

Pulmonary Function Tests in Preschool Children with Asthma

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Pulmonary function tests are seldom performed in preschool children with asthma. The aim of this multicenter study was to compare pulmonary function in 74 preschool children with asthma (height of 90–130 cm) and 84 healthy control subjects. Functional residual capacity (helium dilution technique) and expiratory interrupter resistance (interrupter technique) were measured. As compared with control children, children with asthma had a significantly higher resistance (0.77 ± 0.20 vs. 0.92 ± 0.22 kPa · L⁻¹ · second, $p < 0.001$) and significantly lower specific expiratory interrupter conductance ($p < 0.005$) values. Resistance values were significantly higher in children with asthma with than without symptoms on exertion ($p < 0.05$). The effect of bronchodilator administration, expressed as the percentage of baseline and predicted resistance values, was significantly greater in children with asthma than in control subjects ($-18.6 \pm 13.6\%$ vs. $-11.2 \pm 15.2\%$, $p \leq 0.001$, and $-23.2 \pm 19.2\%$ vs. $-12.6 \pm 17.8\%$, $p < 0.001$), respectively. A 35% decrease in resistance after bronchodilation expressed as the percentage of predicted values had a likelihood ratio of 3 for separating the bronchodilator response in children with asthma from that in healthy control subjects. Pulmonary function tests that do not require active cooperation may help in the management and follow-up of preschool children with asthma who are unable to perform forced expiratory maneuvers.

Keywords: functional residual capacity; expiratory interrupter resistance; bronchodilator

The incidence of pediatric asthma is increasing in most countries (1). Pulmonary function tests (PFTs) are used to determine asthma severity, along with clinical symptoms and medication requirements (2). Normal lung function is one of the goals of asthma management in international guidelines (3, 4). Furthermore, long-term cohort studies have established that PFT results in children with asthma are correlated with asthma severity and with pulmonary function impairment in adulthood (5).

Forced expiratory maneuvers are used in school children and in adults. However, preschool children may be too young to perform acceptable and reproducible forced expiratory maneuvers (6). As a result, PFTs are seldom performed in clinical practice in preschool children with asthma.

In recent years, PFTs that do not require active cooperation,

such as the interrupter technique or the forced oscillation technique, have been evaluated for estimating airflow resistance in healthy (7–10) and in preschool children who have asthma or who are wheezing (9, 11–14). We recently reported prebronchodilator and postbronchodilator expiratory interrupter resistance ($R_{int_{exp}}$) values in healthy preschool children (15) and then used these normative data to study preschool children with respiratory disorders (16).

The aim of this multicenter study in preschool children with asthma was to evaluate pulmonary function using tests that do not require active cooperation. We measured FRC using the helium dilution technique and $R_{int_{exp}}$ before and after administration of a short-acting bronchodilator. We determined whether PFT data were correlated with the clinical characteristics of asthma. Furthermore, we evaluated the bronchodilator response threshold that may separate children with asthma from healthy control children.

METHODS

Subjects

The study was part of a multicenter investigation whose design has been described elsewhere (15) (additional detail is provided in the online supplement). The control subjects were 91 healthy white preschool children in the 90- to 130-cm height range included in a previously reported French multicenter study (15). The patients were 77 white preschool outpatients with a medical diagnosis of asthma. The diagnosis was based on typical asthma symptoms such as recurrent wheeze and breathlessness resolving spontaneously or with an inhaled bronchodilator. The only exclusion criterion was the presence of an acute exacerbation, defined as asthma symptoms requiring oral corticosteroids, an emergency visit, or hospitalization during the last 4 weeks. Physical examination, including height and weight measurements, was performed on the day of the study. In the children with asthma, we recorded age at onset of symptoms, history of atopy and of hospitalization, frequency and circumstances of symptoms, asthma-related absences from school, and antiasthma treatments in the last year. Exposure to environmental tobacco smoke was recorded in all participants. None of the study children with asthma had had PFTs previously. The study was approved by the local ethical committees, and written informed consent was obtained from both parents of each child.

Procedures

Short-acting bronchodilator therapy was withheld for at least 8 hours and long-acting bronchodilator therapy for at least 24 hours. Pulse oximetry was recorded (Nellcor N-200, Hayward, CA) in the children with asthma. FRC was measured using the helium dilution method as the mean of two measurements differing by less than 10%, as previously described (16). The conditions and validation of $R_{int_{exp}}$ measurements have been described previously (15). Briefly, the flow signal used to calculate R_{int} was obtained just before the interruption. Linear-back extrapolation of mouth pressure was used to estimate alveolar pressure for $R_{int_{exp}}$ calculation. Seven $R_{int_{exp}}$ measurements with an intrasubject coefficient of variation that was smaller than 20% were validated. The

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20% limit for acceptance was chosen because it was equal to the mean baseline $R_{int_{exp}}$ coefficient of variation plus 2 SDs (15). Specific expiratory interrupter conductance was the ratio of expiratory interrupter conductance over FRC ($sG_{int_{exp}}$). Data collection was performed as previously reported (15).

The mean $R_{int_{exp}}$ was calculated at baseline and 10 minutes after bronchodilator administration (200 μ g of salbutamol administered using a metered-dose inhaler and a spacer; Volumatic, Glaxo, Badollesloe, Germany). The effects of the bronchodilator were presented in three ways: (1) as raw data, (2) as the percentage of the baseline $R_{int_{exp}}$ values (prebronchodilator values), and (3) as the percentage of the predicted $R_{int_{exp}}$ values.

Statistical Analysis

Data were expressed as frequencies (percentages) for categorical variables and as means $\pm$ SD or medians (interquartile range) for normally and nonnormally distributed continuous variables, respectively. Normality plots were constructed to check that assumptions of normality were met. Comparisons between groups used the chi-square or Fisher's exact test, as appropriate, for categorical variables and the Student's or Wilcoxon test, as appropriate, for continuous variables. Correlations between quantitative variables were studied by the Spearman correlation coefficient. Receiver-operating characteristic (ROC) curves for the bronchodilator effect expressed as the percentages of baseline and predicted values were generated to assess diagnostic performance. The comparison between ROC curves was performed with the Mann-Whitney U-statistic (17). The likelihood ratios (sensitivity/1 – specificity) were calculated (18).

RESULTS

Subjects

Eighty-four of the 91 healthy children completed the baseline and postbronchodilator $R_{int_{exp}}$ measurements. Among the 77 children with asthma, 2 were excluded by the coordinating center because they had fewer than seven validated R_{int} measurements at baseline, and another was excluded because the coefficient of variation was more than 20% at baseline. The 74 other children with asthma performed the baseline and postbronchodilator $R_{int_{exp}}$ measurements. Table 1 reports anthropometric data in the children with asthma and healthy control subjects. There were no differences between the groups except for a larger proportion of boys among the children with asthma. Table 2 reports the clinical data of the children with asthma. The median age at disease onset was 1.9 years (range, 0.2–6), and 34 (46%) patients experienced their first symptoms before 2 years of age. A large majority of the children with asthma (85.1%) were on daily inhaled steroid therapy. Most of the children with asthma were in stable condition, with 49 (66.2%) having fewer than one episode of asthma per month (excluding symptoms on exertion). Symptoms on exertion occurred in 32 (43.2%) children with asthma. The questionnaire was not set up to differentiate between symptoms that occurred early during exercise, suggesting

TABLE 1. DESCRIPTION OF THE STUDY POPULATION

	Healthy Subjects (n = 84)	Patients with Asthma (n = 74)
Girls/boys	42/42	24/50*
Age, yr	5.3 $\pm$ 1.4 (2.9–7.9)	5.2 $\pm$ 1.2 (3.2–7.8)
Height, cm	111.7 $\pm$ 9.1 (92–129)	110.7 $\pm$ 8.6 (92–130)
Weight, kg	19.3 $\pm$ 3.6 (12–29)	19.5 $\pm$ 3.8 (13–28)
BMI, kg/m ²	15.4 $\pm$ 1.3 (11.6–18.8)	15.7 $\pm$ 1.5 (12.6–19.4)
Passive smoke, n (%)	28 (33)	30 (40.5)

Definition of abbreviation: BMI = body mass index.

Results are means $\pm$ SD and (range).

* Sex ratio significantly different ($p < 0.03$).

TABLE 2. CLINICAL CHARACTERISTICS OF THE POPULATION WITH ASTHMA

	Children with Asthma (n = 74) Median (range) or n (%)
Asthma	
Age at onset, yr	1.9 (0.2–6)
Disease duration, yr	3.05 (0.3–6.8)
Previous hospitalization	30 (40.5)
Atopy*	48 (64.9)
In the last year	
Attack(s) of asthma	
≥ 1 in the last yr	63 (85.1)
≥ 1 in the last wk	2 (2.7)
Hospitalization for an attack	11 (14.8)
Frequency of symptoms (excluding symptoms on exertion)	
$\geq 1/d$	0
$\geq 1/wk$	5 (6.7)
$\geq 1/mo$	18 (24)
$< 1/mo$	49 (66.2)
At night	41 (55.4)
Symptoms on exertion	32 (43.2)
Preschool missed	40 (54)
Number of days	11.6 $\pm$ 9.3
Daily antiasthmatic treatment	70 (95)
Inhaled bronchodilator	30 (40.5)
Inhaled steroids	63 (85.1)

* Atopy diagnosis based on a positive prick test to allergens and/or specific IgE elevation.

poorly controlled asthma, and symptoms occurring after prolonged exercise, suggesting exercise-induced asthma. Forty (54%) patients had missed school at least once during the last year because of their asthma.

PFT Data

Pulse oximetry. Sa_{O_2} (mean $\pm$ SD) was $98 \pm 1\%$ (range, 95–100%) at baseline in the children with asthma.

FRC measurements. Mean $\pm$ SD baseline FRC values in the healthy control subjects and children with asthma are shown in Table 3. FRC values were not different between the healthy control subjects and children with asthma.

Baseline $R_{int_{exp}}$ values. Mean $\pm$ SD $R_{int_{exp}}$ and $sG_{int_{exp}}$ values in the healthy children are reported in Table 3. There was no effect of center or sex on these PFT data in healthy children. Figure 1 shows the relationship between $R_{int_{exp}}$ and height in the patients with asthma.

The children with asthma had significantly higher $R_{int_{exp}}$ (Fig-

TABLE 3. COMPARISON OF PULMONARY FUNCTION TEST RESULTS AT BASELINE BETWEEN HEALTHY CONTROL SUBJECTS AND PATIENTS WITH ASTHMA

	Healthy (n = 84)	With Asthma (n = 74)
FRC, L	0.82 $\pm$ 0.20	0.80 $\pm$ 0.26
FRC, % predicted	99 $\pm$ 19	98 $\pm$ 24
$R_{int_{exp}}$ kPa $\cdot$ L ⁻¹ $\cdot$ s	0.77 $\pm$ 0.20	0.92 $\pm$ 0.22*
$R_{int_{exp}}$ % predicted	101 $\pm$ 22	118 $\pm$ 23†
$sG_{int_{exp}}$	1.74 $\pm$ 0.55	1.50 $\pm$ 0.46‡

Definition of abbreviations: $sG_{int_{exp}}$ = expiratory interrupter conductance over FRC; $R_{int_{exp}}$ = expiratory interrupter resistance.

Results are means $\pm$ SD.

Patients with asthma are significantly different from healthy control subjects.

* $p < 0.001$.

† $p < 0.0001$.

‡ $p < 0.005$.

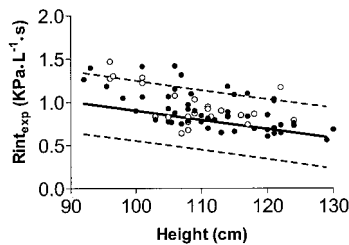


Figure 1. Individual expiratory interrupter resistance (R_{int_exp}) measurements in children with asthma (closed circle, boys; open circle, girls) related to regression lines (solid lines) and 95% confidence limits (dotted lines) for healthy children.

ure 1 and Table 3) values than did the healthy children ($p < 0.001$), with 15% having values greater than the 95% confidence interval. The intrasubject coefficient of variation of R_{int_exp} was not significantly different between the healthy control subjects and children with asthma (Table 4). As shown in Table 3, sG_{int_exp} values were significantly decreased in the children with asthma as compared with the healthy control subjects ($p < 0.005$). No effect of sex was observed for R_{int_exp} or sG_{int_exp} in the children with asthma.

Effect of bronchodilator on R_{int_exp} . R_{int_exp} decreased significantly after bronchodilator inhalation in both the children with asthma and the healthy control subjects ($p < 0.03$; Table 4). The effect of the bronchodilator was greater in the group with asthma whether the response was expressed as the percentage of baseline R_{int_exp} values or as the percentage of predicted R_{int_exp} values ($p \leq 0.001$) (Table 4). These differences persisted after exclusion of the 15% of children with asthma with significantly abnormal baseline R_{int_exp} values ($p < 0.03$). The postbronchodilator R_{int_exp} values were significantly higher in the group with asthma than in the control group (Table 4). Furthermore, children with asthma with abnormal baseline R_{int_exp} had higher postbronchodilator values expressed as the percentage of predicted than those with baseline R_{int_exp} values in the normal range (median [interquartile range] 103% [90%–137%] vs. 90% [78–103%], $p < 0.03$). In both the control group and the group with asthma, the bronchodilator response expressed as the percentage of baseline R_{int_exp} values was significantly correlated with absolute baseline R_{int_exp} ($r = -0.24$, $p < 0.04$, and $r = -0.24$, $p < 0.05$, respectively) and with baseline R_{int_exp} expressed as the percentage of predicted R_{int_exp} ($r = -0.29$, $p < 0.008$, and $r = -0.37$, $p < 0.002$, respectively); in addition, the bronchodilator response expressed as the percentage of predicted R_{int_exp} was significantly correlated with baseline R_{int_exp} values expressed as the percentage of predicted R_{int_exp} ($r = -0.37$, $p < 0.001$, and $r = -0.55$, $p < 0.001$, respectively). In the control group and group with asthma, the distribution of bronchodilator responses was unimodal, and marked overlap occurred between the two populations (Figure

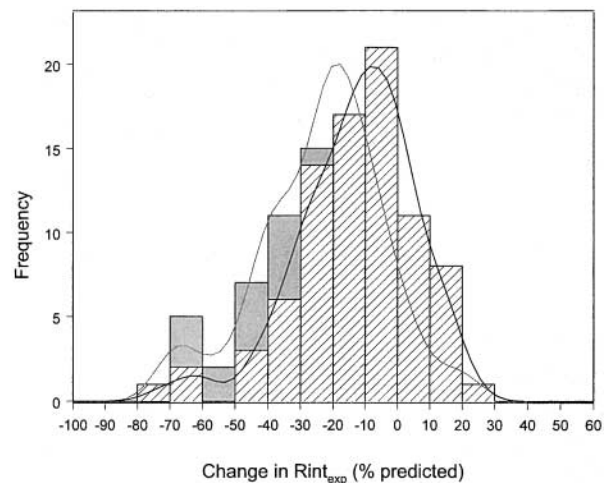


Figure 2. Relative frequency distribution of bronchodilator response expressed as the percentage of predicted R_{int_exp} values in children with asthma and healthy control children (open bars, children with asthma; slashed bars, healthy children).

2). The area under the curve of the ROC curve for the bronchodilator response expressed as the percentage of predicted R_{int_exp} values was significantly greater than the area under the curve of the ROC curve for the bronchodilator response expressed as the percentage of baseline R_{int_exp} values (area under the curve = 0.67 vs. 0.64, $p < 0.05$). A cutoff of 35% of the predicted post-bronchodilator R_{int_exp} decrease had a specificity of 92% and a sensitivity of 24% for separating children with and without asthma (Table 5). With this cutoff, there was a likelihood ratio of 3 for separating the bronchodilator response in children with asthma from that in healthy control subjects.

Relationships between PFT Data and Clinical Characteristics in Children with Asthma

Children with asthma with symptoms on exertion had significantly higher R_{int_exp} values at baseline (R_{int_exp} 1.00 ± 0.23 kPa · L⁻¹ · s vs. 0.86 ± 0.18 kPa · L⁻¹ · s, $p < 0.005$; corresponding to median values [interquartile range] 123% [107–140%] vs. 110% [96–120%] of predicted; $p < 0.02$) and significantly higher post-bronchodilator R_{int_exp} values (R_{int_exp} 0.79 ± 0.17 kPa · L⁻¹ · s vs. 0.70 ± 0.18 kPa · L⁻¹ · s; $p < 0.03$; corresponding to median values [interquartile range] of 96% [87–104%] vs. 87% [77–106%] of predicted, $p < 0.05$) than did the children with asthma without symptoms on exertion (Table 2).

TABLE 4. EFFECT OF BRONCHODILATOR

	R_{int_exp} BD (kPa · L ⁻¹ · s)	R_{int_exp} BD%P	BD-B (kPa · L ⁻¹ · s)	BD-B%B	BD-B%P	CV%B	CV%BD
Healthy							
Mean ± SD	$0.68 \pm 0.18^*$	88.4 ± 19.6	-0.10 ± 0.14	-11.2 ± 15.2	-12.6 ± 17.8	12.2 ± 3.4	$14.0 \pm 4.9^§$
Asthma							
Mean ± SD	$0.74 \pm 0.18^{*†}$	$94.8 \pm 19^†$	$-0.18 \pm 0.15^‡$	$-18.6 \pm 13.6^‡$	$-23.2 \pm 19.2^‡$	11.7 ± 3.9	12.2 ± 3.4

Definition of abbreviations: BD = values after bronchodilator administration; P = predicted; B = baseline (see R_{int_exp} values in Table 3); CV = intrasubject coefficient of variation; R_{int_exp} = expiratory interrupter resistance.

* R_{int_exp} BD is lower than R_{int_exp} B, $p < 0.003$.

Difference between patients with asthma and healthy subjects:

† $p < 0.05$.

‡ $p \leq 0.001$.

§ Coefficients of variation for BD values in the healthy control subjects are different from all other coefficient of variation values, $p < 0.01$.

TABLE 5. SPECIFICITY AND SENSITIVITY OF THE BRONCHODILATOR EFFECT IN 74 CHILDREN WITH ASTHMA AND 84 HEALTHY CHILDREN

Effect of BD, % predicted	-20	-25	-30	-35	-40	-50
Specificity	69	76	86	92	93	96
Sensitivity	54	38	34	24	19	9

Definition of abbreviation: BD = values after bronchodilator administration.

DISCUSSION

The aim of this multicenter study was to compare PFT data in preschool children with asthma and healthy control subjects using methods that do not require active cooperation of the child. Children with asthma had significantly higher $R_{int_{exp}}$ and lower $sG_{int_{exp}}$ values than did the healthy control children. Baseline $R_{int_{exp}}$ and postbronchodilator $R_{int_{exp}}$ values were significantly higher in the children with asthma with than without symptoms on exertion. The effect of short-acting bronchodilator inhalation, expressed as the percentages of baseline and predicted $R_{int_{exp}}$ values, was significantly greater in the children with asthma than in the control children. A 35% decrease in $R_{int_{exp}}$ expressed as the percentage of the predicted values had a likelihood ratio of 3 for separating the bronchodilator response in children with asthma from that in healthy control subjects.

Measurement Methods and PFT Data in Healthy Control Children

All of the centers used the same standardized procedure for PFT measurements and data collection (15). Of the 91 healthy preschool children in our previous study (15), we included the 84 in whom both pre- and post- $R_{int_{exp}}$ measurements were obtained. To calculate the predicted FRC and $R_{int_{exp}}$ values, we used the equations of FRC and $R_{int_{exp}}$ according to height that we had established previously in healthy preschool children (15, 16). $R_{int_{exp}}$ was not measured after placebo administration in the healthy preschool children. Previous studies have reported little or no change after placebo in either resistance at 5 Hz measured using the oscillation technique (R_{rs5}) or R_{int} in healthy preschool children (9, 10, 13). Our study is in line with previous studies in healthy subjects showing a reduction in bronchial tone after bronchodilator administration in healthy infants (19), preschool children (9, 10, 13), school-age children (20–22), and adults (23). The distribution of the bronchodilator effect on $R_{int_{exp}}$ was continuous and unimodal (Figure 2) in the healthy children in our study, as was FEV_1 in a large group of healthy subjects (23). The wide variability of the bronchodilator response in healthy subjects (9, 15, 23) may be due to differences in environmental conditions and/or in genetic make-up (24).

PFT Data in Preschool Children with Asthma

Baseline PFT data. All of the children with asthma had baseline SA_{O_2} values that were more than 95%, and their FRC values were within the range of those in the control children. The baseline coefficient of variation of $R_{int_{exp}}$ in the children with asthma was not significantly different from that in the healthy control children. The children with asthma had higher $R_{int_{exp}}$ and lower $sG_{int_{exp}}$ values than did the control subjects. However, only 15% of the children with asthma had baseline $R_{int_{exp}}$ values above the 95% confidence interval of $R_{int_{exp}}$ in the healthy control subjects. $R_{int_{exp}}$ values were significantly higher in the children with asthma with than without symptoms on exertion.

Few comparisons of PFT data in children with asthma and control preschool children are available. Hellinckx and coworkers found that R_{rs5} was within the normal range in 34 preschool

children with asthma, half of whom were on asthma medications (9). Nielsen and Bisgaard collected PFT data in 55 preschool children with asthma, including 73% on inhaled steroid therapy (13), and found higher specific airway resistance, R_{rs5} , and R_{int} in the children with asthma than in the control children. However, they performed R_{int} measurements using the opening interrupter method, in which the pressure used for R_{int} calculation was measured at the end of an 80-ms occlusion and the flow shortly after airway reopening. R_{int} measured by this method is thought to represent flow resistance plus the resistance of the tissue viscoelastic component of the respiratory system (25, 26). Therefore, R_{int} values measured by the opening interrupter method are higher than those obtained in this study. Consequently, our R_{int} data cannot be compared with those reported by Nielsen and Bisgaard (13) in children with asthma.

Effect of bronchodilator on $R_{int_{exp}}$. We found that the effect of bronchodilator inhalation was significantly greater in the children with asthma than in the control children. Nielsen and Bisgaard (13) found a similar difference, whereas Hellinckx and colleagues (9) did not. Differences in asthma severity and asthma treatment may explain these differences in the magnitude of bronchodilator effects in children with asthma. The slightly but significantly higher postbronchodilator values in the group with asthma than in the control group suggest that relaxation of bronchial smooth muscle was less marked in the children with asthma. The bronchodilator was less effective in the children with asthma with abnormal baseline $R_{int_{exp}}$ who had higher postbronchodilator $R_{int_{exp}}$ values expressed as the percentage of predicted values than in the children with asthma with normal baseline $R_{int_{exp}}$ values. Residual obstruction in the children with asthma who were less responsive to the bronchodilator would perhaps have been lifted by a higher bronchodilator dose than used in this study.

There is no consensus on the best way to express the bronchodilator response in children (27). Waalkens and colleagues recommended the percentage of predicted values rather than the percentage of baseline values in a group of children with asthma with relatively severe obstruction as assessed by FEV_1 measurements (27). They based this recommendation on their finding that the bronchodilator response as the percentage of baseline was significantly dependent on baseline FEV_1 , whereas the bronchodilator response as the percentage of predicted was not (27). We studied preschool children with moderately severe asthma, in whom the bronchodilator responses were related to baseline obstruction whether they were expressed as percentage of baseline or as percentage of predicted. Further investigations are needed in preschool children with asthma with more severe obstruction to determine whether the bronchodilator response remains dependent on baseline obstruction when expressed as the percentage of predicted values.

Bronchodilator response cutoffs for separating children with asthma from control children. Previous reports in healthy and adults with asthma and school children have shown that reversibility of airway obstruction in response to a bronchodilator is a continuous rather than a dichotomous trait (27, 28). In keeping with these data, we found a marked overlap in bronchodilator responses between the control and the children with asthma groups (Figure 2). This overlap complicates the determination of a cutoff for defining a positive bronchodilator response in patients with respiratory disorders. Various approaches have been proposed for defining a cutoff separating bronchodilator responses in healthy subjects from those in patients (28). One possibility is to consider that bronchodilator responses outside the 95% confidence interval in healthy subjects are abnormal. This definition would identify only seven (9%) of the children with asthma in our study (Table 4). Another approach is to take into account the intrinsic variability of $R_{int_{exp}}$ measurements, de-

fining a bronchodilator response as abnormal if it exceeds the 95th percentile of the distribution of $R_{int_{exp}}$ variability (Table 4). In this study, this definition results in overclassification of bronchodilator responses as positive (Figure 2 and Table 5). A third possibility is to calculate the cutoffs from ROC curves. Using the ROC curve for bronchodilator response expressed as the percentage of predicted values, we found that a 35% decrease in $R_{int_{exp}}$ had high specificity (92%) (Table 5) and a likelihood ratio of 3 for separating bronchodilator responses in children with asthma from those in healthy control subjects. Because only 15% of the children with asthma had abnormal baseline $R_{int_{exp}}$ values, sensitivity of the 35% cutoff was low. Further studies are needed to evaluate the clinical usefulness of the proposed cutoff.

In summary, PFTs that do not require active cooperation of the child are well accepted by preschool children. They can be used to evaluate baseline pulmonary function and the effect of bronchodilator inhalation. This study provided a snapshot of the use of $R_{int_{exp}}$ measurements in preschool children with asthma. Longitudinal studies are needed to determine how variables such as baseline $R_{int_{exp}}$, postbronchodilator $R_{int_{exp}}$, and bronchodilator response correlate with clinical symptoms and disease severity. Furthermore, PFT follow-up would show whether early PFTs improve the management of young children with asthma who are unable to perform reproducible expiratory forced maneuvers.

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