Influence of treatment on peak expiratory flow and its relation to airway hyperresponsiveness and symptoms

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Abstract

Background — Despite effective treatments, the morbidity and mortality of obstructive airways disease (asthma and COPD) remains high. Home monitoring of peak expiratory flow (PEF) is increasingly being advocated as an aid to better management of obstructive airways disease. The few available studies describing effects of treatment on the level and variation of PEF have involved relatively small numbers of subjects and did not use control groups.

Methods — Patients aged 18–60 years were selected with PC_{20} \leq 8 mg/ml and FEV_{1} <95% confidence interval of predicted normal. They were randomised to receive, in addition to a \beta_{2} agonist, either an inhaled corticosteroid (BA + CS), an anticholinergic (BA + AC), or a placebo (BA + PL). One hundred and forty one of these subjects with moderately severe obstructive airways disease completed seven periods of two weeks of morning and afternoon PEF measurements at home during 18 months of blind follow up.

Results — Improvements in PEF occurred within the first three months of treatment with BA + CS and was subsequently maintained: the mean (SE) increase in morning PEF was 51 (8) l/min in the BA + CS group compared with no change in the other two groups. Similarly, afternoon PEF increased by 22 (7) l/min. Diurnal variation in PEF (amplitude %mean) decreased from 18-0% to 10-2% in the first three months of treatment with BA + CS. Within-subject relations between changes in diurnal variation in PEF and changes in PC_{20} were found to be predominantly negative (median \rho = 0-40) but with a large scatter. Relations between diurnal variation in PEF and changes in symptom scores, FEV_{1}, and bronchodilator response were even weaker.

Conclusions — In patients with moderately severe obstructive airways disease, PEF rates and variation are greatly improved by inhaled corticosteroids. Since the relation of diurnal PEF variation with PC_{20} symptoms, FEV_{1}, and bronchodilator response were all weak, these markers of disease severity may all provide different information on the actual disease state. PEF measurements should be used in addition to the other markers but not instead of them.

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Peak expiratory flow (PEF) measurements are increasingly recommended to aid in the diagnosis and management of asthma. The National Asthma Education Program, for instance, has recently stated that PEF measurements are a valuable clinical tool for assessing the degree of airflow obstruction and monitoring the response to therapy. To date, however, the effect of different treatments on level of PEF — and especially on PEF variation — has not been extensively documented. An improvement in PEF with inhaled corticosteroids, for instance, has been shown only in two relatively small controlled studies. In a recent long term study of mild, newly detected adult asthmatic patients, Haahela and colleagues compared the results of treatment with budesonide and terbutaline and showed improvements in both morning and evening PEF with budesonide. The effects of treatment on diurnal variation in PEF were not presented.

To our knowledge, a decrease in diurnal variation in PEF with inhaled corticosteroids has been documented only in children. The variation in PEF is thought by many to reflect the degree of airway hyperresponsiveness. It is important to note, however, that most of the epidemiological and clinical studies are cross sectional, whereas longitudinal, within-subject relations between PC_{20} and PEF variation (and symptom scores) are more relevant. This is especially pertinent for self-management plans which rely on home measurements of PEF. Only one report has documented this within-subject relation between diurnal PEF variation and PC_{20}; a weak relationship was found in a small cohort study of asthmatic patients not receiving standardised therapy.

We have recently completed a double blind, controlled, multicentre clinical trial in patients with obstructive airways disease and a broad range of patient characteristics. In the current report the influence of treatment with inhaled corticosteroids and/or bronchodilators on morning and afternoon PEF levels, as well as on diurnal variation in PEF, is tested. Subsequently, the interrelationships between diurnal PEF variation, PC_{20} and symptoms are...
described, both cross sectionally between subjects, and longitudinally within subjects.

Methods

Patients aged 18-60 years with respiratory symptoms and no other major illnesses were selected according to the following criteria: (1) FEV, ranging between 4-5 and 1-64 residual standard deviations (RSD) below the predicted value—that is, between 2-30 and 0-84 litres below predicted normal FEV, for men or between 1-71 and 0-62 litres below predicted for women—or FEV,IVC (inspiratory vital capacity) more than 1-64 RSD (men: 11-76%; women: 10-68%) below the predicted value, provided that total lung capacity was normal (higher than 1-64 RSD (men: 1-15; women: 0-98 litres) below the predicted level). FEV, had to be larger than 1-2 litres; and (2) concentration of histamine causing a 20% fall in FEV, (PC_{20}) < 8 mg/ml.

Inhaled corticosteroids were tapered off and discontinued completely four weeks before a prerandomisation visit. Other maintenance medication was withheld for at least six weeks (ketoen, antihistamines), four weeks (cromolyn sodium), or 48 hours (theophyllines) before the start of the study. Maintenance medication with oral corticosteroids was not allowed. Atopy was defined on the basis of skin tests.

The study was designed as a randomised double blind clinical trial with three parallel treatment arms. Patients were allocated to one of three double blind regimens from identical metered dose inhalers: all patients received an inhaled β₂ agonist (terbutaline 250 µg, two puffs four times daily) combined with either an inhaled corticosteroid (beclometasone 100 µg, two puffs four times daily (BA + CS)), or an inhaled anticholinergic (ipratropium bromide 20 µg, two puffs four times daily (BA + AG)), or an inhaled placebo, two puffs four times daily (BA + PL). Additional bronchodilator medication was supplied as salbutamol dry powder inhalations (400 µg) on demand. No other concomitant pulmonary medication was allowed, except during exacerbations when a 12 day course of oral prednisolone was administered.

Follow up visits were scheduled every three months during which FEV₁ and, at alternate visits, bronchodilator response and PC_{20} were measured. FEV₁ and PC_{20} were only measured during clinically stable periods and not within four weeks of completion of a prednisolone course. Pulmonary medication was discontinued at least eight hours before each test. For bronchodilator response testing FEV₁ was measured before and 20 minutes after four separate inhalations of 250 µg terbutaline sulphate from metered dose inhaler (1) administered through a 750 ml spacer device (Nebulizer). Histamine provocation tests were performed using a two minute tidal breathing test.

Patients were asked to keep PEF records and a diary card for 14 consecutive days before each visit. After standardisation instruction in the outpatient clinic, patients used a Wright mini peak flow meter (Clement Clarke International Ltd, London, UK) to record PEF values at home. The best of three blows was recorded in the morning (directly after rising, before bronchodilator therapy) and in the afternoon (before the evening meal, before bronchodilator therapy). Other values were recorded on a separate sheet in the diary. Symptom scores were noted on a four-point scale (0 = no symptoms, 3 = severe symptoms) daily for wheeze, dyspnoea, cough, and phlegm, separately.

Using data from a standardised history, different syndromes were identified which adhered to the criteria of the American Thoracic Society. Patients reporting attacks of breathlessness and wheeze (asthmatic attacks) without chronic (that is, for more than three months per year) cough and sputum production were identified as having asthma. Current or former smokers without a history of asthmatic attacks, reporting either chronic cough with or without sputum production or dyspnoea when walking quietly on level ground, or both, were included in the chronic obstructive pulmonary disease group (COPD). Patients with both asthmatic attacks or recurrent wheeze and chronic cough and sputum production were labelled asthmatic bronchitics. Subjects with insufficient data to establish a diagnosis from history taking were included in an undefined diagnosis group.

DATA ANALYSIS

PEF records and symptom scores on the diary cards were accepted only if at least nine of 14 days were filled in completely. Of the 274 patients who entered the study, 222 provided acceptable PEF records at the baseline visit and 235 acceptable diary cards. As the objectives of the current analyses were focused on time and treatment effects on PEF, the analyses are limited to those patients with acceptable baseline PEF and diary cards (n = 204) and to patients who also had at least 18 months of follow up (n = 141). These patients had a slightly higher PEF value in l/min (as measured from flow-volume curves) at the baseline visit than the patients excluded from the current analyses (384 vs. 351 l/min, p<0.05), but no significant difference in PEF as % predicted (69-6% and 74-2% respectively). There were no significant differences between the entered and excluded patients with respect to age, smoking habits, FEV₁, logPC_{20}, and bronchodilator response.

Mean morning and afternoon PEF values were calculated for each patient for every period of 14 days before attending the outpatient clinics. PEF variation was assessed as mean diurnal variation = absolute value of ((afternoon reading - morning reading)/mean of these two) X 100%. PEF values were recorded calculated. At every visit to the outpatient clinic the PEF meters were checked visually for malfunction due, for example, to sputum retention. In order to check long term accuracy the morning PEF values at home were compared with PEF values from a pneumotachograph at the baseline visit and after 2-5 years. These were
not significantly different neither at the start nor at the end of the study. Symptom scores over 14 days were averaged for each of the symptoms in the diary and added to obtain a mean symptom score.

Calculations with PC<sub>20</sub> were performed using the base 2 logarithm as this reflects doubling doses and normalised the distribution. For the purposes of analysis, patients already responding to saline or to the lowest concentration of histamine (0·03 mg/ml) were assigned a PC<sub>20</sub> value of 0·015, being half the lowest concentration applied. The data are presented as mean (SE) values unless otherwise stated.

Skewness of distributions was assessed with Kolmogorov-Smirnov tests. If a p value <0·05 was obtained, non-parametric techniques were applied (Spearman’s r for correlation, Wilcoxon signed rank sum test, and Kruskal-Wallis non-parametric analysis of variance to compare group means); otherwise parametric analyses were used (Pearson’s r for correlation, Student’s t test, or one way analysis of variance to compare group means). Although patient selection was based on the number of residual standard deviations below predicted FEV<sub>1</sub>, or FEV<sub>1</sub>/FVC<sup>21</sup> results are presented with FEV<sub>1</sub>% predicted. This made no difference to the results or to the associated p values, and facilitates interpretation. All analyses were performed with SPSS/PC<sup>+</sup>.<sup>24</sup>

**Results**

The results of the intervention study in terms of differences in withdrawal rate, FEV<sub>1</sub> and PC<sub>20</sub> between patients treated with and without inhaled corticosteroids have been presented in a separate paper.<sup>19</sup> Baseline characteristics for the 141 patients in the current analysis are shown in table 1.

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**Table 1  Baseline characteristics by treatment group**

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>BA + PL</th>
<th>BA + AC</th>
<th>BA + CS</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>41</td>
<td>38</td>
<td>62</td>
</tr>
<tr>
<td>Sex: no. (%) male</td>
<td>27 (66%)</td>
<td>27 (71%)</td>
<td>45 (73%)</td>
</tr>
<tr>
<td>Mean (SD) age</td>
<td>8.4 (10·8)</td>
<td>39·9 (13·2)</td>
<td>42·0 (12·4)</td>
</tr>
<tr>
<td>FEV&lt;sub&gt;1&lt;/sub&gt;, prebronchodilatation:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD) litres</td>
<td>2·41 (0·74)</td>
<td>2·32 (0·80)</td>
<td>2·43 (0·79)</td>
</tr>
<tr>
<td>Mean (SD) % predicted</td>
<td>60·4 (17·7)</td>
<td>62·2 (15·6)</td>
<td>64·9 (15·1)</td>
</tr>
<tr>
<td>Mean (SD) number RSD from predicted FEV&lt;sub&gt;1&lt;/sub&gt;,</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>-2·66 (1·5)</td>
<td>-2·92 (1·2)</td>
<td>-2·72 (1·2)</td>
</tr>
<tr>
<td>Mean (SD) BDR</td>
<td>13·9 (9·1)</td>
<td>12·3 (7·9)</td>
<td>11·2 (7·7)</td>
</tr>
<tr>
<td>Mean (SD) log&lt;sub&gt;10&lt;/sub&gt;PC&lt;sub&gt;20&lt;/sub&gt; histamine (mg/ml)</td>
<td>-2·04 (2·37)</td>
<td>-1·81 (2·27)</td>
<td>-1·58 (2·16)</td>
</tr>
<tr>
<td>Geometric mean PC&lt;sub&gt;20&lt;/sub&gt; (mg/ml)</td>
<td>0·24</td>
<td>0·29</td>
<td>0·33</td>
</tr>
<tr>
<td>Mean (SD) morning PEF (l/min)</td>
<td>373 (93)</td>
<td>364 (103)</td>
<td>393 (130)</td>
</tr>
<tr>
<td>Mean (SD) afternoon PEF (l/min)</td>
<td>431 (90)</td>
<td>415 (100)</td>
<td>456 (122)</td>
</tr>
<tr>
<td>PEF variation (amplitude %mean)</td>
<td>16·9 (11)</td>
<td>16·4 (11)</td>
<td>18·0 (13)</td>
</tr>
<tr>
<td>Smoking: no. (%) never</td>
<td>14 (34%)</td>
<td>12 (32%)</td>
<td>18 (29%)</td>
</tr>
<tr>
<td>no. (%) ex</td>
<td>13 (32%)</td>
<td>11 (29%)</td>
<td>19 (31%)</td>
</tr>
<tr>
<td>no. (%) current</td>
<td>14 (34%)</td>
<td>15 (39%)</td>
<td>25 (40%)</td>
</tr>
<tr>
<td>Atopy: no. (%) atopic</td>
<td>25 (61%)</td>
<td>21 (55%)</td>
<td>35 (56%)</td>
</tr>
<tr>
<td>Symptom-based diagnosis groups: no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthma</td>
<td>17 (41%)</td>
<td>17 (45%)</td>
<td>20 (32%)</td>
</tr>
<tr>
<td>Asthmatic bronchitis</td>
<td>13 (32%)</td>
<td>13 (34%)</td>
<td>23 (37%)</td>
</tr>
<tr>
<td>COPD</td>
<td>11 (27%)</td>
<td>8 (21%)</td>
<td>16 (26%)</td>
</tr>
<tr>
<td>Undefined diagnosis</td>
<td>0</td>
<td>0</td>
<td>3 (5%)</td>
</tr>
</tbody>
</table>

BA + PL = β<sub>2</sub> agonist plus placebo; BA + AC = β<sub>2</sub> agonist plus anticholinergic; BA + CS = β<sub>2</sub> agonist plus corticosteroid; BDR = bronchodilatation response to 1000 μg terbutaline (ΔFEV<sub>1</sub>/predicted); PEF = peak expiratory flow (for calculation of diurnal variation, see methods); RSD = residual standard deviation (from predicted FEV<sub>1</sub>, see ref 21).

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**Figure 1**

**A** Mean (SE) morning peak flow (l/min). **B** Mean (SE) afternoon peak flow (l/min). **C** Mean (SE) variation in diurnal peak flow (amplitude % mean). —— BA + CS = β<sub>2</sub> agonist + corticosteroid (n = 62), —— BA + AC = β<sub>2</sub> agonist + anticholinergic (n = 38), —— BA + PL = β<sub>2</sub> agonist + placebo (n = 41).

**EFFECT OF TREATMENT ON PEF LEVELS AND DIURNAL VARIATION IN PEF**

Changes with treatment in morning PEF are shown in fig 1A. After three months the mean increase in morning PEF was 51 (8) l/min in the BA + CS group compared with −4 (7) in the BA + PL group. The mean difference of 55 l/min (p<0·001) was subsequently maintained during the 18 months of follow up. After three months the mean increase in afternoon PEF was 22 (7) l/min in the BA + CS group compared with −5 (7) in the BA + PL group. The mean difference of 27 l/min (p<0·01) was again maintained during the 18 months of follow up (fig 1B). Changes in diurnal variation in PEF are shown in fig 1C. A significant decrease of 8·2 (1·5%) was seen in the first three months in the BA + CS group, with no change in the BA + PL group (0·0 (1·2%), p<0·001). There were no significant differences in morning and afternoon PEF, or in diurnal PEF variation, between the BA + PL and BA + AC groups at any of the follow up visits.
Twenty three of the 62 patients (37%) on BA + CS had a diurnal PEF variation greater than 20% at the baseline visit; after three months of treatment this proportion dropped to 14% (χ² test, p<0.001) to remain approximately constant at further follow up visits. There were no significant changes in the proportions of patients having a diurnal variation in PEF greater than 20% in the other two treatment arms.

**BETWEEN-SUBJECT RELATION OF DIURNAL VARIATION IN PEF TO OTHER MARKERS OF DISEASE SEVERITY**

The cross sectional correlation between diurnal variation in PEF and log$_{2}$PC$_{20}$ at the baseline visit (ρ = -0.39, p<0.001) became somewhat stronger at later visits (ρ = -0.50, -0.60, and -0.59 after six, 12, and 18 months, respectively), but a large scatter persisted (fig 2); the relation was comparable in the three treatment arms (BA + CS; ρ = -0.48, BA + AC: ρ = -0.54, and BA + PL: ρ = -0.48 after 18 months of treatment).

Changes in diurnal variation in PEF from the baseline to the first follow up visit were negatively related to changes in PC$_{20}$ (ρ = -0.31, p<0.001, table 2), largely due to changes in the BA + CS group. Similarly, changes in diurnal variation in PEF were negatively related to changes in FEV$_{1}$,%pred (ρ = -0.31, p<0.05). There was no relation between changes in diurnal variation in PEF and changes in symptom scores (table 2).

For the BA + CS group, the temporal relationships of changes in diurnal variation in PEF, PC$_{20}$ and symptom scores are shown in fig 3. It is clear that the long term changes in these parameters on BA + CS treatment do not run parallel. The mean change of 1·3 (0·27) doubling dose in PC$_{20}$ from baseline to the six month visit was significantly greater than the 0·13 (0·33) doubling dose change in the BA + PL group (p<0.01). The additional mean improvement of 0·51 (0·24) doubling dose from six to 18 months was significantly greater than zero (p=0·04). The mean decrease of −0·55 (0·19) in symptom score from baseline to three months was significantly greater than in the BA + PL group (−0·29 (0·24), p<0.01). The changes in the BA + AC group were not significantly different from the changes in the BA + PL group. Diurnal variation in PEF at the baseline visit in the BA + CS group was only weakly prognostic for the change in FEV$_{1}$,%pred to the first follow up visit (ρ = 0·29, p=0·02), and not at all related to the change in PC$_{20}$ (p=0·07).

**WITHIN-SUBJECT RELATION OF DIURNAL VARIATION IN PEF TO OTHER MARKERS OF DISEASE SEVERITY**

To determine the strength of the association between diurnal variation in PEF and PC$_{20}$ within patients, individual rank correlation coefficients were calculated (table 3). Although a predominantly negative association was found (median ρ = −0·40), the scatter was rather large (90% range −1·00 to 0·80, fig 4A). Within patients there was also a significant, though weak, relation between changes in diurnal variation in PEF and changes in symptom scores (fig 4B). The relations between diurnal variation in PEF and the other markers of disease severity were similar between the different treatment and diagnostic groups (table 3).

**Discussion**

To our knowledge this is the first report of the long term effects of double blind treatment with inhaled corticosteroids and β₂ agonists on PEF rates and variation in adults. Mean morning and afternoon PEF values improved with the combination of inhaled corticosteroid and β₂ agonist (BA + CS) therapy in patients with moderately severe obstructive airways dis-
occurred within the first six months, the improvement continued until at least one year (fig 3). This is an important finding as airway hyperresponsiveness continued to improve even when changes in PEF and FEV₁ could no longer be demonstrated. The longitudinal relation between variation in PEF and PC₂₀ cannot therefore be as close as is suggested from some cross sectional analyses, although not from others. More important than these between-subject analyses, however, is the weakness of the within-subject correlations between changes in PEF variation and other markers of disease severity such as symptoms, FEV₁, and PC₂₀. Our results in a large group of patients on standardised treatment confirm and extend the observations of Josephs et al in an open and uncontrolled follow up study of eight children and 12 adults with mild asthma. Although in our study the relation between diurnal variation in PEF and PC₂₀ was stronger (median \( \rho = -0.40 \)) than between PEF variation and either FEV₁, bronchodilator response, or symptom scores (median \( \rho = -0.23, 0.20 \), and 0.25 respectively), considerable scatter existed for all four measurements (table 3, fig 4A,B). This implies that PEF variation and the other three markers of disease severity (PC₂₀, FEV₁, symptom scores) are not interchangeable and perhaps provide different information on the actual state and are informative in their own right.

The within-subject relation between diurnal variation in PEF and PC₂₀ was not significantly different between patients with a symptom based diagnosis of asthma, asthmatic bronchitis, or chronic obstructive pulmonary disease (COPD) (table 3). Although a high variation in PEF is considered characteristic of asthma, considerable variation in PEF has been found to be present in many current or former smokers without asthmatic attacks. Our study group was selected on the basis of objective criteria of age, FEV₁, and PC₂₀. Increased responsiveness to methacholine has recently been shown to be present in more than two thirds of patients with early COPD. In our population a large overlap was found, not only in PC₂₀ but also in PEF variation between patients with a symptom based diagnosis of asthma and COPD. Both PEF levels and PC₂₀ are also unimodally distributed in the general population. Reliable separation of patients

![Figure 4](http://thorax.bmj.com/)

**Figure 4** Frequency distribution of Spearman’s \( \rho \) for within-subject correlations of diurnal peak flow variation to (A) \( \log_PC_{20} \) and (B) symptom scores. Arrows indicate median \( \rho \).

The improvement in PEF levels and variation with inhaled corticosteroids was paralleled by an improvement in FEV₁ and by an improvement in symptom scores. By contrast, although the greatest improvement in PC₂₀ occurred within the first six months, the improvement continued until at least one year (fig 3). This is an important finding as airway hyperresponsiveness continued to improve even when changes in PEF and FEV₁ could no longer be demonstrated. The longitudinal relation between variation in PEF and PC₂₀ cannot therefore be as close as is suggested from some cross sectional analyses, although not from others. More important than these between-subject analyses, however, is the weakness of the within-subject correlations between changes in PEF variation and other markers of disease severity such as symptoms, FEV₁, and PC₂₀. Our results in a large group of patients on standardised treatment confirm and extend the observations of Josephs et al in an open and uncontrolled follow up study of eight children and 12 adults with mild asthma. Although in our study the relation between diurnal variation in PEF and PC₂₀ was stronger (median \( \rho = -0.40 \)) than between PEF variation and either FEV₁, bronchodilator response, or symptom scores (median \( \rho = -0.23, 0.20 \), and 0.25 respectively), considerable scatter existed for all four measurements (table 3, fig 4A,B). This implies that PEF variation and the other three markers of disease severity (PC₂₀, FEV₁, symptom scores) are not interchangeable and perhaps provide different information on the actual state and are informative in their own right.

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Table 3: Within-subject Spearman’s \( \rho \) rank correlation coefficients for longitudinal relations between diurnal variation in PEF and other markers of disease severity by treatment and diagnosis group (median values)

<table>
<thead>
<tr>
<th></th>
<th>log_PC₂₀</th>
<th>Symptom score</th>
<th>FEV₁ (Increased)</th>
<th>BDR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total group</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>median</td>
<td>-0.40</td>
<td>0.25</td>
<td>-0.23</td>
<td>0.20</td>
</tr>
<tr>
<td>90% range</td>
<td>-1.0 to 0.80</td>
<td>-0.66 to 0.76</td>
<td>-1.0 to 1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>( \rho^* )</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>0.04</td>
<td>0.05</td>
</tr>
<tr>
<td>BA + PL</td>
<td>-0.26</td>
<td>0.20</td>
<td>-0.20</td>
<td>0.20</td>
</tr>
<tr>
<td>BA + AC</td>
<td>-0.32</td>
<td>-0.40</td>
<td>-0.20</td>
<td>0.40</td>
</tr>
<tr>
<td>BA + CS</td>
<td>-0.40</td>
<td>0.20</td>
<td>-0.20</td>
<td>0.20</td>
</tr>
<tr>
<td>pf</td>
<td>0.05</td>
<td>0.48</td>
<td>0.78</td>
<td>0.56</td>
</tr>
<tr>
<td>Asthma</td>
<td>-0.40</td>
<td>0.32</td>
<td>-0.40</td>
<td>0.40</td>
</tr>
<tr>
<td>Asthmatic bronchitis</td>
<td>-0.40</td>
<td>0.20</td>
<td>-0.40</td>
<td>0.26</td>
</tr>
<tr>
<td>COPD</td>
<td>-0.40</td>
<td>0.13</td>
<td>0.20</td>
<td>-0.20</td>
</tr>
<tr>
<td>pf</td>
<td>0.75</td>
<td>0.21</td>
<td>0.03</td>
<td>0.02</td>
</tr>
</tbody>
</table>

* Wilcoxon one sample signed rank sum test; non-parametric testing for symmetric distribution about zero.† Kruskal-Wallis one way analysis of variance; non-parametric testing for differences in means between diagnoses or treatment groups. Three patients with an undefined diagnosis are left out of the comparison of diagnoses. For abbreviations see table 1.
with asthma from both normal subjects and those with COPD on the basis of any one single parameter is not therefore possible.

From a clinical point of view, it would be very valuable if diurnal variation in PEF, measured before institution of treatment, was a good predictor of improvement with inhaled corticosteroids as not all patients respond to corticosteroids.  

In our study, however, baseline diurnal variation in PEF was too weakly related to changes in FEV₁ and PC_{20} (p = 0.29 and 0.07, respectively) to help in deciding to whom to administer inhaled corticosteroids. Baseline PC_{20} FEV₁, bronchodilator response, allergy, and smoking habits may be more useful in this respect.  

To date it is unclear how the variation in PEF should best be measured and expressed. Several points are currently unresolved: firstly, how many PEF readings should be taken each day, and when.  

It is clear that more readings will not only increase diurnal (circadian) PEF variation, but will also lead to somewhat more stable figures for PEF variation. However, in this 2-5 year clinical trial, as perhaps in routine patient care, it was thought that too frequent measurements of PEF, especially at night, would seriously hamper patient compliance.

Secondly, Ryan and coworkers have advocated the computation of the PEF amplitude as the highest postbronchodilator value minus the lowest prebronchodilator value. Expressing amplitude in this way they found a considerably higher correlation coefficient with PC_{20} (r = 0.81) than when calculating amplitude from prebronchodilator values only (r = 0.41). This might effectively make home PEF measurements more informative, probably by adding another component of disease severity – namely, the degree of reversibility to a β₂ agonist – to the equation. When performing analyses with this measure of variation in PEF one should then be aware of a higher interrelationship between the different markers of disease severity.

A limitation of the current analysis is the reduction in number of patients from the original group, even though the analysed group was not significantly different from the group not selected. PEF records and symptom scores on the diary cards were accepted only if reliable – that is, sufficiently completed – data of the prerrandomisation visit were available (n = 204). This is a prerequisite to study changes with treatment. As a result of withdrawal before the 18-month visit, the number of patients was further reduced to 141. This second criterion was employed in order to study long term variability and within-subject correlation coefficients in a complete set of data. We reanalysed the data including all patients who achieved a follow up of at least three months (n = 187 instead of 141) and found the changes in PEF levels and variation with treatment to be highly comparable and all significance levels unchanged. We therefore feel confident that the data presented are representative of the control group, even though a relatively large reduction of patients occurred.

No change (improvement or deterioration) in PEF levels and variation in PEF was found with bronchodilator treatment alone. We are, however, cautious to suggest the absence of a deleterious effect of regular β₂ agonist treatment alone, both because of our large withdrawal rate (mainly due to increases in pulmonary complaints) and because all our patients received regular treatment with a β₂ agonist (2000 µg terbutaline per day).

In conclusion, this randomised controlled longitudinal study of 141 patients shows that inhaled corticosteroids improve morning and afternoon PEF levels, thereby reducing diurnal variation in PEF. This should be kept in mind when interpreting PEF variation for diagnostic classification in research and clinical practice. The relationship between diurnal variation in PEF and both symptoms and objective parameters such as PC_{20} and FEV₁ is relatively weak. We therefore regard home PEF monitoring as an informative and valuable aid to physicians but always in conjunction with other markers of disease severity.

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