

Recent Diagnosis Techniques in Pediatric Asthma

Impulse Oscillometry in Preschool Asthma and Use of Exhaled Nitric Oxide



Karen M. McDowell, MD

KEYWORDS

• Preschool asthma • Pulmonary function testing • Impulse oscillometry • Impedance
• Resistance • Reactance • Coherence • Tidal breathing

KEY POINTS

- Objective measures of lung function are important in the diagnosis and management of asthma, yet most preschoolers cannot perform spirometry.
- Impulse oscillometry, which is performed during tidal breathing, is a method by which lung function measures can be obtained in preschool children.
- Impulse oscillometry can be useful in determining baseline lung function, demonstrating response to bronchodilator or bronchoprovocation, and predicting asthma exacerbations and loss of disease control.
- Fractional exhaled nitric oxide (FeNO) levels reflect eosinophilic inflammation and predict responsiveness to corticosteroids.
- Although FeNO has been used to discriminate among wheezing phenotypes, the role of FeNO in preschool wheezing remains unclear.

INTRODUCTION

Objective assessment of lung function is important in the diagnosis of asthma and assessment of disease control.¹ Spirometry is the pulmonary function test most widely used to evaluate for airway obstruction in children and is recommended as part of asthma evaluation and management by both US¹ and European guidelines.² Spirometry requires a child to be able to follow directions and perform maximal respiratory maneuvers, such as full inspiration to total lung capacity and forced exhalation to residual volume, ideally over 6 seconds. In addition, the child must be able to provide

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Division of Pulmonary Medicine, Cincinnati Children's Hospital Medical Center, Department of Pediatrics, University of Cincinnati College of Medicine, 3333 Burnet Avenue, MLC 7041, Cincinnati, OH 45229, USA

E-mail address: karen.mcdowell@cchmc.org

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reproducible efforts. Children less than 5 years of age are rarely able to perform such a skilled, effort-dependent test. Thus, preschool asthma is most often diagnosed and managed based on clinical findings. Although not as readily available as spirometry, impulse oscillometry (IOS) is a lung function test that can be performed by younger children and those unable to perform spirometry to provide important objective information in those diagnosed with or suspected to have asthma.

IMPULSE OSCILLOMETRY

Because IOS requires minimal cooperation and measurements are made during tidal breathing, it is an ideal method for assessing lung function in preschool children. It has been performed reliably and consistently even by children unable to perform spirometry.^{3,4} However, a recent large multicenter study of inner-city children at risk for asthma found that of 485 children who attempted lung function testing, a higher percentage was able to perform acceptable spirometry than IOS at ages 3, 4, and 5 years.⁵ It is worth noting, though, that the study used forced expiratory volume in 0.5 second (FEV_{0.5}) rather than the more commonly used forced expiratory volume in 1 second (FEV₁) in determining acceptable and repeatable spirometry. Nevertheless, these investigators and others have shown IOS to be more sensitive than spirometry in detecting small-airway obstruction and distinguishing children with asthma from those who did not.^{6–9} IOS has also shown utility in not only identifying inadequate asthma control¹⁰ but also predicting future loss of control and asthma exacerbations.^{11,12} An additional advantage of IOS is that it can measure airway resistance, which cannot be obtained through spirometry and typically requires body plethysmography.

IOS is a form of the forced oscillation technique described in 1956 by Dubois and colleagues.¹³ Forced oscillation measures airway mechanics by superimposing pressure waves on the subject's tidal breathing. IOS uses sound waves to transmit pressure into the airways and thereby determine pressure and flow over a range of frequencies. Once pressure and flow have been determined, other characteristics of the airway, such as resistance, can be calculated. Sound waves of lower frequencies (<15 Hz) travel deeper into the airways, allowing measurement of small-airway parameters. Higher-frequency sound waves are of higher amplitude and move over a shorter distance. Thus, measurements derived from sound waves with a frequency of greater than 20 Hz reflect large airway characteristics. By obtaining measurements over both high and low frequencies, IOS can reflect function of both proximal and distal airways.

Commercially available IOS systems contain a loudspeaker that generates sound waves over a range of frequencies, usually 2 to 35 Hz. The loudspeaker is attached to a mouthpiece, through which the oscillations of the sound and the concomitant pressure fluctuations are transmitted into the oropharynx, through the glottis, and into the lower airways. A pneumotachograph and transducer are connected to the tubing between the loudspeaker and the mouthpiece, allowing measurement of pressure and flow during inspiration and expiration. The generated sound waves are superimposed on the normal tidal breathing of the child, and a signal filter separates the externally produced oscillations from those of the child's breathing pattern. Computer analysis of amplitude and phase differences of pressure and flow during inspiration and expiration calculates respiratory impedance. Impedance of the respiratory system comprises all the forces that inhibit airflow.

CONCEPTS IN IMPULSE OSCILLOMETRY

Several concepts, including *impedance*, are important in understanding IOS. Total respiratory system impedance, represented as *Z_{rs}*, is composed of *resistance* (*R_{rs}*)

and *reactance* (X_{rs}). Resistance can be conceptualized as the energy a sound wave requires to travel through the airways and inflate the lung. The resistance of the entire respiratory system (R_{rs}) includes that found in the extrathoracic airways, intrathoracic airways, lung parenchyma, and the chest wall. The resistance at low frequencies, such as 5 Hz (R_5), is that of both the central and the distal airways, whereas resistance at higher frequencies such as 20 Hz (R_{20}) represents that of the large airways. Resistance of the peripheral airways can be determined by subtracting resistance of the large airways from that of the respiratory system, or $R_5 - R_{20}$. This value is commonly referred to as the R_5-R_{20} . Peripheral airway obstruction results in more resistance in the lower-frequency sound waves (R_5), which travel deeper into the lungs than the higher-frequency waves (R_{20}) representing the large airways. Thus, R_5 will be disproportionately elevated relative to R_{20} in peripheral airway obstruction, and consequently, a higher value for R_5-R_{20} is obtained under such circumstances. This disproportionate effect on low-frequency resistance compared with high-frequency resistance in small-airway obstruction is called *frequency dependence of resistance*, which is an alternate term for R_5-R_{20} . In small-airway obstruction, the value of both R_5 (resistance at low frequencies representing large and small airways) and R_5-R_{20} (resistance of more peripheral airways) will be elevated.

Reactance of the respiratory system, represented as X_{rs} , is composed of the inert and elastic properties of the respiratory system. The elastic properties of the pulmonary system are manifested as the elastic recoil of the airways and lung parenchyma in response to distension. Reactance is the energy generated by the elastic recoil of the lung parenchyma and the airways added to the inertance of the system. Inertance is the force opposing movement of the sound wave through the respiratory system. Reactance can also be thought of as the “stored energy” of the respiratory system or rebound energy that is generated in response to the sound wave moving through the lungs. In contrast, resistance is the pressure opposing the forward movement of the sound wave and is a force occurring in front of and in phase with the sound wave. Reactance occurs in response to the sound wave and therefore is the energy echoed back to the system after, and out of phase with, the sound wave. The sum of the forces ahead of the sound wave (resistance) and those generated behind the sound wave in response to the pressure of the wave (reactance) equal the impedance of the entire respiratory system. In other words, $R_{rs} + X_{rs} = Z_{rs}$. Inertance is the force opposing movement of the sound wave through the respiratory system. At low frequencies where sound waves have reached the more distal airways, elastic recoil (reactance) will be high compared with inertance. At higher frequencies, where sound waves travel only as far as the larger, more proximal, airways, elastic recoil (reactance) will be low compared with the inertive properties of the airways. It is not surprising then that reactance at low frequencies has been shown to correlate with peripheral airway obstruction.¹⁴ When reactance is zero ($X = 0$), the elastic recoil of the airways and lungs is equal and opposite to the inertance of the system, and all of the impedance in the system is created by the forward movement of the sound wave. At this frequency, known as *resonant frequency* or *Fres*, low-frequency and high-frequency reactance can be discriminated. At frequencies above *Fres*, inertance is greater than elastic recoil as is seen in the large airways. Frequencies below *Fres* will be those at which elastic recoil is greater than inertance, a property of the small airways. Therefore, *Fres* is the dividing point between large and small airways based on the mechanical properties of the airways. It is important to realize that the distinction between large and small airways based on *Fres* is determined by the airway mechanics rather than the size or generation of the airway.¹⁴ The value of *Fres* is higher in children than in adults and decreases with age.¹⁵ *Fres* is also increased in airway obstruction.^{16,17}

During IOS testing, curves for the resistance and reactance at all frequencies between 5 and 20 Hz are generated. Both curves are then plotted against frequency and displayed on a single graph called a Goldman graph⁴ (Fig. 1). The area under the reactance curve between the values at 5 Hz (X5) and at Fres is called the *area of reactance* (AX). Both AX and X5 provide information about distal airway obstruction because reactance (elastic recoil) is greatest in the small airways, where low-frequency sound waves can reach. Obstruction of the small airways results in lower (more negative) values for X5 (reduced reactance or elastic recoil). Similarly, the Fres is higher in airway obstruction because the point in the airways where reactance (elastic recoil) is zero is more proximal, and the more proximal, larger airways are represented by values obtained at higher frequencies. Lower X5 and/or higher Fres will increase the area under the reactance curve, and therefore, the value of AX. It follows then that AX is elevated in proportion to small-airway obstruction.^{18,19} AX has been reported to be the most sensitive measure in discriminating between asthmatics and healthy controls.^{6,9}

A final concept is that of *coherence*. Coherence is based on the ratio of the pressure of the sound wave entering the lung and the pressure of its reflection back from the respiratory system. Coherence is measured in units of cm H₂O between 0 and 1.

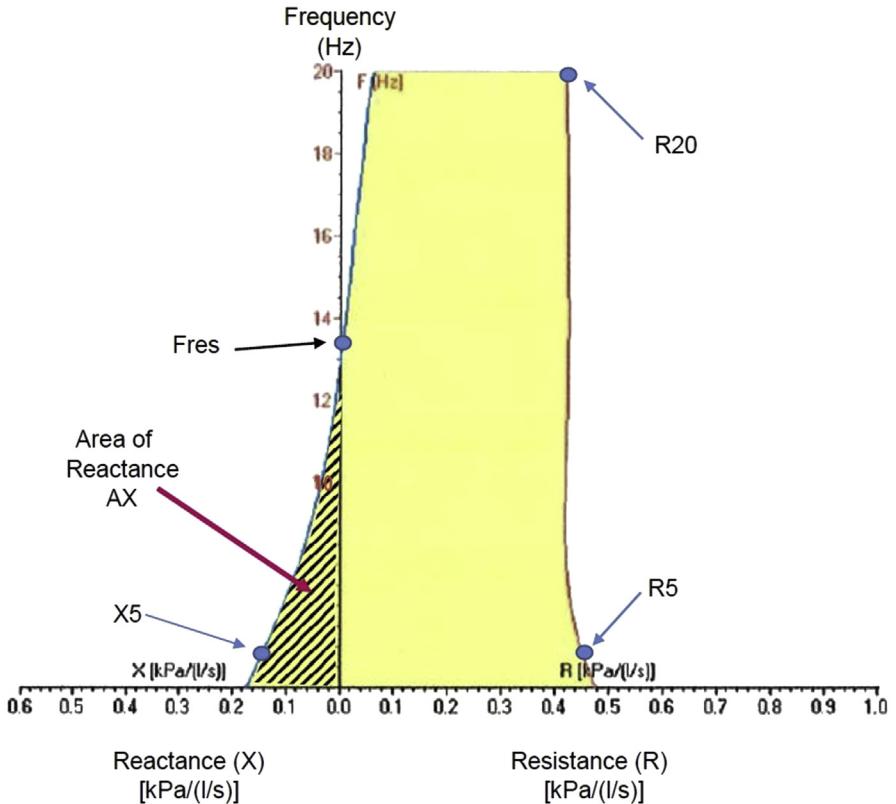


Fig. 1. A Goldman graph displaying reactance (X) (blue line) and resistance (R) (red line) plotted as a function of frequency. Fres is the frequency where X = 0. X5 and R5 are reactance at 5 Hz and resistance at 5 Hz, respectively. The AX is the shaded triangle represented by the area under the reactance curve between Fres and 0 Hz. R5, Fres, and AX will be increased in peripheral airway obstruction. X5 will be more negative in peripheral airway obstruction.

Perfect coherence, where the pressure of the entering sound wave is equal to the pressure of the echoing sound wave, is valued at 1 cm H₂O. Hence, coherence can be used as a measure of the quality or validity of the IOS measurements with coherence closer to 1 representing better validity. In general, a coherence of ≥ 0.8 is acceptable.

OBTAINING IMPULSE OSCILLOMETRY MEASUREMENTS

IOS may be performed with the child seated in a chair or seated on the parent's lap. Legs must be uncrossed to prevent contraction of the abdominal muscles, which can result in lower-end expiratory lung volumes. Nose clips are used to prevent leakage of pressure through the nose. With the head in neutral position, the child places the mouthpiece into his or her mouth and makes a seal with the lips. The cheeks are supported by an adult to prevent shifting of impulses to the upper airway and to limit the compliance of the cheeks.^{20,21} Sound waves are generated by the loudspeaker while the child performs tidal breathing for 20 to 30 seconds. Rrs and Xrs are measured and displayed in real time for inspection by the operator. Rrs and Xrs for all frequencies between 5 and 20 Hz are derived and stored for each trial. A minimum of 3 acceptable trials with less than 10% variation among trials are performed. All equipment calibration and testing should be done in accordance with American Thoracic Society (ATS)/European Respiratory Society standards.²⁰ The performance of the test takes only a few minutes; however, in young children, additional time should be allowed for acclimation to the equipment and testing environment before the IOS procedure is performed.

REFERENCE VALUES FOR IMPULSE OSCILLOMETRY

Reference values in spirometry are affected predominantly by height, but also by age, gender, race, and ethnicity, and predicted normal values are accessible for diverse racial and ethnic groups. In contrast, predicted values in IOS are also based principally on height but are derived from an ethnically homogeneous sample, which is largely white. The equations are based almost exclusively on data obtained from white children of European descent.^{22–25} However, a literature review by Galant and colleagues²⁶ and subsequent comparison of values obtained from diverse populations and commercially available regression equations revealed that normative values for R5 and X5 in healthy children and adults are comparable despite differences in geographic and ethnic origin, and these values correlate with the values obtained from regression equations programmed into commercially available software. Thus, predicted values programmed into commercially available software should be considered reasonable reference values for R5 and X5. Unfortunately, because of a paucity of data, there is still a need to establish reference values for other important IOS parameters, such as AX.

INTERPRETATION OF IMPULSE OSCILLOMETRY

The most commonly used parameters in interpretation of IOS are R5, R20, X5, Fres, and AX. Values for R5 and R20 that are greater than 150% of predicted should be considered abnormal and are consistent with increased airway resistance. An R5-R20 value is considered elevated, and consistent with peripheral airway obstruction, if it is greater than 30% in children and greater than 20% in adults. The within-individual variability of airway resistance when measured by IOS is approximately 16% for children and 10% for adults, which is comparable to the 5% to 15% individual variability in airway resistance obtained by body plethysmography.²²

Decreasing values for X5 indicate a loss of elastic recoil to the system at 5 Hz as would be present in peripheral airway obstruction. X5 is abnormal if the value is greater than 150% of predicted. The Fres (where reactance is zero), is abnormal if it is greater than 25 Hz in children or greater than 20 Hz in adults. A higher value for Fres indicates increased resistance. Fres naturally decreases with age. There are no accepted reference values for AX.

IOS measurements are considered accurate when coherence at 5 Hz is greater than 0.8 and coherence at 20 Hz is between 0.9 and 1.^{27,28} Causes of decreased coherence include swallowing, glottis closure, coughing, mouthpiece obstruction by the tongue, or irregular respiratory pattern. The parameters measured in IOS, their definitions, and normal values are summarized in [Table 1](#).

IMPULSE OSCILLOMETRY AND ASTHMA

One of the most useful areas of application for IOS is pediatric asthma. IOS can provide objective measures of lung function even in children who cannot perform spirometry,

Table 1 Description, abbreviations, and normal values for common impulse oscillometry parameters			
IOS			
Parameter	Symbol	Description	Reference Values
Respiratory impedance	Zrs	Impedance = resistance + reactance	
Respiratory resistance	Rrs	Airway + tissue + chest wall resistance	
	R5	Resistance at frequency of 5 Hz = resistance of proximal and distal airways	R5 normal if $\leq 150\%$ predicted
	R20	Resistance at frequency of 20 Hz = resistance of proximal airways	R20 normal if $\leq 150\%$ predicted
	R5-R20	Value at R5 – value at R20 = resistance of small airways	None established but increase suggestive of elevated small-airway resistance
Respiratory reactance	Xrs	Elastic + inertive properties of airways + lung tissue	
	X5	Reactance at frequency of 5 Hz Increased value suggests small-airway obstruction	Abnormal if X5 $> 150\%$ predicted
Resonant frequency	Fres	Frequency at which elastic forces = inertive forces; X = 0 Increased value suggests peripheral airway obstruction	Adults: Normal < 12 Hz Abnormal > 20 Hz Children: Normal $< 20\text{--}25$ Hz Abnormal > 25 Hz
Reactance area	AX	Area under the reactance curve bounded by Fres and X5 Increased value suggests peripheral airway obstruction	None established but increase suggestive of peripheral airway obstruction
Coherence	Co	Indicator of quality control	Test acceptable if:
	Co 5	Assessment of reproducibility	Co 5 Hz 0.7–0.9
	Co 20	Coherence at 5 Hz	Co 20 Hz 0.9–1.0
		Coherence at 20 Hz	

allowing earlier detection of airway obstruction and response to treatment. IOS has been studied extensively in asthma, including during acute exacerbations. Children with asthma have elevated resistance, specifically R5, as well as decreased Xrs at baseline compared with children without asthma,^{8,29} and R20 and Fres have also been shown to be increased in asthmatics compared with healthy controls^{9,30,31} (Figs. 2 and 3). Response to bronchodilator is the hallmark of bronchial hyperreactivity and a diagnostic criterion for asthma (see Figs. 2 and 3). Following administration of a bronchodilator, children with asthma demonstrate a decrease in resistance, both R5 and R5-R20, and in Xrs and AX.^{7,8} However, the degree of response to bronchodilator reported has varied widely, anywhere from 8.6%⁶ to more than 40%.¹⁵ A review of pediatric studies revealed that when change greater than the upper limit of the 95% confidence interval for R5 is used, the mean bronchodilator response (BDR) in healthy children was 39%.²⁶ Thus, a decrease in R5 or X5 greater than or equal to 40% following administration of a bronchodilator should be considered a positive response in pediatric asthma. Even lower BDR cutoff values have been shown to distinguish between children with asthma and healthy controls. A BDR decrease of 20% in R5 or R10 differentiated asthmatic preschoolers from those without asthma.^{28,32} Similarly, decreases of 8.6% at R10 and 29.1% in AX were found to identify asthma in school-aged children.⁷ These same studies demonstrated changes in IOS parameters even without concomitant change in spirometry, indicating that IOS may be more sensitive than spirometry in distinguishing asthma from healthy controls. This increased sensitivity is most likely because IOS reflects changes in the caliber of the small airways where changes of asthma occur earlier, before the abnormalities in the larger airways characterized by spirometry.¹¹

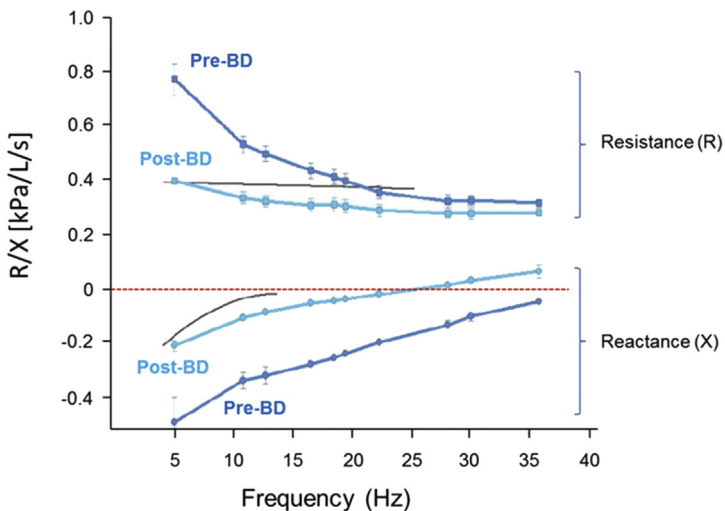


Fig. 2. Prebronchodilator and postbronchodilator IOS showing resistance (R) and reactance (X) plotted against frequency (Hz). At 5 Hz, there was 48% improvement in resistance and 58% improvement in reactance after 2 puffs (400 mg) of albuterol. There was a 23% decrease in resistance at 20 Hz. The R5-R20, which reflects peripheral airway resistance, improved from 75% to 58% after bronchodilator (BD). Measurements were made using Tremoflo airway oscillometry. (Courtesy of Thorasys, Montreal, Quebec, Canada; and From Galant SP, Komarow HD, Hye-Won S, et al. The case for impulse oscillometry in the management of asthma in children and adults. *Ann Allergy Asthma Immunol* 2017;118(6):667; with permission.)

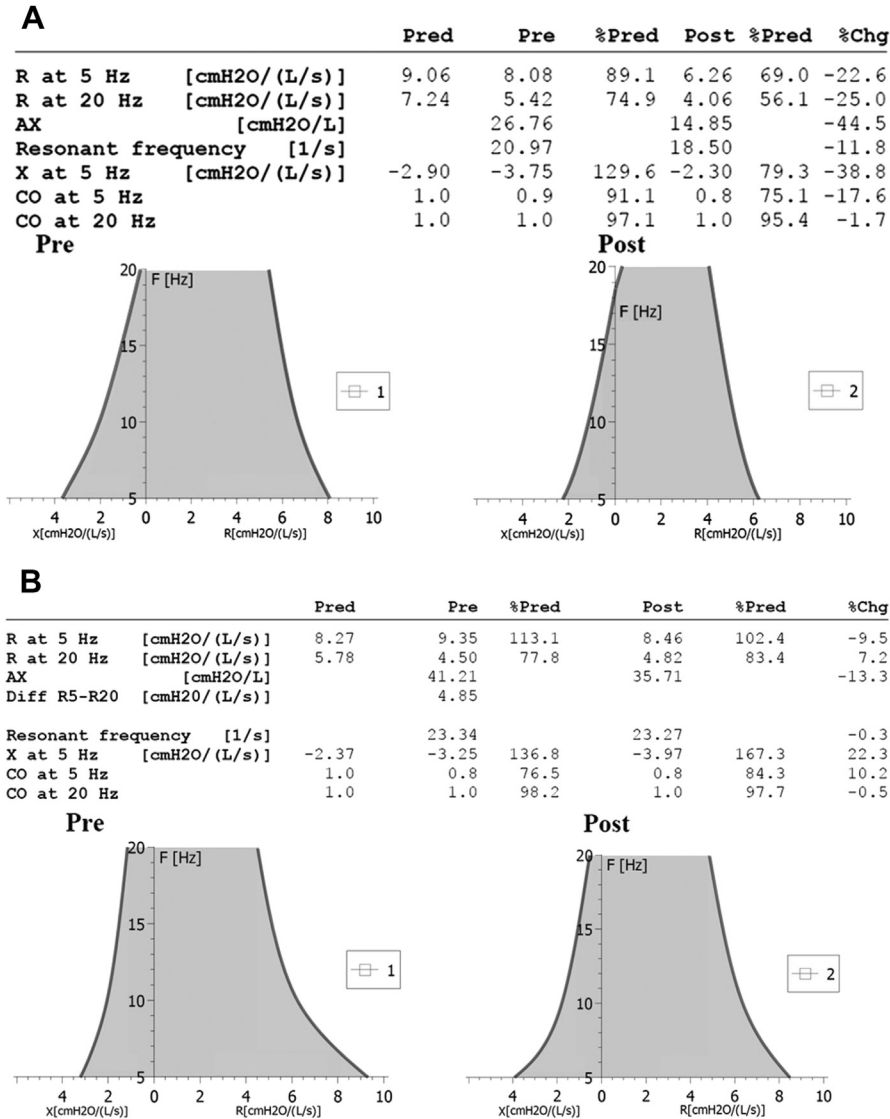


Fig. 3. (A) IOS from a 6-year-old girl with chronic cough and normal spirometry without BDR. IOS reveals normal resistance (R) at 5 Hz and 20 Hz but decreased reactance at 5 Hz and increased AX. These results indicate peripheral airway obstruction. Following administration of bronchodilator, she had a 44.5% decrease in AX and 39% decrease in X5 signifying a positive response to bronchodilator. (B) IOS results from a 9-year-old boy with a history of corrected double aortic arch, tracheomalacia, and suspected asthma. Spirometry was persistently abnormal with flow volume loop suggestive of intrathoracic obstruction. IOS shows normal resistance at 5 Hz and 20 Hz. Reactance at 5 Hz is mildly decreased. There was no significant change in any parameter after bronchodilator. (From Bickel S, Popler J, Lesnick B, et al. Impulse oscillometry: interpretation and practical applications. *Chest* 2014;146(3):845; with permission.)

Investigators have also examined change in IOS parameters after bronchoprovocation tests. Schulze and colleagues³³ evaluated IOS and spirometry during methacholine challenge in 48 children with recurrent wheezing. In the 28 children who had significant changes in both FEV₁ and R5 during the challenge, a lower provocation dose was needed to attain a decrease in R5 than to achieve a 20% decrease in FEV₁,³⁴ implying that IOS may be more sensitive than spirometry in detecting response to methacholine. The investigators also noted that a 45% increase in R5 and/or a decrease in X5 of 0.69 kPa s L⁻¹ predicted a 20% decrease in FEV₁ with adequate sensitivity and specificity. Peripheral airway resistance measurements after methacholine, especially R5-R20, have also been shown to significantly correlate with asthma severity.³⁴ Accordingly, IOS may be more helpful than spirometry in identifying children with more severe disease.

Shi and colleagues¹⁰ studied lung function by spirometry and IOS in more than 100 healthy and asthmatic children. They demonstrated R5-R20 and AX to be useful and more sensitive than spirometry in identifying poorly controlled asthma. In a subsequent study of children with well-controlled asthma (based on clinical and spirometric measures), R5-R20 and AX predicted loss of disease control within 8 to 12 weeks better than spirometry, even when including measurements of forced expiratory flow between the 25th and 75th percentile of forced vital capacity (FVC).¹² A 1-year study of 4- to 7-year-old children with asthma revealed that R5 and R5-R20 were more predictive of asthma exacerbation than FEV₁, FEV₁/forced vital capacity, or methacholine challenge, and that IOS could identify with 80% accuracy which children would have exacerbations.¹¹ A recent report by Knihtilä and colleagues³⁵ determined that abnormalities in IOS measurements of R5 and R5-R20 at age 2 to 7 years were predictive of persistently abnormal FEV₁ after bronchodilator in adolescence. Thus, IOS may allow early detection of peripheral airway obstruction and provide opportunity for intervention to prevent additional decline in lung function.

FRACTIONAL EXHALED NITRIC OXIDE

Measurement of fractional exhaled nitric oxide (FeNO) is a noninvasive technique used to determine eosinophilic airway inflammation and has been studied as a tool to assist with the diagnosis and management of asthma. Nitric oxide (NO) is produced by respiratory epithelial cells, and production is increased in response to inflammatory cytokines in the airways.³⁶ In addition, NO results in dilatation of both blood vessels and airways in the human lung.³⁷ NO is present in exhaled breath, and measurements correlate with sputum eosinophil level.³⁸ Importantly, FeNO levels are elevated in children with asthma compared with those without asthma.^{39,40} Because FeNO can be easily measured in children and reflects eosinophilic airway inflammation, it has significant potential to be useful in the diagnosis and management of asthma in children, especially those too young to perform spirometry. The ATS published an official Clinical Practice Guideline in 2011 addressing use of FeNO for diagnosis of eosinophilic airway inflammation.⁴¹

REFERENCE VALUES FOR FRACTIONAL EXHALED NITRIC OXIDE

An FeNO value greater than 50 parts per billion (ppb) is consistent with eosinophilic airway inflammation and an indication of responsiveness to corticosteroids; however, in children younger than 12 years old, the cutoff may be as low as 35 ppb. Values less than 20 ppb imply that little to no eosinophilic inflammation is present and are considered to be in the normal range.⁴¹ In fact, a study of 150 children demonstrated that using a level of less than 20 ppb as normal had a sensitivity of 86%, specificity of 89%,

positive predictive value of 92%, and negative predictive value of 80%.⁴⁰ Other investigators found increased risk of asthma and low false positive rates of asthma diagnosis for similar cutoff values.^{42–44} Clinical information, such as recent use of inhaled or systemic steroids, is important in interpreting the significance of FeNO, especially intermediate FeNO levels (those between 20 and 35 ppb).

There is more variability in the mean levels reported among studies of FeNO in healthy infants and toddlers than in older children and adults. Meyts and colleagues⁴⁵ measured FeNO during tidal breathing in 89 healthy 4-year-old children and found the mean level of NO was 13 ± 0.4 ppb. A larger study of 121 normal children from 2 to 7 years of age yielded a mean tidal NO level of 3.0 (95% confidence interval 2.7–3.3) ppb.⁴⁶ More recently, a study of 53 healthy children ages 1 to 5 years without current asthma, history of asthma, viral wheezing, allergic rhinitis, eczema, other chronic airway disease, or active respiratory infection and who were not receiving any respiratory medications found a mean FeNO level of 7.1 ppb during tidal breathing (95% CI, 2.8–11.5 ppb).⁴⁷ Larger studies are needed to determine normative values for healthy infant and preschoolers.

There are numerous factors that influence FeNO values, including age, sex, height, atopy, smoking (active or passive exposure to tobacco smoke), consumption of nitrite-containing foods or caffeine,^{48,49} and prematurity.^{50,51} Thus, these factors must be taken into consideration when interpreting FeNO. Testing technique and analyzer type can also affect FeNO levels.⁴¹ However, in children from 1 to 5 years of age, height, weight, age, and sex have been shown not to affect FeNO.⁴⁷ Prematurity has been shown to decrease FeNO levels.^{50,51}

FRACTIONAL EXHALED NITRIC OXIDE AND DIAGNOSIS OF ASTHMA

Measurement of exhaled NO may be useful early in life to determine risk for developing asthma because eosinophilic airway inflammation precedes other criteria for the diagnosis of asthma.⁵² However, FeNO has been shown to be elevated in conditions other than asthma and in both atopic and nonatopic children. For example, in children with recurrent wheezing, FeNO is significantly higher in those who have a positive Asthma Predictive Index (API) compared with those with a negative API (even though the median levels were low in both groups)^{53,54} and children with no wheezing.⁵⁵ FeNO is higher for children with allergic asthma compared with nonallergic asthma⁵⁶ but also in those with allergic sensitization even without asthma.^{56–58}

Despite the overlap in asthma and allergy in producing elevated FeNO, an association between high FeNO levels in childhood and subsequent asthma diagnosis has been reported by several investigators. The Prevention and Incidence of Asthma and Mite Allergy study, a large birth cohort study of 848 children from the Netherlands, demonstrated that elevated FeNO at age 4 is associated with increased physician-diagnosed asthma at age 7.⁵⁹ Similar results were found in a prospective study by Singer and colleagues.⁶⁰ Interestingly, FeNO levels are higher in children with bronchial hyperresponsiveness regardless of atopic status.^{57,61}

FeNO has also been shown to distinguish among wheezing phenotypes in infants, preschoolers, and school-aged children. Gouvis-Echraghi and colleagues⁶² reported that among children less than 3 years of age, those with uncontrolled, nonatopic moderate to severe asthma had the highest levels of exhaled NO. Children with viral-induced wheezing had the lowest levels of FeNO, and those with atopic wheezing had values intermediate to the other 2 wheezing phenotypes. Although FeNO represents eosinophilic inflammation that is typically responsive to steroids, in this population of 79 children, those whose asthma was uncontrolled despite

use of ICS had the highest FeNO levels. Another investigation of FeNO levels in a large cohort of more than 970 children revealed the highest levels in subjects with late-onset wheezing.⁶³ The association between FeNO level and wheezing phenotype was present at age 4 but was even greater by 8 years of age. The same study reported that among atopic children, FeNO was higher in those with transient or occasional wheezing. It is clear that more investigation is necessary in order to understand the role of FeNO measurements in younger children given the complexity of preschool wheezing.

SUMMARY AND FUTURE CONSIDERATIONS

In summary, IOS is a method of obtaining objective measures of lung function in preschool children and others unable to perform spirometry. It is easily performed even by very young children because the test is performed during tidal breathing. IOS measures lung function in both the proximal and the peripheral airways and thereby is more sensitive to detecting airway obstruction and response to bronchodilator than spirometry. Airway resistance measurements that are not available through spirometry are a seminal feature of IOS. Furthermore, the resistance measurements obtained through IOS do not need to be corrected for lung volume, unlike resistance measurements made by plethysmography. IOS has demonstrated utility in distinguishing children with asthma from healthy controls, identifying poorly controlled disease, and predicting asthma exacerbation and loss of disease control. IOS, although not as readily available as spirometry, can be a useful tool in diagnosis and management of asthma in preschoolers. However, reference values for key parameters in IOS, such as AX, are still lacking, highlighting the need for further study of IOS in order to make this valuable technique more universally applicable.

FeNO is a simple noninvasive tool to measure eosinophilic airway inflammation, and levels can be used to predict response to corticosteroids. Both asthma and atopy can produce elevated FeNO. Although elevated FeNO levels have been shown to discriminate among wheezing phenotypes in infancy and school-aged children and correlate with later diagnosis of asthma diagnosis, the best use of FeNO remains unclear. FeNO levels are affected by numerous factors, and thus, interpretation of levels must be done in clinical context. FeNO levels should be viewed as easily obtainable data that, when used with other clinical and objective data, may be helpful in the diagnosis of asthma.

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