

# Variability of bronchodilator response and effects of inhaled corticosteroid treatment in obstructive airways disease

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## Abstract

**Background**—In the day to day care of obstructive airways diseases (asthma and chronic obstructive pulmonary disease) important decisions such as disease classification and choice of therapy are based on assessment of the bronchodilator response. However, surprisingly little is known of the long term course of the bronchodilator response in patients with obstructive airways disease.

**Methods**—Data from a multicentre trial were used in which 274 patients aged 18–60 years with airways obstruction were selected with  $PC_{20} < 8$  mg/ml and  $FEV_1 < 95\%$  CI of predicted.  $FEV_1$  was measured before and 20 minutes after 1000  $\mu$ g terbutaline and 40 minutes after an additional 80  $\mu$ g ipratropium bromide. Data were analysed from 185 patients who were followed up for 21 months (five measurements). Four different expressions of bronchodilator response (BDR) were examined for change under long term therapy, long term variability, and prognostic value in predicting response to inhaled corticosteroids.

**Results**—There was a significant reduction in BDR of 117 ml after three months of treatment with a  $\beta_2$  agonist plus a corticosteroid (BA + CS), but not after bronchodilators only. Significant reductions with BA + CS were also found in BDR as a percentage of initial  $FEV_1$ , and in BDR as a percentage of predicted  $FEV_1$ . Bronchodilator tests were quite variable (SD 186 ml or 11% of initial value) and less than half of the patients could consistently be classified as “irreversible” with recommended cutoff levels. The bronchodilator response at the start of the study proved to be a poor predictor of improvement in  $FEV_1$  under BA + CS treatment (correct prediction 60%).

**Conclusions**—Bronchodilator responses decrease substantially with inhaled corticosteroid therapy, and within subject variability is considerable both in asthma and chronic obstructive pulmonary disease. Dichotomous decisions on whether patients are “irreversible” according to any single bronchodilator measurement should therefore be made with great caution. The bronchodilator response can-

not be used accurately as a predictor of response to inhaled corticosteroids in obstructive airways disease.

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Assessment of bronchodilator response (BDR) in patients with obstructive airways disease is a routine procedure both in clinical practice and research. The results of the test are used to separate patients with asthma both from normal subjects and from those with chronic obstructive pulmonary disease (COPD) and to make therapeutic decisions.<sup>1</sup> There are, however, numerous problems associated with bronchodilator testing.

The interpretation of any test requires knowledge about its variability. Although data are available for patients with COPD,<sup>2</sup> no such data exist on the variability of bronchodilator testing in patients with asthma. In addition there is no consensus on how to express the BDR. The most commonly used expression—the response as a percentage of the initial value—has the disadvantage that the response is highly dependent on the initial (baseline) value.<sup>3-5</sup> There is also no consensus on what constitutes a “significant” BDR.<sup>2-7</sup> The American Thoracic Society has recently issued new guidelines recommending that a “significant” BDR should be both larger than a 12% increase over baseline and larger than 200 ml.<sup>8</sup> To our knowledge, no published data exist to support this recommendation. Finally, the use of the BDR for therapeutic decisions has been studied in patients with COPD where a larger BDR predicted, to some extent, a larger improvement with oral corticosteroids,<sup>9-11</sup> but whether a higher BDR predicts a more favourable reaction to inhaled corticosteroid therapy in obstructive airways disease is unknown.

We have studied the BDR prospectively in a large group of patients with obstructive airways disease (asthma and COPD) and a broad range of clinical presentations and lung function. They were randomly allocated to one of three different treatment regimens (inhalation of a single bronchodilator, two bronchodilators, or a bronchodilator and a corticosteroid), and followed up for 2-5 years.<sup>12,13</sup> In this report we specifically address the following questions:

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1. Is the degree of BDR affected by maintenance treatment with inhaled bronchodilators, or corticosteroids, or both? How large is the long term variability of bronchodilator tests? Does a significant treatment effect or a high variability, or both, have consequences for classification of disease as irreversible on the basis of a single measurement?
2. Does a greater response to bronchodilators predict an improvement in airways obstruction during long term maintenance therapy with inhaled corticosteroids (immediate *v* long term reversibility)?

### Methods

Patients aged 18–60 years with respiratory symptoms and no other major illnesses<sup>12</sup> were selected from the respiratory outpatient departments according to the following criteria: (1) Forced expired volume in one second (FEV<sub>1</sub>) ranging between 4.5 and 1.64 residual standard deviations (RSD) below the predicted value—that is, 2.30–0.84 l below predicted FEV<sub>1</sub> for men or 1.71–0.62 l below predicted FEV<sub>1</sub> for women—or FEV<sub>1</sub>/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 l, woman 0.98 l) below the predicted level). The rationale of using RSDs and predicted values has been detailed elsewhere.<sup>14,15</sup> FEV<sub>1</sub> had to be larger than 1.2 l. (2) Concentration of histamine causing a 20% fall in FEV<sub>1</sub> (PC<sub>20</sub>) < 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 (ketotifen, antihistamines), four weeks (cromolyn sodium), or 48 hours (theophyllines) before the start of the study. Maintenance medication with oral steroids was not allowed. Patients were randomly allocated to one of three double blind regimens using identical metered dose inhalers: all patients received an inhaled  $\beta_2$  agonist (terbutaline 250  $\mu$ g, two puffs four times daily) combined with either an inhaled corticosteroid (beclomethasone 100  $\mu$ g, two puffs four times daily (BA + CS)), an inhaled anticholinergic (ipratropium bromide 20  $\mu$ g, two puffs four times daily (BA + AC)), or an inhaled placebo, two puffs four times daily (BA + PL). Additional bronchodilator medication was supplied as salbutamol dry powder inhalations (400  $\mu$ g) on demand. During exacerbations a 12 day course of oral prednisolone was administered.<sup>12</sup> The primary criterion for physician initiated withdrawal was the need for more than two courses of prednisolone over a three month period or more than four courses over a year.<sup>13</sup>

At alternate three month visits BDR and PC<sub>20</sub> histamine were assessed. FEV<sub>1</sub> and PC<sub>20</sub> were measured only during clinically stable periods and not within four weeks of termina-

tion of a course of prednisolone. Eight hours before these tests all study medication was discontinued. FEV<sub>1</sub> was measured with calibrated water sealed spirometers according to standardisation guidelines.<sup>14</sup> At least three reproducible (less than 5% difference) recordings were obtained and the highest value was then used for analyses. Histamine provocation tests were performed with a two minute tidal breathing method.<sup>12,16</sup>

### ASSESSMENT OF BDR

BDRs were measured as the change in FEV<sub>1</sub> before and 20 minutes after four separate inhalations of 250  $\mu$ g 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 coffee, tea, and smoking between measurements. Results are expressed in four different ways: (1) absolute response in millilitres (BDR[ml]); (2) percentage of initial (prebronchodilator) FEV<sub>1</sub> (BDR%init); (3) percentage of the predicted normal FEV<sub>1</sub> (BDR%pred); (4) difference between the standardised residuals (SR) of the FEV<sub>1</sub> values before and after use of a bronchodilator (BDR-SR). An SR is obtained by subtracting a patient's FEV<sub>1</sub> from the predicted FEV<sub>1</sub> and dividing this difference by the RSD of the predicted FEV<sub>1</sub>.<sup>14</sup> An SR therefore indicates how many RSDs a patient's FEV<sub>1</sub> is away from the predicted FEV<sub>1</sub>.<sup>15</sup>

Immediately after the BDR measurement with terbutaline, four single inhalations of 20  $\mu$ g ipratropium were administered and 40 minutes later the FEV<sub>1</sub> was assessed again.

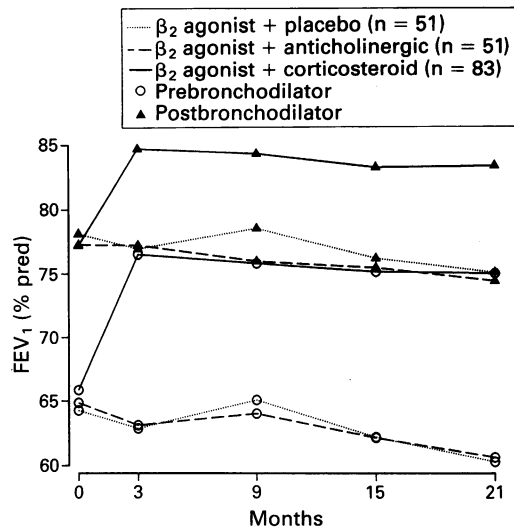
### DIAGNOSTIC CLASSIFICATION

Using data from a standardised questionnaire we identified different syndromes, adhering to the criteria of the American Thoracic Society.<sup>1</sup> 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 COPD group. 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.<sup>12</sup>

### DATA ANALYSIS

Analyses of PC<sub>20</sub> values were performed with the base-2 logarithm as this reflects doubling concentrations. In the analyses 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 mg/ml, being half the lowest concentration applied.<sup>12</sup> Means (SE) are presented unless otherwise

Figure 1 Prebronchodilator and postbronchodilator percentage predicted FEV<sub>1</sub> values for patients with a follow up of at least 21 months. FEV<sub>1</sub> values are corrected for sex, height, and age at every time point.<sup>14</sup>



stated. Statistical methods used included *t* tests and one way analysis of variance (ANOVA) to compare group means,  $\chi^2$  tests for differences in proportions, and Wilcoxon signed rank test for non-parametric testing of distribution.<sup>17</sup> To study variability, within subject standard deviations were calculated<sup>18</sup> as well as intraclass correlation coefficients (ICC: between subject variance/total variance); ICC ranges between 0 and 1. An ICC of 1 signifies the ideal situation where all vari-

ation in results is due to differences between subjects and a value of 0 denotes that all variation is due to within subject variation alone (biological + measurement error).<sup>18</sup> Linear regression analysis was employed to study the relationship between variables over time for the group as a whole, and within subject Spearman rank correlation coefficients (*p*) for within subject relations over time. The rate of change of FEV<sub>1</sub> and BDR over 21 months and the associated standard deviations were calculated for each patient by least squares linear regression. Analyses were performed using the SPSS/PC + package.<sup>19</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 published elsewhere.<sup>13</sup> Briefly, 12 of 91 patients on BA + CS were withdrawn, compared with 44 of 91 on BA + PL and 45 of 92 on BA + AC, *p* < 0.0001; 70% of withdrawals were due to increases in pulmonary symptoms.<sup>13</sup> Mean (SE) prebronchodilator FEV<sub>1</sub> improved by 374 (51) ml in patients receiving BA + CS in the first three months and remained stable afterwards, while no increases in FEV<sub>1</sub> were detected in the BA + AC and BA + PL groups (fig 1). These group differences remained significant at all follow up visits (*p* < 0.001). Over the 2.5 years of follow up, PC<sub>20</sub> improved on average by 2.0 doubling concentrations in the BA + CS group compared with no change in the other two groups (*p* < 0.001). No significant differences were detected between the BA + AC and BA + PL group in terms of changes in prebronchodilator and postbronchodilator FEV<sub>1</sub>, PC<sub>20</sub>, and exacerbation rates.<sup>13</sup>

As the current analyses were focused on long term variability in BDR and effects of inhaled corticosteroid treatment we only analysed data of those patients who had a follow up of at least 21 months (five measurements). Withdrawals (those not reaching 21 months of follow up) had slightly lower baseline prebronchodilator FEV<sub>1</sub>%pred than non-withdrawals (60.8% (1.5%) *v* 65.1% (1.2%), *p* < 0.05), lower postbronchodilator FEV<sub>1</sub>%pred (72.1% (1.7%) *v* 77.5% (1.2%), *p* < 0.01), and lower log<sub>2</sub> PC<sub>20</sub> (-2.44 (2.3) *v* -1.71 (2.3), *p* < 0.05). There were no significant differences at baseline between withdrawals and non-withdrawals in BDR (*p* > 0.15 for all four expressions). Baseline characteristics for the 185 patients with a follow up of at least 21 months are shown in table 1.

CHANGE IN BDR DURING TREATMENT

In fig 2A-D time courses are shown of the BDR expressed in four different ways. After three months the BDR[ml] had decreased in the BA + CS group by 117 (38) ml compared with an increase of 11 (39) ml in the BA + PL group (*p* < 0.05). This mean difference of 127 ml remained approximately

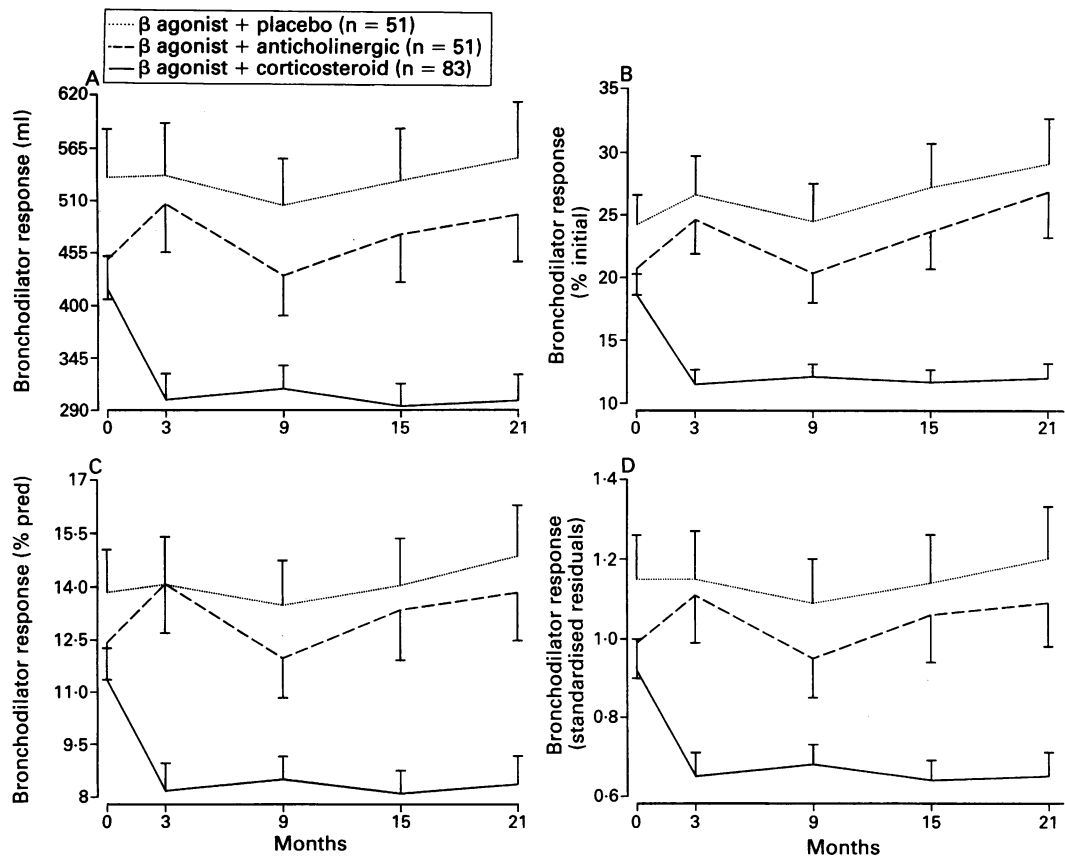
Table 1 Mean (SD) baseline characteristics by treatment group

	Treatment group		
	BA + PL	BA + AC	BA + CS
n	51	51	83
No. men	36 (71%)	34 (67%)	55 (66%)
Age (y)	37.9 (11.2)	41.2 (13.5)	40.1 (12.4)
FEV <sub>1</sub> prebronchodilation			
litres	2.40 (0.77)	2.37 (0.78)	2.45 (0.77)
% predicted	64.3 (17.5)	64.9 (15.2)	65.8 (15.0)
number of RSD below predicted	2.84 (1.42)	2.70 (1.15)	2.70 (1.22)
FEV <sub>1</sub> postbronchodilation (terbutaline)			
litres	2.93 (0.89)	2.82 (0.85)	2.86 (0.86)
% predicted	78.1 (17.7)	77.3 (16.1)	77.2 (16.1)
Bronchodilator response (terbutaline)			
BDR[ml]	535 (357)	448 (296)	417 (314)
BDR%init	24.2 (17.0)	20.7 (14.9)	18.6 (15.3)
BDR%pred	13.9 (8.5)	12.4 (7.6)	11.4 (8.2)
BDR-SR	1.15 (0.78)	0.99 (0.67)	0.92 (0.69)
FEV <sub>1</sub> postbronchodilation (terbutaline + ipratropium)			
% predicted	83.6 (16.9)	81.4 (16.0)	82.8 (15.4)
Histamine challenge			
log <sub>2</sub> PC <sub>20</sub> histamine (mg/ml)	-2.06 (2.33)	-1.57 (2.33)	-1.60 (2.20)
Geometric mean PC <sub>20</sub> (mg/ml)	0.24	0.34	0.33
Allergy	33 (65%)	26 (51%)	50 (60%)
Smoking			
never	18 (35%)	16 (31%)	27 (33%)
ex-smoker	15 (29%)	15 (29%)	27 (33%)
current	18 (35%)	20 (39%)	29 (35%)
Symptom based diagnosis groups			
asthma	21 (41%)	22 (43%)	32 (39%)
asthmatic bronchitis	16 (31%)	21 (41%)	28 (34%)
COPD	14 (28%)	8 (16%)	18 (22%)
undefined diagnosis	0 (0%)	0 (0%)	5 (6%)

BA + PL— $\beta_2$  agonist plus placebo; BA + AC— $\beta_2$  agonist plus anticholinergic; BA + CS— $\beta_2$  agonist plus corticosteroid; RSD—residual standard deviation: a larger figure denotes more abnormality; BDR[ml]—bronchodilator response expressed as absolute response in ml; BDR%init—bronchodilator response expressed as a percentage of initial (prebronchodilator) FEV<sub>1</sub>; BDR%pred—bronchodilator response expressed as a percentage of the predicted normal FEV<sub>1</sub>; BDR-SR—bronchodilator response expressed as the difference between the standardised residuals of the postbronchodilator and prebronchodilator FEV<sub>1</sub>.



Figure 2A–D Mean (SE) bronchodilator response expressed in four different ways (see text).



stable afterwards (fig 2A). In the BA + PL and BA + AC groups there were no significant changes in BDR[ml] from baseline to any of the follow up visits; the slopes of the BDR in the BA + AC and BA + PL groups were not significantly different from zero (mean slope expressed as  $\Delta$ BDR[ml]/year of +12 (19) and +13 (19) in the BA + PL and BA + AC groups respectively, fig 2A).

Similarly, when expressed as BDR%init, BDR%pred, and BDR-SR, the BDR dropped markedly in the first three months of corticosteroid treatment to remain stable afterwards (decrease in BDR%init:  $-7.1$  (1.8)  $p < 0.005$  compared with BA + PL, fig 2B), BDR%pred:  $-3.2$  (1.0),  $p < 0.01$ , fig 2C, BDR-SR:  $-0.27$  (0.08),  $p < 0.01$ , fig 2D). In the BA + AC and BA + PL groups there were no significant changes from baseline over time with any of the BDR expressions, nor were the slopes of the changes over time significantly different from zero.

The decrease in BDR in three months in the BA + CS group was correlated to the increase in prebronchodilator  $FEV_1$ %pred in three months, more strongly so when expressed as BDR%init ( $r = -0.65$ ) than as BDR[ml] ( $-0.52$ ), BDR%pred ( $-0.51$ ), or BDR-SR ( $-0.51$ ), all  $p < 0.001$ .

To determine to what degree the decrease in BDR in the BA + CS treated group was caused by the  $FEV_1$  reaching normal levels the data were recalculated for a subgroup of 49 patients whose  $FEV_1$  value after terbutaline remained more than 1.64 RSD below the predicted value after three months of treatment—that is, whose post-terbutaline  $FEV_1$  remained abnormal. The decrease in BDR[ml] in the first three months diminished to  $-61$  (39) ml ( $p > 0.1$ ), the decrease in BDR%init to  $-5.0\%$  (2.1%) ( $p < 0.05$ ), BDR%pred to  $-2.0\%$  (1.1%) ( $p > 0.05$ ), and BDR-SR to  $-0.16$  (0.1) ( $p > 0.05$ ).

Additional administration of 80  $\mu$ g of ipratropium bromide immediately after terbutaline (1000  $\mu$ g) gave a mean additional dilatation of 197 (30) ml before and 200 (24)

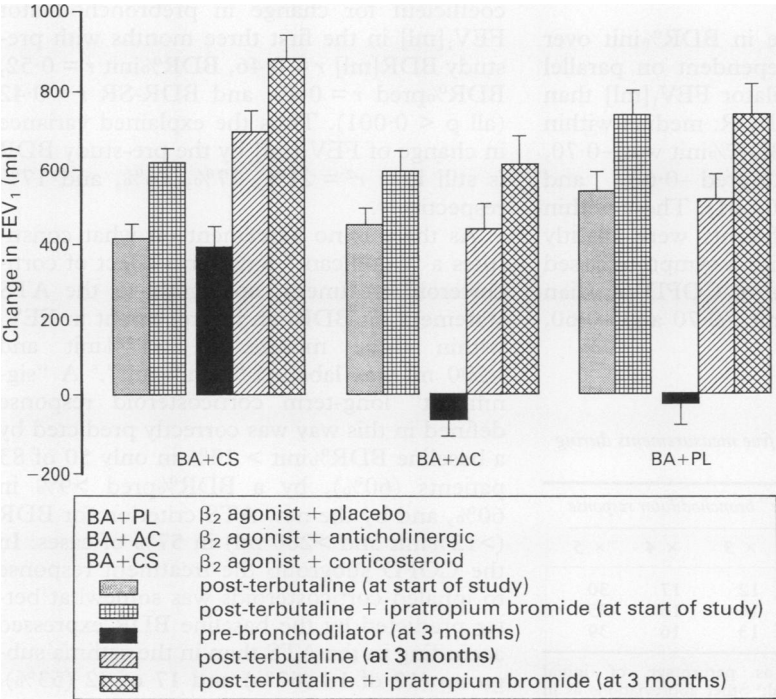


Figure 3 Mean (SE) change in  $FEV_1$  (ml) from baseline prebronchodilator  $FEV_1$ .

Table 2 Intraclass correlation coefficients (ICC) \* and within subject standard deviations (SD) \* according to treatment and diagnosis groups

	Total group		BA + PL (SD)	BA + AC (SD)	BA + CS (SD)	Asthma† (SD)	AB† (SD)	COPD† (SD)
	ICC	SD						
BDR[ml]	0.76	186	195	184	182	193	169	195
BDR%init	0.76	10.7	13.4	11.7	7.9	11.8	10.3	9.1
BDR%pred	0.74	5.1	5.2	5.0	5.3	5.1	4.6	5.9
BDR-SR	0.77	0.41	0.43	0.40	0.39	0.43	0.37	0.41

\*ICC and SD are calculated for measurements under double blind treatment, i.e. without the baseline visit (see methods section); †five of 185 patients had an undefined diagnosis as specified in the methods section and are left out of the comparison of diagnosis groups; AB—asthmatic bronchitis; COPD—chronic obstructive pulmonary disease. Other abbreviations as in table 1.

ml after three months of treatment with inhaled corticosteroids (fig 3). In the subgroup of 49 patients whose post-terbutaline FEV<sub>1</sub> value remained more than 1.64 RSD below predicted as described above, the additional increase with ipratropium bromide after terbutaline amounted to 227 ml (more than 100 ml in 39 of 49 patients).

LONG TERM VARIABILITY OF BRONCHODILATOR RESPONSES

Since it is clear from fig 2A-D that there was a considerable decrease in BDR in the BA + CS group in the first three months, the long term variability of the various BDRs was calculated for measurements under double blind treatment only—that is, without the baseline visit. The within subject standard deviations were quite high: 10.7%init, 186 ml, 5.1%pred, and 0.41 RSD (table 2). The variability in BDR was comparable between the symptom based diagnosis groups of asthma and COPD (table 2). It tended to diminish during treatment with inhaled corticosteroids, most notably so when expressed as BDR%init (table 2). The decrease in variability with inhaled corticosteroids existed only in the symptom based asthma and asthmatic bronchitis groups.

Within subject change in BDR%init over 21 months was more dependent on parallel changes in prebronchodilator FEV<sub>1</sub>[ml] than the other expressions of BDR: median within subject  $\rho$  for FEV<sub>1</sub> and BDR%init was -0.70, BDR[ml] -0.56, BDR%pred -0.60, and BDR-SR -0.60 (all  $p < 0.001$ ). These within subject correlation coefficients were slightly stronger for the group with a symptom based diagnosis of asthma than for COPD (median  $\rho$  for FEV<sub>1</sub> and BDR%init, -0.70 and -0.60, respectively).

Table 3 Frequency of "significant" BDRs in 97 patients with five measurements during 21 months of bronchodilator treatment

	Cut off level (reference)	Frequency of a "significant" bronchodilator response					
		× 0	× 1	× 2	× 3	× 4	× 5
BDR%init	15%init <sup>1</sup>	12	18	8	12	17	30
BDR%pred	9%pred <sup>6</sup>	8	15	7	16	16	35
BDR[ATS]	12%init and 200 ml <sup>8</sup>	6	14	9	13	16	39

BDR[ATS]—significant bronchodilator response expressed as percentage of initial (prebronchodilator) FEV<sub>1</sub> > 12%init if absolute response > 200 ml;<sup>8</sup> other abbreviations as in table 1.

SHIFTS IN DIAGNOSTIC CLASSIFICATION AS "REVERSIBLE" SPONTANEOUSLY AND WITH CORTICOSTEROID TREATMENT

Published criteria for "significant" reversibility<sup>6, 20</sup> were applied to the data in order to determine how many patients measured only in a stable condition would shift from classification category ("reversible" or not) during five measurements in 21 months (table 3). Five patients with one missing value have been left out of the table. High proportions of patients shifted from "reversible" to "irreversible" and back several times. Consistent classification—for example, for BDR%init >15%—occurred in only 42 of 97 (43%) patients (table 3).

The proportion of patients that would be labelled as having "reversible" airways disease by the various criteria fell significantly during maintenance treatment with BA + CS, but not in both non-steroid treated groups (table 4).

PROGNOSTIC VALUE OF BDR FOR CHANGE IN FEV<sub>1</sub> WITH INHALED CORTICOSTEROIDS

BDRs at the start of the study were to some extent predictive of improvement in FEV<sub>1</sub> during BA + CS treatment: correlation coefficient for change in prebronchodilator FEV<sub>1</sub>[ml] in the first three months with pre-study BDR[ml]  $r = 0.46$ , BDR%init  $r = 0.52$ , BDR%pred  $r = 0.40$ , and BDR-SR  $r = 0.42$  (all  $p < 0.001$ ). Thus the explained variance in change of FEV<sub>1</sub>[ml] by the pre-study BDR is still low:  $r^2 = 21\%$ ,  $27\%$ ,  $16\%$ , and  $17\%$  respectively.

As there is no agreement on what constitutes a "significant" long term effect of corticosteroid treatment, analogous to the ATS statement on BDR, an improvement in FEV<sub>1</sub> within three months of >12%init and >200 ml was labelled "significant".<sup>8</sup> A "significant" long-term corticosteroid response defined in this way was correctly predicted by a baseline BDR%init > 15% in only 50 of 83 patients (60%), by a BDR%pred >9% in 60%, and by the new ATS criterion for BDR (>12%init and >200 ml) in 57% of cases. In the COPD subgroup the treatment response to inhaled corticosteroids was somewhat better predicted by the baseline BDR expressed according to the ATS than in the asthma subgroup (12 of 18 (67%) and 17 of 32 (53%), respectively).

Table 4 Number of patients with a "significant" BDR per treatment group before and after treatment

	Cut off level (reference)	Months	Percentage with "significant" response (no/total)			p*	p†
			BA + PL	BA + AC	BA + CS		
BDR%init	15%init <sup>1</sup>	0	63 (32/51)	63 (32/51)	52 (43/83)	0.33	0.00
		3	60 (30/50)	61 (31/51)	29 (24/83)	0.00	
		21	67 (33/49)	57 (29/51)	26 (21/82)	0.00	
BDR%pred	9%pred <sup>6</sup>	0	65 (33/51)	73 (37/51)	54 (45/83)	0.10	0.08
		3	68 (34/50)	65 (33/51)	46 (38/83)	0.02	
		21	71 (35/49)	65 (33/51)	39 (32/82)	0.00	
BDR[ATS]	12%init and 200 ml <sup>8</sup>	0	65 (33/51)	73 (37/51)	58 (48/83)	0.26	0.05
		3	68 (34/50)	71 (36/51)	46 (38/83)	0.04	
		21	69 (34/49)	65 (33/51)	42 (34/82)	0.06	

\*p value for  $\chi^2$  comparison of proportions between the three treatment groups; †p value for  $\chi^2$  comparison of trend with time in proportions within BA + CS group; all p values for trends in BA + AC and BA + PL >0.50. Abbreviations as in tables 1 and 3.

Discussion

Bronchodilator responses in our study are substantially reduced by treatment with inhaled corticosteroids and  $\beta_2$  agonists (BA + CS), but not by treatment with  $\beta_2$  agonists alone (BA + PL), or  $\beta_2$  agonists with an anti-cholinergic drug (BA + AC). Both prebronchodilator and postbronchodilator FEV<sub>1</sub> improved within three months of treatment with corticosteroids, but the prebronchodilator FEV<sub>1</sub> improved to a greater extent causing the reduction in BDR.

We hypothesised that part of the decrease in BDR in patients treated with BA + CS could be explained by the fact that patients reach normal levels of FEV<sub>1</sub>: in those patients whose post-terbutaline FEV<sub>1</sub> remained abnormal after three months of treatment a smaller decrease in BDR was found (61 ml *v* 117 ml, or 5%init *v* 7%init). However, in both the complete BA + CS group and the subgroup mentioned above the FEV<sub>1</sub> measured after 1000  $\mu$ g of terbutaline was not the individual's personal maximum FEV<sub>1</sub>, since the administration of an additional 80  $\mu$ g of ipratropium bromide caused a further 200 ml bronchodilatation (both at the start of the study and after three months of treatment). Since FEV<sub>1</sub> was measured before, 20 minutes after terbutaline, and 40 minutes after ipratropium bromide, it could be argued that part of this further improvement with ipratropium bromide could in fact have been due to a further improvement with terbutaline after the first 20 minutes. An additional effect of ipratropium bromide added to a betamimetic, however, has been documented by several others, though usually at lower dosages of  $\beta_2$  agonist than the 1000  $\mu$ g of terbutaline given in our study.<sup>21-24</sup>

Theoretically airway calibre can be decreased by at least five mechanisms<sup>25</sup>: decreased preload, increased smooth muscle tone, increased smooth muscle strength (hypertrophy, hyperplasia), airway wall thickening due to hypertrophy and hyperplasia of muscles and glands, oedema, influx of inflammatory cells, and secretions within the airway lumen. In this study prebronchodilator FEV<sub>1</sub> after three months of treatment with corticosteroids rose to approximately the post-terbutaline value at the start of the study. This could indicate that the improvement in airways obstruction with inhaled corticosteroids

is due to a decrease in bronchomotor tone only. However, after three months the mean BDR to terbutaline was still 300 ml, compared with 417 ml at the initial visit. This suggests that inhaled corticosteroids also cause an alteration in airway geometry apart from the change in bronchomotor tone, which is well in line with the proposed 'anti-inflammatory effects of inhaled corticosteroids (reduction of number of inflammatory cells and decreases in release of cytokines and mediators thereby reducing airway wall thickness, airway secretions and muscle tone).<sup>26</sup> Although in our study FEV<sub>1</sub> and BDR showed no further change after three months of corticosteroid treatment and hence the maximum improvement in smooth muscle tone and airway geometry had been achieved, airway hyperresponsiveness to histamine nevertheless continued to improve until at least one year of treatment in the same patient population.<sup>13</sup> It is possible that more sensitive measurements than FEV<sub>1</sub> would still detect improvements in airway resistance in parallel with further improvements in the extent of inflammation as measured by PC<sub>20</sub>. Other explanations for continuing improvement in PC<sub>20</sub> without concomitant change in airway calibre seem more appealing, however, such as improvements in epithelial healing and decreases in permeability which would not by itself affect airway geometry.

As indicated above, only part of the improvement in the level of airways obstruction is caused by a decrease in bronchomotor tone. This by itself already suggests that a BDR measured before treatment with inhaled corticosteroids will not accurately predict the change in FEV<sub>1</sub> caused by their use. Although significant regression coefficients were found between baseline BDR and long term improvement in FEV<sub>1</sub>, the maximum correlation coefficient was 0.52 signifying 27% explained variance. The correct prediction of a favourable long term response was calculated using the baseline BDR as the test: only approximately 60% of patients would have been correctly given or withheld inhaled corticosteroids. This correct prediction of an "inhaled corticosteroids responder" by a pre-treatment BDR was slightly better in COPD than in asthma, but because of the small numbers it is uncertain whether any firm



conclusions should be attached to the difference—that is, whether a single bronchodilator test is more useful as a prognostic test for inhaled corticosteroids in COPD than it is in asthma.

Surprisingly few data have hitherto been published on long term variability of BDR in asthma and COPD. Considerable within subject variability of BDR was found in this study, which was performed under rigorously controlled trial conditions, all patients being on maintenance medication and without measurements during or shortly after exacerbations (table 2). The standard deviations of BDR found are comparable to those reported by Anthonisen *et al* in patients with COPD participating in the IPPB trial.<sup>2</sup> Even though we found significant differences (but with a large overlap) in BDR between the different diagnosis groups,<sup>4</sup> within subject standard deviations were quite comparable for patients with a symptom based diagnosis of asthma or COPD (table 2).

The American Thoracic Society has recently recommended a new criterion for the definition of a “significant” bronchodilator response, again from one test (a change in FEV<sub>1</sub> larger than 12%init and larger than 200 ml). Table 3 shows that in this large group of patients with a broad range of clinical characteristics, variability in the result of a single test is not reduced by the new ATS criterion.

Although the decrease in BDR with inhaled corticosteroids is probably not surprising, to our knowledge it has not been documented to date. In many guidelines for the management of obstructive airways disease it is recommended that healthy subjects should be distinguished from those with obstructive airways disease, and reversible airways obstruction should be distinguished from irreversible airways obstruction on the basis of a (single) bronchodilator test.<sup>1,27</sup> The results of our study suggest that this is hazardous, both because of a high within subject variability and because of a decrease in BDR during treatment with inhaled corticosteroids. We feel that one single bronchodilator test is clearly insufficient to make a diagnosis of “(ir)reversible” airways obstruction, and hence to classify a patient as having asthma or COPD on the basis of the test.

From cross sectional data several authors have stressed the dependence on baseline FEV<sub>1</sub> of the BDR when expressed as a percentage of the initial value.<sup>2–4</sup> From our longitudinal data we document further manifestations of this baseline dependency: changes in BDR%init were more dependent on improvements in prebronchodilator FEV<sub>1</sub> with corticosteroid treatment than the other expressions employed. Similarly, in the non-steroid treated groups the within subject variability of BDR was most closely linked to variability in prebronchodilator FEV<sub>1</sub> when expressed as %init.<sup>5</sup> From the data presented in this report no clearcut argument can be given in favour of any one of the expressions of BDR. Expressing the BDR relative to the predicted FEV<sub>1</sub>, however, makes some cor-

rection for gender, height, and age which makes comparison between patients and between studies easier.<sup>4</sup> Expressing the FEV<sub>1</sub>, and hence the BDR, relative to the standardised residual offers theoretical advantages<sup>14,15</sup> but no advantages in the sense of decreased baseline dependency or decreased variability in this study.

The study population was selected on the basis of symptomatic respiratory disease, age, and objective functional criteria of airways obstruction (FEV<sub>1</sub>, FEV<sub>1</sub>/VC) and airway responsiveness (PC<sub>20</sub> histamine). Selection bias of a certain level of reversibility to a  $\beta_2$  agonist was therefore not introduced. Because considerable dropout occurred in both treatment arms without inhaled corticosteroids, however, the current selection from our original population introduced bias to some extent. Withdrawals had slightly lower baseline FEV<sub>1</sub>%pred and lower PC<sub>20</sub> than non-withdrawals, but no significant differences were found in BDR. Since more than 70% of withdrawals resulted from increases in respiratory symptoms it seems likely that, if anything, variability of the BDR in the currently selected group is a conservative estimate of the true variability in our original population.

In conclusion, BDR decreases substantially with inhaled corticosteroid therapy. This improvement is related to the improvement in FEV<sub>1</sub> which is caused by both altered airway geometry and a decrease in bronchomotor tone as measured by a decreased BDR. Moreover, measurements of BDR are very variable over 21 months. These results suggest that a single BDR should not be used as the basis for therapeutic decisions nor as a selection criterion for clinical trials. These problems are greatest with a BDR expressed as a percentage of the initial value because of its dependency on baseline FEV<sub>1</sub>. Finally, because of the imperfect relation between the bronchodilator test before inhaled corticosteroids and the future response to them, we think that therapeutic decisions on whether or not to prescribe corticosteroids should not be made on the basis of bronchodilator tests, but probably on combined information from symptoms, FEV<sub>1</sub>, PC<sub>20</sub>, peak flow, atopy, and BDR.

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