Acceptability, Reproducibility, and Sensitivity of Forced Expiratory Volumes and Peak Expiratory Flow During Bronchial Challenge Testing in Asthmatic Children*

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Objectives: To compare the acceptability, reproducibility, and sensitivity of spirometric outcome measures of airway caliber during challenge testing in children.

Design: FEV1, forced expiratory volume in 0.75 s, forced expiratory volume in 0.5 s, and peak expiratory flow (PEF) were recorded during stepwise dosimetric histamine challenge tests. The responses were compared, and the reproducibility at baseline and from duplicate measurements at each challenge step was determined.

Patients: One hundred five children with newly diagnosed asthma, aged 5 to 10 years.

Results: Compared to PEF, FEV1 showed better baseline reproducibility (p < 0.002) and higher sensitivity (p < 0.0001) during challenge testing, determined as the change normalized to the baseline variation, while the forced expiratory volumes were not significantly different in these respects. During challenge testing in subjects with acceptable flow-volume tracings, paired recordings of FEV1 agreed within 0.1 L in 85% and within 0.2 L in 93% of measurements. During challenge testing, the reproducibility of FEV1 measurements was not better than that of the other indexes. Failure to exhale long enough precluded the use of FEV1 in 16 of the children, particularly the youngest children.

Conclusions: The results demonstrated that the recently published guidelines for FEV1 measurements during challenge tests can be applied to children. During challenge tests in asthmatic children, the advantage of the shorter fractions of forced expiratory volume was that they were more often acceptably recorded than FEV1, while they showed as good reproducibility and were also equally sensitive in assessing changes in airway obstruction.

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Key words: bronchial provocation tests; child; guidelines; reproducibility; respiratory function tests; sensitivity; spirometry

Abbreviations: ATS = American Thoracic Society; CV = coefficient of variation; FEF = forced expiratory flow; FEV0.5 = forced expiratory volume in 0.5 s; FEV0.75 = forced expiratory volume in 0.75 s; PD20 = provocative dose causing a 20% reduction; PEF = peak expiratory flow

The FEV1 and peak expiratory flow (PEF) are usually considered as indexes of airway caliber and, therefore, are useful in the assessment of the variable airways obstruction that is characteristic of asthma. However, the physiologic determinants of these variables, as well as other indexes derived from the forced expiratory maneuver, relate to the dynamic properties of the respiratory system at various levels of lung volumes. Therefore, it is obvious that PEF, FEV1, or any other estimate of forced expiratory maneuver are not interchangeable indexes of airway caliber, and their sensitivity and reproducibil-

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Correspondence to: L. Pekka Malmberg, MD, PhD, Division of Allergology, Helsinki University Central Hospital, PO Box 160, FIN-00029 Helsinki, Finland; e-mail: pekka.malmberg@hus.fi
ity may differ. Previous studies on adult1–4 and child asthmatics5,6 during challenge testing suggest that PEF is not as sensitive an index of airway obstruction as FEV1. Due to its good reproducibility and sensitivity, FEV1 is usually recommended as the primary outcome measure for assessing changes in airway caliber.7–11 In young children, however, due to faster time constants during forced expiration, FEV1 almost equals FVC. Alternative indexes such as forced expiratory volume in 0.75 s (FEV0.75) or forced expiratory volume in 0.5 s (FEV0.5) have been suggested to be even more sensitive indicators of airway patency.12 The reproducibility of these indexes during normal spirometric testing has been described,13 but to our knowledge, there are no comparative data clarifying the reproducibility or the sensitivity of the shorter fractions of forced expiratory volume in asthmatic children during challenge tests.

The usefulness of a measurement index is also dependent on its acceptability and reproducibility in the conditions in which it is applied. Acceptability and reproducibility criteria for ordinary spirometric testing are available,7–9 but they cannot be directly applied to challenge. Recently published standards11 for methacholine challenge tests present reproducibility criteria for FEV1 measurements that are applicable to adult patients, to be used as a basis for quality control during challenge tests. However, as pointed out in this American Thoracic Society (ATS) statement,11 studies are needed to better define the reproducibility criteria for challenge tests. In children, the question of reproducibility should be even more important because failure in exhalation technique is expected to occur more commonly than in adults, and this may jeopardize the validity of challenge testing, both in clinical and research settings.

In this study, we compared responses of FEV1, FEV0.75, FEV0.5, and PEF derived from forced expiratory curves during histamine-induced bronchoconstriction in a series of asthmatic children aged 5 to 10 years. The applicability of each of the indexes was evaluated, with special reference to their acceptability, reproducibility, and sensitivity during the challenge testing.

**Materials and Methods**

The subjects consisted of 105 children aged 5 to 10 years, with newly diagnosed asthma. The demographic data for those completing the study are shown in Table 1. The children were selected in consecutive order from subjects attending rolling measurements in an early intervention study of childhood asthma. All had experienced episodes of acute shortness of breath, wheezing, or prolonged cough, and all had demonstrated a 15% exercise-induced decrease in PEF or FEV1, or had shown at least 20% diurnal variation or at least 15% improvement in FEV1 in response to bronchodilators during home spirometry recordings.14 According to skin prick tests, 60 children (67.4%) were atopic. All of the children were familiar with spirometric testing, having participated in at least one test, performed 2 weeks prior to the challenge test. Within 2 months prior to the time of testing, none of the study subjects had been treated with anti-inflammatory asthma medication (inhaled or oral corticosteroids, or cromones). Treatment with short-acting β2-agonists was withheld for at least 12 h preceding the test. Prior to testing, the children were examined by a pneumologist, and excluded if they had experienced a respiratory tract infection in the preceding 2 weeks, or if they had acute bronchial obstruction.

Witten consent for the intervention study was obtained from the parents, and the study was approved by the institutional ethics committee.

At baseline, two series of flow-volume tracings were recorded with a pneumotachograph (Spirotrac III; Vitalograph Ltd; Buckingham, UK), with an interval of 10 to 15 min between the series. The first series consisted of full FVC maneuvers that were repeated in order to get three acceptable recordings.14 According to skin prick tests, 60 children (67.4%) were atopic. All of the children were familiar with spirometric testing, having participated in at least one test, performed 2 weeks prior to the challenge test. Within 2 months prior to the time of testing, none of the study subjects had been treated with anti-inflammatory asthma medication (inhaled or oral corticosteroids, or cromones). Treatment with short-acting β2-agonists was withheld for at least 12 h preceding the test. Prior to testing, the children were examined by a pneumologist, and excluded if they had experienced a respiratory tract infection in the preceding 2 weeks, or if they had acute bronchial obstruction. Written consent for the intervention study was obtained from the parents, and the study was approved by the institutional ethics committee.

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After baseline measurements, a bronchial provocation test was performed with a stepwise dosimetric method employing increasing doses (0.025 mg, 0.1 mg, 0.4 mg, 0.8 mg, and 1.6 mg) of histamine diphosphate and a controlled inhalation technique.16 Flow-volume recordings were performed 90 s after the inhalation, using the same FEV1 maneuver as in the second series of baseline measurements. At each step, repeated attempts were made to obtain two acceptable flow-volume tracings. The criteria for acceptability were not based on the reproducibility of any of the measured indexes, but on visual evaluation of the maneuver and the tracings, according to ATS recommendations.15 These criteria included observation of adequate inspiration, satisfactory effort and start of test, sufficient exhalation time for recording of FEV1, and a smooth flow-volume curve, without signs of coughing.

### Table 1—Anthropometric and Baseline Lung Function Data of Study Subjects in the Final Analysis (n=89)*

<table>
<thead>
<tr>
<th>Variables</th>
<th>Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>7.6 (5.1–10.9)</td>
</tr>
<tr>
<td>Height, cm</td>
<td>128 (104–158)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>29 (17–51)</td>
</tr>
<tr>
<td>Female/male sex, No.</td>
<td>30/59</td>
</tr>
<tr>
<td>FVC, L</td>
<td>1.92 (1.03–3.25)</td>
</tr>
<tr>
<td>FVC, % predicted†</td>
<td>101 (65–130)</td>
</tr>
<tr>
<td>FEV1, L</td>
<td>1.56 (0.95–2.51)</td>
</tr>
<tr>
<td>FEV1, % predicted†</td>
<td>94 (70–122)</td>
</tr>
<tr>
<td>FEV1/FVC, % predicted†</td>
<td>94 (68–109)</td>
</tr>
</tbody>
</table>

*Data are presented as mean (range) unless otherwise indicated.
†From Quanjer et al.15
or obstructed mouthpiece. Unacceptable tracings were rejected on site. The highest values for FEV\(_1\), FEV\(_{0.75}\), FEV\(_{0.5}\), and PEF were recorded in order to calculate changes in relation to baseline. In addition, the difference between the paired recordings was calculated in order to determine reproducibility at each measurement. The test was discontinued if PEF decreased by at least 20% or when the maximum dose of histamine had been inhaled. Thereafter, the children were administered bronchodilators in order to resolve the bronchoconstriction.

The decrease in FEV\(_1\), FEV\(_{0.75}\), FEV\(_{0.5}\), and PEF during the histamine challenge test was expressed as percentages from the baseline values. The changes were also normalized to the baseline variation of each parameter, by dividing the nominal change by the within-subject SD for the corresponding parameter. This quotient expresses the changes as dimensionless multiples of the within-subject SD.

The baseline reproducibility was calculated using analysis of variance, and the coefficients of variation (CVs) were compared according to Sokal and Rohlf. Reproducibility during the challenge test was estimated for each of the parameters by calculating the difference between the two obtained values, and by assessing the distribution of paired measurements within ±20% or when the maximum dose of histamine had been inhaled. Ten percent reproducibility was achieved in 21 of the FEV\(_1\) measurements (5%) and in 3 of the FEV\(_{0.75}\) measurements (5%) and in the FEV\(_{0.5}\) measurements (10%).

The distribution of reproducibility in the measured parameters during the challenge tests is illustrated in Figure 1. In the measurements during the challenge test (n = 415), the mean differences between the two determinations of FEV\(_1\), FEV\(_{0.75}\), FEV\(_{0.5}\), and PEF were 0.056 L, 0.051 L, 0.041 L, and 5.9 L/s, respectively. The differences as percentages (4.0%, 4.1%, 4.2%, and 3.4%, respectively) were not significantly different (χ\(^2\) = 1.92, p = 0.58). Ten percent reproducibility was achieved somewhat less frequently in FEV\(_1\) (83%) than in FEV\(_{0.75}\) (91%), FEV\(_{0.5}\) (93%), or PEF (96%). In FEV\(_1\), the two best values agreed to within 0.1 L in 85% and within 0.2 L in 93% of measurements. Due to short exhalations, the result was based on only 1 record in 21 of the FEV\(_1\) measurements (5%) and in 3 of the FEV\(_{0.75}\) measurements (0.1%).

### Sensitivity

The number of subjects completing the dose steps of 0.025 mg, 0.1 mg, 0.4 mg, 0.8 mg, and 1.6 mg were 89, 84, 79, 51, and 24, respectively. In 11 children, the decrease of FEV\(_1\) remained < 20% even after the highest dose of histamine. The changes in the spirometric variables at different dose steps of the challenge test have been illustrated in Figure 2, where, for comparison, the dose steps are related to the individual highest (last) dose. The results after the last dose have been summarized in Table 3. Using linear regression analysis, the decrease of 20% in FEV\(_1\) corresponded approximately to the decrease of 17% in PEF. As percentages from the baseline, the maximum changes after the final dose of histamine were not significantly different between PEF and FEV\(_1\), but slightly larger by ranks in FEV\(_{0.75}\) (p = 0.012) and FEV\(_{0.5}\) (p = 0.0002) than in FEV\(_1\) (Table 3). When normalized to the within-subject baseline reproducibility of each parameter, the change in PEF was significantly smaller than that in FEV\(_1\) (p < 0.0001), FEV\(_{0.75}\) (p < 0.0001), or FEV\(_{0.5}\)

### Results

#### Acceptability

In 16 children, recording of FEV\(_1\) was not acceptable during some of the test phases, due to exhalation times < 1 s. This occurred in eight children already in the baseline phase, and in eight children after histamine inhalation; in some of the children, this failure in exhalation technique was associated with coughing. These 16 children were significantly younger (mean age, 6.9 years; range, 5.1 to 9.3 years) than the children with acceptable exhalations (p = 0.002). Due to missing data points, they were excluded from the final analysis. In six cases, the exhalations were < 0.75 s; in no cases were exhalations < 0.5 s.

#### Reproducibility

The baseline results for the remaining 89 children are shown in Table 2. Expressed as CV, the baseline reproducibility for FEV\(_1\) (2.8%) was better than that for PEF (4.3%, p = 0.002), but did not differ significantly from that for FEV\(_{0.75}\) (2.9%) or FEV\(_{0.5}\) (3.1%). The baseline CV was not related to age in any of the parameters.

#### Table 2—Baseline Reproducibility of PEF and FEV\(_1\), FEV\(_{0.75}\), and FEV\(_{0.5}\)*

<table>
<thead>
<tr>
<th>Variables</th>
<th>Baseline Test 1</th>
<th>Baseline Test 2</th>
<th>Within-Subject SD</th>
<th>CV, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEF, L/min</td>
<td>202 (5)</td>
<td>202 (5)</td>
<td>8.6</td>
<td>4.3</td>
</tr>
<tr>
<td>FEV(_1), L</td>
<td>1.56 (0.04)</td>
<td>1.55 (0.04)</td>
<td>0.044</td>
<td>2.8</td>
</tr>
<tr>
<td>FEV(_{0.75}), L</td>
<td>1.41 (0.03)</td>
<td>1.40 (0.03)</td>
<td>0.040</td>
<td>2.9</td>
</tr>
<tr>
<td>FEV(_{0.5}), L</td>
<td>1.16 (0.03)</td>
<td>1.15 (0.03)</td>
<td>0.035</td>
<td>3.1</td>
</tr>
</tbody>
</table>

*Data are presented as mean (SEM) unless otherwise indicated.

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Thus, PEF showed the poorest sensitivity. The forced expiratory volumes showed no significant differences in this analysis.

Using the exponential model,\textsuperscript{18} the bronchial responsiveness was calculated for each parameter by interpolating the provocative dose causing a reduction of 20\% (PD\textsubscript{20}). Extrapolation was used in cases in which the decrease in a parameter after the last dose remained < 20\% (11 cases for PEF and FEV\textsubscript{1}, 10 cases for FEV\textsubscript{0.75}, and 7 cases for FEV\textsubscript{0.5}). The geometric means of PD\textsubscript{20} in FEV\textsubscript{1} (0.41 mg), PD\textsubscript{20} in FEV\textsubscript{0.75} (0.39 mg), PD\textsubscript{20} in FEV\textsubscript{0.5} (0.37 mg), and PD\textsubscript{20} in PEF (0.43 mg) were similar, but the ranks of the test results showed statistically significant differences ($\chi^2 = 47.5$, $p < 0.0001$). PD\textsubscript{20} in FEV\textsubscript{1} correlated significantly with PD\textsubscript{20} in PEF ($r = 0.76$, $p < 0.0001$) but more closely with PD\textsubscript{20} in FEV\textsubscript{0.75} ($r = 0.93$, $p < 0.0001$) and PD\textsubscript{20} in FEV\textsubscript{0.5} ($r = 0.91$, $p < 0.0001$).

**DISCUSSION**

This study compared a set of spirometric indexes, thought to be useful in the assessment of variable airways obstruction, during histamine-induced bronchoconstriction in asthmatic children. An ideal marker of airway caliber would be one with good acceptability, reproducibility, and sensitivity, in the test conditions in which it is to be applied. According to the present results, the use of FEV\textsubscript{1} as the primary outcome measure may be motivated due to its good baseline reproducibility and sensitivity. Particularly in the youngest children, however, FEV\textsubscript{1} failed to satisfy the criteria of an ideal index due to its low acceptability, and its reproducibility was not better than that of the other spirometric indexes in the challenge test. The present results demonstrate that the standards for acceptability and reproducibility for ordinary spirometry\textsuperscript{7–9} are not directly applicable for challenge testing, and other modified guidelines for spirometric testing must be followed in these conditions.

All the investigated spirometric parameters showed good baseline reproducibility, although PEF was inferior to forced expiratory volumes in this respect. This has also been reported earlier.\textsuperscript{13} Kan-ner et al\textsuperscript{19} have shown that the guidelines for normal spirometric testing are reasonable for children 8 years and 9 years of age. Ninety-five percent of their subjects achieved acceptable flow-volume tracings, and of these almost all were capable of producing FEV\textsubscript{1} measurements that were reproducible to within 5\% or 100 mL, whichever was greater. These results are close to those for our baseline data, both in acceptability (92\%) and in reproducibility in children with acceptable exhalations (99\%), although our series also included younger children.

For the measurement of forced expiratory volumes, the exhalation should meet a specified time in order to be considered acceptable. Short exhalations limited the acceptability of FEV\textsubscript{1} recordings in many
(15%) of our children, either at baseline or in the challenge test, particularly among the youngest children. Desmond et al.20 found that only 19% of children aged 5 to 18 years met ATS end-of-test criteria, and 37% of those aged <7 years failed to reach 95% of the theoretical FVC determined using fitted curves. The shorter exhalation times in young children may arise from differences in physiologic time constants of respiratory mechanics compared to adults, or may simply be due to technical failure to exhale completely. In our study, histamine-induced cough21 was probably the reason for short exhalations in some of the subjects. Short exhalations precluded the measurement of FEV0.75 less frequently than of FEV1, and never of FEV0.5. This is an important advantage of the shorter fractions of forced expiratory volumes.

Compared to baseline, the poorer reproducibility of measurements during challenge test may have various reasons: the cooperation of the child may be influenced by tiredness, or may be affected by symptoms such as cough or shortness of breath. If several attempts are performed, the effect of histamine may change over time and cause variation. Since the conditions are not the same as in ordinary spirometric testing, a different quality control scheme must be followed during challenge tests. Recently published standards for methacholine challenge testing11 suggest that FEV1 measurements during challenge should be classified to five categories (A, B, C, D, and F) depending on whether two acceptable values agree within 0.1 L, 0.2 L, or >0.2 L, or if there is only one acceptable or no acceptable measurements, respectively. These criteria seemed also to fit for our children with asthma, since most of them (93%) were capable of producing acceptable FEV1 measurements within reproducibility categories A and B. However, as underlined in the ATS guidelines, these reproducibility criteria are to be used only to assist the technician and the interpreter, and not to exclude data from analysis. Since the variation between the paired measurements is typically homoscedastic (ie, not proportional to the mean), it is recommendable to express target reproducibility as liters rather than percentages. In order to compare the reproducibility of different indexes, we also calculated the difference between the paired measurements as percentages. Since the exhalation technique is easier when shorter fractions of forced expiratory volumes or PEF are to be recorded,

Table 3—Changes in PEF, FEV1, FEV0.75, and FEV0.5 After the Last Dose of Histamine*

<table>
<thead>
<tr>
<th>Variables</th>
<th>Change, %</th>
<th>Change, Within-Subject SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEF</td>
<td>-27.9 (1.0)</td>
<td>-6.7 (0.3)</td>
</tr>
<tr>
<td>FEV1</td>
<td>-29.1 (1.4)</td>
<td>-10.4 (0.6)</td>
</tr>
<tr>
<td>FEV0.75</td>
<td>-30.2 (1.3)</td>
<td>-10.9 (0.6)</td>
</tr>
<tr>
<td>FEV0.5</td>
<td>-30.9 (1.3)</td>
<td>-10.4 (0.5)</td>
</tr>
<tr>
<td>χ²</td>
<td>-41.9</td>
<td>110.6</td>
</tr>
<tr>
<td>p Value</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*Data are presented as mean (SEM) unless otherwise indicated.
†Friedman’s analysis of variance.
reproducible measurements (within 5% or 10%) were obtained slightly more frequently in these parameters than in FEV₁. However, the mean reproducibilities were not statistically significantly different.

The study also showed that in 5- to 10-year-old asthmatic children during graded histamine-induced bronchoconstriction, the changes in PEF and FEV₁ correlate with each other, but changes in PEF as percentages were less pronounced: on average, a decrease of 20% in FEV₁ corresponded to a decrease of 17% in PEF. The changes in shorter fractions of forced expiratory volume (FEV₀.₇₅ and FEV₀.₅) were very close to those in FEV₁. As each of these parameters showed a different baseline variation, the changes that would be considered statistically significant were also different. Consequently, a given percentage decrease reflects a different deviation from normalcy in each of the parameters. In order to compare the relative sensitivities of the spirometric indexes during histamine challenge testing, the changes were normalized to the baseline variation of each parameter, by expressing them as multiples of the within-subject SD of the corresponding parameter. This analysis showed that PEF was the least sensitive parameter in assessing changes in airway caliber, but the different fractions of forced expiratory volume showed no significant differences in this respect. Although the PD₂₀ values calculated using different indexes correlated closely, in individual cases the result would have differed considerably, depending on the outcome measure chosen. Thus, these indexes cannot be used interchangeably to assess bronchial responsiveness.

Although previous comparative studies during bronchial challenge tests are limited in number for asthmatic children, they suggest that PEF is less sensitive to changes in airway caliber than FEV₁. Murray and Ferguson²² described this order of sensitivity in both the early and late asthmatic reaction to dust mite challenges. Limna⁶ found that during methacholine-induced bronchoconstriction, a reduction of 20% in FEV₁ corresponded to a decrease of 15% in PEF measured with a Wright peak flowmeter. These studies as well as comparable reports on asthmatic adults³⁴ are in agreement with the present results. In the previous studies, however, the different within-subject variation of the spirometric indexes was not accounted for in the analysis. Although shorter fractions of forced expiratory volume (FEV₀.₇₅ and FEV₀.₅) have been claimed to be more sensitive indexes than FEV₁ in children,¹² their relative sensitivity in different degrees of airway obstruction has not been previously investigated. Our results do not suggest that any benefit in sensitivity is to be expected when using these indexes but, rather, that the sensitivity of FEV₀.₇₅ and FEV₀.₅ is similar to that of FEV₁.

PEF was chosen to be the follow-up parameter during challenge tests, because it was evident in a pilot study that not all of the youngest children were capable of producing acceptable FEV₁ measurements. During the challenge test, the children were urged to exhale not until residual volume level, but for at least 1 s, in order to record FEV₁. This is less demanding and strenuous for the children than exhaling full FVCs. The change in maneuver did not have any significant effect on the test results, when the two series of baseline measurements were compared. Since full FVC recordings were not made, it was not possible to measure forced expiratory flows (FEFs) at specified volumes, i.e., FEF at 50% of FVC, or FEF at 25 to 75% of FVC. Therefore, their sensitivity in reflecting changes in airway caliber compared to forced expiratory volumes remains to be studied. However, it is probable that the technical difficulties encountered in measuring FEV₁ would have been even more pronounced if full FVC tracings had been recorded. Finally, it should be emphasized that the present study describes the relationship between the measured spirometric indexes during histamine-induced bronchoconstriction, and the physiologic determinants of airway narrowing may be different during acute exacerbations of asthma. We would therefore be cautious in extrapolating the present results to the latter conditions.

We conclude that the recently published standards for FEV₁ measurements during challenge testing are applicable as quality control guidelines also when children are to be investigated. As an outcome measure, FEV₁ is characterized by good baseline reproducibility and better sensitivity than PEF or FEV₀.₅ in assessing changes in airway obstruction. However, failure to exhale long enough precluded the use of FEV₁ in some children, particularly in the youngest children. Compared to FEV₁, the shorter fractions of forced expiratory volume were more often acceptably recorded in the children, showed as good reproducibility during the challenge test and were equally sensitive in assessing changes in airway obstruction.

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