, which is widely accessible today, and help to personalize asthma treatment strategies.

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Conflicts of interest

The authors have no conflicts of interest to declare.

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