Can Peak Expiratory Flow Measurements Estimate Small Airway Function in Asthmatic Children?*

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Background: Asthma is characterized in part by small airways dysfunction. Peak expiratory flow (PEF) measurement has been suggested by all international guidelines as an important tool in asthma management. The correlation between PEF and FEV₁ but not with forced expired flow at 50% of vital capacity (FEF₅₀) is well-established.

Study objective: To determine the value of PEF measurement as a predictor of small airways status as expressed by FEF₅₀.

Design: Analysis of the association between PEF and FEF₅₀ in single and multiple determinations.

Patients: One hundred eleven asthmatic children (mean age, 11.8 years), grouped in the following way according to FEV₁ values: within normal range (n = 46); mildly reduced FEV₁ (n = 44); and moderately/severely reduced FEV₁ (n = 21).

Results: Overall, FEF₅₀ and PEF were significantly correlated (r = 0.49; p < 0.0001). However, in 41.6% of the patients, the actual FEF₅₀ differed by > 20% from the calculated FEF₅₀. PEF has a high specificity (82.4%) but a poor sensitivity (51.7%) to detect FEF₅₀ status. PEF was better able to reflect abnormal FEF₅₀ in the patients with more severe asthma and to reflect normal FEF₅₀ values in the healthier patients. In patients with multiple measurements (n = 40), the correlation between FEF₅₀ and PEF was significantly better than that derived from a single determination (multiple measurements r = 0.77; single measurement, r = 0.49).

Conclusions: Although PEF is an important tool in the management of asthmatic patients, it does not yield a complete picture because it is not sensitive in detecting small airways function. It is best used at home along with regular spirometry measurements at the clinic. PEF may serve as a better index of changes in small airways function once an individual regression is determined.

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Key words: forced expiratory flow at 50% of vital capacity; FEV₁; lung function tests

Abbreviations: FEF₅₀ = forced expiratory flow at 50% of vital capacity; FEF₅₀(calc) = value calculated from the overall regression of forced expiratory flow at 50% of vital capacity values for all subjects on peak expiratory flow; group M = mildly obstructed group; group MS = moderately to severely obstructed group; group N = normal group; MEFV = maximal expiratory flow-volume; NPV = negative predictive value; PEF = peak expiratory flow; PPV = positive predictive value

Asthmatic patients with no respiratory difficulties or wheeze on examination may still have bronchial obstruction detected by spirometry. As many as one third of the patients who are in clinically stable condition have FEV₁ values below the lower limit of the normal range, and about 50% of clinically stable asthmatic patients have abnormal values for forced expiratory flow at 50% of vital capacity (FEF₅₀).³ Peak expiratory flow (PEF) has been found to correlate well with FEV₁ in different studies with r values ranging from 0.74 to 0.93. Since measuring PEF at home using a simple peak flowmeter is easier than measuring FEV₁, the use of PEF measurement on a daily basis has been recommended by international guidelines for asthmatic patients having more than mild disease.⁴,15–19

However, it is common to find clinically stable asthmatic patients who do not wheeze but present reduced values of FEF₅₀ while the values for PEF and FEV₁ are within normal limits.⁵ Meijer et al²⁰ reviewed the five most cited asthma guidelines and revealed considerable differences between them, in particular with regard to the use of PEF-
FEV1 value differed by possibly by small airways closure. The obstruction of the large and small airways, which may be unevenly distributed throughout the airways. Thus, it was not surprising to see that in about 30% of patients in the study of Meltzer et al., the actual FEV1 value differed by > 20% from that calculated from the PEF. Moreover, other evidence has cast doubt on the ability of PEF home monitoring to reflect the clinical status of the asthmatic patient or to significantly alter management.24

Based on the leading theories, the shape of the maximal expiratory flow-volume (MEFV) curve is determined by the location and the inherent characteristics of the flow-limiting segment (the choke point),25 the size and properties of the small airways,26 and possibly by small airways closure.27 The obstruction of small peripheral airways usually causes a reduction in flows at low lung volume, which commonly are believed to be due to the flow-limiting segment moving peripherally as the lung empties, and this is readily detected from the concave shape of the MEFV curve.28,29 PEF, however, is determined by effort, is thought to reflect mainly large airway function, and commonly serves as a global indicator of airway function. Thus, it is not clear whether PEF can reflect small airways status as measured by FEF50.

The aim of the present study was to define the sensitivity and specificity of PEF measurements in detecting peripheral airways obstruction as represented by FEF50 in young asthmatic patients.

MATERIALS AND METHODS

In a retrospective study, FVC maneuvers of 111 asthmatic children were extracted from the lung function results stored in the laboratory database. The patients were selected in alphabetical order, and the first 111 patients < 18 years of age who had technically acceptable flow-volume curves were included in the study. The diagnosis of asthma was made on clinical grounds by one of the pediatric pulmonologists of the Institute of Pulmonology at Hadassah University Hospital (Jerusalem, Israel). Of the 111 patients tested, 61 (55%) were male and 50 were female. The mean (± SD) age of the whole group was 11.8 ± 3.0 years. The mean weight was 40.6 ± 13.4 kg, and the mean height was 147 ± 40 cm. As many patients had tests performed on several occasions, we arbitrarily selected the most recent test for analysis. All lung function tests were performed in the lung function laboratory at Hadassah University Hospital by a trained technician between 8 AM and 4 PM, using a portable electronic spirometer (Compact; Vitalograph; Buckinghamshire, UK). The best FVC maneuver from at least three attempts was chosen based on American Thoracic Society criteria (ie, the highest sum of FEV1 and FVC). By laboratory practice, all our spirometers with pneumotachograph (No. 3; Fleisch) are calibrated on a daily basis, and it is our experience that day-to-day variations never exceed ± 1%. All patients refrained from taking any sympathomimetic bronchodilator drugs for at least 6 h before undergoing the test. To enable comparison between children of different ages and heights, the percent of predicted values for PEF, FEV1, and FEF50 were calculated.20 The lower limits of the normal range (ie, 95% confidence interval) were calculated to be 56% for FEF50, 76% for PEF, and 79% for FEV1.

In order to investigate whether the correlation between FEF50 and PEF is affected by the severity of airway obstruction, we divided the population studied into three subgroups according to their FEV1 values. The normal group (group N) was defined as those patients with FEV1 values ≥ 80% of predicted normal values, the mildly obstructed group (group M) was defined as those patients with FEV1 values ranging between 65% and 79%, and the moderately to severely obstructed group (group MS) was defined as those patients with FEV1 values of < 65%. Of the 111 patients, 46 (41.4%) fell into group N, 44 (39.6%) fell into group M, and 21 (18.9%) fell into group MS.

Forty patients had five or more FVC measurements over a period of 2.6 ± 1.3 years (range, 6 months to 8 years). We analyzed the individual correlations between PEF and FEF50 in these patients (n = 40) and compared the mean of the individual correlation coefficients to the intersubject correlation of the whole group, which was based on a single determination in each patient (n = 111).

Statistical Analysis

Linear regression, Pearson correlation coefficient, and paired t test were used to compare PEF to FEF50. Based on the normal range of predicted values as described above,20–24 four-quadrant graphs were constructed as well as 2 × 2 contingency tables, and the χ2 test (with Yates continuity correction) was used to yield χ2 and two-sided p values. Sensitivity, specificity, the positive predictive values (PPVs), and negative predictive values (NPVs) of PEF were then calculated for the total sample and for each of the severity subgroups. Thus, for example, sensitivity, which is also known as positivity of disease,25 was defined as the ability of an abnormal value of PEF to correctly detect an abnormal value of FEF50.

\[
\text{Sensitivity} = \frac{\text{FEF}_{50}(\text{ABN}) \text{ having } \text{PEF}(\text{ABN})}{\text{all } \text{FEF}_{50}(\text{ABN})} \times 100
\]

where ABN refers to values below the normal range. Similar calculations were used with appropriate modification to estimate specificity, PPV, and NPV. The agreement rate between the two parameters, which is known as the overall accuracy of the test, was defined as the proportion of tests in which both PEF and FEF50 were within the normal or abnormal range at the same time (that is, how well PEF reflected the true state of the patient as described by FEF50).

To further investigate the ability of a single determination of PEF to correctly predict FEF50, we defined FEF50(calc) as the value calculated from the overall regression of FEF50 values for all subjects on PEF. We then defined the individual deviation of FEF50 as the difference between FEF50(calc) and the measured FEF50 (FEF50(calc))

\[
\text{Deviation} = \frac{\text{FEF}_{50}(\text{calc}) - \text{FEF}_{50}(\text{act})}{\text{FEF}_{50}(\text{calc})} \times 100
\]

The significance of the difference between the r values of different linear regressions was determined by the method of standardized z scores.

RESULTS

The correlation between individual values of FEF50 and PEF is shown in Figure 1, top. The
The regression equation was: $\text{FEF}_{50} = 0.575 \times \text{PEF} + 10.8$ ($r = 0.49$; $p < 0.0001$). A second-order regression analysis did not yield a better correlation, and we therefore limited ourselves to linear analyses. A good correlation also was found between individual values of $\text{FEV}_1$ and $\text{PEF}$, with the regression equation $\text{PEF} = 0.831 \times \text{FEV}_1 + 17.5$ ($r = 0.69$; $p < 0.0001$). The best correlation was found between individual values of $\text{FEV}_1$ to $\text{FEF}_{50}$, with the regression equation $\text{FEF}_{50} = 1.021 \times \text{FEV}_1 - 20.1$ ($r = 0.72$; $p < 0.0001$).

The individual deviation of $\text{FEF}_{50}(\text{act})$ from $\text{FEF}_{50}$ predicted by the regression line defined above was calculated and summarized in Figure 1, bottom. It can be seen that in only 34 of the patients (31.5%) the difference was $\leq 10\%$, and only 65 patients in the total study population (58.6%) had deviation rates of $\leq 20\%$. In other words, in as many as 46 patients (41.4%), $\text{FEF}_{50}(\text{act})$ was either higher or lower than $\text{FEF}_{50}(\text{calc})$ by $> 20\%$. When $\text{FEV}_1$ was used to predict $\text{FEF}_{50}$ by the regression line defined above, the outcome was only slightly improved. In only 44 of the patients (39.6%), the difference was $\leq 10\%$, and in 78 patients (70.3%) the difference was $\leq 20\%$.

The correlations between $\text{FEF}_{50}$ and $\text{PEF}$ in three groups of patients classified by their $\text{FEV}_1$ values (group N, group M, and group MS) are shown in Figure 2. There was only a borderline significant correlation between $\text{FEF}_{50}$ and $\text{PEF}$ for patients in group N ($r = 0.24$; $p = 0.05$). No significant correlation was found in patients in group M ($r = 0.010$; $p = \text{NS}$). The best correlation was found for the patients in group MS ($r = 0.45$; $p < 0.05$). The $r$ value for group MS was significantly different from that of the other two groups ($p < 0.05$).

Two-by-two contingency tables were constructed, and the results are summarized in Table 1. Overall, $\text{PEF}$ had a poor sensitivity (51.7%) but good specificity 82.4 (%) in representing $\text{FEF}_{50}$. That is, $\text{PEF}$ values were good in detecting normal $\text{FEF}_{50}$ values but were disappointing in detecting abnormal $\text{FEF}_{50}$ values. Most of the patients of group N (70%) were in the right upper quadrant of Figure 2, top, representing reasonable agreement concerning normality. This fact contributes to the high specificity, NPV, and accuracy seen for group N. In the MS group (Fig 2, bottom), most of the patients (85%) were in the left lower quadrant, representing reasonable agreement concerning abnormality, which contributes to a good sensitivity. This fact contributes to the high sensitivity, PPV, and accuracy seen for group MS.

We defined 76% of the predicted value of $\text{PEF}$ as the lower limit of the normal range. Had we taken 80% instead of 76% of the predicted value as the lower limit of the normal range, as many clinicians do, the agreement between the two parameters would have been even lower. There were 13 patients with $\text{PEF}$ values between 76% and 79%, 8 of them with normal $\text{FEF}_{50}$ values. Thus, using the higher cutoff, the agreement rate for the whole group would hardly change (higher cutoff, 65.8%; lower cutoff, 63.1%), with no change in NPV but a fall in PPV (from 77.5% to 67.9%).
The correlation between FEF$_{50}$ and PEF in the 40 patients who had five or more FVC tests is shown in Figure 3, which depicts the individual regression lines for each patient. There was a high variability in the $r$ values of the patients with a mean value of 0.77 (range, 0.25 to 0.97). The difference between the $r$ value of the whole group ($r = 0.49$) and the mean $r$ value of the 40 individuals with multiple determinations was significant ($p < 0.05$). As can also be seen, most of the individual slopes fall along the direction of the line of identity, implying that individual changes in FEF$_{50}$ and PEF occur in concert.

**Discussion**

A significant correlation ($r = 0.49; p < 0.0001$) was found between FEF$_{50}$ and PEF in our asthmatic children similar to that reported in a study of healthy adults. However, the ability of a single determination of PEF to predict FEF$_{50}$ based on this correlation was found to be limited, in that FEF$_{50}$(act) deviated by $>-20\%$ in 45 of the patients (40.5\%) and by $>-30\%$ in 22 of the patients (19.8\%). We have further shown that repeated measurements of both parameters enabled us to establish an individual regression that increases the ability to predict FEF$_{50}$ more accurately. Thus, we have shown in this study that a single measure of PEF may only have limited power in estimating FEF$_{50}$ in the general pediatric asthmatic population. For the individual patient with repeated FVC measurements, though, it is possible to estimate FEF$_{50}$ from the PEF measurements with much greater certainty.

We also found that the correlation between PEF and FEF$_{50}$ was related to the severity of airways obstruction as assessed by FEV$_1$ values. In the patients with normal lung function or with moderate-to-severe obstruction, there was a positive but weak correlation, while no correlation was found in the mildly obstructed patients. Thus, it is possible that in the patient with normal lung function or with moderate-to-severe obstruction the degree of patency or obstruction is similar throughout the bronchial tree, whereas in the patient with mild asthma the obstructive process may be distributed nonhomogeneously and may affect large or small airways to different degrees. In order to test this hypothesis, we examined the individual correlations between PEF and FEF$_{50}$ in 40 individuals with multiple determinations. We speculated that if the obstructive process in a mild asthmatic patient, for example, is manifested by more pronounced changes in FEF$_{50}$ than in PEF, the individual slopes at the upper right-hand corner will be steeper and those at the lower left-hand corner will be less steep, yielding an overall...
nonlinear regression. However, on inspection, individual correlations did not exhibit nonlinear characteristics and presented a wide variety of slopes, invalidating the possibility that obstruction of one region along the bronchial tree precedes that in the other region (ie, peripheral vs central airways). Thus, it is quite possible that the wide variety of processes is the reason for the poor overall power of PEF to predict FEF50 as a measure of small airways function. This conclusion also can be reached if one considers the wide distribution of the normal range of FEF50 (95% confidence interval, 56 to 144%).31 It is further noted that Berube and colleagues34 attributed the variability in response to bronchial challenge tests to the nonhomogeneous distribution of the obstructive process.

The PPV of PEF to accurately represent small airways obstruction was found to be 77.5%. This implies that the probability of the subjects with abnormal PEF having an abnormal FEF50 is 77.5%. Ferguson5 found the PPV to be much lower (35%) in 20 asthmatic children, but his findings refer to symptom-free periods only. Hence, the low PPV value for group N that we reported on (17%) seems to explain the low values reported by Ferguson.5 Interestingly, this choice of a lower normal limit for forced expiratory flow in the midexpiratory phase was 70% and not the 56% used by us,31 having counted patients who usually have accepted normal FEF50 as abnormal, which yields a poor agreement rate of 30%. Overall, NPV was found to be only 59%, implying that relying on normal PEF readings may be misleading in giving a false sense of security that the patient does not have small airways obstruction.

When spirometry was performed repeatedly in 40 patients over a period of up to 8 years, the mean individual correlation between PEF and FEF50 improved significantly (r = 0.77 vs r = 0.49). Kelly and Gibson7 compared the correlation between PEF and FEV1 in 8 subjects studied longitudinally to the correlation between these parameters in a cross-sectional study of 61 patients. They found the mean within-individual relationship to be similar to those seen in their cross-sectional study. It is possible that their lack of ability to reveal a significant improvement was masked by their better overall correlation between PEF and FEV1.5–14

Although the measurement of PEF was shown to be effort-dependent and the technique of testing to significantly influence the outcome, the correlation between PEF measured with different devices was nevertheless reasonable5–7,14,35 when performed under the supervision of a skilled technician. However, since most tests are routinely performed at home using mechanical peak flowmeters with no supervision, an even greater discrepancy between measured PEF and calculated FEF50 is to be expected.36

The clinical implications of measuring FEF50 in the management of asthma remain to be defined, since FEF50 has not been shown to date to be related to asthma clinical status. Small airways disease can be detected by simple spirometry from the concave shape of the MEFV curve and from FEF50 values being reduced in such patients.28,29 Over the

<table>
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<th>p Value</th>
<th>Sens, %</th>
<th>Spec, %</th>
<th>PPV, %</th>
<th>NPV, %</th>
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<td>94.4</td>
<td>0</td>
<td>81.0</td>
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*Sens = sensitivity; Spec = specificity; Acc = accuracy of test, agreement between parameters.

Figure 3. The relationship between PEF and FEF50 (percent predicted) in 40 asthmatic patients in whom lung function tests were performed on at least five occasions. For clarity, only individual regression lines, as calculated from available data, are presented herein. See the text for further details.
years, many have hoped to be able to detect early changes in small airways function, and FEF_{50} seems to be an excellent candidate for the job. However, the large intrasubject and intersubject variability hinders these efforts as the lower limit of the normal range is as low as 56%.^{31,32} A renewed hope arises from some studies^{37–40} that have used high-resolution CT scans that directly confirm small airway caliber changes during induced bronchoconstriction in animals and in healthy humans. Thus, it is possible that a direct association between anatomic measures and physiologic parameters of small airways function (such as FEF_{50}) can be inferred in the near future. It is only logical to expect that the relationship between FEF_{50} and asthma clinical status will be looked into formally.

In conclusion, the present study casts further doubt on the sensitivity and specificity of PEF measurements to detect small airways obstruction in asthmatic children. While PEF measurement is recommended for the follow-up of patients with asthma, it is best used at home along with regular spirometry measurements at the clinic. It is further suggested that a better estimate of small airways function from the PEF measurements may be achieved in any individual patient in whom repeated spirometric measurements have established a unique relationship.

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