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Impulse oscillometry for the evaluation and management of pediatric asthma

Pasquale Comberiati[1*], Marcello Cottini[2], Massimo Landi[3], Alvise Berti[4,5], Carlo Lombardi[6], Diego Peroni[1]

[1]Department of Clinical and Experimental Medicine, Section of Pediatrics, University of Pisa, 56126 Pisa, Italy
[2]Allergy and Pneumology Outpatient Clinic, 24125 Bergamo, Italy
[3]Pediatric National Healthcare System, 10135 Turin, Italy
[4]Center for Medical Sciences (CISMed) and Department of Cellular, Computational and Integrative Biology (CIBIO), University of Trento, 38123 Trento, Italy
[5]Santa Chiara Regional Hospital, Azienda Provinciale per i Servizi Sanitari, 38123 Trento, Italy
[6]Departmental Unit of Allergology, Immunology & Pulmonary Diseases, Fondazione Poliambulanza, 25124 Brescia, Italy

***Correspondence:** Pasquale Comberiati, Department of Clinical and Experimental Medicine, Section of Pediatrics, University of Pisa, Via Roma 67, 56126 Pisa, Italy. pasquale.comberiati@unipi.it
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Abstract

Asthma is the most common chronic disease during childhood. While most of characteristic structural changes in asthma have been identified in the large airways, there is a growing recognition of peripheral airway dysfunction as a crucial factor in the development of asthma. This dysfunction is a defining feature in adults with persistent asthma. However, little is known about the contribution of small airway impairment in children with asthma due to the relatively low sensitivity of conventional lung function tests, such as spirometry. Recently, new diagnostic tools that are sensitive to both large and small airway function and inflammation have been introduced in clinical practice. The most widely studied of these tools in preschool and school-aged children is impulse oscillometry (IOS). This review addresses the latest findings on the usefulness of IOS in identifying small airway dysfunction, predicting the risk of uncontrolled asthma, and ultimately improving the diagnosis and management of asthma in children.

Keywords

Asthma, children, small airways, dysfunction, impulse oscillometry

Introduction

Asthma is a chronic inflammatory disease that occurs frequently, affecting all age groups, and results in a significant health and economic burden [1]. While asthma affects the entire bronchial tree, most of the characteristic structural changes are detected in the large airways [2]. Small airways refer to those with an internal diameter of < 2 mm, extending from the 8th-generation airways to the periphery of the bronchial

tree [3]. In healthy individuals, small airways have traditionally been considered the "quiet zone" because they contribute minimally to airway resistance [4]. However, emerging evidence shows that small airway dysfunction (SAD) is an important component in the pathogenesis and persistence of asthma in both children and adults [5].

Surgical resection and autopsy analyses have shown small airway involvement in adults affected by asthma [6], with some data suggesting more inflammation and remodeling in small than in large airways [7]. Clinical studies have shown that SAD correlates with the risk of asthma development and exacerbations [8–10], worse asthma control [11–13], greater bronchial hyperresponsiveness [14], and loss of pulmonary function with age [15].

Until recently, SAD in asthma was largely unrecognized due to the limited sensitivity of conventional lung function tests (e.g., spirometry) [16]. The forced expiratory volume in 1 s (FEV1) and FEV1/forced vital capacity (FVC) ratio, which are the spirometry parameters commonly used to classify asthma status, tend to reflect the variability of large airway rather than small airway obstructions [17–19]. There is evidence that almost 2/3 of the small airways need to be obstructed before there is a reduction in FEV1 [17]. The forced expiratory flow between 25% and 75% of vital capacity (FEF25–75%) may be a more sensitive parameter of small and medium airway obstruction than FEV1 [20–22]. However, it is not specific to small airways [23] and has a high coefficient of variability, which limits its use in identifying poor asthma control [24]. In addition, it is often difficult to obtain reliable spirometry before the age of 6 years, due to limited breathing coordination and cooperation in this age group.

Recently, advanced techniques have been developed and are available in clinical practice, which may be more sensitive to identifying SAD in patients with asthma than spirometry (Table 1). Among these lung function tests, which are extensively reviewed by McNulty and Usmani [16], impulse oscillometry (IOS) is the most studied in pediatric patients [25]. IOS can detect airway obstruction in both adults and children [26, 27] and bronchial hyperresponsiveness during bronchoprovocation testing [9, 28], with comparable results to spirometry. IOS may have greater sensitivity than spirometry in identifying SAD and predicting the risk of future exacerbations [26].

Table 1. Non-invasive available techniques for small airway function and their feasibility in children

Method	Small airway function	Feasibility in children
IOS	R5–R20, X5, AX, Fres	H
SBNW or MBNW test	Slope phase III, CV, CC, Sacin, Scond	H
Spirometry	FEF25–75%, FVC, FVC/SVC	M
Body plethysmography	RV, RV/TLC	M
eNO	Alveolar eNO	M
Sputum induction	Late phase sputum	L
Bronchoscopy	Transbronchial biopsy, BAL	L
HRCT	Air trapping, airway wall thickness	L
CT and computational fluid dynamics	Changes in airway volume and resistance	L
Nuclear medicine (scintigraphy, SPECT, PET)	Regional ventilation defects	L
3He-MRI	Non-ventilated lung volume	L

R5: respiratory system resistance (Rrs) at 5 Hz; X5: respiratory system reactance (Xrs) at 5 Hz; AX: area of reactance; Fres: resonant frequency; SBNW: single breath nitrogen washout; MBNW: multiple breath nitrogen washout; CV: closing volume; CC: closing capacity; Sacin: ventilation heterogeneity in the acinar airways; Scond: ventilation heterogeneity in the conducting airways; SVC: slow vital capacity; RV: residual volume; TLC: total lung capacity; eNO: exhaled nitric oxide; BAL: bronchoalveolar lavage; CT: computerized tomography; HRCT: high resolution CT; SPECT: single-photon emission CT; PET: positron emission tomography; 3He-MRI: 3helium-magnetic resonance imaging; H: high; M: medium; L: low (The abbreviations "H", "M", and "L" for "high", "medium", and "low", respectively, are only applicable in the Table)

Note. Adapted from "Small airway dysfunction and poor asthma control: a dangerous liaison," by Cottini M, Licini A, Lombardi C, Bagnasco D, Comberiati P, Berti A. Clin Mol Allergy. 2021;19:7 (https://clinicalmolecularallergy.biomedcentral.com/articles/10.1186/s12948-021-00147-8#Abs1). CC BY.

This review aims to present the latest evidence on the role of IOS in the diagnosis and management of asthma in children.

IOS: technical use in children with wheezing and asthma

IOS is a modified form of the forced oscillation technique (FOT), which uses an impulse generator to transmit small oscillation pressure impulses to the respiratory system of a patient breathing normally. These impulses are multifrequency oscillations in nature ranging from 5 Hz to 50 Hz. Sound waves of high frequency (> 20 Hz signals) are of higher amplitude and travel over a shorter distance, thus reaching the proximal large airways, whereas low frequency sound waves (5 Hz signals) move deeper into the airways and reach the entire bronchial tree. The ratio of oscillatory pressure to oscillatory flow generated from this oscillatory stimulus is used to calculate the respiratory system impedance (Zrs), which includes the Rrs and Xrs. Rrs reflects the pressure opposing the forward movement of the sound wave into the airways and may be largely interpreted as airway caliber. Thus, narrower and longer airways have higher Rrs. Xrs reflects the energy generated by the elastic recoil of the lung parenchyma and the airways (i.e., the capacitance of the lungs) added to the inertance of the system, and may be largely interpreted as the stiffness of the entire system [26, 29–31]. The other two parameters used in interpreting IOS are the "Fres" and the "AX". Fres corresponds to the frequency at which, in normal conditions, the elastic forces of the airways and lungs are equal to the inertial properties of the system. The AX comprises all the frequencies measured by IOS where the elastic properties of the lung prevail over the inertance of the system [26, 29–31].

Therefore, a peripheral airway obstruction will result in: a) a greater R5 than R20, and thus an increase in the differential R5–R20; b) a more negative value of X5, due to the hyperinflation (i.e., greater stiffness) and reduced elasticity, which is normally greatest in the small airways; and c) increase of the "AX", due to lower (more negative) values for X5 and higher Fres.

The IOS test is a non-invasive lung function test that is particularly useful for young children aged three years and older, as well as individuals who cannot perform spirometry because it only requires passive cooperation during tidal breathing [30].

To standardize IOS measurement, recommended technical standards have been published [32, 33] to uniform the different commercially available IOS devices, which are not necessarily comparable at present [34]. Reference values for IOS have been established for both preschool and school-aged children, as well as for Caucasian and non-Caucasian patients [31, 35, 36], although baseline and positive bronchodilator reference values for R5–R20 and AX still need to be established.

Studies have reported conflicting results regarding the use of IOS for distinguishing healthy preschool children from those with wheezing [37–39], with some reporting significant differences and others not [40, 41]. Using a *z*-score > 2 as a cut-off for Rrs and X5 may increase the sensitivity of IOS, especially when completed with a bronchodilator reversibility test [42] or bronchial challenge test [43]. Recent guidelines recommend using, in both adults and children, a 40% decrease in R5, a 50% increase in X5, and an 80% decrease in AX to define a positive bronchodilator response (BDR) [31–33]. However, asthma studies have reported different AX values to identify a positive BDR, ranging from over 30% in children to over 40% in adults according to previous studies [25].

SAD and risk of developing asthma

Observational studies have indicated that SAD can occur in children with suspected asthma before traditional diagnostic tools, such as spirometry, detect any abnormalities, particularly in the reduction of the FEV1 [25].

One study conducted on 117 American school-aged children referred to a Pediatric Allergy Clinic for asthma suspicion showed that the IOS AX parameter and BDR detected with IOS could differentiate between asthmatics and non-asthmatics, whereas spirometry FEV1 could not [44].

Another study involving 2,600 Swedish children found that those with transient or persistent asthma had lower FEV1 at the age of 16 compared to their peers who did not develop asthma [45]. SAD, as measured by the IOS index R5–R20, was significantly associated with active persistent asthma in adolescence but not with transient asthma [45].

In a longitudinal study of 64 school-aged children who were hospitalized for bronchiolitis in their first 6 months of life, IOS reactance parameters measured at preschool age (mean age 6.3 years) predicted spirometry results in early adolescence, showing a significant correlation, particularly between the reduction in X5 and FEV1 or FVC in both baseline and post-bronchodilation measurements [46].

In another longitudinal study, IOS was measured in 255 Finnish children with asthma-like symptoms at 4–7 years [47]. In addition to baseline IOS measurements, an exercise challenge and a bronchodilation test were performed. Asthma symptoms and the need for asthma medication in adolescence were both predicted by a positive modified asthma-predictive index and altered lung function at preschool age. However, only an R5 *z*-score ≥ 1.645 standard deviation (SD) at baseline was able to predict the persistence of abnormal lung function in adolescence. These findings show that IOS is an objective diagnostic method for preschool asthma that can be easily combined with asthma-predictive clinical indexes [47].

Evidence also suggests that SAD may precede the occurrence of asthma in children with allergic rhinitis [8]. In a cohort of 73 children with moderate-to-severe allergic rhinitis, SAD, as measured by significant post-bronchodilation changes in R5 and X5, was the most efficient predictor of asthma occurrence in the subsequent 5-year follow-up, superior to spirometry and other risk factors such as a family history of asthma and personal history of atopy [8].

Prevalence of SAD in children with asthma

The prevalence of SAD in adults with persistent asthma ranges from 50% to over 90%, depending on the lung function test used [48]. Increasing evidence shows that small conducting airways are affected in the early stages of the disease and are a major site of airflow limitation, even in childhood asthma [25].

In a retrospective study of 139 children and adolescents (aged 4–18 years) with moderate-to-severe asthma, IOS was able to identify SAD and distinguish lack of asthma control to a greater extent than spirometry [49]. Participants with non-controlled asthma had evidence of SAD in 69–73% of cases when defined by the IOS X5 age-specific threshold compared to 35–50% when using spirometry FEF25–75% ($P < 0.05$). Similarly, in the subgroup with well-controlled asthma, IOS identified SAD in 20% of participants < 12 years and 45% of teenagers, compared with 0–10% when using FEF25–75%, respectively ($P < 0.05$) [49].

In the longitudinal BAMSE birth cohort study, among the 2,600 adolescents who participated, those with allergic asthma showed SAD, as measured by increased IOS index R5–R20 and AX, in addition to markers of type-2 inflammation, such as elevated fraction of eNO (FeNO) and blood eosinophils [50]. In contrast, the group of non-allergic asthmatics had no evidence of SAD, despite having reduced FEV1/FVC on spirometry. These findings suggest that peripheral airway impairment could be related to eosinophilic inflammation in adolescents with allergic asthma [50].

Notably, a recent analysis of induced sputum samples from 197 adults with asthma showed that eosinophilic airway inflammation (i.e., eosinophils ≥ 2%) is the main driver of SAD and related poor asthma outcomes [51].

Relationship between SAD and asthma control in children

Recent studies have highlighted the role of persistent inflammation in the small airways as a significant contributor to poor asthma control and an increased risk of exacerbations in both adults and pediatric patients with asthma [52, 53].

Observational studies have shown that the measurement of SAD through IOS parameters and FeNO can increase the accuracy of identifying uncontrolled asthma in pediatric patients [54, 55]. In a study of 79 preschool children (ages 3–6 years), those with uncontrolled asthma had greater evidence of SAD, as measured by IOS parameters X5, AX, R5–R20, and FeNO levels, compared to children with controlled asthma [54]. The combination of IOS and FeNO improved the accuracy of the test in distinguishing controlled *versus* uncontrolled patients. The area under the curves in the receiver operating characteristic (ROC) analysis was 0.786 for FeNO alone, 0.751 for the IOS X5 parameter alone, and 0.866 for X5 combined with FeNO (cut-off value: 27 ppb) [54]. Similarly, in a large cohort of 560 school-age children (ages 6–12 years), the IOS parameter R5–R20 was the strongest predictor of uncontrolled asthma among lung function tests, including spirometry and FeNO [55]. However, the combination of IOS with FeNO > 20 ppb significantly increased the specificity of identifying poor asthma control [55].

Furthermore, IOS parameters have been shown to be a better predictor of future asthma exacerbations than spirometry and bronchoprovocation test. A prospective study of 75 children (4–7 years of age) with intermittent asthma, showed that IOS (R5) was a better predictor of future asthma exacerbations than spirometry (FEV1) and methacholine challenge [9]. In another prospective study on 111 preschool children (age 3–6 years) with mild-to-moderate asthma using inhaled corticosteroids (ICS), IOS was shown to predict loss of asthma control at the 8- to 12-week follow-up visit [13]. Children who had persistent uncontrolled asthma at the follow-up showed significantly altered IOS parameters [R5, R5–R20, AX, and Zrs at 5 Hz (Z5)] compared with those in the controlled asthma group and those without asthma. The AX value of 37.435 cmH_2O/L (1 cmH_2O = 0.098 kPa) at baseline turned out to be the best cut-off point to predict future loss of asthma control. In this study, FeNO did not predict the risk for persistent uncontrolled asthma [13]. Shi et al. [12] also showed that school-age children with mild-to-moderate controlled asthma who had evidence of SAD, as measured by IOS (AX, R5–R20), were at high risk of uncontrolled asthma at the 8- to 12-week follow-up visit.

Recently, Galant et al. [56] demonstrated that SAD, defined by all available standardized IOS reference values (especially X5), was consistently linked to uncontrolled asthma risk in children, including those treated with a step 3 or higher ICS therapy, and across ethnicities.

A previous report by Shi et al. [11] showed that neither FEV1 nor FEF25–75% was as effective as IOS indexes in detecting poor asthma control in children aged 6 years to 17 years [11]. Finally, a recent systematic review and meta-analysis involving a total of 615 patients from six trials confirmed that IOS parameters R5, AX, and X5 can predict asthma exacerbations in children [57].

Current research confirms that both pre- and post-bronchodilation values of IOS indexes (R5, X5, and AX) are better predictors of future loss of asthma control than spirometry parameters [58, 59]. However, combining IOS and spirometry increases the prognostic accuracy for poor asthma control [58].

Impact of SAD on asthma therapy

Current guidelines recommend using asthma control and spirometry to guide treatment [60]. However, accumulating evidence in both adults and children suggests that spirometry measures, especially FEV1, have a weak correlation with validated asthma control questionnaires [61, 62] and disease severity [63, 64].

SAD is often undetected by conventional spirometry, but it could impact asthma control. Therefore, recognizing SAD early and providing targeted treatment could reduce the number of children with uncontrolled asthma and exacerbations.

Traditional inhaled therapy for asthma may not reach the small airways adequately, leading to the inefficacy of ICS therapy in a subset of patients with refractory asthma. With a mass median aerodynamic diameter as low as 1 μm to 1.5 μm, the “extra-fine” ICS formulations can better penetrate small airways than traditional ICS. Observational studies have shown that the use of extra-fine particle ICS reduces exacerbations and improves asthma control [65]. Further studies are necessary to determine whether children with asthma and evidence of SAD would benefit from extra-fine ICS over conventional ICS.

Assessing SAD using IOS could also be important when monitoring the response to asthma treatments. Pediatric patients with severe, therapy-resistant asthma may particularly benefit from multidomain lung function assessments [66, 67]. It would be particularly interesting to apply IOS to document and monitor the impact of new biologicals on children with severe asthma, as has already been shown in adults receiving treatment with monoclonal antibodies such as anti-interleukin-5 (IL-5) mepolizumab [68, 69].

Future of IOS in real life clinical practice

IOS is a non-invasive and effort-independent lung function test that can detect airway obstruction and bronchial hyperresponsiveness and is feasible in children from the age of 3. Compared to spirometry, IOS may be more sensitive in identifying SAD and the risk of poor asthma control.

In real life clinical practice, IOS can complement spirometry in the diagnostic workup of children with asthma or suspected asthma. IOS is also able to identify children with inadequately controlled asthma despite normal spirometry. This ability of IOS is further increased by combination with FeNO [70]. Thus, IOS can improve asthma management, especially in high-risk categories such as adolescents, who often report poor adherence to therapy, and children with severe asthma, who require frequent follow-ups and have now access to biological therapies.

Preschool children with recurrent wheezing can also benefit from the use of IOS. In this group of patients, spirometry and FeNO are usually not performed due to technical difficulties in carrying out these tests. Thus, most decisions on whether to start a preventive therapy or on the timings of the follow-ups are based on the clinical scenario or clinically-based predictive index.

However, there are still knowledge gaps that prevent IOS from being widely implemented in clinical practice. While current reference values for R5 and X5 appear appropriate, further evidence is needed to define reference values for R5–R20 and AX. Various IOS devices are now available, offering in-office diagnostic tools that can detect SAD, but there is not necessarily an interdevice agreement and the final report might differ from one to another device both in terms of readability and reference values.

Conclusions

Currently, a significant proportion of children still experience poor asthma control, despite available effective treatment. Since SAD can have a considerable impact on asthma control, it should be routinely assessed as part of asthma management in both children and adolescents. IOS is emerging as a non-invasive and feasible technique to assess SAD in pediatric age and provide additional information about lung pathology that spirometry might not detect. Therefore, it is a high priority to implement access to IOS to complement spirometry in asthma management.

Abbreviations

AX: area of reactance

BDR: bronchodilator response

CT: computerized tomography

eNO: exhaled nitric oxide

FEF25–75%: forced expiratory flow between 25% and 75% of vital capacity

FeNO: fraction of exhaled nitric oxide

FEV1: forced expiratory volume in 1 s

Fres: resonant frequency

FVC: forced vital capacity

ICS: inhaled corticosteroids

IOS: impulse oscillometry

R5: respiratory system resistance at 5 Hz

Rrs: respiratory system resistance

SAD: small airway dysfunction

X5: respiratory system reactance at 5 Hz

Xrs: respiratory system reactance

Declarations

Author contributions

PC, MC, ML, and AB: Conceptualization, Investigation, Writing—original draft, Writing—review & editing. CL and DP: Writing—review & editing, Validation, Supervision. All authors read and approved the submitted version.

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The authors declare that they have no conflicts of interest.

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