

Peripheral airway impairment measured by oscillometry predicts loss of asthma control in children

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Background: We previously showed that impulse oscillometry (IOS) indices of peripheral airway function are associated with asthma control in children. However, little data exist on whether dysfunction in the peripheral airways can predict loss of asthma control.

Objective: We sought to determine the utility of peripheral airway impairment, as measured by IOS, in predicting loss of asthma control in children.

Methods: Fifty-four children (age, 7-17 years) with controlled asthma were enrolled in the study. Spirometric and IOS indices of airway function were obtained at baseline and at a follow-up visit 8 to 12 weeks later. Physicians who were blinded to the IOS measurements assessed asthma control (National Asthma Education and Prevention Program guidelines) on both visits and prescribed no medication change between visits.

Results: Thirty-eight (70%) patients maintained asthma control between 2 visits (group C-C), and 16 patients had asthma that became uncontrolled on the follow-up visit (group C-UC). There was no difference in baseline spirometric results between the C-C and C-UC groups, except for FEV₁/forced vital capacity ratio (86% vs 82%, respectively; $P < .01$). Baseline IOS results, including resistance of the respiratory system at 5 Hz (R5; 6.4 vs 4.3 cm H₂O · L⁻¹ · s), frequency dependence of resistance (difference of R5 and resistance of the respiratory system at 20 Hz [R5-20]; 2.0 vs 0.7 cm H₂O · L⁻¹ · s), and reactance area (13.1 vs 4.1 cm H₂O · L⁻¹), of group C-UC were significantly higher than those of group C-C ($P < .01$). Receiver operating characteristic analysis showed baseline R5-20 and reactance area effectively predicted asthma control status at the follow-up visit (area under the curve, 0.91 and 0.90).

Conclusion: Children with controlled asthma who have increased peripheral airway IOS indices are at risk of losing asthma control. (J Allergy Clin Immunol 2013;131:718-23.)

Key words: Impulse oscillometry, pediatric, lung function, longitudinal

Abbreviations used

AIC:	Akaike information criterion
AUC:	Area under the curve
AX:	Reactance area
BMI:	Body mass index
C-C:	Patients who maintained asthma control between 2 visits
C-UC:	Patients whose asthma became uncontrolled on the follow-up visit
FEF ₂₅₋₇₅ :	Forced expiratory flow at 25% to 75% of forced vital capacity
FVC:	Forced vital capacity
ICS:	Inhaled corticosteroid
IOS:	Impulse oscillometry
ROC:	Receiver operating characteristic
R5:	Resistance of the respiratory system at 5 Hz
R5-20:	Difference of R5 and R20
R20:	Resistance of the respiratory system at 20 Hz

The goal of asthma care in children is to achieve and maintain control of the disease at the lowest step and dose of inhaled corticosteroid (ICS), thereby maximizing the safety of treatment.¹⁻³ The Global Initiative for Asthma suggests that treatment can be stepped down if asthma control has been maintained for at least 3 months.⁴ However, previous studies have noted that a certain proportion of patients who previously had well-controlled asthma do not maintain control at follow-up visits, despite adherence to prescribed controller therapy.^{5,6} Thus for effective asthma care, it is important to identify the factors that might predict future loss of asthma control before attempting step-down treatment in children with controlled asthma.

Current symptoms and spirometric results are associated with future asthma exacerbations in children.^{7,8} However, current symptoms, spirometric results, exhaled nitric oxide levels, or bronchial provocation test results are not predictive of a decline in asthma control.^{5,9-11} Moreover, many children have poor perceptions of their disease symptoms,^{12,13} and discrepancies in perceived symptoms exist between children and their parents.^{14,15} Finally, traditional spirometry and exhaled nitric oxide tests might be difficult for young children because they require forced expiratory maneuvers. An inability to perform acceptable-quality spirometry is also a relative contraindication to bronchial hyperresponsiveness testing.¹⁶ Increasing evidence demonstrates that the peripheral airways play an important role in asthma control^{9,17,18}; however, none of the traditional tests (eg, spirometry) measure the peripheral airways specifically, and thus the clinical assessment of asthma control in children using these tests has been particularly challenging.

Impulse oscillometry (IOS) assesses airways resistance and reactance during tidal breathing and has been increasingly used to separately quantify the degree of obstruction in the central and peripheral airways.¹⁹⁻²¹ Because low oscillation frequencies can

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Supported by National Institutes of Health grant HL070645.

Disclosure of potential conflict of interest: S. P. Galant has received research support from the University of California, Irvine. The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication June 6, 2012; revised September 7, 2012; accepted for publication September 25, 2012.

Available online November 10, 2012.

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0091-6749/\$36.00

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<http://dx.doi.org/10.1016/j.jaci.2012.09.022>

be transmitted more distally in the lungs compared with higher frequencies, resistance of the respiratory system at 5 Hz (R5) reflects obstruction in both the peripheral and central airways, resistance of the respiratory system at 20 Hz (R20) reflects the central airways only, and the difference between R5 and R20 (R5-20), an indicator of frequency dependence of the resistance, is an index of the peripheral airways only. The low-frequency reactance area (AX) is the total reactance at all frequencies between 5 Hz and the resonant frequency and reflects changes in the degree of obstruction in the peripheral airways.²⁰ However, there have been no studies to determine whether IOS indices predict a decline in asthma control. We previously showed in a cross-sectional study that IOS indices of peripheral airway dysfunction were associated with uncontrolled asthma in children.²⁰ Thus we hypothesized that IOS indices of peripheral airway function might predict future loss of asthma control in children with controlled asthma.

METHODS

Children aged 7 to 17 years who were being actively treated for asthma by the Children's Hospital of Orange County Breathmobile were enrolled in the study. The Breathmobile is a mobile asthma clinic that travels to schools in low-income neighborhoods throughout Orange County, California, and provides comprehensive asthma care to children. Children were included if they had a physician's clinical diagnosis of mild-to-moderate asthma that was controlled according to the guidelines published by the National Asthma Education and Prevention Program/National Heart, Lung, and Blood Institute guidelines.² Patients were excluded 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. Short- and long-acting β -agonists were withheld for 12 hours before the study. The Institutional Review Boards of the University of California, Irvine, and the Children's Hospital of Orange County approved the study. Written informed assent and consent were obtained from all participants and their parents or guardians, respectively.

All study procedures were performed on the Breathmobile vans.²² Participants were required to complete 2 consecutive visits and remain compliant with their asthma medications between the visits. At the initial visit (visit 1), 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. Each subject was required to report a complete symptom history during the past 6 to 8 weeks. Baseline IOS and standard spirometric maneuvers were performed in accordance with American Thoracic Society/European Respiratory Society standards.²³ Percent predicted normal values of spirometry (best of 3 repeated maneuvers) were used for later analyses. IOS was performed before spirometry to avoid the influence of forced exhalation maneuvers on airway function.²⁴ The mean values from 3 IOS maneuvers, including R5, R20, R5-20, and AX values, were calculated as previously described.²⁰ Physicians were blinded to the IOS data and evaluated the participants' control and treatment plan by using criteria defined in the National Asthma Education and Prevention Program/National Heart, Lung, and Blood Institute guidelines, 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 fewer days per week of daytime symptoms or short-acting β -agonist use, 80% or greater FEV₁ and FEV₁/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. Because we aimed to identify the asthmatic patients who are at risk of losing asthma control without the influence of step-down treatment, participants received no medication change on visit 1 and returned for a follow-up visit (visit 2) within 8 to 12 weeks. At the follow-up visit, nursing assessment, symptom history, IOS results, spirometric results, and physician evaluation were repeated.

TABLE I. Demographic characteristics of study participants

	C-C group (n = 38)	C-UC group (n = 16)	P value
Age (y)	13 (7-17)	11 (7-17)	.02*
Male/female sex (%)	55/45	38/62	.37†
Ethnicity (%), Hispanic	80	75	.73†
BMI (kg/m ²)	22 (16-34)	25 (18-35)	.03*
Atopic (%)	82%	63%	.17†
Medication step (%), 1/2/3/4	29/47/21/3	25/56/6/13	.32†

Data are presented as medians (ranges).

*The Mann-Whitney *U* test and †Fisher exact test were applied to detect the group difference between patients who maintained asthma control (C-C group) and patients whose asthma became uncontrolled (C-UC group) on the follow-up visit. *P* values of less than .05 are shown in boldface.

On the basis of our previous cross-sectional study, the difference between prebronchodilator R5-20 values in patients with controlled asthma and postbronchodilator R5-20 values in patients with uncontrolled asthma was 0.38 cm H₂O · L⁻¹ · s (0.90 vs 1.28 cm H₂O · L⁻¹ · s), and the SD of R5-20 was 0.8 cm H₂O · L⁻¹ · s.²⁰ Thus we estimated a difference (effect size) of 0.5 in peripheral airway IOS results between patients who maintained asthma control between 2 visits (group C-C) and patients whose asthma became uncontrolled on the follow-up visit (group C-UC) at baseline. Power analysis showed 17 subjects were needed in each group to detect an effect size of 0.5 with a power of 0.8 and significance level of .05 by using 1-way ANOVA. Scott et al⁶ previously demonstrated that the percentage of patients with well-controlled asthma at follow-up visits across all severities was 69.9% in Orange County. Therefore 57 subjects were required for a sample size of approximately 17 in the C-UC group.

Because of the nonnormal distributions of the measurements and small sample size, the parameters were summarized by medians with ranges, unless indicated otherwise. The nonparametric Mann-Whitney *U* test or Fisher exact test was used to detect the difference in the outcomes at baseline and follow-up visits between groups. The paired Wilcoxon signed-rank test was applied to test the difference of the measurements between the 2 consecutive visits. The interdependency of each predictor was tested by using correlation coefficients. The logistic regression and backward stepwise variable selection method with demographic, spirometric, and IOS data were applied to find the best model in predicting asthma control. The receiver operating characteristic (ROC) method was conducted to evaluate the utility of different baseline oscillometric variables in predicting physician-assessed loss of asthma control. ROC areas under the curve (AUCs) with estimated SEs and optimal IOS cut points based on maximizing the sum of sensitivity and specificity were calculated for each of the IOS variables. The statistical analyses were made with the R package software (2.11.0). Statistical significance was established at a *P* value of less than .05.

RESULTS

Fifty-four children with controlled asthma were consented for the study at the initial visit. On the basis of physicians' assessments, 38 (70%) of these subjects continued to have controlled asthma, and 16 (30%) of these subjects lost asthma control on their follow-up visit. The demographics of the 2 groups are presented (Table I). The majority of our study population identified themselves as of Mexican descent, and the rest were a mixed ethnic population primarily of Caucasian and Asian descent. No statistical differences between the 2 groups were detected in sex, ethnicity, atopic status, or step level of management between the 2 visits. However, subjects in group C-C were older than those in group C-UC, and the body mass index (BMI) for group C-C was lower compared with that of group C-UC subjects (*P* < .05).

TABLE II. Comparison of standard spirometric results between groups

	Visit 1			Visit 2		
	C-C group	C-UC group	<i>P</i> value*	C-C group†	C-UC group	<i>P</i> value*
FEV ₁	96 (81-134)	98 (80-109)	.68	100 (81-143)	91 (74-106)‡	.07
FVC	98 (61-142)	105 (88-118)	.10	99 (80-141)	105 (84-117)	.21
FEV ₁ /FVC ratio	86 (80-95)	82 (80-90)	<.001	86 (80-97)	79 (70-88)§	<.001
FEF ₂₅₋₇₅	89 (71-147)	82 (66-103)	.06	96 (64-140)	71 (54-97)‡	<.001

Data are presented as medians (ranges). FEV₁, FVC, and FEF₂₅₋₇₅ values are shown as percent predicted values.

The paired Wilcoxon signed-rank test was used to test differences between visits within groups: ‡*P* < .05 and §*P* < .01.

*The Mann-Whitney *U* test was applied to detect the group difference on both visits. *P* values of less than .05 are shown in boldface.

†One subject could not perform standard spirometry on visit 2 (*n* = 37).

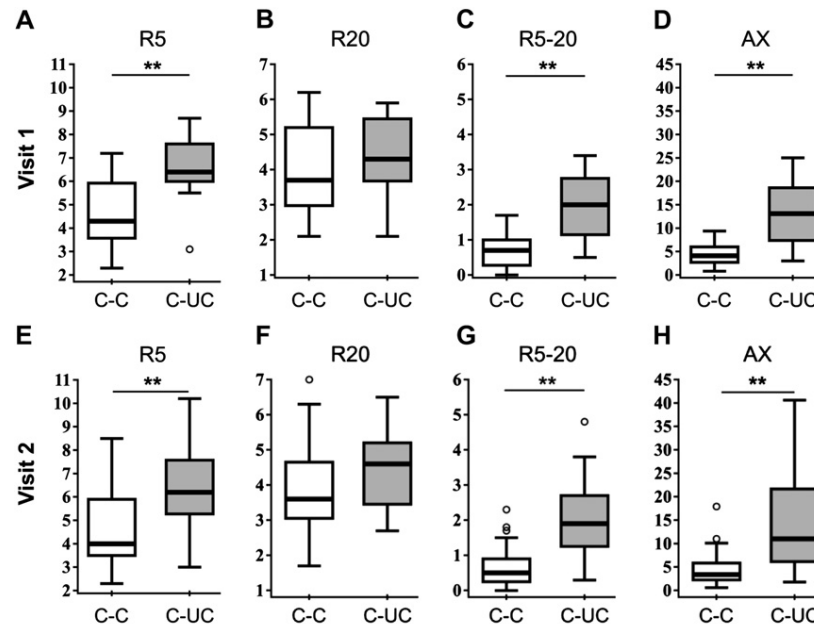


FIG 1. Box plots of IOS measurements at baseline (A-D) and the follow-up visit (E-H) for groups C-C (*n* = 38) and C-UC (*n* = 16). R5, R20, and R5-20 values are shown in centimeters of H₂O per liter per second, and AX values are shown in centimeters of H₂O per liter. The boxes represent 25th to 75th 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. The significance level of group difference was determined by using the Mann-Whitney *U* test: ***P* < .01.

The comparison of standard spirometric results between the C-C and C-UC groups are presented (Table II). There was no difference at baseline between the 2 groups, except that the FEV₁/FVC ratio was significantly higher in group C-C than in group C-UC (86% vs 82%, respectively; *P* < .01). At the follow-up visit, the FEV₁/FVC ratio (86% vs 79%), and forced expiratory flow at 25% to 75% of forced vital capacity (FEF₂₅₋₇₅; 96% vs 71%) were significantly higher for patients with controlled (group C-C) than those with uncontrolled (group C-UC) asthma (*P* < .01). The spirometric outcomes in group C-UC, including FEV₁ percent predicted (98% vs 91%, *P* = .04), FEV₁/FVC ratio (82% vs 79%, *P* < .01), and FEF₂₅₋₇₅ percent predicted (82% vs 71%, *P* = .05), were statistically decreased from visit 1 to visit 2. In group C-C no difference was detected between visits.

The comparison of IOS results between the C-C and C-UC groups is presented using box plots (Fig 1). Baseline R5 (4.3 vs 6.4 cm H₂O · L⁻¹ · s), R5-20 (0.7 vs 2.0 cm H₂O · L⁻¹ · s), and AX (4.1 vs 13.1 cm H₂O · L⁻¹) values were all significantly

lower in subjects whose symptoms remained controlled compared with those in whom asthma control was lost (*P* < .01). R20 values were not different between the groups (3.7 vs 4.3 cm H₂O · L⁻¹ · s, *P* = .19). Similarly, on the second visit, R5 (4.0 vs 6.2 cm H₂O · L⁻¹ · s), R5-20 (0.5 vs 1.9 cm H₂O · L⁻¹ · s), and AX (3.4 vs 11.0 cm H₂O · L⁻¹) values were all significantly lower in group C-C than in group C-UC (*P* < .01). However, IOS measurements were not different between the 2 consecutive visits for either of the 2 groups.

The discriminative properties of the oscillometric variables in predicting the loss of asthma control are shown using ROC curves (Fig 2). Three indices, R5-20, AX, and R5, had the estimated AUC of greater than 0.8 (0.91, 0.90, and 0.80, respectively), and were thus easily able to distinguish group C-UC from group C-C. The optimal cut points of the baseline IOS results in prescreening patients who lost asthma control on visit 2 were presented (Table III). Although R5-20 had a higher overall AUC than AX, the optimal cut point of AX of 7.0 cm H₂O · L⁻¹ or greater (correctly classified ratio, 91%) was able to distinguish the 2 groups better than the

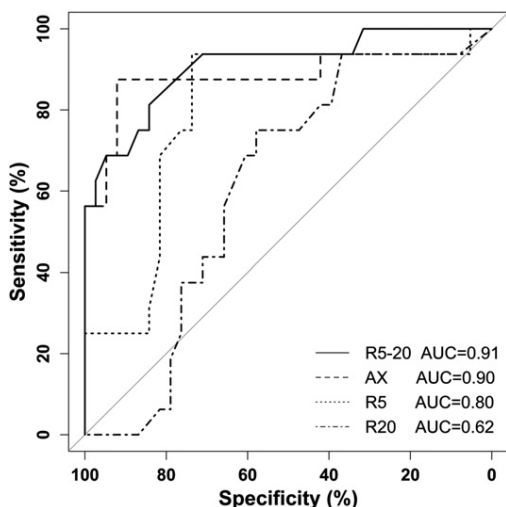


FIG 2. ROC curves of baseline IOS measurements in predicting physician-assessed loss of asthma control on a follow-up visit. R5, R5-20, and AX values all predict future loss of asthma control (AUC \geq 0.8).

cut point of R5-20 of $1.0 \text{ cm H}_2\text{O} \cdot \text{L}^{-1} \cdot \text{s}$ or greater (correctly classified ratio, 83%).

General linear regression was applied to assess the interdependency among the 3 predictors of baseline R5, R5-20, and AX values. The correlation coefficient (r) for R5 with R5-20 was 0.59, for R5 with AX was 0.72, and for R5-20 with AX was 0.92. The strong correlation between baseline R5-20 and AX values suggested that only one of them was needed in the logistic regression model predicting loss of asthma control. According to Goldman et al,²⁴ AX provides complementary information over a wide range of frequencies compared with the low-frequency resistance data R5-20. Thus AX was selected over R5-20 for inclusion in the model.

Correlation coefficients of the 2 predictors (R5 and AX) with age, BMI, and FEV₁/FVC ratio were also calculated. Results showed that age correlated with R5 values ($r = 0.71$) and that the interaction between the 2 needed to be included in the model. BMI did not correlate with any IOS indices, and FEV₁/FVC ratio correlated weakly with R5 and AX values ($r = 0.44$ and 0.51 , respectively). Thus BMI and the FEV₁/FVC ratio could be 2 independent predictors. Baseline R5, AX, BMI, age, and FEV₁/FVC ratio, as well as interactions between age and R5, R5 and AX, were included in the initial model for variable selection to determine whether they were independent predictors of loss of asthma control.

Backward stepwise elimination based on the Akaike information criterion (AIC) showed that the best model to predict loss of asthma control on visit 2 contained 2 variables: AX and BMI (AIC, 38.4). In this model baseline AX values were significantly correlated with asthma control ($P = 3.5 \times 10^{-8}$); however, BMI was not ($P = .15$). The AIC for one predictor model (AX) was 38.7 ($P = 4.8 \times 10^{-9}$). Thus by introducing 1 more variable (BMI), AIC only improved by 0.3 (or <1%).

DISCUSSION

Our study demonstrates that peripheral airway obstruction, as measured by IOS in a field clinical setting, was associated with future loss of asthma control in a pediatric population. Although

asthma control was assessed by the physician independently of IOS, the cut points of peripheral airway IOS indices, including R5-20 and AX, were able to correctly classify up to 91% of our population. These findings suggest that IOS indices of peripheral airway function are useful in identifying asthmatic patients who are at risk of losing control, and may be able to assist clinical decisions and treatment plans.

Previous studies showed that peripheral airway conditions are associated with asthma control^{9,18,20,25} and can predict symptom change after ICS titration.¹¹ Our study also found that peripheral airway conditions play an integral role in asthma, specifically asthma control. Farah et al¹¹ showed that baseline resistance and reactance at 6 Hz, as measured by the forced oscillation technique, were not associated with symptom change after ICS titration. However, resistance at 6 Hz reflects resistance in both the peripheral and central airways^{26,27} and is thus not as specific to the peripheral region as R5-20 or AX. In our study although the equivalent measure, R5, was statistically higher in group C-UC than in group C-C at baseline, ROC analysis showed that it was not as good as R5-20 or AX in predicting asthma control. Although it is peripheral airway specific, reactance at 6 Hz reflects the signal at only 1 frequency and is more variable compared with AX.²⁴ This feature of reactance at 6 Hz, combined with the limited sample size (20 total subjects), might explain why reactance at 6 Hz did not predict symptom change.

The cut points of peripheral airway IOS established by using ROC analysis might have important clinical implications. For example, the optimal cut point of AX had a positive predictive value of 82.3%. It indicates that children with a baseline AX value of $7.0 \text{ cm H}_2\text{O} \cdot \text{L}^{-1}$ or greater have a greater than 80% chance of losing asthma control in the following 8 to 12 weeks, even if they remain compliant with current medication. We previously published that an AX value of $9.5 \text{ cm H}_2\text{O} \cdot \text{L}^{-1}$ or greater had a sensitivity of 0.86 to identify uncontrolled asthma in children.²⁰ Together, these results indicate that if a child has traditionally defined controlled asthma with an AX range of between 7.0 and 9.5 $\text{cm H}_2\text{O} \cdot \text{L}^{-1}$, the asthma control might not be stable, and the patient is at risk of losing control. R5-20 behaves in a similar fashion in the range between 1.0 and 1.5 $\text{cm H}_2\text{O} \cdot \text{L}^{-1} \cdot \text{s}$.

In our study baseline spirometric results for the FEV₁/FVC ratio were significantly lower in children who lost asthma control compared with those who maintained controlled at the follow-up visit (Table II). Because physicians had access to the patient's spirometric history during the clinical assessment of control, baseline spirometric results might not be an independent predictor. Although not rigorous, ROC analysis was still performed to gauge the utility of the FEV₁/FVC ratio in predicting loss of asthma control. An FEV₁/FVC ratio cut point of less than 85% had an AUC of 0.82 and was able to correctly classify 77% of the population, with a sensitivity of 0.69 and specificity of 0.81. This cut point was specific but not very sensitive in detecting loss of asthma control compared with IOS indices of R5-20 or AX. Importantly, the cut point was greater than seen in current guidelines, which define airway obstruction as an FEV₁/FVC ratio of less than 80%.² It is generally accepted that the FEV₁/FVC ratio assesses primarily the large airways.²⁸ Surprisingly, we noticed that at baseline, the FEV₁/FVC ratio was weakly correlated with R5-20 ($r = 0.45$) and AX ($r = 0.51$) values but not with R20 values ($r = 0.22$). These results indicate that the FEV₁/FVC ratio might reflect obstruction in the peripheral airways and that the current guideline to define the normal (>80%) might be too low.

TABLE III. Performance of baseline IOS cut points in predicting uncontrolled asthma on a follow-up visit

	Cut point	Sensitivity	Specificity	PPV (%)	NPV (%)	Correctly classified (%)
R5 AUC = 0.80 (0.66-0.94)	≥5.2	0.938	0.711	57.7	96.5	77.8
	≥5.4	0.938	0.737	60.0	96.6	79.7
	≥5.5	0.875	0.737	58.3	93.3	77.8
	≥5.6	0.813	0.737	56.6	90.3	76.0
	≥5.9	0.750	0.763	57.1	87.9	75.9
R5-20 AUC = 0.91 (0.82-1.0)	≥0.8	0.938	0.605	50.0	95.9	70.4
	≥0.9	0.938	0.711	57.7	96.5	77.8
	≥1.0	0.813	0.842	68.4	91.4	83.3
	≥1.1	0.750	0.842	66.7	88.9	81.5
	≥1.2	0.750	0.868	70.5	89.2	83.3
AX AUC = 0.90 (0.79-1.0)	≥6.0	0.875	0.789	63.6	93.7	81.4
	≥6.5	0.875	0.816	66.7	93.9	83.3
	≥7.0	0.875	0.921	82.3	94.6	90.7
	≥7.5	0.750	0.921	80.0	89.7	87.0
	≥8.0	0.688	0.947	84.5	87.8	87.0

AUCs are presented as means (95% CIs). Cut points of R5 and R5-20 values are in centimeters of H₂O per liter per second, and the cut points of AX are in centimeters of H₂O per liter. Values in boldface are the optimal cut points.

NPV, Negative predictive value; PPV, positive predictive value.

We did not include FEF₂₅₋₇₅ values in the regression model because they did not differ between the 2 groups ($P = .06$) and ROC analysis (data not shown) demonstrated that FEF₂₅₋₇₅ values do not predict asthma control (AUC, 0.66). It has been well accepted that the FEF₂₅₋₇₅ value is more reflective of the small airways. However, in this study we found FEF₂₅₋₇₅ values correlate with R5 ($r = 0.8$) and R20 ($r = 0.7$) values better than R5-20 ($r = 0.4$) or AX ($r = 0.5$) values. These results suggest that although FEF₂₅₋₇₅ reflects small-airway function better than other spirometric outcomes, it is still a combination of both the large and small airways.

The spirometric measurements, including FEV₁, FEV₁/FVC ratio, and FEF₂₅₋₇₅ values, decreased significantly in the C-UC group on visit 2 (Table II); however, the IOS indices showed no differences between visits. It is possible that IOS is sensitive to obstruction in the peripheral airways, which precedes worsening of spirometric values or symptoms yet places the subject at risk of losing control. This observation is consistent with the report by Larsen et al,²⁹ who demonstrated a continued improvement in AX values over a prolonged period of time after spirometry and that symptoms had stabilized after treatment. These results suggest that IOS identifies deterioration or improvement in the peripheral airways, which cannot be detected based on spirometric results or symptoms.

Reports have shown that obesity is associated with worsening asthma control and increased risk of exacerbations in children^{20,30,31} and that obese patients are poorly responsive to conventional ICS therapy.^{32,33} We observed that children who lost asthma control had a higher BMI at visit 1 compared with those who maintained controlled asthma (Table I). Airway obstruction measured based on IOS results does not correlate with weight,^{34,35} and thus BMI could provide additional information to AX measurement in predicting loss of control. However, adding BMI to the prediction model provided only a marginal improvement. Thus IOS indices of the peripheral airways (eg, AX values) appear to be far more useful in predicting loss of asthma control, but BMI may provide additional useful information and could be explored in a larger and more targeted study.

In our study subjects who lost asthma control were younger compared with those who maintained asthma control (Table I),

which is consistent with previous reports.⁶ However, in our study age was eliminated from the regression model after stepwise variable selection. One possibility is that IOS outcomes are correlated with age, decreasing as age increases.³⁵ As a result, the variability of age is captured by the IOS indices in the model. The medication step was not significantly different between groups in our study (Table I), and therapy included traditional ICSs, which preferentially target the large airways. Thus on the basis that AX and R5-20 values are indicative of peripheral airway dysfunction, we speculate that preferentially targeting the peripheral airways with ICSs might improve asthma control in a subset of children with asthma. Finally, it should be noted that our study subjects are predominantly of Mexican descent. Therefore our findings might not be generalizable to other ethnic populations, and results from this study need to be validated in studies with a larger sample size.

In conclusion, the ability to predict loss of asthma control in children can reduce morbidity and potentially the long-term health effects of asthma. However, an objective tool to assist the clinician in predicting loss of control does not currently exist. Our study demonstrates that IOS indices of peripheral airway function (R5-20 and AX) are elevated in children with controlled asthma who subsequently lost control in the following 8 to 12 weeks. Thus IOS might be a clinically useful tool to identify children with controlled asthma who are at risk of losing asthma control and might benefit from a change in medication.

We thank Michael D. Goldman, MD (in memoriam), Geffen School of Medicine, University of California–Los Angeles, and David Sinks, Director, Technical Marketing of Carefusion, for their expertise in the IOS instrumentation, as well as their input and discussions of the clinical application of IOS. We also thank the staff of the Children's Hospital of Orange County Breathmobile, including Jennifer Nguyen, BA, Olga Guijon, MD, and Linh Pham, MD, for their collaborative efforts during data collection and analysis.

Clinical implications: Increased peripheral airway indices of IOS predict loss of asthma control in children with mild-to-moderate asthma.

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