Interpretation of bronchodilator response in patients with obstructive airways disease

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Abstract

**Background** There is no agreement on how a bronchodilator response should be expressed. Ideally, the index used should be able 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 bronchiectasis (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 (∆FEV1) 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. ∆FEV1 was expressed as a percentage of initial FEV1, ∆FEV1, absolute value (∆FEV1, [I]), percentage of predicted FEV1, ∆FEV1, %pred, standardised residual (∆SR-FEV1), and percentage of maximal possible increase (A FEV1, %init).

**Results** ∆FEV1, %init was more dependent on initial FEV1, (r = -0.405) than ∆FEV1, [I] (r = -0.145), ∆FEV1, %pred (r = -0.166), and ∆SR-FEV1, ∆FEV1, %pred - init reached infinity when initial FEV1, approached predicted levels. ∆FEV1, %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 ∆SR-FEV1, (F=9.19) and ∆FEV1, %pred (F=9.03); it was much smaller for ∆FEV1, %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** ∆FEV1, %pred 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. 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 researchers. Despite these important functions of bronchodilator response testing, there is no agreement on how the results should be expressed. The mode of expression of the results depends on the reason the test is performed. There is also no consensus on what constitutes a “positive” response. 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 FEV1.6-9,13 This dependence of bronchodilator response on initial FEV1 may be undesirable, especially when responses of patients with different initial FEV1 levels are being compared.14

Although several expressions of bronchodilator response have been discussed from a theoretical point of view in some detail,11,12 few comparative clinical studies have been carried out. Most studies have been confined to patients with chronic obstructive lung disease13,14,16,19; other results have been obtained in relatively small groups of patients with unstandardised treatment.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 FEV1 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 (β2 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.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 FEV1 level greater than 1.2 litres and 1–64–4.5 residual standard deviations (RSD) below the predicted value, or if their FEV1/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.20 Another selection criterion was hyperresponsiveness to inhaled histamine (the provocative concentration of histamine causing a 20% decrease in FEV1, PC20 < 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, β2 blocking drugs, nitrates, or anticoagulants, 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:17

• 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 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.20 FEV1 and FVC 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.20

Histamine provocation tests were performed according to a two minute tidal breathing method, the details of which have been published.19 Results were expressed in terms of PC20 histamine.

ASSESSMENT OF BRONCHODILATOR RESPONSE

FEV1 measurements were carried out before and 20 minutes after the separate inhalation of four puffs of 225 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 FEV1

In a subgroup of 45 patients from one centre spontaneous changes in FEV1 were assessed. Spirometric values before bronchodilatation were determined twice in these subjects with an
Table 1 Characteristics of the patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean (SD)</th>
<th>Median (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Height (cm)</td>
<td>174 (10 0)</td>
<td>40 (18 to 60)</td>
</tr>
<tr>
<td>FEV, % predicted</td>
<td>2.33 (0.74)</td>
<td></td>
</tr>
<tr>
<td>FEV, % predicted</td>
<td>63.7 (15.3)</td>
<td></td>
</tr>
<tr>
<td>FEV, /IVC % predicted</td>
<td>55.3 (11.0)</td>
<td></td>
</tr>
<tr>
<td>FEV, % predicted</td>
<td>68.5 (13.2)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Bronchodilator response</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔFEV, [1]</td>
<td>0.44 (0.33)</td>
<td></td>
</tr>
<tr>
<td>ΔFEV, % predicted</td>
<td>11.9 (8.9)</td>
<td></td>
</tr>
<tr>
<td>ΔSR-FEV,</td>
<td>0.97 (0.75)</td>
<td></td>
</tr>
</tbody>
</table>

| PC_{20} (mg/ml)                  | 7.95 (2.30)        |                  |
| Geometric mean (with 1 SD)       | 0.28 (0.05, 1.27)  |                  |

FEV,—forced expiratory volume in one second; IVC—inspiratory vital capacity; SR—standardised residual; PC_{20}—provocative concentration of histamine causing a 20% fall in FEV,

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

**EXPRESSION OF FEV, AND BRONCHODILATOR RESPONSE**

Initial FEV, and postbronchodilator FEV, (FEV,pb) were expressed as percentages of predicted normal values (FEV, %pred and FEV, %pred, respectively). Standardised residuals (SR) of prebronchodilator and postbronchodilator FEV, were computed by subtracting the patient’s FEV, from the predicted FEV, and dividing this difference by the residual standard deviation (RSD) of the FEV, reference formula. The SR indicates how many RSDs a patient’s FEV, is away from the predicted FEV,.

Bronchodilator responses to terbutaline were expressed in five ways:

- as a percentage of initial (prebronchodilator) FEV, (ΔFEV, %init)
- as absolute values in litres (ΔFEV, [1])
- as a percentage of the predicted normal FEV, (ΔFEV, %pred)
- as a percentage of the achievable reversibility, i.e. the difference between predicted and initial FEV, (ΔFEV, %pred - init)
- as standardised residuals, i.e. the difference between the SRs of the post- and prebronchodilator FEV, (ΔSR-FEV,).

**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.
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 (r = -0.405, p < 0.001). The relation between ΔFEV₁, %init 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 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, %init, and less clear for ΔFEV₁, %init (table 3); this was also true when non-parametric ANOVA was applied (Kruskall-Wallis procedure). Despite these differences in mean response considerable 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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Figure 4. Relation of ΔFEV₁ expressed as standardised residuals (ΔSR-FEV₁), to initial FEV₁% pred. r = -0.127, p = 0.035. y = -0.006 x + 1.368.

Interpretation of FEV₁, AFEV₁, (AFEV₁, % of LL, V₀), -200 to 200. 100 to +x -x'

Discussion

This study shows that expressing a bronchodilator response as a percentage of the initial FEV₁ is more dependent on initial FEV₁ 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 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 ΔAFEV₁ %init because they assume that the clinical relevance of a bronchodilator response is reflected by expressing it as an increase in FEV₁ relative to the initial value, 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 ΔAFEV₁ %init clinically is that spuriously suggests that patients with a low initial FEV₁ are more responsive to bronchodilator drugs.

The pronounced dependence of ΔAFEV₁ %init on initial FEV₁ (fig 1) has important drawbacks for research. If a certain level of ΔAFEV₁ %init is used as an inclusion criterion in clinical studies, as is commonly the case, patients with a low initial FEV₁ will be selected preferentially. 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 FEV₁ is related to an unfavourable prognosis in chronic obstructive lung disease and in these patients ΔAFEV₁ %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 ΔAFEV₁ %init is usually not associated with a better outcome in chronic obstructive lung disease. In studies where initial FEV₁ was corrected for or where ΔAFEV₁ % [pred - init] was used 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 ΔAFEV₁ % [pred - init], an index of the capacity to respond, has little dependence on initial FEV₁. This expression gives progressively higher results with higher initial FEV₁ 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 FEV₁ levels can then be compared. Because spontaneous changes in FEV₁ appear to be unrelated to the

Figure 5. Relation of ΔAFEV₁ expressed as a percentage of achievable response (ΔAFEV₁ % of [pred - init]), to initial FEV₁ % pred.
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>( \Delta \text{FEV,} % \text{init} )</td>
<td>15 (^{\text{I}})</td>
<td>156</td>
<td>0.687</td>
<td>0.529</td>
<td>1.459</td>
</tr>
<tr>
<td>( \Delta \text{FEV,} % \text{init} )</td>
<td>0.200 (^{\text{II}})</td>
<td>210</td>
<td>0.879</td>
<td>0.353</td>
<td>1.359</td>
</tr>
<tr>
<td>( \Delta \text{FEV,} % \text{init} )</td>
<td>&gt; 15 (^{\text{III}})</td>
<td>155</td>
<td>0.687</td>
<td>0.549</td>
<td>1.523</td>
</tr>
<tr>
<td>( \Delta \text{AFEV,} % \text{init} )</td>
<td>&gt; 0.2 (^{\text{IV}})</td>
<td>165</td>
<td>0.737</td>
<td>0.569</td>
<td>1.710</td>
</tr>
<tr>
<td>( \Delta \text{SR-} \text{FEV,} )</td>
<td>0.5 (^{\text{V}})</td>
<td>188</td>
<td>0.408</td>
<td>0.451</td>
<td>1.472</td>
</tr>
<tr>
<td>( \text{FEV,} % \text{pred} )</td>
<td>80 (^{\text{VI}})</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>( \Delta \text{FEV,} % \text{init} )</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>( \Delta \text{AFEV,} % \text{init} )</td>
<td>2.56 (0.79)</td>
<td>1.85 (1.72)</td>
<td>1.48 (1.99)</td>
<td>1.99 (2.84)</td>
<td>5.89</td>
<td>0.001</td>
</tr>
<tr>
<td>( \Delta \text{SR-} \text{FEV,} )</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>9.03</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>( \text{FEV,} % \text{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>( \text{FEV,} % \text{pred} )</td>
<td>79.02 (1.62)</td>
<td>75.95 (1.75)</td>
<td>66.95 (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 \( \Delta \text{FEV,} \) is related to the predicted \( \text{FEV,} \), the choice lies between \( \Delta \text{FEV,} \% \text{pred} \) and \( \Delta \text{SR-} \text{FEV,} \). 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 \( \text{FEV,} \) 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 of 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 PC<sub>20</sub> 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 ml or 8-55% of predicted have been derived. Our results (235 ml and 6-04%) 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 postbronchodilator 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 prebronchodilator or postbronchodilator 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. 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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