Relating small airways to asthma control by using impulse oscillometry in children

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Background: Previous reports suggest that the peripheral airways are associated with asthma control. Patient history, although subjective, is used largely to assess asthma control in children because spirometric results are many times normal values. Impulse oscillometry (IOS) is an objective and noninvasive measurement of lung function that has the potential to examine independently both small- and large-airway obstruction.

Objective: We sought to determine the utility of IOS in assessing asthma control in children.

Methods: Asthmatic and healthy children (6-17 years) were enrolled in the study. Spirometric and IOS (resistance of the respiratory system at 5 Hz [R5] and 20 Hz [R20], reactance of the respiratory system at 5 Hz [X5], resonant frequency of reactance [Fres], and area under the reactance curve between 5 Hz and Fres [reactance area {AX}]) values were collected in triplicate before and after a bronchodilator was administered. The physicians were blinded to the IOS measurements and assessed asthma control using American Thoracic Society guidelines.

Results: Small-airway IOS measurements, including the difference of R5 and R20 [R5-20], X5, Fres, and AX, of children with uncontrolled asthma (n = 44) were significantly different from those of children with controlled asthma (n = 57) and healthy children (n = 14), especially before the administration of a bronchodilator. However, there was no difference in large-airway IOS values (R20). No differences were found between children with controlled asthma and healthy children in any of the end points. Receiver operating characteristic analysis showed cut points for baseline R5-20 (1.5 cm $H_2O \cdot L^{-1} \cdot s$) and AX (9.5 cm $H_2O \cdot L^{-1}$) that effectively discriminated controlled versus uncontrolled asthma (area under the curve, 0.86 and 0.84) and correctly classified more than 80% of the population.

Conclusion: Uncontrolled asthma is associated with small-airways dysfunction, and IOS might be a reliable and noninvasive method to assess asthma control in children.

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Key words: *Reactance, resistance, control, pediatric, lung function*

Asthma is a lung disease characterized by airway obstruction and is one of the most common chronic disorders in children. Early diagnosis and control of asthma in children is very important because appropriate treatments can affect the course of the disease. Current guidelines emphasize that treatment decisions should be based on achieving and maintaining asthma control.[1] However, assessing asthma control in children is particularly challenging for many reasons, including a discrepancy in perceived symptoms between child and parents[2,3] and the poor correlation between symptoms and traditional objective tests, such as spirometry.[4,5] Therefore the development of new, reliable, and noninvasive methods to assess asthma control in children remains a priority and is essential for the effective treatment of asthma.

Increasing evidence indicates that peripheral-airway function is associated with asthma control.[6-10] Conventional spirometry is regarded as the gold standard assessment of airflow obstruction; however, it has a limited capacity to distinguish the distal and proximal airways. For example, the most frequently used measurement, FEV_1, mainly reflects the large airways,[11,12] and forced expiratory flow at 25% to 75% of forced vital capacity (FEF_{25-75}), which is believed to be a marker of the small airways,[13,14] suffers from poor reproducibility.[15] Finally, traditional spirometry requires the subject to perform forced expiratory maneuvers (ie, effort-dependent maneuvers), which are difficult for young children and also hamper reproducibility.

There are different techniques to detect small-airway obstruction, such as heliox flow-volume loops[16]; however, they generally require forced exhalation maneuvers, which can be difficult for young children to perform.

More recently, a much simpler technique, impulse oscillometry (IOS), has been increasingly used as a noninvasive method to assess airway resistance and reactance in children.[17,18] IOS requires minimal patient cooperation, is effort independent, and separately quantifies the degree of obstruction in the central and peripheral airways.[19] IOS has been shown to be useful in the diagnosis of asthma[20,21] and small-airway impairment in children[7]; however, studies on the utility of IOS to assess asthma control are limited, and there are no published cut points for IOS measurements to determine asthma control in children. Therefore the aim of the study was to investigate the utility of IOS in a pediatric population to detect uncontrolled asthma and to determine the cut points that discriminate controlled versus uncontrolled asthma.

METHODS

Study participants

Children aged 6 to 17 years who were being actively treated for asthma on the Children's Hospital of Orange County Breathmobile were enrolled in the

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Abbreviations used
AUC: Area under the curve
AX: Reactance area
BDR: Bronchodilator response of FEV_1
FEF_{25-75}: Forced expiratory flow at 25% to 75% of forced vital capacity
Fres: Resonant frequency of reactance
FVC: Forced vital capacity
IOS: Impulse oscillometry
R5: Resistance of the respiratory system at 5 Hz
R20: Resistance of the respiratory system at 20 Hz
R5-20: Difference of R5 and R20
ROC: Receiver operating characteristic
X5: Reactance of the respiratory system at 5 Hz

study. The Breathmobile is a mobile asthma clinic that travels to schools, community clinics, and child development centers in low-income neighborhoods throughout Orange County, California, and provides comprehensive asthma care to children who have or are at risk for asthma. Children were included in the study if they were 6 to 17 years of age and had a physician's clinical diagnosis of asthma. Patients were excluded from the study if they were given a diagnosis of any other pulmonary or cardiac disease, had any history of smoking within 12 months of enrollment, or were not able to perform a standard spirometric maneuver. Healthy children without a history of asthma, allergies, or other lung diseases were also enrolled in the study as control subjects. The study was approved by the Institutional Review Boards of the University of California, Irvine, and the Children's Hospital of Orange County. Written informed consent and assent were obtained from all participants and their parents or guardians.

Protocol

All study procedures were performed on the Breathmobile vans.[22] Participants received a nursing assessment to identify their health status and underwent skin prick testing to 12 common allergens to assess atopic status. Categorization as atopic was based on a single positive wheal response (3 mm larger than that elicited by the negative control). Each subject was required to report a complete symptom history during the past 6 to 8 weeks, which included, for example, daytime symptoms, nighttime symptoms, exercise symptoms, and exacerbations. Baseline IOS and standard spirometric maneuvers were performed in accordance with American Thoracic Society/European Respiratory Society standards.[23] IOS was performed before spirometry to avoid the influence of forced exhalation maneuvers on airway function.[24] Albuterol (2 puffs of 180 μg) was then administered through a metered-dose inhaler with a spacer to assess bronchodilator responsiveness. Spirometric and IOS measurements were repeated 10 minutes after bronchodilator administration. Physicians were blinded to the IOS data. They evaluated the participants' asthma severity, control, and treatment plan by using criteria defined in the National Asthma Education and Prevention Program/National Heart, Lung, and Blood Institute guidelines,[25] which included traditional spirometry. For subjects 5 to 11 years of age, controlled asthma is defined as 1 or fewer nighttime symptoms per month, 2 or less days per week of daytime symptoms or short-acting β-agonist use, 80% or greater FEV_1 and FEV_1/forced vital capacity (FVC) ratio, and no interference with normal activities. For subjects 12 years and older, criteria for control are similar except for 2 or fewer nighttime symptoms per month.

Spirometry

Standard spirometry was performed in the sitting position with the Vmax Encore 20c spirometer (CareFusion Respiratory, Yorba Linda, Calif). The best spirometric measures of at least 3 reproducible attempts were recorded for analysis. In accordance with American Thoracic Society guidelines,[23] reference values from the Third National Health and Nutrition Examination Study were used to interpret spirometric results for participants aged 8 to 17 years.[26] For participants younger than 8 years, Morris/Polgar reference values were used.[27]

IOS

The Vmax Encore 20c is fully integrated with an IOS system. IOS requires the subject to breath normally (tidal breathing) into a mouthpiece while a loudspeaker generates an impulse-shaped pressure signal into the respiratory system. The IOS system was calibrated each day before the measurements with a 3-L syringe. IOS measurements were performed in the sitting position with participants wearing nose clips. Participants breathed tidally into the IOS mouthpiece for 30 seconds, with the cheeks supported by the hands of trained technicians. The technicians evaluated the efforts and made sure each observation consisted of at least 3 reproducible maneuvers that did not have artifacts caused by coughing, swallowing, vocalization, or breath holding.

LabManager Version 4.67.0.1 (CareFusion Germany GmbH, Hoechberg, Germany) was used to calculate the pressure-flow relationship and calculate the resistance and reactance of the respiratory system as a function of oscillation frequency. The representative tracing and definitions of the IOS indices, including resistance of the respiratory system at 5 Hz (R5), resistance of the respiratory system at 20 Hz (R20), reactance of the respiratory system at 5 Hz (X5), resonant frequency of reactance (Fres), and reactance area (AX) are presented schematically (Fig 1). Acceptable coherence values ($r^2 > 0.6$ at 5 Hz and $r^2 > 0.9$ at 10 Hz and higher frequencies) were used as recommended[28] to exclude nonlinear data. Results were acceptable if the coefficient of variation of at least 2 sets of data was less than 10%. Mean values of R5, R20, X5, Fres, and AX calculated from the measurements were used for further analysis.

The resistance is the in-phase component of lung impedance. Because low oscillation frequencies (<15 Hz) can be transmitted more distally in the lungs compared with higher frequencies,[19] R5 reflects obstruction in both the small and large airways, R20 reflects the large airways only, and the difference of R5 and R20 (R5-20) is an index of the small airways only.[29] The resistance will become more frequency dependent if peripheral resistance increases.[30] Reactance is the out-of-phase component related to the capacitative and the inertive properties of the airways. At low frequencies, capacitative pressure loss is large compared with inertive pressure loss, whereas at higher frequencies, the inertive properties dominate. The intermediate frequency at which the total reactance is 0 is known as the resonant frequency (Fres) when the magnitudes of the capacitative and inertive pressure loss are the same. AX is the total reactance (area under the curve [AUC]) at all frequencies between 5 Hz and Fres (Fig 1). Thus X5, Fres, and AX all reflect changes in the degree of obstruction in the peripheral airways.[19]

Sample size and statistical analysis

Gaylor et al[31] reported a 20% to 30% decrease in the frequency dependence of resistance and Saadeh et al[32] found a 40% to 50% decrease in AX after inhaled corticosteroid treatment. Thus we estimated a difference in distal airway IOS of 35% between subjects with controlled and uncontrolled asthma before bronchodilator. On the basis of this difference, a sample size of 44 subjects in each asthma group is needed to provide 90% statistical power to detect a 35% difference at a significance level of .05 by using 1-way ANOVA.

Because of the nonnormal distributions of the measurements and relatively small sample size, the parameters were summarized by medians with ranges, unless indicated otherwise. The nonparametric Mann-Whitney *U* test was used to detect the difference in the outcomes between groups. The paired Wilcoxon signed-rank test was applied to test the difference before and after bronchodilator within groups. The receiver operating characteristic (ROC) method was conducted to evaluate the utility of different oscillometric variables in distinguishing children with uncontrolled asthma from those with controlled asthma. ROC areas with estimated SEs were calculated for each of the IOS and spirometric variables. In addition, optimized IOS cut points were calculated, and sensitivity, specificity, positive predictive value, negative predictive value, and the correctly classified ratio were estimated at each of the cut points.

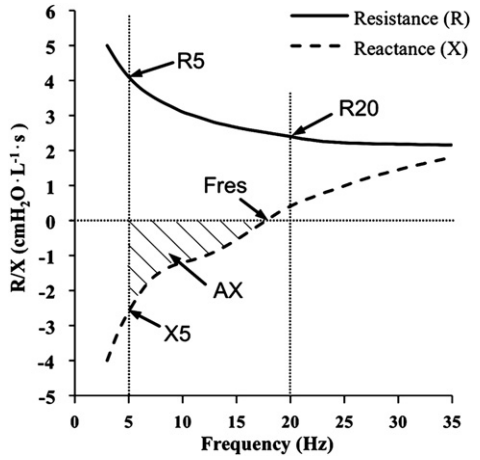

FIG 1. Schematic illustration of IOS indices over oscillation frequency, including R5, R20, Fres, X5, and AX.

General linear regression and ANOVA were later applied to describe the relationships between small-airway IOS versus asthma control and demographic parameters. The criterion for this analysis was the physician's assessed asthma control status, which included standard spirometric results. The statistical analyses were made with the R package (2.11.0). Statistical significance was established at a *P* value of less than .05.

RESULTS

Study sample

Fourteen healthy control subjects and 107 asthmatic subjects were consented for the study. One hundred one (94%) of the asthmatic subjects were able to perform acceptable IOS maneuvers; 6 patients were excluded from the study because their IOS measurements had coherence lower than the recommended values. On the basis of a physician's assessment, 57 (56%) of the 101 asthmatic subjects had controlled asthma and 44 (44%) had uncontrolled asthma. The demographics of the 3 asthma groups are presented in Table I. The majority of our study population identified themselves as Hispanic (71% of healthy control subjects and 82% of asthmatic subjects). Of the subjects with asthma, both controlled and uncontrolled, 77% had positive skin test results and were categorized as atopic. Ninety-two percent of the asthmatic subjects were given a diagnosis of mild-to-moderate asthma. Unpaired Mann-Whitney *U* tests showed no statistical difference in age, sex, height, or weight across groups. There was no statistical difference between controlled and uncontrolled asthma in the step level of management. However, body mass indexes of subjects with uncontrolled asthma were higher compared with those of subjects with controlled asthma and healthy subjects ($P < .05$).

Standard spirometry

Results of standard spirometry were compared between healthy subjects, subjects with controlled asthma, and subjects with uncontrolled asthma (Table II). Results of spirometry were very similar for healthy subjects and subjects with controlled asthma. FEF_{25-75}, FEV_1 (percent predicted), FEF_{25-75} (percent predicted), and FEV_1/FVC ratio were higher in healthy subjects and subjects with controlled asthma compared with values seen in subjects with uncontrolled asthma. Bronchodilator response of FEV_1 (BDR; percentage change from baseline) in healthy subjects and subjects with controlled asthma was statistically lower than that seen in subjects with uncontrolled asthma. Although significant differences were detected, the sensitivities of spirometric outcomes for assessing uncontrolled asthma were low, especially for FEV_1 and BDR. In the uncontrolled asthma group, there were 42 (95%), 16 (36%), 17 (39%), and 28 (64%) subjects who had FEV_1 percent predicted, FEF_{25-75} percent predicted, FEV_1/FVC ratio, and BDR values, respectively, within the normal range based on the guidelines.[25,33]

IOS

The comparison of IOS measurements between the 3 groups before and after bronchodilator administration and the bronchodilator responses are presented using box plots (Fig 2). Healthy subjects and subjects with controlled asthma had no statistical differences in IOS measurements. For subjects with uncontrolled asthma, R20 was also not different from values seen in healthy subjects or subjects with controlled asthma. However, R5, R5-20, Fres, X5, and AX values were all statistically different in subjects with uncontrolled asthma compared with those in healthy subjects and subjects with controlled asthma. For each of the 5 indices, the most significant differences were detected before bronchodilator administration. Paired Wilcoxon signed-rank tests showed that all IOS outcomes were significantly improved after bronchodilator in all 3 groups.

Distinguishing uncontrolled and controlled asthma

The discriminative properties of the oscillometric variables to distinguish subjects with uncontrolled asthma from subjects with controlled asthma are shown by using ROC (Fig 3). Before bronchodilator, the estimated AUCs for R5-20, R5, and R20 were 0.86, 0.71, and 0.5, respectively. The AUCs for AX, Fres, and X5 before bronchodilator were all greater than 0.8, with AX being slightly better than the other 2. After bronchodilator, the AUCs for R5-20, AX, and Fres decreased to less than 0.8, AUCs for R5 and X5 decreased to less than 0.7, and AUCs for R20 remained near 0.5. The trends for the bronchodilator response (change from baseline) for the 3 resistances were similar to those of the postbronchodilator values. For the bronchodilator response of the reactance indices, the AUC for ΔAX (0.81), where Δ refers to the change from baseline, and ΔX5 (0.79) were similar to the prebronchodilator AUC, whereas the AUC for ΔFres decreased to 0.66.

The ROCs were used to determine the performance of the optimized IOS cut points in screening uncontrolled from controlled asthma for prebronchodilator and the bronchodilator response indices (Table III). The cut points were selected by maximizing the sum of sensitivity and specificity. Before bronchodilator, the best indices were R5-20 and AX, which correctly classified 83.2% and 85.1% of the patients at a cut point of 1.5 cm $H_2O \cdot L^{-1} \cdot s$ and 9.5 cm $H_2O \cdot L^{-1}$, respectively. These cut points also had positive and negative predictive values of greater than 0.80.

The best index for the bronchodilator response was ΔAX, which correctly classified 75% of the patients at a cut point of 2.7, with positive and negative predictive values of 73.1% and 87.5%, respectively. Therefore the bronchodilator response of AX was not as useful as AX before bronchodilator in screening for uncontrolled asthma. The cut points for the change in other IOS

TABLE I. Demographics for different asthma status

	Asthma status			*P* value*		
	Healthy (n = 14)	Controlled (n = 57)	Uncontrolled (n = 44)	Healthy vs controlled	Healthy vs uncontrolled	Controlled vs uncontrolled
Age (y)	13	12	11	.6945	.6807	.4050
Male/female sex (%)	36/64	51/49	59/41	.3163	.1327	.4157
Height (cm)	156	154	151	.6962	.2373	.2525
Weight (kg)	50	51	54	.9137	.5487	.2837
Body mass index (kg/m^2)	20.9	20.8	23.8	.7560	.0299	.0086
Atopic (%)	0	77	77	<.0001	<.0001	.8831
Medication step (%), noncompliant/1/2/3/4		27/12/35/21/5	27/18/34/16/5			.5295

Demographic measurements are presented as medians.
*The Mann-Whitney *U* test was applied to detect the group difference between healthy subjects versus subjects with controlled asthma, healthy subjects versus subjects with uncontrolled asthma, and subjects with controlled asthma versus subjects with uncontrolled asthma.

TABLE II. Standard spirometry for different asthma status

	Asthma status			*P* value*		
	Healthy (n = 14)	Controlled (n = 57)	Uncontrolled (n = 44)	Healthy vs controlled	Healthy vs uncontrolled	Controlled vs uncontrolled
FVC (L)	3.3	3.1	3.1	.9819	.7359	.6662
FEV_1 (L)	3.0	2.7	2.4	.6130	.0982	.0587
FEF_{25-75} ($L \cdot s^{-1}$)	3.1	3.0	2.3	.2914	.0008	<.0001
FVC (% predicted)	102	106	107	.2140	.2477	.7365
FEV_1 (% predicted)†	104 (100)	100 (95)	94 (95)	.4391	.0195	.0196
FEF_{25-75} (% predicted)†	100 (100)	92 (96)	74 (36)	.1218	.0001	<.0001
FEV_1/FVC ratio (%)†	89 (93)	87 (79)	79 (39)	.2102	<.0001	<.0001
BDR (%)†	1.6 (100)	3.2 (95)	6.4 (64)	.3145	.0046	.0009

Spirometric measurements are presented as medians.
*The Mann-Whitney *U* test was applied to detect the group difference between healthy subjects versus subjects with controlled asthma, healthy subjects versus subjects with uncontrolled asthma, and subjects with controlled asthma versus subjects with uncontrolled asthma.
†Percentage of patients with the spirometric parameter in the normal range are presented in parentheses. FEV_1 percent predicted of less than 80% of predicted value, FEF_{25-75} percent predicted of less than 65% of predicted value, FEV_1/FVC ratio of less than 80%, and BDR of greater than 10% are considered abnormal.

parameters before and after bronchodilator had AUCs of less than than 0.8 and were not good for discriminating asthma control.

DISCUSSION

Our study compared IOS indices of small- and large-airway resistance and reactance in children with controlled and uncontrolled asthma and established cut points to identify uncontrolled asthma. Prebronchodilator (or baseline) values for small-airway resistance (R5-R20) and reactance (AX) performed best, resulting in sensitivities, specificities, positive predictive values, and negative predictive values that all exceeded 0.80. To our knowledge, this is the first study to investigate the utility of IOS parameters to determine asthma control status in a pediatric population. Our results suggest that indices from IOS are useful in determining control status in asthmatic children and add additional information to standard spirometry.

Resistance versus reactance

Previous investigators have shown that peripheral- or small-airway function evaluated based on IOS correlates with healthy status and asthma symptoms in children and adults,[9,34,35] which is consistent with our results in children. We compared the utility of 4 peripheral airway variables (R5-20, Fres, X5, and AX) from IOS, which characterize both airways resistance and reactance, in distinguishing asthma control. The results suggested that increased indices representing both resistance (R5-20) and reactance (AX) were the best indicators of uncontrolled asthma. This suggests that both a decrease in small-airway caliber and an increase in airway wall tone contribute to asthmatic symptoms in children. The resistance to flow through a tube is inversely related to the radius of the tube to the fourth power[36]; thus a larger pressure is required to force air through a tube of smaller diameter. In contrast, AX reflects the reactance of the peripheral airways at low frequencies and thus reflects the ability of the peripheral lung to store capacitative energy. As the peripheral lung becomes less compliant (stiffer), it cannot store as much capacitative energy and requires a larger pressure to inflate. Thus an increase in small-airway wall tone will decrease (larger negative value) the reactance and increase AX.

R5-20 and AX values at baseline are strongly correlated (r^2 = 0.837), which is consistent with previous reports.[19,30] Airway resistance and reactance are likely coupled because, at equivalent airway pressures, a stiffer small airway will have a smaller caliber, which would increase the resistance to flow. In either case the increase in resistance and reactance of the small airways results in a larger pressure during inspiration to inflate the lungs. A larger pressure requires more exertion by the respiratory muscles and is thus the probable mechanism underlying the relationship between the IOS parameters and asthma control. Therefore as indices determining asthma control, R5-20 and AX do not provide independent information.

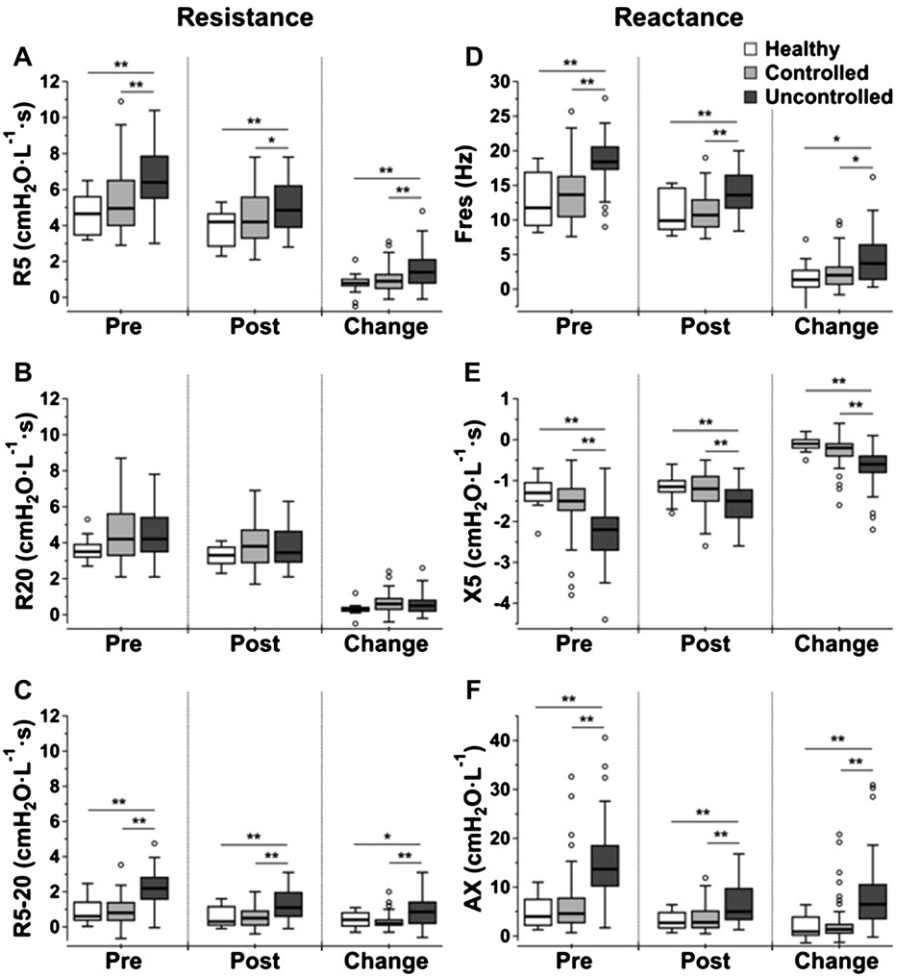

FIG 2. Box plots of IOS measurements (**A,** R5; **B,** R20; **C,** R5-20; **D,** Fres; **E,** X5; and **F,** AX) for different asthma groups before and after bronchodilator and the bronchodilator response. The *boxes* represent 25th-75th percentiles with medians, and the *top* and *bottom tails* represent the highest/lowest scores without outliers. An outlier is defined as any value that lies more than 1.5 times the interquartile range from either end of the box. Significance level of group difference by using the unpaired Mann-Whitney *U* test: $*P < .05$ and $**P < .01$.

The enhanced discriminatory power of AX relative to the other parameters that reflect reactance in the small airways (Fres and X5) is likely due to the fact that AX is an index that captures the integrated response over the entire range of low frequencies (Fig 1).[18,37,38] As a result, AX is less variable than the reactance at a specific frequency, as is the case for both Fres and X5. This is supported by previous work that demonstrates a large variance for X5 in children.[24,34]

Healthy subjects versus subjects with controlled asthma

Our study demonstrates that the controlled asthma group and healthy control subjects have no differences in any of the IOS measurements (Fig 2). In contrast, studies have shown that the IOS parameters at baseline were statistically different between children with and without asthma.[20,39,40] However, these latter studies did not consider asthma control. A potential limitation of our study is the relatively small number of healthy subjects, which could result in failure to detect more subtle differences between healthy children and children with controlled asthma.

Bronchodilator response

Previous reports have shown that the IOS-assessed bronchodilator response was useful in discriminating healthy versus asthmatic children.[20,21,34] This is consistent with our results; however, our results suggest that baseline values of IOS are even more effective at detecting uncontrolled asthma. This is different compared with traditional BDR (percentage change in FEV_1), which has been shown to be a more sensitive indicator of asthma control compared with baseline spirometric results.[41] This difference might be related to techniques, population, status of control, and the fact that IOS can distinguish small and large airways, as well as airways resistance and reactance.

Finally, we chose to use the change in the absolute value of the IOS parameters to define the bronchodilator response instead of the percentage change, which is commonly used for FEV_1. This choice is based on the fact that IOS indices (eg, AX) increase as asthma symptoms increase, thus creating a larger baseline value, and decrease after administration of a bronchodilator. In contrast, indices from traditional spirometry (eg, FEV_1) decrease with increasing asthma symptoms, creating a smaller baseline. Thus the percentage change for IOS will tend to be

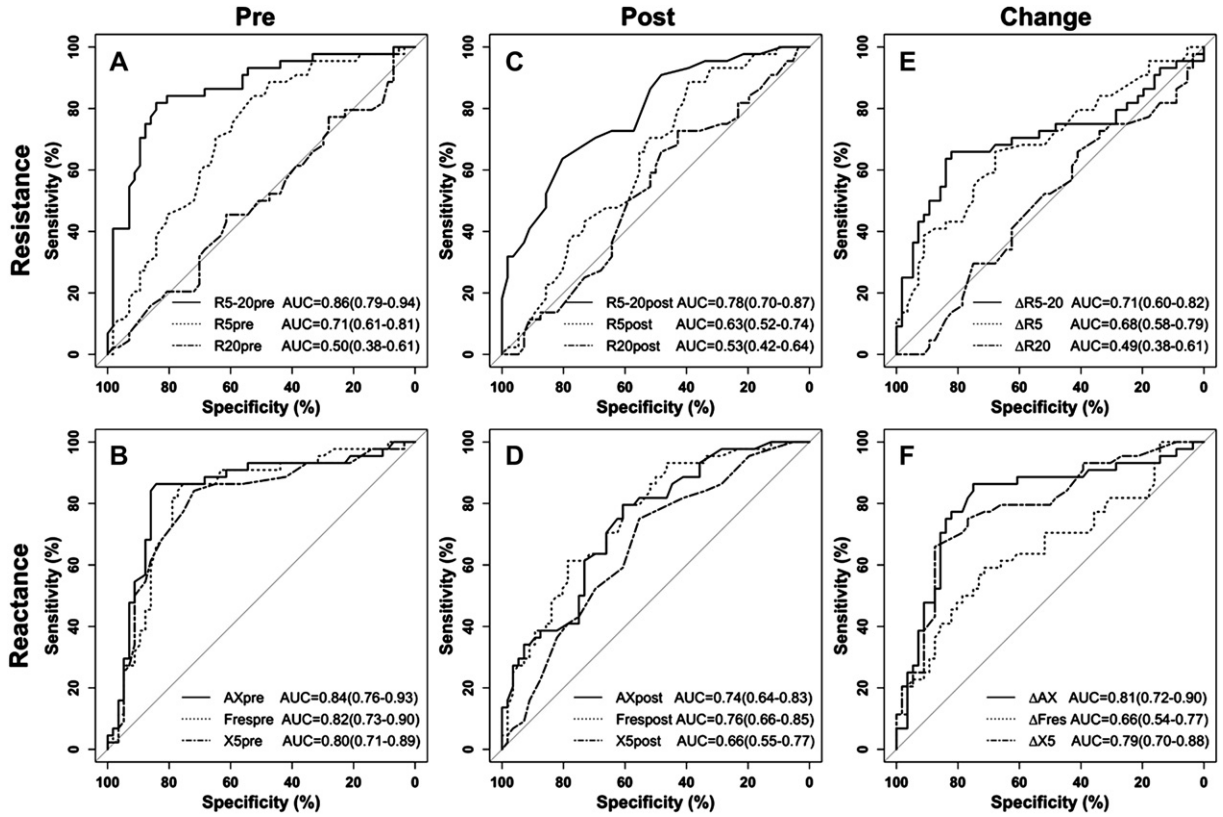

FIG 3. ROC curves of IOS measurements in predicting physicians' assessed uncontrolled asthma, including resistance **(A)** and reactance **(B)** before bronchodilator, resistance **(C)** and reactance **(D)** after bronchodilator, and the bronchodilator response of resistance **(E)** and reactance **(F)**. R5-20, X5, Fres, and AX values before bronchodilator and the bronchodilator response of AX all predict asthma control status (AUC > 0.8). AUCs are presented as means (95% CIs).

TABLE III. Performance of IOS cut points in screening uncontrolled versus controlled asthma

	Cut point*	Sensitivity	Specificity	PPV (%)	NPV (%)	Correctly classified (%)	AUC
Before bronchodilator							
R5	5.2	0.84	0.53	57.8	81.1	66.3	0.71
R5-20	1.5	0.82	0.84	80.0	85.7	**83.2**	**0.86**
Fres	16.0	0.86	0.68	67.9	86.7	76.2	**0.82**
X5	−1.8	0.84	0.72	69.8	85.4	77.2	**0.80**
AX	9.5	0.86	0.84	80.9	88.9	**85.1**	**0.84**
Bronchodilator response							
ΔR5	1.0	0.68	0.59	56.6	70.2	63.0	0.68
ΔR5-20	0.6	0.66	0.82	74.4	75.4	75.0	0.71
ΔFres	3.0	0.59	0.66	57.8	67.2	63.0	0.66
ΔX5	−0.5	0.71	0.79	72.1	77.2	75.0	0.79
ΔAX	2.7	0.86	0.75	73.1	87.5	75.0	**0.81**

NPV, Negative predictive value; *PPV*, positive predictive value.
*Cut points of R5, R5-20, and X5 are in centimeters of H_2O per liter per second, the cut point of Fres is in hertz, and the cut point of AX is in centimeters of H_2O per liter. The cut points were selected by maximizing the total of sensitivity and specificity. Correctly classified ratios of greater than 80% and AUCs of greater than 0.80 are in boldface.

smaller than for traditional spirometry, and the effect of the bronchodilator will be blunted.

Spirometry versus IOS

Numerous studies have investigated the correlation between traditional spirometry and IOS. For example, R5 correlates with FEV_1 at baseline[42,43] and during mannitol or methacholine challenge.[44,45] Although FEV_1 measurement is the most widely used test for airflow obstruction, it is generally considered an index of large airway caliber. In our study no differences in FEV_1 were detected between subjects with controlled versus uncontrolled asthma, and we found a large proportion (95%) of asthmatic children whose FEV_1 percent predicted values were in the normal range (>80% of predicted value) despite a physician's diagnosis of uncontrolled asthma. One possible explanation is

that asthma control status primarily reflects small- or peripheral-airway obstruction. Alternatively, FEF_{25-75} is considered to be a more specific marker for obstruction in the distal airways. Our results suggest that FEF_{25-75} percent predicted was more sensitive in detecting uncontrolled asthma than FEV_1 because a lower percentage (36%) of children with uncontrolled asthma had values greater than the normal cutoff (65% of predicted value).[33] These observations are consistent with our findings in IOS in which only those indices that reflect the small airways could predict asthma control. However, neither FEV_1 nor FEF_{25-75} was as effective as small-airway IOS indices in detecting poorly controlled asthma.

Finally, although not rigorously correct because the physician used spirometric results as part of the criteria to determine control, we performed additional ROC analysis to gauge the performance of spirometry in detecting uncontrolled asthma. The AUCs for FEF_{25-75}, FEF_{25-75} percent predicted, FEV_1/FVC ratio, and BDR (0.74, 0.79, 0.81, and 0.69, respectively) were all less than the small-airway IOS indices or resistance and reactance, despite the fact that spirometric results were part of the criteria used by the physician to assess control.

Cut points of IOS to discriminate asthma control

Our study was able to determine cut points of R5-20 and AX for discriminating asthma control by using the absolute value of each index. However, the cut points might be affected by other variables, such as age, sex, height, weight, body mass index, and race. Previous studies have shown that IOS measurements correlate with age, sex, and height.[46-49] In our study ANOVA showed that R5-20 or AX had no correlation with sex, weight, or body mass index but did correlate with age and height ($P <$ .01). Thus caution should be exercised in using absolute values for cut points in children who differ in age or height. Furthermore, our population of children was primarily of Hispanic ethnicity, which has been shown to affect baseline values of traditional spirometry.[26] There are limited IOS references for baseline values in healthy children for our study age group, and thus additional data are necessary before cut points expressed as percent predicted of normal values can be used.

Conclusion

The standard asthma history, which incorporates impairment and risk factors, as defined by National Asthma Education and Prevention Program guidelines, remains a subjective tool in assessing control. Standard spirometric criteria provide important objective information, but values are usually normal in children with mild-to-moderate asthma. In addition, spirometric results might not accurately reflect small-airway dysfunction, which is an important determinant of asthma control. As suggested by our study, IOS, which measures small-airway obstruction, can provide additional objective information useful for assessing asthma control in children as an adjunct to the traditional history and spirometry.

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Clinical implications: Small-airway indices of IOS identify children with uncontrolled asthma and thus might be useful in the clinical assessment of asthma control.

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