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Relating small airways to asthma control using impulse oscillometry in children

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Abstract

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

Objective—To determine the utility of IOS in assessing asthma control in children.

Methods—Asthmatic and healthy children (6–17 yrs) were enrolled in the study. Spirometry and IOS (resistance at 5 and 20 Hz, R5 and R20, respectively, reactance at 5 Hz, X5, resonant frequency, Fres, and area under the reactance curve between 5 Hz and Fres, AX) were collected in triplicate before and after a bronchodilator was administered. The physicians were blinded to the IOS measurements and assessed asthma control using ATS guidelines.

Results—Small airway IOS measurements, including R5-20, X5, Fres and AX, of children with uncontrolled asthma (n=44) were significantly different from those of controlled asthmatic (n=57) and healthy (n=14) children, especially prior to the administration of a bronchodilator. However, there was no difference in large airway IOS (R20). No differences were found between controlled asthmatic and healthy children in any of the endpoints. ROC analysis showed cut-points for baseline R5-20 (1.5 $cmH_2O{\cdot}L^{-1}{\cdot}s$) and AX (9.5 $cmH_2O{\cdot}L^{-1}$) that effectively discriminated controlled versus uncontrolled asthma (AUC=0.86 and 0.84), and correctly classified more than 80% of the population.

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Conclusion—Uncontrolled asthma is associated with small airways dysfunction, and IOS may be a reliable non-invasive method to assess asthma control in children.

Keywords

reactance; resistance; control; pediatric; lung function

INTRODUCTION

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 may impact 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 the 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 non-invasive methods to assess of 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 distal and proximal airways. For example, the most frequently used measurement (the forced expiratory volume in one second, FEV_1) mainly reflects the large airways (11, 12), and the mid-forced expiratory flow ($FEF_{25–75}$), believed to be a marker of small airways (13, 14), suffers from poor reproducibility (15). Finally, traditional spirometry requires the subject to perform forced expiratory maneuvers (i.e. effort-dependent), which is difficult for young children and also hampers 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 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 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 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 asthma, or are at risk for asthma. Children were included in the study if they were 6–17 years of age and had a clinical diagnosis of asthma by a physician. Patients were excluded from the study if they were diagnosed with

any other pulmonary or cardiac disease, had any history of smoking within 12 months of their enrollment, or if they were not able to perform a standard spirometry maneuver. Healthy children without 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 skin prick testing of eight common allergens to assess atopic status. Categorization of atopic was based on a single positive wheel (3 millimeters greater than negative control). Each subject was required to report a complete symptom history during the past 6–8 weeks, which includes daytime symptoms, nighttime symptoms, exercise symptoms and exacerbations, etc.. Baseline IOS and standard spirometry maneuvers were performed in accordance with ATS/ERS standards (23). IOS was performed prior to spirometry to avoid influence of forced exhalation maneuvers on airway function (24). Albuterol (2 puffs; 180 mcg) was then administered from a metered dose inhaler with a spacer to assess bronchodilator responsiveness. Ten minutes after bronchodilator administration, spirometry and IOS measurements were repeated. Physicians were blinded to the IOS data. They evaluated the participants' asthma severity, control, and treatment plan using criteria defined in the NAEPP/NHLBI guidelines (25), which included traditional spirometry. For age 5–11, controlled asthma is defined as ≤1/month nighttime symptoms, ≤2 days/wk daytime symptoms or SABA use, ≥80% FEV_1 and FEV_1/FVC and no interference with normal activities. For ages 12 and older, criteria for control are similar except ≤2/month nighttime symptoms.

Spirometry

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

Impulse Oscillometry (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 prior to the measurements using a 3-liter syringe. IOS measurements were performed in the sitting position with participants wearing nose clips. Participants tidally breathed 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 which 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 R5, R20, X5, Fres and AX are presented schematically (Fig. 1). Acceptable coherence values (r^2>0.6 at 5Hz and r^2>0.9 at 10Hz and higher frequencies) were used as recommended (28) to exclude non-linear data. Results

were acceptable if the coefficient of variation of at least 2 sets of data was < 10%. Mean values of R5, R20, X5, Fres and AX calculated from the measurements were used for further analysis.

The resistance (R) is the in-phase component of the lung impedance. Because low oscillation frequencies (<15Hz) can be transmitted more distally in the lungs compared to higher frequencies (19), R5 reflects obstruction in both small and large airways, R20 reflects large airways only, and R5-20 is an index of the small airways only (29). The resistance will become more frequency-dependent if peripheral resistance increases (30). Reactance (X) 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 to inertive pressure loss, while 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) at all frequencies between 5Hz 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 20–30% decrease in the frequency-dependence of resistance and Saadeh et al (32) found a 40%–50% decrease in AX after inhaled corticosteroid treatment. Thus, we estimated a difference in distal airway IOS of 35% between controlled and uncontrolled asthma pre bronchodilator. Based on this difference, a sample size of 44 subjects in each asthmatic group is needed to provide 90% statistical power to detect a 35% difference at a significance level of 0.05 using one-way analysis of variance.

Because of the non-normal distributions of the measurements and relatively small sample size, the parameters were summarized by medians with ranges, unless indicated otherwise. The non-parametric Mann-Whitney U Test was used to detect the difference of 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 controlled asthma. ROC areas with estimated standard errors were calculated for each of the IOS and spirometry variables. In addition, optimized IOS cut-points were calculated, and sensitivity and specificity, positive predictive and negative predictive values, and the correctly classified ratio were estimated at each of the cut-points. General linear regression and analysis of variance (ANOVA) were later applied to describe the relationships between small airway IOS versus asthma control and demographic parameters. The criterion for this analysis was physicians' assessed asthma control status which included standard spirometry. The statistical analyses were made using R package (2.11.0). Statistical significance was established at P-value < .05.

RESULTS

Study sample

A total of 14 healthy controls and 107 asthmatic subjects were consented for the study. 101 (94%) of the asthmatics 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. Based on physicians' assessment, 57 (56%) of the 101 asthmatic subjects had controlled asthma and 44 (44%) had uncontrolled asthma. The demographics of the three asthma groups are presented (Table I). The majority of our study population identified themselves as Hispanic (71% of healthy controls and 82% of asthmatics). Of the asthmatics, both controlled and uncontrolled, 77% had positive skin test results, and were

categorized as atopic. 92% of the asthmatic patients were diagnosed with mild to moderate asthma. Unpaired Mann-Whitney U Tests showed no statistical difference in age, gender, height, or weight across groups. There was no statistical difference between controlled and uncontrolled asthma in the step level of management. However, the body mass index for uncontrolled asthma was higher compared to controlled and healthy subjects (P-value < 0.05).

Standard Spirometry

Standard spirometry was compared between healthy, controlled asthma and uncontrolled asthma (Table II). Spirometry was very similar for healthy and controlled asthma. The $FEF_{25–75}$, FEV_1 (% predicted), $FEF_{25–75}$ (% predicted), and the ratio of FEV_1/FVC were higher in healthy and controlled asthma compared to uncontrolled asthma. Bronchodilator response (BDR) of FEV_1 (% change from baseline) in healthy and controlled asthma was statistically lower than uncontrolled asthma. Although significant differences were detected, the sensitivities of spirometry 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%predicted, $FEF_{25–75}$%predicted, FEV_1/FVC and BDR, respectively, within the normal range based on the guidelines (25, 33).

IOS

The comparison of IOS measurements between the three groups pre- and post-bronchodilator administration, and the bronchodilator response are presented using box plots (Fig. 2). Healthy subjects and controlled asthmatics had no statistical differences in IOS measurements. For uncontrolled asthma, R20 was also not different from healthy or controlled asthma. However, R5, R5-20, Fres, X5, and AX were all statistically different in uncontrolled asthma compared to healthy and controlled asthma. For each of the five indices, the most significant differences were detected pre-bronchodilator administration. Paired Wilcoxon Signed Rank Tests showed that all IOS outcomes were significantly improved after bronchodilator in all three groups.

Distinguishing Uncontrolled and Controlled Asthma

The discriminative properties of the oscillometric variables to distinguish uncontrolled from controlled asthma patients are shown using ROC (Fig. 3). Pre-bronchodilator, the estimated area under the curve (AUC) for R5-20, R5 and R20 were 0.86, 0.71 and 0.5, respectively. The AUC for AX, Fres and X5 pre-bronchodilator were all above 0.8, with AX being slightly better than the other two. Post-bronchodilator, the AUC for R5-20, AX, and Fres decreased below 0.8, R5 and X5 decreased below 0.7 and R20 remained near 0.5. The trends for the bronchodilator response (change from baseline) for the three resistances were similar to those of the post-bronchodilator 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 AUC for pre-bronchodilator while the AUC for ΔFres decreased to 0.66.

The receiving operating curves were used to determine the performance of the optimized IOS cut-points in screening uncontrolled from controlled asthma for pre-bronchodilator and the bronchodilator response indices (Table III). The cut-points were selected by maximizing the sum of sensitivity and specificity. Pre-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 $cmH_20{\cdot}L^{-1}{\cdot}s$ and 9.5 $cmH_20{\cdot}L^{-1}$, respectively. These cut-points also had positive and negative predictive values > 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 a positive predictive value and negative predictive value of 73.1% and 87.5%, respectively. Therefore, the bronchodilator response of AX was not as useful as AX pre bronchodilator in screening for uncontrolled asthma. The cut-points for the change in other IOS parameters before and after bronchodilator had AUCs lower 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. Pre-bronchodilator (or baseline) values for small airway resistance (R5-R20) and reactance (AX) performed best, resulting in values for the sensitivity, specificity, positive predictive value, and negative predictive value which 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 by 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 four 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 elevated 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 at baseline are strongly correlated (R^2 =0.837), which is consistent with previous reports (19, 30). Airway resistance and reactance are likely coupled, as, 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.

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 versus controlled asthma

Our study demonstrates that the controlled asthma group and healthy controls 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 a relatively small number of normal subjects, which could fail to detect more subtle differences between healthy children and controlled asthmatics.

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 to the traditional bronchodilator response (percent change in FEV1) that has been shown to be a more sensitive indicator of asthma control compared to baseline spirometry (41). This difference may be related to the techniques, the 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 percent change, which is commonly used for FEV1. This choice is based on the fact that IOS indices (e.g., AX) increase as asthma symptoms increase, thus creating a larger baseline value, and decrease following administration of a bronchodilator. In contrast, indices from traditional spirometry (e.g., FEV1) decrease with increasing asthma symptoms creating a smaller baseline. Thus, the percent change for IOS will tend to be smaller than traditional spirometry, and the effect of the bronchodilator blunted.

Spirometry versus IOS

Numerous studies have investigated the correlation between traditional spirometry and IOS. For example, R5 correlates with FEV_1 at (42, 43) at baseline and during mannitol or methacholine challenge (44, 45). Although FEV_1 is the most widely used test for airflow obstruction, it is generally considered to be an index of large airway caliber. In our study, no differences in FEV_1 were detected between controlled and uncontrolled asthma, and we found a large proportion (95%) of asthmatic children whose FEV_1%predicted was in the normal range (> 80%predicted) despite a physician 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 $FEF_{25–75}$%predicted was more sensitive in detecting uncontrolled asthma compared to FEV_1, as a lower percentage (36%) of children with uncontrolled asthma were above the normal cutoff (65%predicted) (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 since the physician used spirometry 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 $FEF_{25–75}$, $FEF_{25–75}$% predicted, FEV_1/FVC and BDR (0.74, 0.79, 0.81 and 0.69, respectively) were all lower than small airway IOS indices or resistance and reactance, despite the fact that spirometry was part of the criteria used by the physician to assess control.

Cut-point values of IOS to discriminate asthma control

Our study was able to determine cut-point values of R5-20 and AX for discriminating asthma control using the absolute value of each index. However, the cut-point values might be affected by other variables such as age, gender, height, weight, BMI and race. Previous studies have shown that IOS measurements correlate with age, gender and height (46–49). In our study, analysis of variance showed that R5-20 or AX had no correlation with gender, weight, or BMI, but did correlate with age and height (P-value < 0.01). 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 impact 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 is necessary before cut-points expressed as a percent-predicted of normal can be utilized.

Conclusion

The standard asthma history, which incorporates impairment and risk factors as defined by NAEPP 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, spirometry may 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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Abbreviations used

BDR	Bronchodilator response of FEV_1
IOS	Impulse oscillometry
R5	Resistance of the respiratory system at 5Hz
R20	Resistance of the respiratory system at 20Hz
R5-20	The difference of R5 and R20
Fres	Resonant frequency of reactance
X5	Reactance of the respiratory system at 5Hz
AX	Reactance Area
ROC	Receiver operating characteristic
AUC	Area under the curve

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Clinical Implication/Key message

Small airway indices of impulse oscillometry (IOS) identify children with uncontrolled asthma, and thus may be useful in the clinical assessment of asthma control.

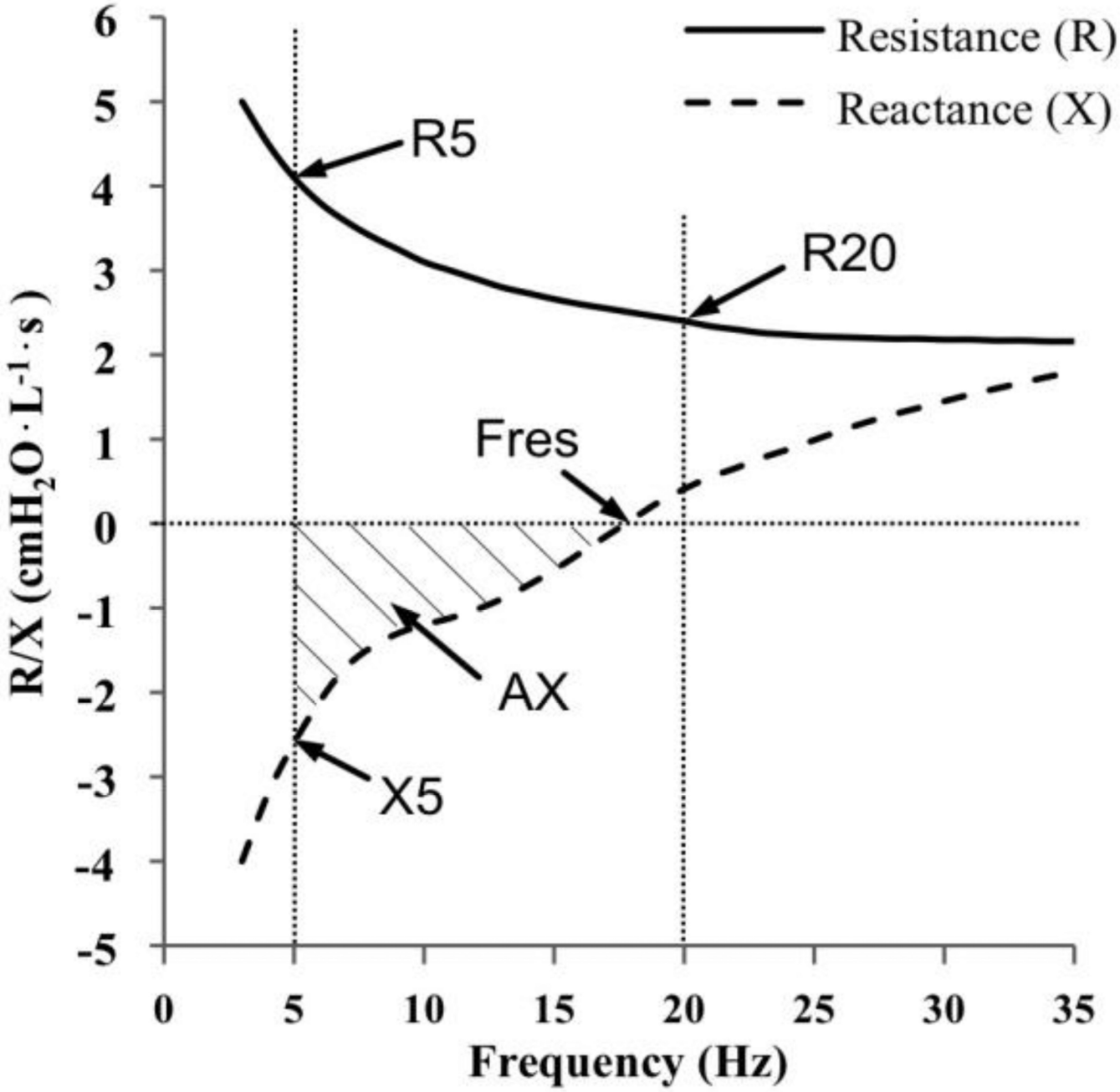

FIG 1.
Schematic illustration of IOS indices over oscillation frequency, including R5, R20, Fres, X5 and AX.

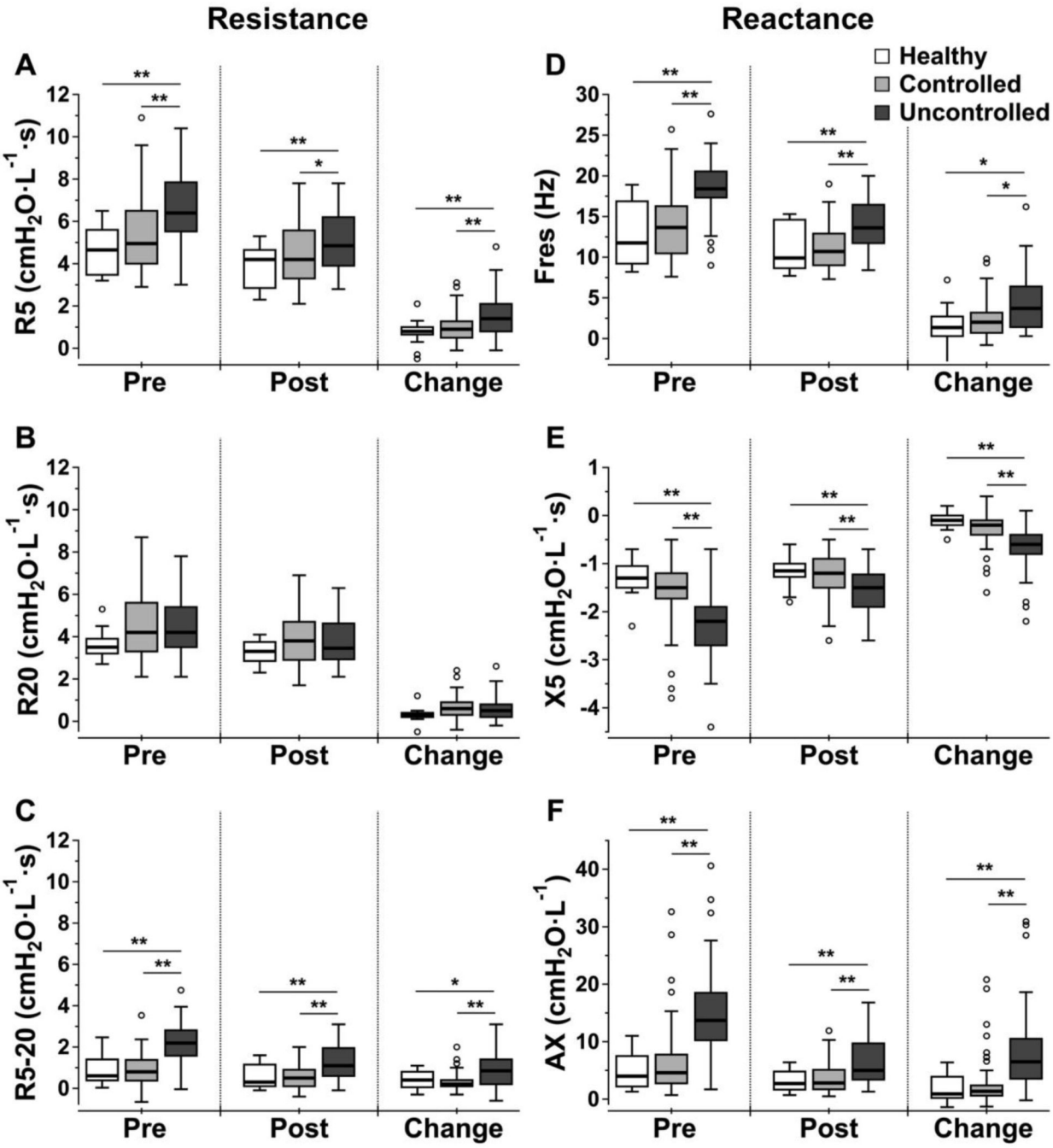

FIG 2.

Box plots of IOS measurements (A. R5, B. R20, C. R5-20, D. Fres, E. X5 and F. AX) for different asthma groups before, after bronchodilator and the bronchodilator response. The boxes represent 25^{th} –75^{th} percentile with median, 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 using unpaired Mann-Whitney U test: * *P*-value < .05; ** *P*-value < .01.

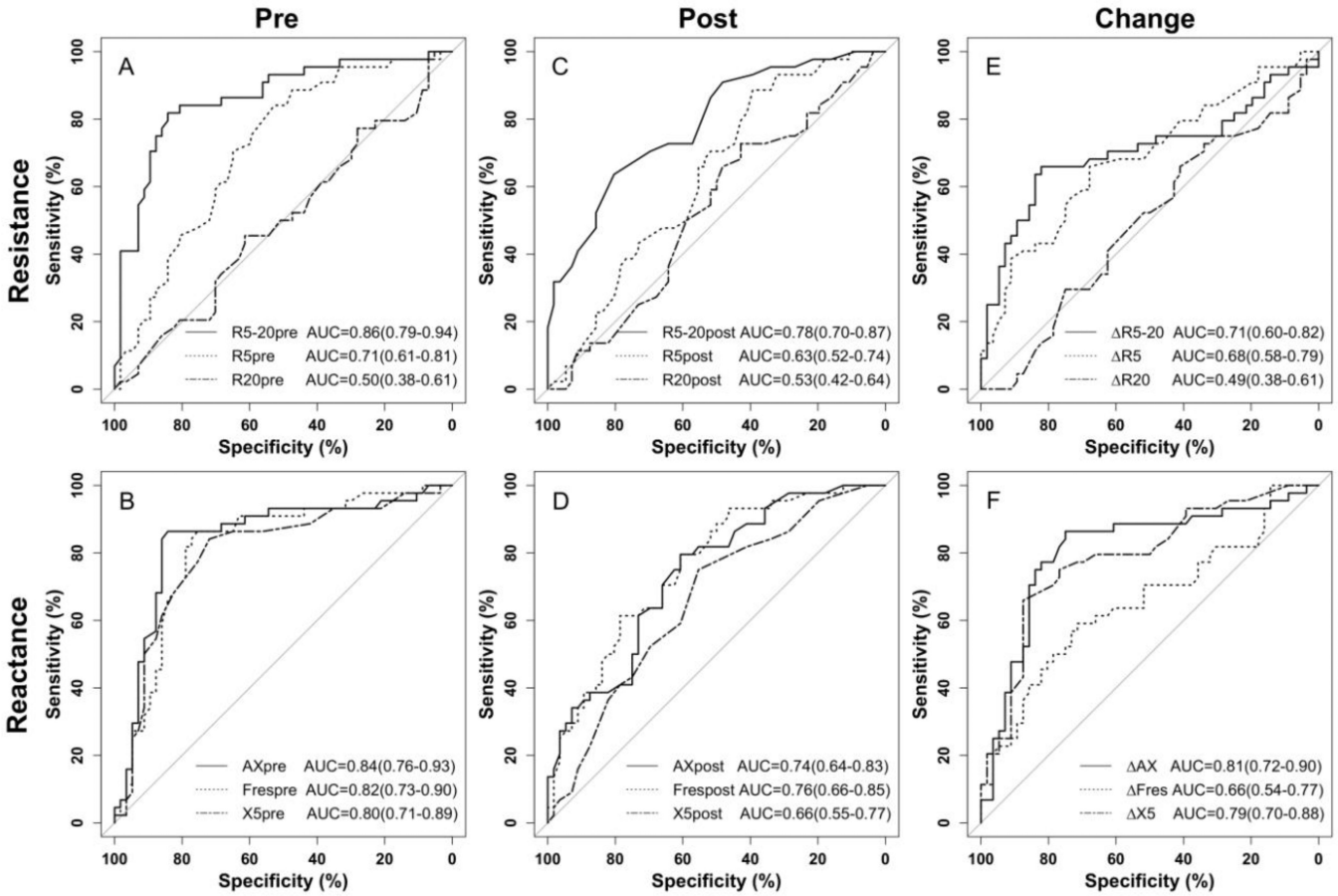

FIG 3.

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 bronchodilator response of resistance (E) and reactance (F). R5-20, X5, Fres, AX before bronchodilator and bronchodilator response of AX all predict asthma control status (area under the curve > 0.8). AUCs are presented as mean (95% confidence interval)

TABLE I

Demographics for different asthma status

	Asthma status			*P* value*		
	Healthy (n=14)	**Controlled (n=57)**	**Uncontrolled (n=44)**	**H vs. C**	**H vs. U**	**C vs. U**
Age, years	13	12	11	.6945	.6807	.4050
Male/Female, %	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	20.9	20.8	23.8	.7560	.0299	.0086
Atopic, %	0	77	77	<.0001	<.0001	.8831
Medication step, % Non-compliant/1/2/3/4		27/12/35/21/5	27/18/34/16/5			.5295

Demographic measurements are presented as median.

*Mann-Whitney U Test was applied to detect the group difference between healthy (H) vs. controlled asthma (C), healthy vs. uncontrolled asthma (U) and controlled asthma vs. uncontrolled asthma.

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TABLE II

Standard spirometry for different asthma status

	Asthma status			*P* value*		
	Healthy (n=14)	**Controlled (n=57)**	**Uncontrolled (n=44)**	**H vs. C**	**H vs. U**	**C vs. U**
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
FEV% 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, %†	89 (93)	87 (79)	79 (39)	.2102	<.0001	<.0001
BDR, %†	1.6 (100)	3.2 (95)	6.4 (64)	.3145	.0046	.0009

Spirometry measurements are presented as median.

†Percentage of patients with the spirometry parameter in normal range are presented in parentheses. FEV_1%predicted lower than 80% of predicted, $FEF_{25–75}$%predicted lower than 65% predicted, FEV_1/FVC lower than 80%, or BDR higher than 10% are considered as abnormal.

*Mann-Whitney U Test was applied to detect the group difference between healthy (H) vs. controlled asthma (C), healthy vs. uncontrolled asthma (U) and controlled asthma vs. uncontrolled asthma.

TABLE III

Performance of IOS cut-points in screening uncontrolled vs. controlled asthma

	Cut-points†	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**

†Cut-points of R5, R5-20, and X5 are $cmH_2O \cdot L^{-1} \cdot s$, cut-point of Fres is Hz and cut-point of AX is $cmH_2O \cdot L^{-1}$. The cut-points were selected by maximizing the total of sensitivity and specificity. Correctly classified ratios higher than 80% and AUCs above 0.80 are in bold.

PPV is positive predictive value; NPV is negative predictive value; AUC is area under the curve.