

Impulse oscillometry provides an effective measure of lung dysfunction in 4-year-old children at risk for persistent asthma

Alex Marotta, MD,^{a,d} Mary D. Klinnert, PhD,^{b,e} Marcella R. Price, MSPH,^b
Gary L. Larsen, MD,^{c,d} and Andrew H. Liu, MD^{a,d} Denver, Colo

Background: Objective lung function measurements are routinely used to diagnose and manage asthma, but their utility for young children has not been defined.

Objective: Bronchodilator responses were measured by means of impulse oscillometry (IOS) and compared with conventional spirometry to determine the value of lung function measures in 4-year-old asthma-prone children.

Methods: The study participants were in the Childhood Asthma Prevention Study (National Institute of Health/National Institute of Allergy and Infectious Diseases) and at risk for asthma. At age 4 years, concurrent asthma was determined by using a previously validated modified American Thoracic Society questionnaire. Children performed IOS and spirometry before and after albuterol administration and underwent skin prick testing to 13 common allergens to assess atopy. IOS measures were as follows: airways resistance at 5 Hz and 10 Hz, airways reactance at 5 Hz and 10 Hz, and resonant frequency. **Results:** Asthmatic patients versus nonasthmatic patients significantly differed in their IOS-assessed bronchodilator responses through Δ resistance at 5 Hz (medians, 27% vs 17%; $P = .02$) and Δ resistance at 10 Hz (24% vs 16%; $P = .03$). Because atopic children who have frequent wheezing are at risk for persistent asthma, the data were analyzed in regard to atopic patients with or without asthma. IOS strongly distinguished atopic asthmatic children through Δ resistance at 5 Hz (36% vs 13%, $P = .007$), Δ resistance at 10 Hz (25% vs 11%, $P = .02$), and Δ reactance at 10 Hz (47% vs 12%, $P = .03$). Conventional spirometry did not establish similar statistically significant findings.

Conclusion: IOS bronchodilator responses are remarkably abnormal in 4-year-old children, who are most likely to have persistent asthma. IOS is a useful diagnostic tool in early asthma development and might be a helpful objective outcome measure of early interventions. (*J Allergy Clin Immunol* 2003;112:317-22.)

Key words: Asthma, atopy, children, early intervention, lung function, bronchodilator response, impulse oscillometry, spirometry

Early intervention for asthma has become a focus of recent research in the hopes that appropriate measures will affect the natural course of the disease. Current tests of lung function have difficulty distinguishing young children who will have persistent asthma (asthma throughout childhood) from those who will have intermittent wheezing episodes only during the early years of life. Objective outcome measures that can be readily used in young children would be valuable to determine whether early intervention is effective. Impulse oscillometry (IOS) has been developed as a measure of lung function that requires only passive cooperation and has been used with success in younger children.¹⁻⁴

The aim of this study was to assess the utility of IOS and spirometry when compared with standardized asthma criteria in a population of primarily minority 4-year-old children from low-income families. This inner-city population is particularly important to study in the light of increasing rates of severe asthma among urban youth⁵⁻⁹ and their notable absence from previous studies of lung function measurement in young children.

METHODS

The children presented in this article were enrolled in the Childhood Asthma Prevention Study (National Institutes of Health/National Institutes of Allergy and Infectious Diseases no. R18-AI41137), a randomized study designed to assess the efficacy of environmental intervention on the development of asthma.¹⁰ The study participants are children in low-income (ie, Medicaid eligible) urban families who are at risk for persistent asthma because of 3 or more documented episodes of wheezing before age 2 years. Children who were born before 34 weeks' gestation or who required supplemental oxygen at birth for greater than 48 hours were excluded from the study. The participants have been followed prospectively since their enrollment between 9 months and 2 years of age. Care givers signed consent forms for this protocol, which was approved by the institutional review board at the National Jewish Medical and Research Center and participating institutions.

When the subjects reached 4 years of age, families came to National Jewish Medical and Research Center for a medical evaluation. The environmental interventions preceding this evaluation might have altered the outcome of the development of asthma, allergy, or both in these children, but this investigation was undertaken to correlate clinical asthma with lung dysfunction and would therefore not be affected. The evaluation included pulmonary function testing (spirometry and IOS) before and after albuterol, allergy skin

From ^athe Division of Pediatric Allergy and Immunology, ^bthe Division of Pediatric Behavioral Health, and ^cthe Division of Pediatric Pulmonary Medicine, National Jewish Medical and Research Center, and ^dthe Department of Pediatrics and ^ethe Department of Psychiatry, University of Colorado Health Sciences Center, Denver.

Supported by National Institutes of Health grants R18-AI41137 and M01-RR00051, HL-67818 (Dr Larsen), and K23-HL04272 (Dr Liu).

Received for publication October 28, 2002; revised April 10, 2003; accepted for publication April 24, 2003.

Reprint requests: Andrew Liu, MD, Department of Pediatrics, National Jewish Medical and Research Center, 1400 Jackson St (K1023), Denver, CO 80206.

© 2003 Mosby, Inc. All rights reserved.

0091-6749/2003 \$30.00 + 0

doi:10.1067/mai.2003.1627

- 1) Wheeze with colds.
- 2) Wheeze apart from colds.
- 3) Dyspnea associated with wheeze.
- 4) Wheeze after exercise.
- 5) Persistent cough.

FIG 1. Modified ATS-B questions for asthma in childhood.¹¹ For the purposes of this study, an affirmative response to at least 4 of 5 questions for the preceding 12 months was considered the definition current asthma.

TABLE I. Demographics of children in this study (n = 73)

Median age, mo (range)	49 (48-60)
Male sex, %	68
Median family income, (dollars/y)*	13,500
Ethnicity, %	
Hispanic	54
African American	23
European American	22
Native American	1
Asthma, %†	38
Atopy, %‡	29

*Income at initial enrollment in study.

†Asthma was defined as 4 or more positive responses to the modified ATS-B questionnaire (Fig 1).

‡Atopy was defined as 1 or more positive skin prick test responses.

Abbreviations used

ATS: American Thoracic Society

IOS: Impulse oscillometry

prick testing, and an interview before lung function testing in which care givers replied to a modified American Thoracic Society (ATS) symptom questionnaire (ATS-B) reflecting respiratory symptoms in the 12 months preceding the interview (Fig 1). A positive response to 4 of 5 questions has been shown to be highly specific for physician-diagnosed asthma and bronchial hyperresponsiveness in inner-city children and was used to define asthma.¹¹

IOS

IOS simply requires the participant to breathe normally into a mouthpiece for a short period of time. At the same time, a loudspeaker delivers a pulse-shaped pressure flow excitation to the respiratory system. The overall impedance of the pulse is due to the resistive and viscoelastic forces of the respiratory system. This is reported as resistance and reactance measured in centimeters of H₂O per liter per second. The point at which reactance is 0 is known as the resonant frequency and is measured in hertz.

A Jaeger MasterScreen Impulse Oscillometry system (Jaeger Co, Wurzburg, Germany) was used. The system was calibrated through a single volume of air (3 L) at different rates (flow) and also with a reference resistance device (0.2 kPa·L⁻¹·s⁻¹) per manufacturer. The machine was also calibrated for body temperature and pressure of saturated gas. The children used nose clips, and the parent or guardian gently held the sides of each child's face to decrease the shunt compliance of the cheeks. Multifrequency impulses were applied over a 30-second interval to the airway through the mouthpiece during tidal breathing. Trained pulmonary function technicians coached and evaluated efforts. Each observation consisted of

an optimum of 3 reproducible (ie, resistance at 10 Hz within 10% of highest obtained value) maneuvers, which did not have artifacts caused by coughing, breath holding, swallowing, or vocalization. The mean resistance and reactance values were calculated at discrete frequencies from 5 to 35 Hz. Measurements from the 3 efforts for each IOS parameter were then averaged for the final result. Albuterol (2.5 mg) was administered through a nebulizer with a mouthpiece, and lung function measurements were repeated 15 minutes afterward. Retrospectively, the coherence values (another measurement of reproducibility) were examined for each IOS attempt used in our data set. Ninety-two percent of the measurements had a coherence of 0.8 or greater, and 82% had coherence values of 0.9 or greater.

Spirometry

A Jaeger MasterScreen Spirometry system (Jaeger Co) was used. This system was also calibrated for body temperature and pressure of saturated gas and volumes, as per ATS standards.¹² The children used nose clips and were coached through standard forced expiratory maneuvers. Each data set consisted of at least 3 reproducible attempts, with no more than 8 attempts made. Because 4-year-old children are rarely able to meet strict ATS criteria for spirometry, modified criteria were used on the basis of the findings of Arets et al¹³ and Eigen et al.¹⁴ These criteria consisted of visually reproducible shapes of flow-volume curves, forced expiratory time of greater than 1 second, consistent peak expiratory flows, and FEV₁ and forced vital capacity values within 0.2 L of each other. The best effort was defined as the greatest sum of forced vital capacity and FEV₁ and used in statistical analysis. Spirometry was also measured after bronchodilator administration with IOS. Percent predicted values for spirometry measurements were based on age, height, sex, and ethnicity.¹⁵ Two children were unable to perform spirometry, and 2 had unacceptable results and were excluded from the analysis.

Allergy skin testing

Children were tested with 13 common Colorado allergens: cat, dog, mouse, dust mite, cockroach, *Alternaria* species, *Cladosporium* species, egg, milk, Bermuda grass, Kentucky Blue/June grass, tree mix, and weed mix, along with glycerol-saline and histamine controls (Bayer, Elkert, Ind). Skin testing was done with the Quin-test instrument (Bayer, Spokane, Wash), and reactions were recorded after 15 minutes. Skin test results were considered positive if the wheal diameter was at least 3 mm. Atopy was defined as 1 or more positive skin test results.

Statistics

Data were analyzed by using SAS statistical software (version 8.0; SAS Institute Inc, Cary, NC). Nonparametric statistical tests were used because of small subject numbers, nonnormal distribution of data, or both. The Wilcoxon rank sum test was used to compare data between groups. Significance was defined at a *P* value of .05.

RESULTS

The 73 subjects studied were primarily young, low-income (58% <\$12,000/y) minority children (Table I). Thirty-eight percent of the children had concurrent asthma, as defined by the ATS-B symptom questionnaire criteria (Fig 1), and 29% had evidence of atopy. Data for this study were obtained from the first 73 children who came in for evaluation and completed IOS.

The children underwent IOS before and after bronchodilator use. Before bronchodilator use, there were no significant differences in resistance or reactance at 5 or

TABLE II. IOS measurements in 4-year-old children with and without asthma

	Asthma (n = 28)	No asthma (n = 45)	P value*
Before bronchodilator			
R5	13.3* (11.4 to 14.3)	12.1 (10.6 to 14.4)	.42
R10	10.2 (8.8 to 11.0)	9.5 (8.5 to 11.0)	.20
X5	-5.5 (-7.0 to -5.0)	-5.4 (-6.4 to -4.3)	.34
X10	-3.9 (-5.1 to -2.7)	-3.6 (-4.8 to -2.9)	.98
Rfo	25.8 (24.3 to 29.0)	25.5 (22.5 to 27.3)	.37
Bronchodilator response			
ΔR5 (%)	26.9 (17.1 to 39.2)	17.0 (9.9 to 32.8)	.02
ΔR10 (%)	23.6 (15.0 to 31.1)	15.6 (9.7 to 25.4)	.03
ΔX5 (%)	35.8 (21.7 to 48.3)	27.8 (6.1 to 38.7)	.09
ΔX10 (%)	46.2 (37.3 to 56.4)	41.0 (12.7 to 51.7)	.09
ΔRfo (%)	15.2 (8.6 to 26.7)	11.9 (6.3 to 19.7)	.25

R5, Resistance at 5 Hz; R10, resistance at 10 Hz; X5, reactance at 5 Hz; X10, reactance at 10 Hz; Rfo, Resonant frequency; Δ, change in measurement after bronchodilator.

*Wilcoxon rank sum test.

†IOS measurements are given in centimeters of H₂O per liter per second, except for resonant frequency, which is given in hertz. Data are represented as medians, with interquartile ranges (25%-75%) in parentheses. In bold are comparisons attaining at least a .05 level of significance. IOS measurements are given as resistance and reactance at 5 and 10 Hz and resonant frequency.

TABLE III. Spirometry measurements in 4-year-old children with and without asthma

	Asthma (n = 27)	No asthma (n = 42)	P value*
Before bronchodilator			
FEV ₁	94.3† (72.4 to 103.4)	91.3 (78.5 to 101.3)	.96
FVC	83.3 (67.8 to 88.2)	78.7 (69.7 to 88.0)	.68
FEV ₁ /FVC	114.9 (112.5 to 116.3)	115.1 (114.9 to 116.3)	.47
FEF ₂₅₋₇₅	86.8 (59.7 to 102.4)	88.7 (72.7 to 102.3)	.68
Bronchodilator response			
ΔFEV ₁ (%)	4.0 (-7.0 to 18.0)	6.5 (-1.0 to 18.0)	.28
ΔFVC (%)	5.0 (-7.0 to 13.0)	8.0 (-1.0 to 18.0)	.13
ΔFEV ₁ /FVC (%)	0 (0 to 2.0)	0 (0 to 0)	.18
ΔFEF ₂₅₋₇₅ (%)	48.0 (21 to 65)	33.0 (10 to 50)	.15

FVC, Forced vital capacity; FEF₂₅₋₇₅, forced expiratory flow at 25% to 75% of forced vital capacity; Δ, change in measurement after bronchodilator.

*Wilcoxon rank sum test.

†Data are represented as median percent predicted, with interquartile ranges (25%-75%) in parentheses. Spirometry measurements (FEV₁, FVC, and FEF₂₅₋₇₅) are presented as percent predicted.¹⁴ The FEV₁/FVC ratio is presented as a percentage.

10 Hz or resonant frequency between the children with or without asthma (Table II). After bronchodilator use, however, significant differences were observed in the percentage change of resistance at 5 and 10 Hz. Nearly significant differences were observed for reactance at 5 and 10 Hz. There were not any significant differences in spirometric values at baseline or with bronchodilator response between the children who had asthma and those who did not (Table III).

Because young atopic children with a history of frequent wheezing are at risk for persistent asthma (asthma throughout childhood),¹⁶⁻²¹ the data were analyzed in regard to atopic patients with and without asthma. IOS measurements showed a remarkable response to albuterol when comparing atopic children with asthma versus atopic children without asthma (Table IV). Bronchodilator response was 2- to 4-fold higher in atopic asthmatic patients versus atopic nonasthmatic patients for all IOS measures. Specifically, significant differences

were observed in the bronchodilator response at resistance at 5 Hz, resistance at 10 Hz, and reactance at 10 Hz. The improved significance of the bronchodilator response in the atopic subset of children compared with the entire group of children is visually represented in Fig 2. In contrast, by using spirometric measures, there were no significant differences at baseline or in the bronchodilator response between the atopic asthmatic children and the atopic nonasthmatic children (Table V). In the subset of nonatopic children, there were no significant differences between the asthmatic and nonasthmatic children at baseline or bronchodilator response measured by means of IOS or spirometry (data not shown).

DISCUSSION

This is the first study to our knowledge to observe lung function differences in young children with a clinical picture of asthma. Previous authors have established correla-

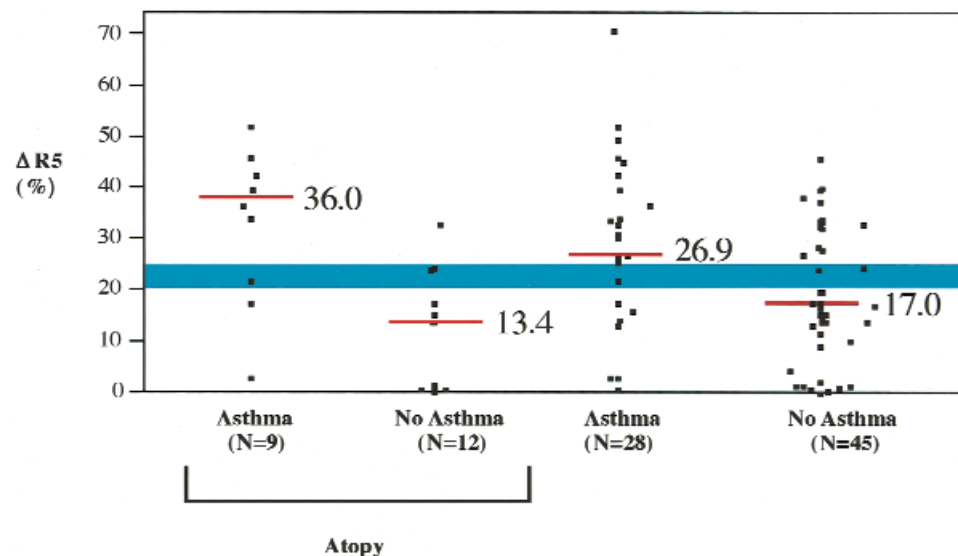


FIG 2. IOS bronchodilator (BD) response at 5 Hz in 4-year-old children. Percentage change in IOS resistance at 5 Hz (R_5) in response to albuterol is represented as individual values (black dots) and medians (number with horizontal line). Bronchodilator changes in the negative range were given a 0 value.

TABLE IV. IOS measurements in 4-year-old atopic children with and without asthma

	Asthma (n = 9)	No asthma (n = 12)	P value*
Before bronchodilator			
R5	13.3 [†] (12.0 to 16.4)	10.8 (9.4 to 13.7)	.13
R10	10.6 (10.1 to 13.0)	8.2 (6.9 to 10.6)	.08
X5	-5.8 (-9.0 to -5.3)	-5.2 (-7.3 to -4.0)	.25
X10	-3.9 (-5.6 to -3.0)	-3.5 (-5.6 to -2.5)	.54
Rfo	29.0 (26.7 to 31.0)	25.4 (21.9 to 29.2)	.21
Bronchodilator response			
ΔR5 (%)	36.0 (21.6 to 42.1)	13.4 (-0.3 to 23.9)	.007
ΔR10 (%)	24.5 (16.8 to 33.2)	10.5 (-16.2 to 19.1)	.02
ΔX5 (%)	36.2 (24.0 to 45.6)	-0.7 (-16.2 to 41.6)	.09
ΔX10 (%)	47.3 (38.0 to 67.5)	12.3 (3.9 to 41.4)	.03
ΔRfo (%)	25.0 (14.0 to 32.0)	12.7 (8.1 to 20.2)	.15

R5, Resistance at 5 Hz; R10, resistance at 10 Hz; X5, reactance at 5 Hz; X10, reactance at 10 Hz; Rfo, resonant frequency; Δ, change in measurement after bronchodilator.

*Wilcoxon rank sum test.

[†]IOS measurements are given in centimeters of H₂O per liter per second, except resonant frequency, which is given in hertz. Data are represented as medians, with interquartile ranges (25%-75%) in parentheses. IOS measurements are resistance and reactance at 5 and 10 Hz and resonant frequency.

tion of oscillometry measurements in children with other forms of lung function testing by means of bronchial challenges^{1,3,22} or bronchodilator response.²³⁻²⁶ Delacourt et al²⁷ used receiver operating characteristic curve analysis of oscillometry data to determine a cutoff that correlated with postbronchodilator change in FEV₁ in older children (mean age, 9.4 years). This cutoff point correlated with a group of younger children who had increased airway resistance that was reversed by means of bronchodilator use but was not compared with their clinical asthma phenotype. None of these above studies have investigated the relationship of IOS with clinical asthma.

Values for IOS bronchodilator response deemed reliable for the diagnosis of asthma have been reported as a 30% decrease in resistance at 10 Hz²⁴ and a 40% decrease in resistance at 5 Hz.² Mazurek et al²⁴ determined their

cutoff point by looking at older children (mean age, 9.2 years) with asthma or cystic fibrosis through their bronchodilator response (Δ FEV₁) compared with baseline values or values after bronchial challenge. Hellinkx et al² established a 40% decrease in resistance at 5 Hz as a positive bronchodilator response in children with a mean age of 4.5 years on the basis of a 95% CI of a healthy nonasthmatic population. However, they did not find a significant difference in IOS measurements at baseline or with bronchodilator response between their asthmatic and nonasthmatic children. Differences in IOS technique, populations, and asthma definitions might account for some of the discrepancy between this study and that of Hellinkx et al. At this institution (ie, National Jewish Medical and Research Center), Gleason et al,²⁸ using the same IOS equipment and methods but a completely dif-

TABLE V. Spirometry measurements in 4-year-old atopic children with and without asthma

	Asthma (n = 9)	No asthma (n = 9)	P value*
Before bronchodilator			
FEV ₁	94.4† (80.6 to 98.3)	98.7 (92.9 to 101.3)	.38
FVC	87.7 (80.0 to 90.5)	87.1 (84.0 to 92.6)	.99
FEV ₁ /FVC	112.5 (102.3 to 114.0)	114.9 (109.3 to 116.3)	.11
FEF ₂₅₋₇₅	48.8 (45.7 to 102.2)	81.8 (60.6 to 91.5)	.54
Bronchodilator response			
ΔFEV ₁ (%)	11.0 (0.0 to 23.0)	0.0 (−8.0 to 14.0)	.35
ΔFVC (%)	9.0 (0.0 to 15.0)	−3.0 (−13.0 to 12.0)	.30
ΔFEV ₁ /FVC (%)	2.0 (0.0 to 11.0)	0.0 (0.0 to 2.0)	.34
ΔFEF ₂₅₋₇₅ (%)	60.0 (44.0 to 146.0)	29.0 (7.0 to 63.0)	.11

FVC, Forced vital capacity; FEF₂₅₋₇₅, forced expiratory flow at 25% to 75% of forced vital capacity; Δ, change in measurement after bronchodilator.

*Wilcoxon rank sum test.

†Data are represented as median percent predicted, with interquartile ranges (25%-75%) in parentheses. Spirometry measurements (FEV₁, FVC, and FEF₂₅₋₇₅) are given in percent predicted.¹⁴ FEV₁/FVC ratio is given as a percentage.

ferent cohort, also found a significant difference in bronchodilator response in 2- to 6-year-old children (mean age, 4 years; n = 43) with and without a history of wheezing. Their results mirrored the findings in this report, with a mean bronchodilator response of wheezers versus non-wheezers in resistance at 5 Hz (24% vs 18%, $P = .01$) and resistance at 10 Hz (19% vs 14%, $P = .03$).

The differences in bronchodilator response between asthmatic patients and nonasthmatic patients are readily visualized when graphing the responses at a given resistance, such as that at 5 Hz (Fig 2). However, there was also some significant variation in bronchodilator response in the nonatopic asthma and nonatopic nonasthmatic groups. The children with large bronchodilator responses in the nonatopic asthma group might represent children who have not yet had positive skin test sensitivity to allergens because inhalant allergen sensitization develops in asthmatic children through age 7 years.²⁹ They might also become nonatopic children with bronchial hyperresponsiveness and persistent wheezing.^{17,30} An increased bronchodilator response is a hallmark of both of these childhood asthma phenotypes. The children in the nonatopic nonasthmatic group had 3 or more episodes of wheezing in early life, and a portion might still have some lung dysfunction despite a lack of clinical symptoms in the last year. The ATS-B symptom questionnaire criteria do not necessarily predict that these children will not have future wheezing manifestations (and thus be counted as having asthma in another year), and some of the asthma symptoms might be under-reported by the parents or caretakers. Considering these variable future outcomes, lung dysfunction demonstrated by an exaggerated bronchodilator response might be a helpful predictor of later childhood asthma and response to therapy. Although the bronchodilator response is statistically different between the asthmatic patients and nonasthmatic patients, there is substantial overlap in the responses between the groups (Fig 2). In the atopic subset of children, however, the difference between the asthmatic and nonasthmatic children is more dramatic, and a

cutoff point in the range of 20% to 25% bronchodilator response distinguishes most of the subjects in the groups. Similar analysis can be done for resistance at 10 Hz, which suggests a bronchodilator response of 15% to 20% as a cutoff point range for asthma in atopic children (not shown). These data suggest that a bronchodilator response of 20% to 25% at resistance at 5 Hz, a bronchodilator response of 15% to 20% at resistance at 10 Hz, or both distinguishes the young child with atopy-associated asthma. This is in contrast to conventional spirometry, presumably because reliable spirometry is difficult to obtain in young children.

Traditionally, the diagnosis of asthma in young children is based on clinical criteria, such as patterns of symptoms and response to medications. A good example of such criteria is the ATS-B asthma questionnaire of respiratory symptoms, which has been shown to have high specificity for physician-diagnosed asthma and bronchial hyperresponsiveness.³¹ Along similar lines, groups such as Castro-Rodriguez et al³² have developed clinical indices to define the risk of asthma in young children with recurrent wheezing. Although these types of standardized criteria are helpful, they had not been correlated with lung function in young children.³³ Our data support ATS-B criteria for asthma with objective lung function measurements in 4-year-old patients.

IOS could be used by clinicians to help target those patients with a significant bronchodilator response as children who might benefit from early medical intervention, environmental intervention, or both. It has been known for some time that preschool children with asthma and atopy are at higher risk than their peers for development of persistent asthma (and might be the most appropriate group for early treatment).^{16-21,34} Four-year-old children might provide an important window of opportunity for such interventions. Longitudinal studies of asthmatic children suggest that loss of lung function in patients with persistent asthma occurs between the ages of 1 and 6 years,³⁴ with little additional loss of function after 7 to 10 years of age.^{35,36} Researchers can apply this

information to focus on children who have early evidence of lung dysfunction, which correlates well with the clinical diagnosis of asthma. IOS will allow intervention studies to develop objective inclusion criteria and follow lung function parameters as outcome measures, even in young children. Recently, IOS served as one of multiple outcome measures for the effectiveness of inhaled budesonide in 2- to 5-year-old children.³⁷

In conclusion, IOS was better than spirometry at discriminating between young children with and without asthma on the basis of their bronchodilator response. It is especially strong in the subgroup of atopic children. Our data build on previous work by suggesting the level of a positive IOS bronchodilator response to a 15% to 20% decrease in resistance at 10 Hz or a 20% to 25% decrease in resistance at 5 Hz in atopic children and correlating objective lung function measurements with a standardized clinical definition of asthma in young children.

We thank the following persons for their contributions to this study: the technicians in the Pulmonary Physiology Unit at the National Jewish Medical and Research Center, including Trish Bangert, Rachel Comfort, Lisa Fails, Becky Kolenbrander, and Nick Morgan; the entire CAPS staff for coordinating patients and gathering data; Jim Murphy in Biostatistics for his analysis and advice; and Jan Manzanarez for help in preparing the manuscript.

REFERENCES

1. Bisgaard H, Klug B. Lung function measurement in awake young children. *Eur Respir J* 1995;8:2067-75.
2. Hellinckx J, DeBoeck K, Bande-Knops J, van der Poel M, Demedts M. Bronchodilator response in 3-6.5 year old healthy and stable asthmatic children. *Eur Respir J* 1998;12:438-43.
3. Klug B, Bisgaard H. Measurement of lung function in awake 2-4-year-old asthmatic children during methacholine challenge and acute asthma: a comparison of the impulse oscillation technique, the interrupter technique, and transcutaneous measurement of oxygen versus whole-body plethysmography. *Pediatr Pulmonol* 1996;21:290-300.
4. Nielsen KG, Bisgaard H. Lung function response to cold air challenge in asthmatic and healthy children of 2-5 years of age. *Am J Respir Crit Care Med* 2000;161:1805-9.
5. Carr W, Zeitel L, Weiss K. Variations in asthma hospitalizations and deaths in New York City. *Am J Public Health* 1992;82:59-65.
6. Marder D, Targonski P, Orris P, Persky V, Addington W. Effect of racial and socioeconomic factors on asthma mortality in Chicago. *Chest* 1992;101(suppl 6):426S-9S.
7. Lang DM, Polansky M. Patterns of asthma mortality in Philadelphia from 1969 to 1991. *N Engl J Med* 1994;331:1542-6.
8. Targonski PV, Persky V, Orris P, Addington W. Trends in asthma mortality among African Americans and whites in Chicago, 1968 through 1991. *Am J Public Health* 1994;84:1830-3.
9. Goodman DC, Stukel TA, Chang CH. Trends in pediatric asthma hospitalization rates: regional and socioeconomic differences. *Pediatrics* 1998;101:208-13.
10. Klinnert MD, Price MR, Liu AH, Robinson JL. Unraveling the ecology of risks from early childhood asthma among ethnically diverse families in the southwest. *Am J Public Health* 2002;92:792-8.
11. Joseph CLM, Foxman B, Leickly FE, Peterson E, Ownby D. Sensitivity and specificity of asthma definitions and symptoms used in a survey of childhood asthma. *J Asthma* 1999;36:565-73.
12. American Thoracic Society. Standardization of spirometry: 1994 update. *Am J Respir Crit Care Med* 1995;152:1107-36.
13. Arets HGM, Brackel HJL, van der Ent CK. Forced expiratory maneuvers in children: do they meet ATS and ERS criteria for spirometry? *Eur Respir J* 2001;18:655-60.
14. Eigen H, Bieler H, Grant D, Christoph K, Terrill D, Heilman DK, et al. Spirometric pulmonary function in healthy preschool children. *Am J Respir Crit Care Med* 2001;163:619-23.
15. Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. *Am J Respir Crit Care Med* 1999;159:179-87.
16. Brooke AM, Lambert PC, Burton PR, Clarke C, Luyt DK, Simpson H. The natural history of respiratory symptoms in preschool children. *Am J Respir Crit Care Med* 1995;152:1872-8.
17. Stein RT, Holberg CJ, Morgan WJ, Wright AL, Lombardi E, Taussig LM, et al. Peak flow variability, methacholine responsiveness and atopy as markers for detecting different wheezing phenotypes in childhood. *Thorax* 1997;52:946-52.
18. Kulig M, Gergmann R, Tacke U, Wahn U, Guggenmoos-Holzmann I, et al. Long-lasting sensitization to food during the first two years precedes allergic airway disease. *Pediatr Allergy Immunol* 1998;9:61-7.
19. Lau S, Illi S, Sommerfeld C, Niggemann B, Bergmann R, von Mutius E, et al. Early exposure to house-dust mite and cat allergens and development of childhood asthma: a cohort study. *Lancet* 2000;356:1392-7.
20. Rhodes HL, Thomas P, Sporik R, Holgate ST, Cogswell JJ. A birth cohort study of subjects at risk of atopy. Twenty-two-year follow-up of wheeze and atopic status. *Am J Respir Crit Care Med* 2002;165:176-80.
21. Wolfe R, Carlin JB, Oswald H, Olinsky A, Phelan PD, Robertson CF. Association between allergy and asthma from childhood to middle adulthood in an Australian cohort study. *Am J Respir Crit Care Med* 2000;162:2177-81.
22. Duiverman EJ, Neijens HJ, Van der Snee-van Smaalen M, Kerrebijn KF. Comparison of forced oscillometry and forced expirations for measuring dose-related responses to inhaled methacholine in asthmatic children. *Bull Eur Physiopathol Respir* 1986;22:433-6.
23. Konig P, Hordvik NL, Pimmel RL. Forced random noise resistance determination in childhood asthma. *Chest* 1984;86:884-90.
24. Mazurek HK, Marchal F, Derelle J, Hatahet R, Moneret-Vautrin D, Monin P. Specificity and sensitivity of respiratory impedance in assessing reversibility of airway obstruction in children. *Chest* 1995;107:996-1002.
25. Klug B, Bisgaard H. Lung function and short-term outcome in young asthmatic children. *Eur Respir J* 1999;14:1185-9.
26. Delacourt C, Lorino H, Fuhrman C, Herve-Guillot M, Reinert P, Harf A, et al. Comparison of the forced oscillation technique and the interrupter technique for assessing airway obstruction and its reversibility in children. *Am J Respir Crit Care Med* 2001;164:965-72.
27. Delacourt C, Lorino H, Herve-Guillot M, Reinert P, Harf A, Housset B. Use of the forced oscillation technique to assess airway obstruction and reversibility in children. *Am J Respir Crit Care Med* 2000;161:730-6.
28. Gleason M, Covar R, Gelfand E, Szeffler SJ, Larsen G. Lung function measurements using forced oscillation in young children. In: *Proceedings of the World Asthma Meeting*; Chicago, Ill; 2001.
29. Illi S, von Mutius E, Lau S, Nickel R, Niggemann B, Sommerfeld C, et al. The pattern of atopic sensitization is associated with the development of asthma in childhood. *J Allergy Clin Immunol* 2001;108:709-14.
30. Palmer LJ, Rye PJ, Gibson NA, Burton PR, Landau LI, LeSouef PN. Airway responsiveness in early infancy predicts asthma, lung function, and respiratory symptoms by school age. *Am J Respir Crit Care Med* 2001;163:37-42.
31. Leone FT, Mauger EA, Peters SP, Chinchilli VM, Fish JE, Boushey HA, et al. The utility of peak flow, symptoms scores, and β -agonist use as outcome measures in asthma clinical research. *Chest* 2001;119:1027-33.
32. Castro-Rodriguez JA, Holberg CJ, Wright AL, Martinez FD. A clinical index to define risk of asthma in young children with recurrent wheezing. *Am J Respir Crit Care Med* 2000;162:1403-6.
33. Remes ST, Pekkanen J, Remes K, Salonen RO, Korppi M. In search of childhood asthma: questionnaire, tests of bronchial hyperresponsiveness, and clinical evaluation. *Thorax* 2002;57:120-6.
34. Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ, et al. Asthma and wheezing in the first six years of life. *N Engl J Med* 1995;332:133-8.
35. Oswald H, Phelan PD, Lanigan A, Hibbert M, Carlin JB, Bowes G, et al. Childhood asthma and lung function in mid-adult life. *Pediatr Pulmonol* 1997;23:14-20.
36. The Childhood Asthma Management Program Research Group. Long-term effects of budesonide or nedocromil in children with asthma. *N Engl J Med* 2000;343:1054-63.
37. Nielsen KG, Bisgaard H. The effect of inhaled budesonide on symptoms, lung function, and cold air and methacholine responsiveness in 2- to 5-year-old asthmatic children. *Am J Respir Crit Care Med* 2000;162:1500-6.