Use of the Forced Oscillation Technique to Assess Airway Obstruction and Reversibility in Children

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The forced oscillation technique (FOT) is particularly attractive in a pediatric setting as it requires only passive cooperation from the child. We assessed the sensitivity and specificity of this method for detecting airway obstruction and its reversibility in 313 children (3 to 16 yr of age) with asthma or chronic nocturnal cough. Baseline and postbronchodilator (n = 251) resistance were measured (R\textsubscript{0}) with the FOT. Baseline R\textsubscript{0} was normalized for height and weight [R\textsubscript{0}(SD)]. In children able to perform forced expiratory maneuvers (n = 181), R\textsubscript{0}(SD) was independently correlated with FEV\textsubscript{1} (p < 0.02) and maximal expiratory flow at 50% (MEF\textsubscript{50}) (p < 0.004). The optimal R\textsubscript{0}(SD) cutoff value given by receiver operating characteristic (ROC) curves to discriminate between children with baseline FEV\textsubscript{1} < 80% or ≥ 80% of predicted values yielded 84% sensitivity and 73% specificity. Postbronchodilator changes in R\textsubscript{0}(SD) [ΔR\textsubscript{0}(SD)] were mostly correlated to changes in MEF\textsubscript{50}. The optimal ΔR\textsubscript{0}(SD) cutoff value to discriminate between children with the presence or absence of significant reversibility in FEV\textsubscript{1} yielded 69% sensitivity and 78% specificity. In children unable to perform forced expiratory maneuvers (n = 132), this ΔR\textsubscript{0}(SD) cutoff clearly identified a subgroup of young children with high R\textsubscript{0} values at baseline, that returned to normal after bronchodilation. We conclude that FOT measurements allow reliable evaluation of bronchial obstruction and its reversibility in asthmatic children over 3 yr old. 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.


The detection of airflow obstruction and its reversibility is a routine procedure in pediatric pulmonary function laboratories. Measurement of forced expiratory volume in one second (FEV\textsubscript{1}) is considered to be the basic test for the assessment of airway obstruction. However, it is usually difficult to obtain in children younger than 6 yr of age because it is effort-dependent and therefore requires active cooperation from the child. An alternative method is measurement of the total resistance of the respiratory system (R\textsubscript{rs}) with the forced oscillation technique (FOT). This method is particularly attractive as it requires only passive cooperation from the subject, who breathes quietly at tidal volume during the test. In children, the FOT has already proved useful for evaluating bronchial responsiveness to nonspecific agents (1–3). In contrast, few studies have evaluated the ability of this method to detect bronchial obstruction in children and to assess changes following bronchodilator inhalation (4–6). Moreover, there is no consensus on R\textsubscript{rs} criteria for the identification and grading of airway obstruction. A significant correlation has been found between baseline FEV\textsubscript{1} and R\textsubscript{rs} (4, 6), but it was also suggested that R\textsubscript{rs} failed to reflect peripheral obstruction, thus limiting routine use of FOT for detecting bronchial obstruction (6).

In this investigation we first studied children able to perform forced expiratory maneuvers in order to evaluate the ability of FOT to identify those with an abnormal flow-volume curve and to detect a response to a bronchodilator relative to changes in FEV\textsubscript{1}. We then studied the usefulness of R\textsubscript{rs} measurement for assessing bronchial obstruction and its reversibility in a population of young children unable to perform forced expiratory maneuvers.

METHODS

Population

A total of 313 children were referred to our pulmonary function laboratory for evaluation of bronchial disease. The clinical diagnoses were asthma (n = 203), chronic nocturnal cough (n = 99), and allergic rhinitis (n = 11). Of these 313, 181 children (104 boys and 77 girls), age 4.3 to 15.7 yr (9.4 ± 2.0 yr) were able to perform forced expiratory maneuvers and underwent FOT measurements (Group 1). The remaining 132 children (85 boys and 47 girls), age 2.7 to 12.7 yr (4.9 ± 1.0 yr) were unable to perform forced expiratory maneuvers, but had acceptable FOT measurements (Group 2).

Study Design

Baseline measurements were obtained in all children. A bronchodilator (200 μg salbutamol) was administered with a metered-dose and spacer device to 126 children in Group 1 and 125 children in Group 2. Postbronchodilator measurements were obtained after 15 min.
**Measurement of Forced Expiratory Volumes and Flows**

Flow-volume curves were registered with a MedGraphics PF/Dx (Medical Graphics Co., St. Paul, MN) to determine FVC, FEV₁, and maximal expiratory flow at 50% (MEF₅₀) and 25% (MEF₂₅) of FVC. A acceptance of flow-volume curves was subject to the respect of international criteria (7). Results were expressed as the percentage of predicted values (8).

**Measurement of Respiratory Impedance**

Respiratory impedance was determined by the standard forced oscillation technique as previously described (9–11). A forced expiratory maneuvers could induce possible changes in bronchial motor tone, all forced oscillation measurements were performed first. The child was equipped with a mouthpiece and a nose clip and was comfortably seated with the head in the neutral position and the cheeks firmly held by a parent. The child was asked to breathe quietly and avoid swallowing. A pseudorandom noise signal mixing integer frequencies between 4 and 32 Hz was generated by a loudspeaker (Oscilink; Datalink-M SR, Rungis, France) and superimposed on the subject's spontaneous breathing. Mouth flow was sensed by a pneumotachograph (Model 4700; Hans Rudolph, Kansas City, MO) connected to a differential pressure transducer (Validyne DP45 ± 2 cm H₂O; Validyne Co., Northridge, CA). Both signals were low-pass filtered and sampled at 128 Hz for measurement periods of 16 s. The time course of pressure and flow was monitored, and data with glottic closure, swallowing, or episodes of irregular breathing were discarded. A u-to- and cross-spectra of flow and pressure were estimated for adjacent 4-s blocks and averaged over each 16-s period to yield a mean estimate of impedance (Zrs) and coherence function (γ²) for each frequency component. A measurement period was considered acceptable if γ² was higher than 0.9 for more than 80% of the frequency components. The real component of Zrs (Rrs), which is related to the resistive properties of the respiratory system, was submitted to linear regression analysis over the 4 to 16 Hz frequency range to obtain the intercept (R₀, resistance extrapolated to 0 Hz) and the slope of the linear relationship between Rrs and frequency (Slope) (Figure 1). At least three acceptable 16-s measurement periods were averaged to yield the final value of these parameters.

**Data Analysis**

Data are expressed as means ± SEM.

**RESULTS**

In the whole study population, multiple regression analysis of R₀ to anthropometric data showed an inverse correlation of R₀ with height (p < 0.0001) and weight (p < 0.03), but not with age or sex, according to the following equation:

\[ R₀ \text{predicted} (\text{hPa} \cdot \text{s} \cdot \text{L}^{-1}) = 25.76 - 0.149 \times \text{Height(cm)} + 0.058 \times \text{Weight(kg)} \]

The standard deviation of the residual was 2.27. A noninformed regression analysis of R₀ to anthropometric data showed an inverse correlation of R₀ with height (p < 0.0001) and weight (p < 0.03), but not with age or sex, according to the following equation:

\[ R₀ \text{predicted} (\text{hPa} \cdot \text{s} \cdot \text{L}^{-1}) = 25.76 - 0.149 \times \text{Height(cm)} + 0.058 \times \text{Weight(kg)} \]

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TABLE 1
ANTHROPOMETRIC DATA AND BASELINE PULMONARY FUNCTION TEST RESULTS IN CHILDREN ABLE TO PERFORM FORCED EXPIRATORY MANEUVERS, ACCORDING TO THEIR FEV1, AND MEF50 VALUES*

<table>
<thead>
<tr>
<th></th>
<th>FEV1 &gt; 80% pred and MEF50 &gt; 80% pred (n = 90)</th>
<th>FEV1 &gt; 80% pred and MEF50 &lt; 80% pred (n = 47)</th>
<th>FEV1 &lt; 80% pred and MEF50 &lt; 80% pred (n = 44)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>8.9 ± 0.3</td>
<td>9.1 ± 0.3</td>
<td>10.8 ± 0.4†</td>
</tr>
<tr>
<td>Height, cm</td>
<td>132 ± 2</td>
<td>134 ± 2</td>
<td>144 ± 2†</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>31 ± 1</td>
<td>33 ± 2</td>
<td>38 ± 2†</td>
</tr>
<tr>
<td>FEV1, % pred</td>
<td>102 ± 1</td>
<td>92 ± 1†</td>
<td>71 ± 1†</td>
</tr>
<tr>
<td>MEF50, % pred</td>
<td>101 ± 2</td>
<td>67 ± 1†</td>
<td>50 ± 2†</td>
</tr>
<tr>
<td>R0, hPa · s · L⁻¹</td>
<td>6.8 ± 0.2</td>
<td>7.8 ± 0.3†</td>
<td>7.9 ± 0.4†</td>
</tr>
<tr>
<td>Slope(SD)</td>
<td>-0.109 ± 0.010</td>
<td>-0.153 ± 0.017†</td>
<td>-0.165 ± 0.017†</td>
</tr>
</tbody>
</table>

* Values are mean ± SEM.
† Significant difference (p < 0.05) when compared with the group of children with both FEV1 and MEF50 values > 80% of predicted.
‡ Significant difference when compared with the group of children with baseline FEV1 and MEF50 values > 80% or MEF50 > 80% of predicted.
§ Significantly greater salbutamol-induced change (p < 0.05) relative to children with baseline MEF50 < 80%. To discriminate between children with MEF50 < 80% (p < 0.004) but not with FVC or MEF25. Group 1 children were thus divided into three subgroups according to their baseline FEV1 and MEF50 values. Anthropometric data and pulmonary function test results are summarized in Table 1.

Taking the subgroup of children with both FEV1 and MEF50 > 80% of predicted values as reference, there was a gradual and significant increase in R0(SD) in children with low lung function parameters, showing that children with decreased lung function parameters are also those with increased resistance values (Figure 2). Similarly, Slope(SD) was gradually and significantly steeper in children with low lung function parameters.

Figure 3 shows ROC curves corresponding to the sensitivity and specificity of possible cutoff points for R0(SD) and Slope(SD) to discriminate between children with lung function parameters < 80% or ≥ 80% of predicted values. The best results were obtained for R0(SD). To discriminate between children with MEF50 < 80% or ≥ 80% of predicted values, the cutoff point of R0(SD) was −0.10, corresponding to 75% sensitivity and 78% specificity for the detection of children with MEF50 < 80%. To discriminate between children

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**Figure 2.** Spirometric and FOT parameters before (open bars) and after (solid bars) salbutamol inhalation. Children are divided into three subgroups according to their baseline FEV1 and MEF50 values: A: children with both FEV1 and MEF50 > 80% of predicted values; B: children with FEV1 ≥ 80% but MEF50 < 80% of predicted values; C: children with both FEV1 and MEF50 < 80% of predicted values. Asterisk indicates a significantly greater salbutamol-induced change (p < 0.05) relative to children with baseline MEF50 and FEV1 both ≥ 80% of predicted. †Significantly greater salbutamol-induced change (p < 0.05) relative to children with baseline FEV1 ≥ 80% of predicted but MEF50 < 80% of predicted.

**Figure 3.** ROC curve corresponding to the sensitivity and specificity of possible cutoff points for R0(SD) (A) and Slope(SD) (B) for discriminating between children with baseline lung function parameter < 80% and ≥ 80% of the predicted value. Solid lines: baseline MEF50 as reference; dashed line: baseline FEV1 as reference. The closest point to the upper left-hand corner was chosen as the cutoff (closed point on the curve).
TABLE 2

<table>
<thead>
<tr>
<th></th>
<th>∆FEV₁ &lt; 10%</th>
<th>∆FEV₁ &gt; 10%</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>9.6 ± 0.3</td>
<td>9.4 ± 0.4</td>
<td>NS</td>
</tr>
<tr>
<td>Height, cm</td>
<td>137 ± 2</td>
<td>132 ± 2</td>
<td>NS</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>34 ± 1</td>
<td>30 ± 2</td>
<td>NS</td>
</tr>
<tr>
<td>Baseline measurements</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV₁, % pred</td>
<td>92 ± 7</td>
<td>80 ± 3</td>
<td>&lt; 0.002</td>
</tr>
<tr>
<td>MEF₅₀, % pred</td>
<td>80 ± 3</td>
<td>57 ± 4</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>R₀, hPa · s · L⁻¹</td>
<td>7.2 ± 0.2</td>
<td>9.3 ± 0.5</td>
<td>0.0002</td>
</tr>
<tr>
<td>R₅₀(SD)</td>
<td>-0.06 ± 0.08</td>
<td>0.63 ± 0.18</td>
<td>0.0004</td>
</tr>
<tr>
<td>Slope, hPa · s · L⁻¹ · Hz⁻¹</td>
<td>-0.130 ± 0.010</td>
<td>-0.217 ± 0.025</td>
<td>0.0003</td>
</tr>
<tr>
<td>Slope(SD)</td>
<td>-0.005 ± 0.08</td>
<td>-0.63 ± 0.21</td>
<td>&lt; 0.002</td>
</tr>
</tbody>
</table>

Postbronchodilator measurements

|                     |             |             |         |
| FEV₁, % pred        | 91 ± 1      | 98 ± 4      | 0.04    |
| ∆FEV₁, %            | -0.6 ± 0.5 | 17.7 ± 1.6  | < 0.0001|
| MEF₅₀, % pred       | 85 ± 2      | 95 ± 5      | NS      |
| ∆MEF₅₀, %           | 5.0 ± 1.5   | 38.1 ± 3.8  | < 0.0001|
| R₀, hPa · s · L⁻¹   | 5.8 ± 0.2   | 6.1 ± 0.3   | NS      |
| R₅₀(SD)             | -0.69 ± 0.08| -0.77 ± 0.09| < 0.0009|
| ∆R₀(SD)             | -0.62 ± 0.07| -1.39 ± 0.16| < 0.0001|
| Slope, hPa · s · L⁻¹ · Hz⁻¹ | -0.076 ± 0.009 | -0.090 ± 0.016 | NS      |
| Slope(SD)           | 0.46 ± 0.08 | 0.51 ± 0.15 | NS      |
| ∆Slope(SD)          | 0.54 ± 0.09 | 1.10 ± 0.24 | < 0.01  |

* Values are mean ± SEM.

With FEV₁ < 80% or ≥ 80% of predicted values, the cutoff point of R₀(SD) was 0, corresponding to 84% sensitivity and 73% specificity. With the −0.10 cutoff, 89% of children with FEV₁ < 80% of predicted values were identified.

Changes after bronchodilator inhalation. A total of 126 children received 200 µg of inhaled salbutamol and had flow–volume curve and FOT measurements 15 min later. Changes differed significantly between the subgroups in Group 1 (Figure 2). When compared with children with initial MEF₅₀ and FEV₁ values ≥ 80% of predicted, children with initial MEF₅₀ and FEV₁ < 80% had significantly larger changes in MEF₅₀, FEV₁, and R₀(SD). Children with initial MEF₅₀ and FEV₁ < 80% of predicted had the largest changes in all parameters, but only the changes in FEV₁ differed significantly from those in children with initially low MEF₅₀ and FEV₁.

Linear regression analysis showed that ∆R₀(SD) significantly inversely correlated to ∆FEV₁ and ∆MEF₅₀. However, multiple regression with ∆FEV₁ and ∆MEF₅₀ as independent variables and ∆R₀(SD) as the dependent variable showed that ∆R₀(SD) only inversely correlated with ∆MEF₅₀ (p = 0.0002).

Twenty-six children were considered to have a significant reversibility, defined by ∆FEV₁ ≥ 10%. The characteristics of these children are summarized in Table 2. At baseline, responding children had lower FEV₁ and higher resistance than children with no significant response to salbutamol. A flter salbutamol inhalation the decrease in R₀ was significantly more marked in children with a significant increase in FEV₁, so that the difference in postbronchodilator R₀ and R₀(SD) values between the two groups disappeared (Table 2). There was a strong correlation both for FEV₁ and R₀(SD) between baseline values and changes with bronchodilator (r = 0.415, p < 0.0001 and r = 0.621, p < 0.0001 for FEV₁ and R₀(SD), respectively), showing that low baseline FEV₁ and high baseline R₀ values are associated with significant reversibility toward higher FEV₁ and lower R₀ values after salbutamol inhalation in this population, respectively. Figure 4 shows the ROC curves corresponding to the sensitivity and specificity of possible cut-off points for ∆R₀(SD) and ∆Slope(SD) to discriminate between children with significant reversibility (defined by ∆FEV₁ ≥ 10%) and those with no significant reversibility. A decrease in R₀(SD) of one or more ∆R₀(SD) ≤ −1 yielded 69% sensitivity and 78% specificity. ∆Slope(SD) was less useful for discriminating between the two subgroups: an increase of 0.75 or more had 50% sensitivity and 75% specificity.

In clinical practice, the R₀(SD) cutoff corresponded to a decrease in R₀ of 2.27 hPa · s · L⁻¹ or more after bronchodilator, as ∆R₀(SD) = (R₀ postbronchodilator − R₀ prebronchodilator) / 2.27. If changes in R₀ after bronchodilator were expressed as percentage of change from baseline value (data not shown), lower specificities were observed at similar levels of sensitivity. The point of the ROC curve closest to the upper left-hand corner corresponded to a 27.5% decrease in R₀ after bronchodilator and yielded 73% sensitivity and 66% specificity.

Children with Only Resistance Measurements (Group 2)

A total of 132 children were unable to perform forced expiratory maneuvers. Eighty-nine percent of these children were preschool children younger than 6 yr of age. Mean baseline R₀ was 10.8 ± 0.3 hPa · s · L⁻¹ and mean Slope was −0.228 ± 0.012 hPa · s · L⁻¹ · Hz⁻¹. Very high baseline R₀ values were observed in some of these preschool children (up to 19.6 hPa · s · L⁻¹). A s in Group 1, higher baseline R₀ values were clrearly associated with larger decreases after bronchodilation, suggesting basal airway obstruction. Indeed, after salbutamol inhalation (n = 125) there was a strong correlation between baseline R₀(SD) and ∆R₀(SD) (r = 0.740; p < 0.0001).

Significant reversibility in Group 1 children was best reflected by ∆R₀(SD) ≤ −1. Our aim was to test the relevance of this R₀ cutoff to Group 2 children. Sixty Group 2 children (48%) had ∆R₀(SD) ≤ −1, and 65 children had ∆R₀(SD) > −1. When comparing Group 2 children with and without significant reversibility to corresponding Group 1 children, mean postsalbutamol changes in R₀(SD) and Slope(SD) were similar in the two groups (Table 3). Group 2 children with ∆R₀(SD) ≤ −1 had significantly higher baseline R₀(SD) and
lower Slope(SD) values than Group 2 children with \( \Delta R_0(SD) \) > \(-1\), but after salbutamol inhalation \( \Delta R_0(SD) \) and Slope(SD) returned to values similar to postsalbutamol values in Group 2 children without significant reversibility (Figure 5).

**DISCUSSION**

We assessed the FOT method for detecting airway obstruction and its reversibility in the pediatric setting. The study consisted of three phases: (1) a study of the whole population to determine the relation between FOT parameters and anthropometric data, and to express the FOT parameters as \( R_0(SD) \) and Slope(SD); (2) a comparison between FOT and spirometric parameters to define \( R_0(SD) \) and Slope(SD) cutoff values for classifying children with low baseline lung function parameters and significant postbronchodilator changes in FEV1; and (3) extrapolation of these cutoff values to a population of younger children unable to perform forced expiratory maneuvers, which identified a subgroup of subjects with high baseline \( R_0 \) values and significant reversibility after bronchodilator inhalation.

The forced oscillation method used in this study utilized the frequency range 4 to 32 Hz. In children whose respiratory frequency is higher than in adults, respiratory impedance is difficult to be measured below 4 Hz. Furthermore, at frequencies lower than 1 Hz, the tissue viscoelastic component results in a dramatic increase in respiratory resistance (15), which would impede the accurate evaluation of airway resistance. Besides, at frequencies up to several hundred hertz, the acoustic antiresonances of the airways yield information about airway impedance (16). However, in the present study, we were only interested in detecting airflow obstruction and its reversibility, i.e., in investigating total airway resistance which has been proved to be fairly measured over the 4 to 32 Hz frequency range.

The detection of airway obstruction and its reversibility is an important tool in the management of pediatric bronchial diseases such as asthma. FEV1 is usually considered the gold standard for the detection of basal bronchial obstruction and the evaluation of bronchodilatory effects (17). However, children younger than 6 yr are not expected to cooperate sufficiently to perform forced expiratory maneuvers reliably. The forced oscillation technique appears more suitable to young children, as the measurements are performed during tidal volume breathing, and as forced expiratory maneuvers are not required. Despite the advantages offered by FOT, knowledge of its clinical value in children younger than 6 yr is limited. Most available studies of preschool children have evaluated the application of FOT to the measurement of airway reactivity (1, 2). It has thus been shown that impedance measurement by FOT exhibited convincing covariation with measurements of FEV1 and specific airway resistance (sRaw) during methacholine-induced bronchial obstruction (2). Impedance measurements were significantly more sensitive than all subsequent methods tested. There are, however, very few FOT data obtained in children with airway obstruction with reference to children without bronchial obstruction, and there is no consensus on Rs criteria for the identification and grading of airway obstruction (18).

The present study demonstrates that FOT can identify children with low lung function parameters. Second, changes in spirometric parameters after bronchodilation correlated with changes in FOT measurements. Third, our results point to a tight link between FOT measurements in children and the peripheral airway resistance level. Finally, reliable evaluation of bronchial obstruction by FOT was obtained in children as young as 3 yr.

**Identification of Baseline Airway Obstruction**

FOT was able to identify children with airway obstruction. There was a tight correlation between \( R_0 \) and spirometric indices of bronchial obstruction such as FEV1 and MEF50. Children with FEV1 or MEF50 < 80% of predicted had higher mean \( R_0 \) values and more pronounced negative frequency dependence than children with spirometric parameters ≥ 80% of predicted. This increase was related to the degree of lung function abnormalities, the largest increase being observed in children with both low FEV1 and MEF50 values, and intermediate values being obtained in children with only a low MEF50 value. The difference in Slope observed between children with and without low spirometric parameter shows that the greatest difference between these two groups will be observed at lower frequencies. That is why we described the frequency dependence of the resistance by the slope of the corresponding regression equation and by its intercept at zero frequency. \( R_0 \) is a purely empirical intercept and does not represent an estimate of the respiratory resistance measured at the frequency approaching 0 Hz. Indeed, it is derived from resistive impedance measured over 4 to 32 Hz, \( R_0 \) represents respiratory resistance to the exclusion of the resistance caused by tissue viscoelastic properties, i.e., airway and tissue Newtonian resistance plus the resistance due to gas redistribution, if any. Reproducible \( R_0 \) measurements were obtained with this method, with a relatively low coefficient of variation compared with...
other studies (2, 19, 20). The negative frequency dependence of resistance is thought to result from the shunt compliance of the upper airway and/or gas redistribution originating from series and/or parallel intrapulmonary inhomogeneities (18). However, it is worth noting that the effects of both shunt compliance and gas redistribution on respiratory resistance are all the more marked as the bronchoconstriction is severe. Consequently, whatever its origin(s), the frequency dependence of respiratory resistance is a good index of the bronchoconstriction level (9, 21). However, the ability of standard FOT to identify airway obstruction in young children has been questioned because of shunt artifacts resulting from upper airway wall motion during the forced oscillation maneuver. A respiratory impedance is larger in early childhood than in adulthood, the upper airway artifact was considered likely to significantly affect impedance measurements in this age range (18). Supporting the children’s cheeks, as in our study, is one way of reducing the error and yielded reliable measurements even in the youngest children. Spirometric parameters correlated with $R_0$, as previously reported (4, 22). This good correlation suggested that $R_0$ provides as valid a measure of airway obstruction as do forced expiratory parameters. We identified clear $R_0(SD)$ cutoffs to define baseline bronchial obstruction. A $R_0(SD)$ value $> 0.10$ identified children with low lung function parameters with 78% specificity and 75% sensitivity. The children in our population identified as being free of functional abnormalities had baseline resistance values corresponding to reference values obtained in healthy children without airway disease (19, 20, 23, 24) (Figure 6).

**Postbronchodilator Changes in FOT Measurements**

Salbutamol inhalation induced a decrease in $R_0$ that correlated tightly with the degree of basal airway obstruction reflected by the $R_0(SD)$ value. A slight decrease in $R_0$ was also observed in the great majority of children with normal spirometric baseline values. The mechanical consequences of airway smooth muscle relaxation probably accounts for the bulk of this phenomenon. Indeed, relaxation of airway smooth muscle by a bronchodilator increases airway caliber when airflow rates and transmural pressures across the airway walls are low (25). In these conditions, which are fulfilled during tidal breathing, airway conductance and airway wall compliance are increased by bronchodilation (25). This mechanism may also contribute to the apparent discrepancy in some children between the decrease in $R_0$ after salbutamol inhalation and the absence of improvement or even the decrease in FEV$_1$. Indeed, because FEV$_1$ measurement necessitates a forced expiratory maneuver, its changes after bronchodilation are the combined effect of two opposite actions: increased airway caliber (that would result in increased maximal expiratory flow rates) and more compliant airways (that would collapse at lower transmural pressures) (25). In routine procedures, the aim of testing a bronchodilator response is to identify subjects with significant reversibility of an airway obstruction attributable to asthma. A significant improvement in FEV$_1$ was defined in our study by a $\Delta$FEV$_1 \approx 10%$. This index was previously shown to be more suitable than the percentage change in FEV$_1$ in showing the reversibility of airway obstruction resulting from asthma (13, 14). The 10% value has a sensitivity of 0.91 and a specificity of 0.95 for classifying patients according to the presence or absence of asthma (10). We found that children with a significant improvement in FEV$_1$ after salbutamol inhalation also had a larger fall in $R_0$ values than children with no significant change in FEV$_1$. A $R_0(SD)$ as a result, the two subgroups showed similar postsalbutamol values of $R_0$ and Slope. ROC curve analysis defined a $\Delta R_0(SD)$ cutoff value for the identification of children with a significant FEV$_1$ improvement after bronchodilator inhalation. A $\Delta R_0(SD) \approx - 1$, corresponding to a decrease in $R_0$ of 2.3 hPa $\cdot$ L$^{-1}$ or more (i.e., the standard deviation of the residual), had 0.78 specificity and 0.69 sensitivity. Similar results in children have been reported by Mazurek and coworkers, who measured resistance at 10 Hz or 20 Hz with either the standard or the head generator method (5). They obtained 0.65 to 0.78 specificity and 0.74 to 0.83 sensitivity for an optimal cutoff to discriminate between children with a negative or positive response to a bronchodilator, depending on the method used.

**FOT Measurements as a Potential Index of Peripheral Airway Resistance**

FOT measurement of total respiratory resistance has been claimed to reflect mainly the caliber of large airways, and not to be affected by peripheral airway obstruction (6). Our data, however, taking into account low-frequency measurements, argue for a significant contribution of the peripheral airways to FOT resistance. First, $R_0$ at baseline values was higher in younger children, and the frequency dependence of resistance was more pronounced. This pattern had already been described in children (19, 20, 22–24, 26–29) and has been explained on the basis of increased peripheral resistance (28). Indeed, young children have high peripheral resistance which represents a higher fraction of total resistance than in adults (30), and total respiratory resistance becomes more frequency-dependent as peripheral resistance increases (31). Thus, the higher peripheral resistance in younger children in comparison to older children and adolescents would directly explain the more pronounced frequency dependence of their total resistance (28). Second, multiple regression analysis showed that MEF$_{50}$ was a highly significant determinant of the correlations between spirometric parameters and $R_0$ at baseline. A assuming that MEF$_{50}$ reflects small-airway caliber, it appears from our results than FOT might be a sensitive method for early identification of small-airway abnormalities in children. The fact that children with FEV$_1 > 80%$ but MEF$_{50} < 80%$ of predicted had significantly higher baseline $R_0(SD)$ values than children with normal FEV$_1$ and MEF$_{50}$ supports the potential value of FOT in identifying small-airway abnormalities. Similarly, in adults, the slope of FOT resistance versus frequency efficiently distinguishes between smokers and nonsmokers, whereas no difference in spirometric values was observed (9). Finally, changes in MEF$_{50}$ after salbutamol inhalation were the

![Figure 6](image-url)
main factor influencing $R_0$ modifications. This suggests that most of the bronchodilator-induced decrease in resistance occurred in the peripheral airways.

**FOT Measurements in Preschool Children**

FOT appeared to be a promising tool for evaluating baseline airway obstruction and its reversibility in young children. In this age range, the use of the cutoffs defined with reference to spirometric parameters in older children allowed us to clearly identify subgroups of young children according to their variations in $R_0$ after bronchodilator inhalation. Children with large changes in $R_0$ values after bronchodilation had high $R_0$ values at baseline, that returned to normal after bronchodilation. Our results therefore suggest that, in preschool children, FOT can be useful for detecting reversible basal airway obstruction. Although previous studies have demonstrated the usefulness of FOT for the measurement of airway reactivity in preschool children, very few studies have evaluated the ability of FOT to assess airway obstruction and its reversibility. König and coworkers were able to obtain reliable random noise measurements in children as young as 2 yr and to identify reversible airway obstruction to baseline levels after bronchodilator inhalation, but they did not define significance criteria. Finally, Ducharme and Davis demonstrated that measurement of respiratory resistance via FOT was feasible in preschool children with acute asthma and that resistance values correlated with clinical variables indicative of the severity of airway dysfunction.

In conclusion, we defined useful criteria for FOT measurements, permitting reliable evaluation of bronchial obstruction and its reversibility in children as young as 3 yr. Furthermore, many of our results suggest that FOT measurements are strongly influenced by the peripheral airway resistance level. If these findings are confirmed, FOT may be used routinely for lung function evaluation in children with chronic cough or asthma.

**References**