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 FEV_1.**

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. FEV_1 was measured before and 20 minutes after inhalation of 1000 μg terbutaline. Different expressions of bronchodilator response (ΔFEV_1) were compared with respect to their dependence on initial FEV_1 and their efficacy in separating subjects with asthma from those with chronic obstructive lung disease. ΔFEV_1 was expressed as a percentage of initial FEV_1 (ΔFEV_1%init), absolute value (ΔFEV_1[l]), percentage of predicted FEV_1 (ΔFEV_1%pred), standardised residual (ΔSR-FEV_1), and percentage of maximal possible increase (ΔFEV_1%[pred−init]).**

Results **ΔFEV_1%init was more dependent on initial FEV_1 ($\rho = -0{\cdot}405$) than ΔFEV_1[l] ($r = -0{\cdot}145$), ΔFEV_1%pred ($r = -0{\cdot}166$), and ΔSR-FEV_1 ($r = -0{\cdot}127$). ΔFEV_1%[pred−init] reached infinity when initial FEV_1 approached predicted levels. ΔFEV_1%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-FEV_1 ($F = 9{\cdot}19$) and ΔFEV_1%pred ($F = 9{\cdot}03$); it was much smaller for ΔFEV_1%init ($F = 5{\cdot}89$). 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 **ΔFEV_1%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.[1 2] 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.[3–5] The mode of expression may depend on the reason why the test is performed.[3] There is also no consensus on what constitutes a "positive" response.[3–5] 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 (FEV_1) of more than 15% of the initial level is commonly considered to signify a "positive" bronchodilator response,[1] although

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several studies have reported that this criterion provides poor discrimination between patients with asthma and those with chronic obstructive lung disease[6-8]; it also increases the response in patients with a low initial FEV_1.[6 9-13] This dependence of bronchodilator response on initial FEV_1 may be undesirable, especially when responses of patients with different initial FEV_1 levels are being compared.[14]

Although several expressions of bronchodilator response have been discussed from a theoretical point of view in some detail,[5 11 15] few comparative clinical studies have been carried out. Most studies have been confined to patients with chronic obstructive lung disease[7 13 14 16]; 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 FEV_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.[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_1 level greater than 1·2 litres and 1·64–4·5 residual standard deviations (RSD) below the predicted value, *or* if their FEV_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.[20] Another selection criterion was hyperresponsiveness to inhaled histamine (the provocative concentration of histamine causing a 20% decrease in FEV_1 (PC_{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 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[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.[20] FEV_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.[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 PC_{20} histamine.

ASSESSMENT OF BRONCHODILATOR RESPONSE

FEV_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_1

In a subgroup of 45 patients from one centre spontaneous changes in FEV_1 were assessed. Spirometric values before bronchodilatation were determined twice in these subjects with an

Table 1 Characteristics of the patients

	Mean (SD)		
			Median (range)
Height (cm)	174 (10·0)	Age (years)	40 (18 to 60)
FEV_1			
Litres	2·33 (0·74)	Smoking (pack years)	4·5 (0 to 123)
% predicted	63·7 (15·3)	ΔFEV_1% init	18 (−14 to 78)
FEV_1/IVC %	55·3 (11·0)		
% predicted	68·5 (13·2)		
		Smoking	*Number (%)*
Bronchodilator response		Current smoker	98 (35·7)
ΔFEV_1[1]	0·44 (0·33)	Ex-smoker	88 (32·1)
ΔFEV_1%predicted	11·9 (8·9)	Never smoker	88 (32·1)
ΔSR-FEV_1	0·97 (0·75)	Male	176 (64·2)
PC_{20} (mg/ml)		*Diagnosis*	
^{2}log	−1·95 (2·30)	Asthma	99 (36·1)
Geometric mean (with 1 SD)	0·28 (0·05, 1·27)	Asthmatic bronchitis	88 (32·1)
		Chronic obstructive lung disease	51 (18·6)
		No conclusive diagnosis	36 (13·1)

FEV_1—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_1.

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

EXPRESSION OF FEV_1 AND BRONCHODILATOR RESPONSE

Initial FEV_1 and postbronchodilator FEV_1 (FEV_1pb) were expressed as percentages of predicted normal values (FEV_1%pred and FEV_1pb%pred, respectively). Standardised residuals (SR) of prebronchodilator and postbronchodilator FEV_1 were computed by subtracting the patient's FEV_1 from the predicted FEV_1 and dividing this difference by the residual standard deviation (RSD) of the FEV_1 reference formula.[20] The SR indicates how many RSDs a patient's FEV_1 is away from the predicted FEV_1.[21]

Bronchodilator responses to terbutaline were expressed in five ways:

as a percentage of initial (prebronchodilator) FEV_1 (ΔFEV_1%init)

as absolute values in litres (ΔFEV_1[1]

as a percentage of the predicted normal FEV_1 (ΔFEV_1%pred)

as a percentage of the achievable reversibility, i.e. the difference between predicted and initial FEV_1 (ΔFEV_1%[pred − init]

as standardised residuals, i.e. the difference between the SRs of the post- and prebronchodilator FEV_1s (ΔSR-FEV_1).

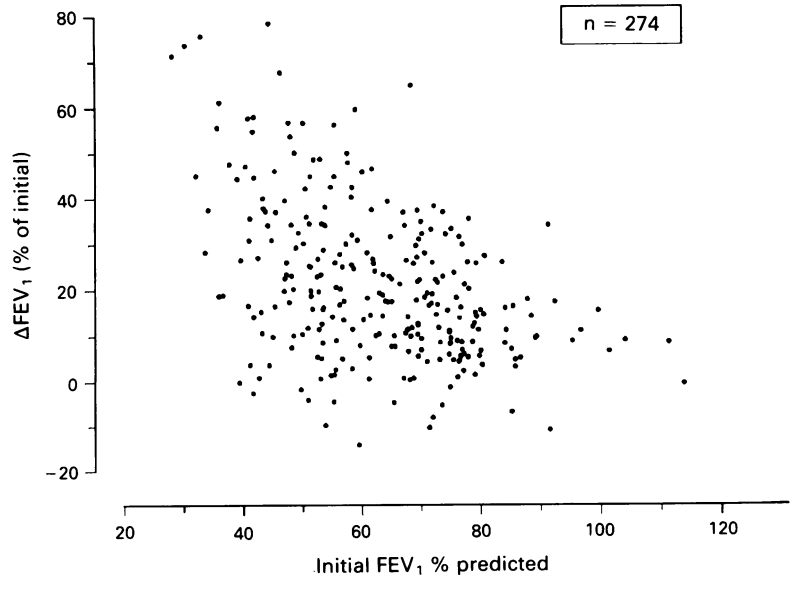

Figure 1 Relation of ΔFEV_1, expressed as a percentage of the initial FEV_1 (ΔFEV_1%init) to initial FEV_1%pred. $\rho = -0{\cdot}405$, $p < 0{\cdot}001$.

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.[19] 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.[22] 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.[23] All analyses were performed with the SPSS/PC+ package.

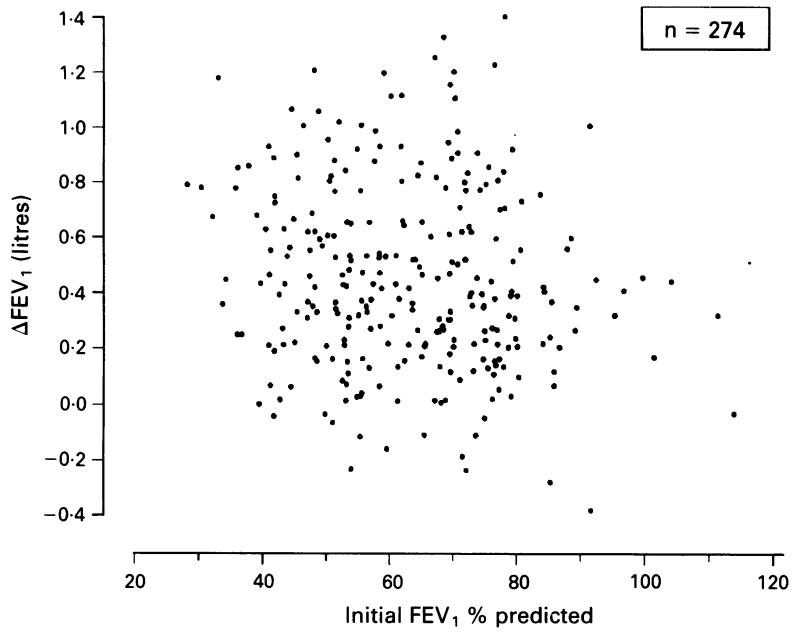

Figure 2 Relation of ΔFEV_1, expressed as absolute values ($\Delta FEV_1[l]$), to initial FEV_1%pred. $r = -0{\cdot}145$, $p = 0{\cdot}017$. $y = -0{\cdot}003x + 0{\cdot}639$.

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, $p < 0{\cdot}01$). The distributions of FEV_1%pred and FEV_1pb%pred were normal ($p = 0{\cdot}74$ and 0·86). ΔFEV_1%init showed a positively skewed distribution (that is, with a long tail to the right) ($p = 0{\cdot}03$), as did ΔFEV_1%(pred − init) to a much stronger extent ($p < 0{\cdot}01$). The distributions of $\Delta FEV_1[l]$ ($p = 0{\cdot}09$) and ΔSR-FEV_1 ($p = 0{\cdot}05$) were only slightly skewed to the left, whereas ΔFEV_1%pred had a normal distribution ($p = 0{\cdot}56$). All distributions were continuous and unimodal.

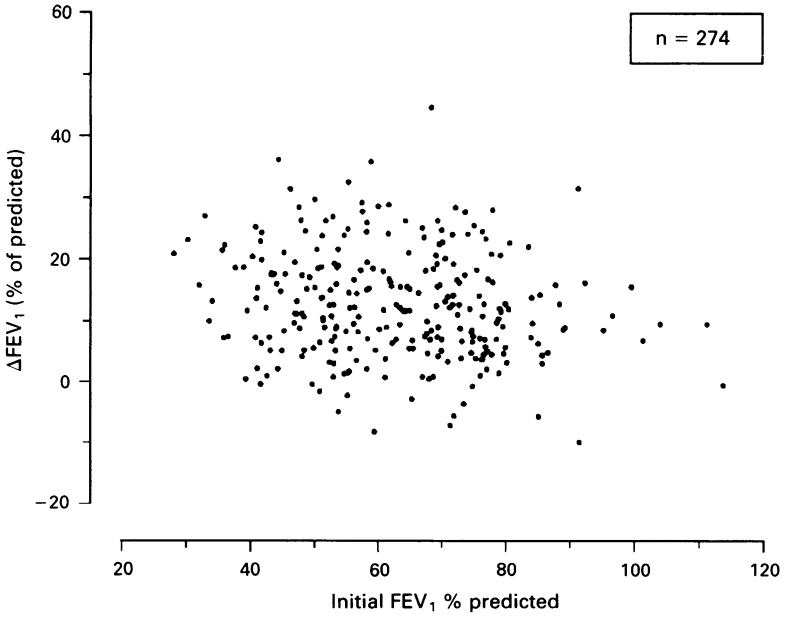

Figure 3 Relation of ΔFEV_1, expressed as a percentage of the predicted FEV_1 (ΔFEV_1%pred), to initial FEV_1%pred. $r = -0{\cdot}166$, $p = 0{\cdot}006$. $y = -0{\cdot}096x + 18{\cdot}101$.

RELATION OF BRONCHODILATOR RESPONSE TO INITIAL FEV_1%PRED

The relation between ΔFEV_1%init and initial FEV_1%pred is plotted in figure 1. Values for ΔFEV_1%init increased substantially when initial FEV_1%pred was low, causing a highly significant negative correlation ($\rho = -0{\cdot}405$, $p < 0{\cdot}001$). The relation between $\Delta FEV_1[l]$ and initial FEV_1%pred did not show a substantial increase at low initial FEV_1%pred (fig 2); the results show a wide scatter with a small, but significant, negative correlation ($r = -0{\cdot}145$, $p = 0{\cdot}017$). A similar relationship was found between initial FEV_1%pred and both ΔFEV_1%pred (fig 3, $r = -0{\cdot}166$, $p = 0{\cdot}006$) and ΔSR-FEV_1 (fig 4, $r = -0{\cdot}127$, $p = -0{\cdot}127$, $p = 0{\cdot}035$). ΔFEV_1%(pred − init) showed values reaching infinity when initial FEV_1 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 ΔFEV_1%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 ΔFEV_1%[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-FEV_1, ΔFEV_1%pred, and $\Delta FEV_1[l]$, and less clear for ΔFEV_1%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 ΔFEV_1%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 FEV_1

The 45 patients in whom spontaneous changes in FEV_1 were assessed were somewhat younger (U test, $p = 0{\cdot}046$) amd taller (t test, $p = 0{\cdot}026$), and had less severe airways hyperresponsive-

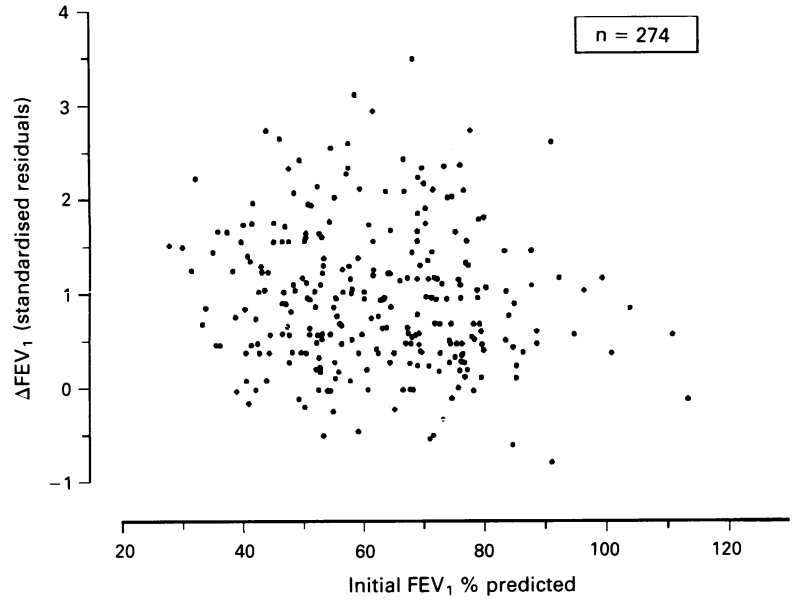

Figure 4 Relation of ΔFEV_1, expressed as standardised residuals ($\Delta SR\text{-}FEV_1$), to initial FEV_1%pred. $r = -0{\cdot}127$, $p = 0{\cdot}035$. $y = -0{\cdot}006\,x + 1{\cdot}368$.

ness (p=0·002) than the rest of the study population. Initial FEV_1%pred was similar in the two groups (p=0·090), as were FEV_1/IVC, the sex distribution, and smoking habits. The median spontaneous change in FEV_1 over 20 minutes was zero. Spontaneous changes in FEV_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_1 were not related significantly to age, sex, smoking habits, PC_{20} level, or the bronchodilator response to terbutaline, expressed in any way (all p values >0·2). The spontaneous change in FEV_1 was also unrelated to initial FEV_1%pred (p=0·602).

Discussion

This study shows that expressing a bronchodilator response as a percentage of the initial FEV_1 is more dependent on initial FEV_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[7 13 14 16] or relatively small groups of patients with unstandardised treatment[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 ΔFEV_1%init because they assume that the clinical relevance of a bronchodilator response is reflected by expressing it as an increase in FEV_1 relative to the initial value,[24] 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 ΔFEV_1%init clinically is that spuriously suggests that patients with a low initial FEV_1 are more responsive to bronchodilator drugs.[6 9–13]

The pronounced dependence of ΔFEV_1% init on initial FEV_1 (fig 1) has important drawbacks for research. If a certain level of ΔFEV_1%init is used as an inclusion criterion in clinical studies, as is commonly the case, patients with a low initial FEV_1 will be selected preferentially.[5 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_1 is related to an unfavourable prognosis in chronic obstructive lung disease,[25–27] and in these patients ΔFEV_1%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 ΔFEV_1% init is usually not associated with a better outcome in chronic obstructive lung disease.[28–30] In studies where initial FEV_1 was corrected for[27] or where ΔFEV_1%[pred−init] was used[13 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 ΔFEV_1%[pred − init], an index of the capacity to respond, has little dependence on initial FEV_1. This expression gives progressively higher results with higher initial FEV_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_1 levels can then be compared.[5 6 14] Because spontaneous changes in FEV_1 appear to be unrelated to the

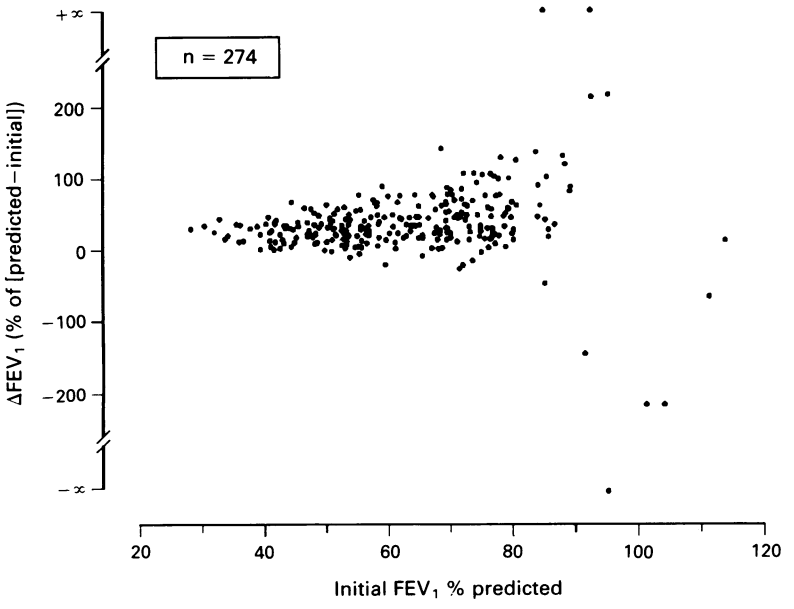

Figure 5 Relation of ΔFEV_1, expressed as a percentage of achievable response (ΔFEV_1%[pred − init]), to initial FEV_1%pred.

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

Expression	Cut off level and reference	Number of "positive" responders	Sensitivity	Specificity	Likelihood ratio
ΔFEV_1 % init	15[1]	156	0·687	0·529	1·459
ΔFEV_1[l]	0·200[18 31]	210	0·879	0·353	1·359
ΔFEV_1 % init and ΔFEV_1[l]	>15 > 0·2[24]	155	0·687	0·549	1·523
ΔFEV_1 % pred	9[32]	165	0·737	0·569	1·710
ΔSR-FEV_1	0·5	188	0·808	0·451	1·472
FEV_1 pb % pred	80[25]	112	0·455	0·686	1·449

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

Expression	Mean (SE) response: Asthma	Asthmatic bronchitis	Chronic obstructive lung disease	No conclusive diagnosis	F*	p
ΔFEV_1 [l]	0·55 (0·04)	0·41 (0·03)	0·28 (0·03)	0·42 (0·05)	8·82	<0·001
ΔFEV_1 % init	25·86 (1·79)	18·57 (1·72)	14·87 (1·99)	19·39 (2·84)	5·89	0·001
ΔFEV_1 % pred	15·18 (0·93)	10·84 (0·86)	7·97 (1·00)	11·73 (1·51)	9·03	<0·001
ΔSR-FEV_1	1·24 (0·08)	0·88 (0·07)	0·61 (0·08)	0·96 (0·13)	9·19	<0·001
FEV_1 % pred	63·84 (2·08)	65·11 (1·71)	60·98 (2·34)	63·92 (2·08)	0·79	0·504
FEV_1 pb % pred	79·02 (1·62)	75·95 (1·75)	68·95 (2·31)	75·65 (2·45)	4·406	0·005

*From analysis of variance.

initial value,[18 31] as in this study, the bronchodilator response expressed in absolute terms (ΔFEV_1[l]) can adequately distinguish a true bronchodilator response from chance variation in FEV_1.[3 18 31] These values are not corrected, however, for determinants of lung size, such as age, height, and sex. Such correction may be achieved by relating change in absolute FEV_1 to the predicted FEV_1.[11 13 32]

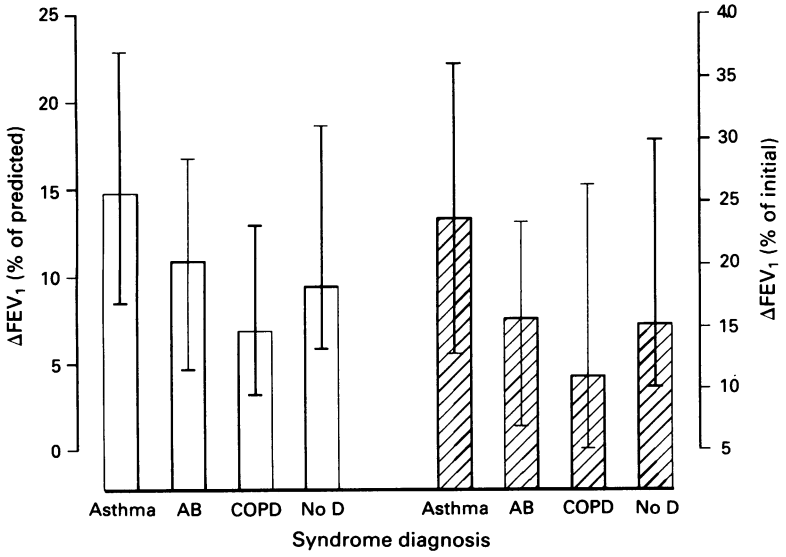

Figure 6 Medians (bars) and interquartile (50%) ranges (error bars) of ΔFEV_1 as a percentage of the predicted FEV_1 (ΔFEV_1%pred, open bars) and as a percentage of the initial FEV_1 (ΔFEV_1%init, hatched bars) in subgroups of patients with different syndromes. AB—asthmatic bronchitis; COPD—chronic obstructive lung disease; No D—no conclusive diagnosis. Despite significant differences, there is considerable overlap between subgroups in the bronchodilator responses of individual patients, which is larger for ΔFEV_1%init than for ΔFEV_1%pred.

When ΔFEV_1 is related to the predicted FEV_1, the choice lies between ΔFEV_1%pred and ΔSR-FEV_1. The use of % predicted values has been criticised as it leaves "hidden bias in the data"[21]; the use of standardised residuals is a more appropriate statistical technique.[21] The % predicted method has been shown to be at least as useful as the SR method in identifying obstructive airways disease epidemiologically, however,[33] 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 FEV_1 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.[9 34] 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.[9 34] In contrast, our inclusion criteria were of a functional nature (age, airway calibre, and PC_{20} 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.[17] The distribution of bronchodilator responses, both in clinical studies such as ours[6 35] and in samples of healthy individuals,[32 36] is continuous and unimodal. Thus any attempt at achieving a cut off level for a "positive" response is arbitrary.[37] 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 FEV_1 have been proposed,[32 36] which were dependent on age, height, and sex.[32] When expressed as ΔFEV_1% pred, a cut off value of 9% was derived, which was much more stable between age-height-sex subgroups.[32] An alternative approach is to study short term spontaneous or placebo induced changes in FEV_1 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[18 31 35] or 8·55% of predicted[35] 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 FEV_1 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 FEV_1 follows from the fact that ΔFEV_1%pred is the difference between initial and postbronchodilator FEV_1%pred, both of which are important outcome predictors in obstructive airways disease.[16 25–27] Knowledge of ΔFEV_1%pred with initial FEV_1%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 ΔFEV_1% 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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