Interpretation of bronchodilator response in patients with obstructive airways disease

Paul L P Brand, Philip H Quanjer, Dirkje S Postma, Huib A M Kerstjens, Gerard H Koeter, P N Richard Dekhuijzen, Henk J Sluiter, and the Dutch chronic non-specific lung disease (CNSLD) study group* 

Abstract

Background There is no agreement on how a bronchodilator response should be expressed. Ideally, the index used should be adequate to distinguish asthma from chronic obstructive lung disease and be independent of initial FEV1.

Methods Two hundred and seventy four adult (aged 18-60 years) outpatients with obstructive airways disease were studied. Patients were divided into syndrome groups on the basis of a standardised history: asthma (n=99), asthmatic bronchitis (n=88), and chronic obstructive lung disease (n=51); 36 subjects could not be attributed to any subgroup. FEV1 was measured before and 20 minutes after inhalation of 1000 µg terbutaline. Different expressions of bronchodilator response (ΔFEV1) were compared with respect to their dependence on initial FEV1, and their efficacy in separating subjects with asthma from those with chronic obstructive lung disease. ΔFEV1 was expressed as a percentage of initial FEV1 (ΔFEV1, %), absolute value (ΔFEV1(I)), percentage of predicted FEV1 (ΔFEV1, %pred), standardised residual (ΔSR-FEV1), and percentage of maximal possible increase (ΔFEV1, %init).

Results ΔFEV1, %init was more dependent on initial FEV1 (r² = 0.405) than ΔFEV1(I) (r² = 0.145), ΔFEV1, %pred (r² = 0.166), and ΔSR-FEV1 (r² = 0.127). ΔFEV1, %pred [pred – init] reached infinity when initial FEV1 approached predicted levels. ΔFEV1, %pred had a higher likelihood ratio (1:71) for separating patients with asthma from those with chronic obstructive lung disease than other expressions of bronchodilator response. Asthmatic patients had larger mean bronchodilator responses than patients in other subgroups; this difference was largest for ΔSR-FEV1 (F = 9.19) and ΔFEV1, %init (F = 5.89). Despite significant differences in mean response, there was a large overlap of individual responses between diagnostic subgroups. The bronchodilator response was continuously and unimodally distributed for all expressions.

Conclusions ΔFEV1, %init appears to be the most useful method of expressing bronchodilator response, both for clinical and for research purposes. Reversibility of airways obstruction in response to a bronchodilator is a continuous variable and not a dichotomous trait. Any cut off level of a “positive” bronchodilator response is therefore arbitrary.

Assessment of a bronchodilator response is a routine procedure both in pulmonary medicine and in research. This response is primarily assessed as a tool to distinguish “mainly reversible” from “irreversible” airways obstruction, a key difference between asthma and chronic obstructive lung disease.1 2 3 The results of bronchodilator response tests are commonly used as a basis for classification of disease and choice of treatment by clinicians and as an inclusion criterion for studies by research workers. Despite these important functions of bronchodilator response testing, there is no agreement on how the results should be expressed.2 3 The mode of expression may depend on the reason why the test is performed.2 There is also no consensus on what constitutes a “positive” response.2 3 As a result numerous criteria are being used, for which the scientific foundation appears to be largely lacking. For example, a change in forced expiratory volume in one second (FEV1) of more than 15% of the initial level is commonly considered to signify a “positive” bronchodilator response, although...
several studies have reported that this criterion provides poor discrimination between patients with asthma and those with chronic obstructive lung disease; it also increases the response in patients with a low initial FEV\textsubscript{1}.\textsuperscript{6,9-13} This dependence of bronchodilator response on initial FEV\textsubscript{1} may be undesirable, especially when responses of patients with different initial FEV\textsubscript{1} levels are being compared.\textsuperscript{14}

Although several expressions of bronchodilator response have been discussed from a theoretical point of view in some detail,\textsuperscript{11,12} few comparative clinical studies have been carried out. Most studies have been confined to patients with chronic obstructive lung disease,\textsuperscript{13,14,16} other results have been obtained in relatively small groups of patients with unstandardised treatment.\textsuperscript{17,18}

We studied bronchodilator response under strictly standardised conditions in a large group of adults with obstructive airways disease, with a broad range of clinical presentations and lung function, during the baseline period of a long term multicentre trial. In this report we compare different expressions of bronchodilator response with respect to their dependence on initial FEV\textsubscript{1}, and to their efficacy in distinguishing asthmatic individuals from patients with chronic obstructive lung disease.

Methods

PATIENTS

For this report we used baseline data from a multicentre trial supported by the Dutch government. The main goal of this trial is to compare the effect of three different treatment regimens (β agonist plus either placebo, anticholinergic agent, or corticosteroid, all given by inhalation) on the long term (30 months) course and outcome of obstructive airways disease.\textsuperscript{19}

We recruited 274 adult patients (aged 18–60 years) with chronic respiratory symptoms from six university hospital pulmonary outpatient clinics if they had a baseline FEV\textsubscript{1} level greater than 1.2 litres and 1-64–4-5 residual standard deviations (RSD) below the predicted value, or if their FEV\textsubscript{1}/inspiratory vital capacity (IVC) ratio was more than 1-64 RSD below the predicted value provided that total lung capacity was less than 1-64 RSD below the predicted level.\textsuperscript{20} Another selection criterion was hyperresponsiveness to inhaled histamine (the provocative concentration of histamine causing a 20% decrease in FEV\textsubscript{1}, (PC\textsubscript{20}) <8 mg/ml—see below). We excluded pregnant women, patients with a history of occupational asthma or other serious diseases (for example, tuberculosis, myocardial infarction, and malignancy), patients who were taking oral corticosteroids, β blocking drugs, nitrates, or antiocoagulants, and patients who were taking antibiotics continuously.

By using data from a standardised history we identified different clinical syndromes, closely adhering to the criteria proposed by the American Thoracic Society:\textsuperscript{1}

- patients reporting attacks of breathlessness and wheeze (asthmatic attacks) without chronic (that is, for more than three months a year) cough or sputum production were labelled as having asthma (n = 99, 36%);
- 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 lung disease group (n = 51, 19%);
- patients with both asthmatic attacks or recurrent wheeze and chronic cough and sputum production were labelled as having asthmatic bronchitis (n = 88, 32%).

In 36 subjects (13%) a clinical syndrome diagnosis could not be made from the data obtained from the history because these were either incomplete or unreliable ("no diagnosis" group).

The study protocol was approved by the medical ethics committees of all participating centres; all patients gave written informed consent.

DATA ACQUISITION

Before entering the study patients discontinued their usual maintenance treatment for the following times: at least one month for ketotifen and antihistamines, two weeks for an inhaled corticosteroid and for sodium cromoglycate, and two days for theophyllines. For the 14 days before the present study only inhaled bronchodilators were used. These were withheld at least eight hours before measurement of lung function. All measurements were performed when subjects were clinically stable, and at least three weeks after discontinuation of a course of oral corticosteroids.

A standardised history of respiratory symptoms was obtained. Spirometry was performed with calibrated water sealed spirometers according to standardised guidelines.\textsuperscript{20} FEV\textsubscript{1} and IVC were measured until three reproducible recordings (less than 5% difference) were obtained. Highest values were used for analyses. Reference values are those of the European Community for Coal and Steel.\textsuperscript{20}

Histamine provocation tests were performed according to a two minute tidal breathing method, the details of which have been published.\textsuperscript{19} Results were expressed in terms of PC\textsubscript{20} histamine.

ASSESSMENT OF BRONCHODILATOR RESPONSE

FEV\textsubscript{1} measurements were carried out before and 20 minutes after the separate inhalation of four puffs of 250 μg of terbutaline sulphate from a metered dose inhaler, administered through a 750 ml spacer device (Nebuhaler, Astra Pharmaceuticals, Rijswijk, The Netherlands). Patients rested at least 15 minutes before the first measurement and refrained from drinking coffee or tea and from smoking between measurements.

ASSESSMENT OF SPONTANEOUS FLUCTUATIONS IN FEV\textsubscript{1}

In a subgroup of 45 patients from one centre spontaneous changes in FEV\textsubscript{1} were assessed. Spirometric values before bronchodilatation were determined twice in these subjects with an
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Table 1  Characteristics of the patients

<table>
<thead>
<tr>
<th>Height (cm)</th>
<th>174 (10 0)</th>
<th>age (years)</th>
<th>40 (18 to 60)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV₁, litres</td>
<td>2-33 (0-74)</td>
<td>Smoking (pack years)</td>
<td>4-5 (0 to 123)</td>
</tr>
<tr>
<td>% predicted</td>
<td>63-7 (15-3)</td>
<td>ΔFEV₁%init</td>
<td>18 (-14 to 78)</td>
</tr>
<tr>
<td>FEV₁/IVC %</td>
<td>55-3 (11-0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>% predicted</td>
<td>68-5 (13-2)</td>
<td></td>
<td></td>
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<tr>
<td>Bronchodilator response</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ΔFEV₁</td>
<td>0-44 (0-33)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ΔFEV₁%predicted</td>
<td>11-9 (8-9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ΔSR-FEV₁</td>
<td>0-97 (0-75)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PC₂₀ (mg/ml)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>log Geometric mean (with 1 SD)</td>
<td>-1.95 (2-30)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Geometric mean</td>
<td>0-28 (0-05, 1-27)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthma</td>
<td>99 (36-1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthmatic bronchitis</td>
<td>88 (32-1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic obstructive lung disease</td>
<td>51 (18-6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No conclusive diagnosis</td>
<td>36 (13-1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV₁—forced expiratory volume in one second; IVC—inspiratory vital capacity; SR—standardised residual; PC₂₀—provocative concentration of histamine causing a 20% fall in FEV₁.</td>
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</tbody>
</table>

interval of 20 minutes, during which they remained seated and refrained from drinking coffee or tea and from smoking.

**Expression of FEV₁ and Bronchodilator Response**

Initial FEV₁ and postbronchodilator FEV₁ (FEV₁,pb) were expressed as percentages of predicted normal values (FEV₁,%pred and FEV₁,pb,%pred, respectively). Standardised residuals (SR) of prebronchodilator and postbronchodilator FEV₁ were computed by subtracting the patient's FEV₁ from the predicted FEV₁ and dividing this difference by the residual standard deviation (RSD) of the FEV₁ reference formula. The SR indicates how many RSDs a patient's FEV₁ is away from the predicted FEV₁. Bronchodilator responses to terbutaline were expressed in five ways: as a percentage of initial (prebronchodilator) FEV₁ (ΔFEV₁,%init) as absolute values in litres (ΔFEV₁), as a percentage of the predicted normal FEV₁ (ΔFEV₁,%pred) as a percentage of the achievable reversibility, i.e. the difference between predicted and initial FEV₁ (ΔFEV₁,%pred – init) as standardised residuals, i.e. the difference between the SRs of the post- and prebronchodilator FEV₁ (ΔSR-FEV₁).

**Quality Control**

All data were recorded on standardised forms and submitted to a data centre, where they were keyed into a data base. Missing or out of range data were noted and referred back to the appropriate clinical centre for clarification. Data input into the computer was double checked with data on the submitted forms.

**Data Analysis**

The baseline period of the main study required two visits. The analyses in this report are based on data from the second visit, immediately before randomisation. Analysis of data from the first visit did not change the results.

Kolmogorov-Smirnov (K-S) tests were used to compare distributions of variables with standard normal distributions: smaller p values indicate a more skewed distribution. If p values below 0.05 were obtained non-parametric techniques were used to analyse those variables; otherwise, parametric techniques were applied. These included computation of correlation coefficients and regression analysis to study the relation between variables, and two tailed t tests and one way analysis of variance (ANOVA) to compare group means. The sensitivity and specificity of a bronchodilator response to terbutaline in separating subjects with asthma from those with chronic obstructive lung disease were computed for various criteria of a "positive" bronchodilator response obtained from published reports. The likelihood ratio (sensitivity/1-specificity) reflects the ability of a test to discriminate between subjects with asthma and chronic obstructive lung disease. All analyses were performed with the SPSS/PC+ package.
Results
Clinical characteristics of the 274 patients who completed baseline measurements are presented in table 1. Age and pack years of smoking are presented as medians and ranges because their distribution was skewed (K-S tests, p < 0.01). The distributions of FEV1%pred and FEV1pb%pred were normal (p = 0.74 and 0.86). ΔFEV1%init showed a positively skewed distribution (that is, with a long tail to the right) (p = 0.03), as did ΔFEV1%pred−init to a much stronger extent (p < 0.01). The distributions of ΔFEV1[1] (p = 0.09) and ΔSR-FEV1 (p = 0.05) were only slightly skewed to the left, whereas ΔFEV1%pred had a normal distribution (p = 0.56). All distributions were continuous and unimodal.

RELATION OF BRONCHODILATOR RESPONSE TO INITIAL FEV1%PRED
The relation between ΔFEV1%init and initial FEV1%pred is plotted in figure 1. Values for ΔFEV1%init increased substantially when initial FEV1%pred was low, causing a highly significant negative correlation (p = −0.405, p < 0.001). The relation between ΔFEV1[1] and initial FEV1%pred did not show a substantial increase at low initial FEV1%pred (fig 2); the results show a wide scatter with a small, but significant, negative correlation (r = −0.145, p = 0.017). A similar relationship was found between initial FEV1%pred and both ΔFEV1%pred (fig 3, r = −0.166, p = 0.006) and ΔSR-FEV1 (fig 4, r = −0.127, p = 0.035). ΔFEV1%pred−init showed values reaching infinity when initial FEV1%pred approached 100% pred (fig 5). No correlation coefficient was computed because of the shape of the scatter.

NUMBER OF RESPONDERS FOR EACH EXPRESSION
The number of patients with a “positive” response was calculated with commonly quoted cut-off levels for different expressions of the bronchodilator response. The sensitivity and specificity of these criteria in separating subjects with asthma from patients with a history of chronic obstructive lung disease was calculated (table 2). The best separation (highest likelihood ratio) of asthma from chronic obstructive lung disease was found for a ΔFEV1%pred of 9%.

BRONCHODILATOR RESPONSES IN DIFFERENT PATIENT GROUPS
To allow comparison of different measures of bronchodilator responsiveness with respect to their distributions among the diagnostic subgroups, parametric analysis of variance was performed for all measures of bronchodilator response except ΔFEV1%pred−init (the distribution of this variable was so clearly non-normal that the condition of normality for the ANOVA was obviously violated). Results are presented in table 3. The difference between groups (expressed as the F ratio of the ANOVA) was most pronounced for ΔSR-FEV1, ΔFEV1%pred, and ΔFEV1[1], and less clear for ΔFEV1%init (table 3); this was also true when non-parametric ANOVA was applied (Kruskall-Wallis procedure). Despite these differences, mean response considered overlap in bronchodilator responses of individual cases occurred between patient groups (fig 6). For example, the interquartile (50%) range of ΔFEV1%pred was 8.49–22.8 for asthma, 4.66–16.7 for asthmatic bronchitis, and 3.23–12.9 for chronic obstructive lung disease.

SPONTANEOUS CHANGES IN FEV1
The 45 patients in whom spontaneous changes in FEV1 were assessed were somewhat younger (U test, p = 0.046) and taller (t test, p = 0.026), and had less severe airways hyperresponsive-
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ness (p = 0.002) than the rest of the study population. Initial FEV\textsubscript{1} %pred was similar in the two groups (p = 0.090), as were FEV\textsubscript{1}/FVC, the sex distribution, and smoking habits. The median spontaneous change in FEV\textsubscript{1} over 20 minutes was zero. Spontaneous changes in FEV\textsubscript{1}, ranged from −0.35 to +0.40 litres, or from −6.94 to +9.78% predicted. Ninety five per cent of all spontaneous changes were less than −0.235 l, or 6.04% predicted. Spontaneous changes in FEV\textsubscript{1} were not related significantly to age, sex, smoking habits, PC\textsubscript{20} level, or the bronchodilator response to terbutaline, expressed in any way (all p values > 0.2).

The spontaneous change in FEV\textsubscript{1} was also unrelated to initial FEV\textsubscript{1} %pred (p = 0.602).

Discussion

This study shows that expressing a bronchodilator response as a percentage of the initial FEV\textsubscript{1} is more dependent on initial FEV\textsubscript{1} than other expressions of the response. It is also less effective than other indices of the bronchodilator response in distinguishing patients with asthma from those with chronic obstructive lung disease. These results were obtained in a large group of patients with obstructive airways disease with a broad range of clinical characteristics under standardised conditions and treatment. Our results thus confirm and extend the results of earlier studies, in which only patients with chronic obstructive lung disease\textsuperscript{12,14,15} or relatively small groups of patients with unstandardised treatments\textsuperscript{17,18} were studied.

This study was not designed to answer the question of which expression of the bronchodilator response gives the most relevant information in a clinical setting. Most clinicians use \(\Delta FEV\textsubscript{1} %\text{init}\) because they assume that the clinical relevance of a bronchodilator response is reflected by expressing it as an increase in FEV\textsubscript{1}, relative to the initial value,\textsuperscript{14} but this has never been formally studied. Which expression of the bronchodilator response correlates best with the clinical improvement of a patient after inhalation of a bronchodilator is unknown. The main disadvantage of using \(\Delta FEV\textsubscript{1} %\text{init}\) clinically is that sparsely suggests that patients with a low initial FEV\textsubscript{1} are more responsive to bronchodilator drugs\textsuperscript{6,15}.

The pronounced dependence of \(\Delta FEV\textsubscript{1} %\text{init}\) on initial FEV\textsubscript{1} (fig 1) has important drawbacks for research. If a certain level of \(\Delta FEV\textsubscript{1} %\text{init}\) is used as an inclusion criterion in clinical studies, as is commonly the case, patients with a low initial FEV\textsubscript{1} will be selected preferentially.\textsuperscript{7,14,15} Furthermore, if bronchodilator response is studied as a predictor of outcome the results will depend on the level of initial airway obstruction. A low initial FEV\textsubscript{1} is related to an unfavourable prognosis in chronic obstructive lung disease,\textsuperscript{5,29} and in these patients \(\Delta FEV\textsubscript{1} %\text{init}\) will be high. Thus when bronchodilator response is related to prognosis in such studies the results reflect an interaction of initial airway calibre and its reversibility rather than the effect of reversibility itself. It is not surprising therefore that a high \(\Delta FEV\textsubscript{1} %\text{init}\) is usually not associated with a better outcome in chronic obstructive lung disease.\textsuperscript{26,30} In studies where initial FEV\textsubscript{1} was corrected for\textsuperscript{29} or where \(\Delta FEV\textsubscript{1} %\text{[pred – init]}\) was used\textsuperscript{16} a larger bronchodilator response was related to a more favourable prognosis when bronchodilator drugs were used regularly. These latter findings may only apply to patients with severe airways obstruction, where \(\Delta FEV\textsubscript{1} %\text{[pred – init]}\), an index of the capacity to respond, has little dependence on initial FEV\textsubscript{1}. This expression gives progressively higher results with higher initial FEV\textsubscript{1} values, however (fig 5).

Other expressions of a bronchodilator response correlate only weakly with prebronchodilator airway calibre (figs 2–4), which is advantageous in a research setting because responses of patients with different initial FEV\textsubscript{1} levels can then be compared.\textsuperscript{5,14} Because spontaneous changes in FEV\textsubscript{1} appear to be unrelated to the
Table 2  Expressions of bronchodilator response according to cut off points used in previous reports: number of "positive" responses with the sensitivity, specificity, and likelihood ratio of a positive result for the distinction between asthma and chronic obstructive lung disease

<table>
<thead>
<tr>
<th>Expression</th>
<th>Cut off level and reference</th>
<th>Number of &quot;positive&quot; responders</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Likelihood ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Δ FEV,%init</td>
<td>15</td>
<td>156</td>
<td>0.687</td>
<td>0.529</td>
<td>1.459</td>
</tr>
<tr>
<td>Δ FEV[II]</td>
<td>0-200</td>
<td>210</td>
<td>0.879</td>
<td>0.353</td>
<td>1.359</td>
</tr>
<tr>
<td>N D</td>
<td>&gt;15</td>
<td>155</td>
<td>0.687</td>
<td>0.549</td>
<td>1.523</td>
</tr>
<tr>
<td>Δ FEV,%init</td>
<td>&gt;0.2</td>
<td>165</td>
<td>0.737</td>
<td>0.569</td>
<td>1.710</td>
</tr>
<tr>
<td>Δ FEV,%pred</td>
<td>0-5</td>
<td>188</td>
<td>0.808</td>
<td>0.451</td>
<td>1.472</td>
</tr>
<tr>
<td>Δ FEV[II]</td>
<td>80</td>
<td>112</td>
<td>0.455</td>
<td>0.686</td>
<td>1.449</td>
</tr>
</tbody>
</table>

Table 3  Response to bronchodilator, expressed in various ways, in the different diagnostic groups

<table>
<thead>
<tr>
<th>Expression</th>
<th>Asthma</th>
<th>Asthmatic bronchitis</th>
<th>Chronic obstructive lung disease</th>
<th>No conclusive diagnosis</th>
<th>F*</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Δ FEV,[I]</td>
<td>0.55 (0.04)</td>
<td>0.41 (0.03)</td>
<td>0.28 (0.03)</td>
<td>0.42 (0.05)</td>
<td>8.82</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Δ FEV,%init</td>
<td>25.86 (1.79)</td>
<td>18.97 (1.72)</td>
<td>14.87 (1.99)</td>
<td>19.39 (2.84)</td>
<td>5.89</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Δ FEV,%pred</td>
<td>15.18 (0.93)</td>
<td>10.84 (0.86)</td>
<td>7.97 (1.00)</td>
<td>11.73 (1.51)</td>
<td>9.03</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Δ SR-FEV1</td>
<td>1.24 (0.08)</td>
<td>0.88 (0.07)</td>
<td>0.61 (0.08)</td>
<td>0.96 (0.13)</td>
<td>9.19</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FEV,%pred</td>
<td>63.84 (2.08)</td>
<td>65.11 (1.71)</td>
<td>60.98 (2.34)</td>
<td>63.92 (2.08)</td>
<td>0.79</td>
<td>0.504</td>
</tr>
<tr>
<td>FEV,%pred</td>
<td>79.02 (1.62)</td>
<td>75.95 (1.75)</td>
<td>68.95 (2.31)</td>
<td>75.65 (2.45)</td>
<td>4.406</td>
<td>0.005</td>
</tr>
</tbody>
</table>

*From analysis of variance.

When ΔFEV1 is related to the predicted FEV1, the choice lies between ΔFEV,%pred and ΔSR-FEV1. The use of % predicted values has been criticised as it leaves "hidden bias in the data"; the use of standardised residuals is a more appropriate statistical technique. The % predicted method has been shown to be at least as useful as the SR method in identifying obstructive airways disease epidemiologically, however, and clinicians probably feel more comfortable with it. Our results suggest that, for the purpose of tests of bronchodilator responsiveness, there is little difference between the two methods. This may not hold true for a differently selected group of patients.

In our study population a bronchodilator response expressed as a percentage of the predicted FEV1 was more powerful than other expressions in separating subjects with asthma from those with chronic obstructive lung disease (table 2). Despite the significant differences in mean response considerable overlap between bronchodilator responses existed between subgroups of patients (fig 6), which implies that results of a single bronchodilator test cannot reliably distinguish asthma from chronic obstructive lung disease. This finding is in contrast with the results of earlier work. Selection factors may be largely responsible for this difference in results. In the earlier studies patients were selected on the basis of a classical history of asthma or chronic obstructive lung disease, which thus created groups with relatively large differences in bronchodilator response. In contrast, our inclusion criteria were of a functional nature (age, airway calibre, and PC20 histamine), deliberately aiming at recruiting a heterogeneous population of
patients with moderately severe airways obstruction. Thus differences in bronchodilator response between various clinical syndromes are dependent on the study population and on the definitions of asthma and chronic obstructive lung disease that are used. The distribution of bronchodilator responses, both in clinical studies such as ours and in samples of healthy individuals, is continuous and unimodal. Thus any attempt at achieving a cut-off level for a "positive" response is arbitrary. With this restriction in mind, two approaches may be used to derive reference values for a bronchodilator response. The first is to consider values higher than the 95th percentile in a distribution of healthy individuals as being "abnormal." Thus, cut off levels of 130 and 417 ml for absolute change in FEV1, have been proposed, which were dependent on age, height, and sex. When expressed as ΔFEV1, % pred, a cut off value of 9% was derived, which was much more stable between age-height-sex subgroups. An alternative approach is to study short term spontaneous or placebo induced changes in FEV1, in patients. A bronchodilator response which exceeds the 95th percentile of the distribution of these spontaneous fluctuations may then be considered a "positive" response. With this approach, cut off levels of 178-190 ml31 35 or 8.5-9.5% of predicted35 have been derived. Our results (235 ml and 6-0.4%) differ somewhat from those previously reported, probably owing to differences in study populations and methods (for example, type, dose, and administration of the bronchodilating agent).

No matter how the bronchodilator response is expressed, the magnitude of the response cannot be interpreted on its own because it gives no information on the severity of post-bronchodilator airways obstruction. An increase of 20% of the initial FEV1, or of 300 ml may hardly be relevant clinically if severe airways obstruction remains after inhalation of the bronchodilator. A bronchodilator response can be reliably interpreted only if pre-bronchodilator or post-bronchodilator airway calibre is known. The clinical usefulness in this respect of expressing the bronchodilator response as a percentage of the predicted FEV1, follows from the fact that ΔFEV1, % pred is the difference between initial and postbronchodilator FEV1, % pred, both of which are important outcome predictors in obstructive airway disease.16-27 Knowledge of ΔFEV1, % pred with initial FEV1, % pred gives clinicians all the information they need on the severity of initial airway obstruction, the magnitude of the bronchodilator response, and the remaining ventilatory deficit after bronchodilatation. The effect of a single bronchodilator dose, however, reflects only acute reversibility, which is probably largely determined by relaxation of airways smooth muscle. The slower improvement of lung function produced by anti-inflammatory drugs is another component of reversibility. It is not clear whether short term reversibility (that is, the bronchodilator response) may be used as a predictor of long term reversibility (that is, the response to anti-inflammatory drugs).

In conclusion, we consider that ΔFEV1, % pred is a useful and valid measure of bronchodilator response both for clinical practice and for many aspects of research. The choice of a cut off level for a "positive" response is arbitrary because acute reversibility of airways obstruction to a bronchodilator is a continuous variable rather than a dichotomous trait.

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