Thorax 1987;**42**:487–490

Short term variability in FEV_1 and bronchodilator responsiveness in patients with obstructive ventilatory defects

P M TWEEDDALE, F ALEXANDER, G J R McHARDY

From the Lothian Area Respiratory Function Service and the Departments of Medicine, Respiratory Medicine, and Medical Computing and Statistics, University of Edinburgh

ABSTRACT Short term variability in FEV_1 and responsiveness to inhaled bronchodilator were measured in 150 patients with obstructive ventilatory defects. The range of initial FEV_1 was 0·5–4·71 and the natural variability over a 20 minute period when expressed in absolute terms was similar over the entire range, and differed insignificantly from that found in normal subjects. The increase in FEV_1 and vital capacity (VC) required to exclude natural variability with 95% confidence in these patients was 160 ml and 330 ml respectively. Natural variability when expressed in percentage terms was negatively correlated with the level of FEV_1 recorded. The analysis of changes in FEV_1 and VC after administration of bronchodilator used absolute and percentage criteria for response. The number of responders differed considerably according to the criterion used. In those defined by the absolute criterion as responders there was no evidence that size of response was related to level of FEV_1. Percentage criteria have traditionally been used to identify responses to bronchodilator that may be clinically useful, while absolute criteria, although statistically valid, have not been favoured. Reappraisal of the criteria used and their limitations and implications is required.

Pulmonary function laboratories report the results of bronchodilator tests to clinicians, who then may make decisions about treatment. The criterion used to define a response to bronchodilators therefore requires scrutiny. Any criterion used to define the change in FEV_1 that is indicative of a response to bronchodilator must take into account the natural short term variability in FEV_1; this is true both in routine clinical work and when patients are selected for entry into clinical trials. We have recently reported[1] that short term variability in FEV_1 was constant over a wide range of FEV_1 in normal subjects and a small group of patients with restrictive ventilatory defects, and therefore suggested that the criterion of response should be an absolute change of 190 ml or more. The possibility remained that patients with severe airflow obstruction might show less natural variability than normal subjects, so that the use of a percentage criterion to define response might be more appropriate in these patients. We have therefore studied prospectively short term variability and response to bronchodilator in patients with airway obstruction.

Address for correspondence: Dr P M Tweeddale, City Hospital, Edinburgh EH10 5SB. (Reprints will not be available.)

Accepted 9 January 1987

Methods

Four laboratories in Edinburgh took part in the study. All patients referred routinely for a bronchodilator test who were found to have an obstructive ventilatory defect on initial testing were asked to take part in the study, which had received the approval of the Physicians' Advisory Ethical Committee in the South Lothian District. Patients who had been using bronchodilators therapeutically were asked to refrain from using them for four hours before the laboratory visit.

FEV_1 and vital capacity (VC) were recorded with bellows spirometers (Vitalograph), which were all calibrated for volume with the same precision syringe (Hans Rudolph, Kansas City). Measurements were read on the BTPS scale of the paper in three laboratories and digitally displayed using the electronic output

from the spirometers in the remaining laboratory. Patients were seated and each had FEV_1 and vital capacity (VC) recorded by a single technician using one sheet of recording paper on one spirometer. The highest of three technically acceptable recordings was taken.[2] Initial values were designated as measurement I. After the patients had sat for 20 minutes in the laboratory measurement II was made. Two puffs of salbutamol (200 μg) or terbutaline (500 μg) were then administered in identical fashion by the technician from a metered dose inhaler, and after a 20 minute interval measurement III was made. The predicted normal values of Hall *et al*[3] were used for women and those of Crapo *et al*[4] for men. An obstructive ventilatory defect was defined as a reduction in the FEV_1/VC ratio of two or more standard deviations from mean predicted values.

Results

One hundred and fifty consecutive patients with reduced FEV_1/VC ratio were included in the study. The group comprised 104 men and 46 women (age 18–88 years, height 1·40–1·86 metres). Sixty two were smokers, 40 ex-smokers, and 48 non-smokers. Before measurement of FEV_1I, 97 patients had been seated, 52 had been walking within the hospital, and one had been walking outdoors. For statistical comparison by analysis of variance the patients were divided, as in the previous study,[1] into three subgroups on the basis of the mean of FEV_1I and FEV_1II (that is, the measurements before administration of bronchodilator): group A (n = 72), range of mean FEV_1 0·5–1·1 l; group B (n = 51), FEV_1 1·15–2·4 l; group C (n = 27), FEV_1 2·45–4·7 l. In addition to the reduced FEV_1/VC ratio used as a criterion for entry, all patients were found to have an FEV_1I value at least 1 SD lower than the predicted value and most patients in each subgroup had an FEV_1 more than 2 SD below the mean predicted value.

The differences in FEV_1 and VC measurements (in millilitres) were expressed both as absolute change (AC) and as percentage change (PC)[5]:

Natural variability

$$\text{AC} = \text{difference (II} - \text{I)} \qquad \text{PC} = \frac{\text{difference (II} - \text{I)}}{\text{mean of (II} + \text{I)}} \times 100$$

Change after bronchodilator

$$\text{AC} = \text{difference (III} - \text{II)} \quad \text{PC} = \frac{\text{difference (III} - \text{II)}}{\text{mean of (III} + \text{II)}} \times 100$$

Mean values of AC and PC for FEV_1 and VC before administration of bronchodilator in the three subgroups are shown in table 1. There was no evidence for any learning effect, the mean changes being insignificantly different from zero. The variations about the means in the three subgroups were then compared by Levene's test.[6] When absolute change in FEV_1 was used there was no significant difference in the variability of FEV_1 between the groups, but with PC there was a decrease in variability with increasing level of FEV_1 ($p < 0·001$). Variability in vital capacity when expressed as AC did not differ significantly between groups A, B, and C; but when PC was used variability decreased with increasing level of FEV ($p = 0·001$).

Table 1 *Natural variability in FEV_1 and vital capacity over 20 minute time interval*

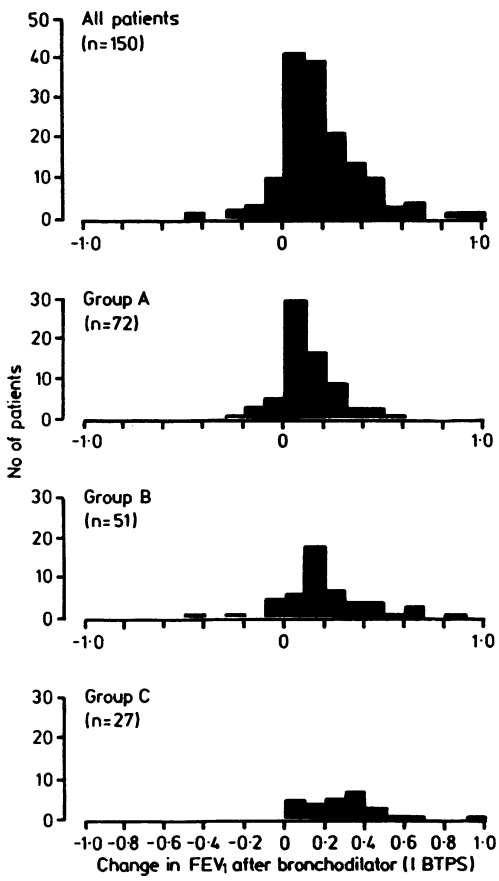
	Group A	*Group B*	*Group C*
No of patients	72	51	27
FEV_1			
Range (l, BTPS)	0·50–1·10	1·15–2·40	2·45–4·70
AC (ml)			
Mean	3	19	21
SD	96	100	84
PC (%)			
Mean	−0·1	−1·6	−0·7
SD	12·4	6·5	3·0
Vital capacity			
Range (l, BTPS)	0·55–4·10	1·95–4·95	3·40–6·80
AC (ml)			
Mean	48	43	−46
SD	211	189	181
PC (%)			
Mean	2·6	1·3	−1·2
SD	12·5	6·6	4·3

AC—absolute change; PC—percentage change.

The absolute increases in FEV_1 and VC necessary to distinguish with 95% confidence between natural variability and a response to bronchodilator in these patients are 160 and 330 ml. The absolute change for FEV_1 does not differ significantly from the 190 ml previously identified for normal subjects and patients with restrictive ventilatory defects. It is not possible to state a single percentage change that would distinguish between natural variability and a response to bronchodilator in these patients because the percentage variability in FEV_1 differed between groups.

Natural variability in FEV_1 and VC, whether expressed in absolute or in percentage terms, was unrelated to the sex, age, or smoking habits of the patients and did not differ between those patients who had been walking on the flat and those who had been sedentary before the test.

The absolute change in FEV_1 found after inhalation of bronchodilator ranged from −450 to +950 ml but the distribution was skewed towards positive differences (figure). Patients were defined as AC responders if they had an increase of 160 ml or more in FEV_1, to distinguish between natural variability and a positive response to bronchodilator (table 2). The proportion of patients within each subgroup defined as AC responders rose significantly



Histograms showing absolute change in FEV_1 after administration of bronchodilator (that is, FEV_1III–FEV_1II) for all the subjects and three subgroups (range of mean FEV_1 prior to bronchodilator for group A 0·5 – 1·1 l, group B 1·15–2·4 l, and group C 2·45–4·7 l).

with the level of the initial FEV_1 ($p < 0.001$). Analysis of the absolute change in VC after administration of bronchodilator showed that 8 of 17 FEV_1 responders in group A, 12 of 23 FEV_1 responders in group B, and 7 of 18 FEV_1 responders in group C also showed significant absolute changes in VC. A response of 330 ml or more in VC without a response in FEV_1 was found in 7 patients in group A, 4 patients in group B, and none in group C; so a total of 24 patients in group A, 27 in group B, and 18 in group C could be identified as being AC responders when changes in both FEV_1 and VC were used.

For defining patients as PC responders we used criteria of 10% and 15% change. Results are shown in table 2. With the 15% criterion the proportion of responders in each subgroup fell as initial level of

Table 2 *Number of patients with FEV_1 response to bronchodilator*

	Group A	*Group B*	*Group C*	*All patients*
No of patients	72	51	27	150
FEV_1 Range (l, BTPS)	0·5 – 1·1	1·15 – 2·4	2·45 – 4·7	0·5 – 4·7
AC responders (% of group)	17 (24)	23 (45)	18 (66)	58 (39)
PC 15% responders (% of group)	22 (31)	15 (29)	2 (7)	39 (26)
PC 10% responders (% of group)	36 (50)	22 (43)	11 (41)	69 (46)

AC responders—patients showing an absolute increase of > 160 ml in FEV_1; PC 15% responders—patients showing a percentage increase of > 15% in FEV_1; PC 10% responders—patients showing a percentage increase of > 10% in FEV_1.

FEV_1 rose (χ^2_1 for trend: $p < 0.025$); but if the 10% criterion was used the proportion of responders was similar in the three subgroups.

Once the patients had been classified as AC and PC responders, natural variability in FEV_1 was re-examined to determine whether natural variability before administration of the bronchodilator had been different in the responders and the non-responders. Regardless of which criterion was used to define a response in FEV_1, there was no significant difference in AC or PC variability between those who responded and those who did not.

In those defined as AC responders the range of response in FEV_1 after administration of bronchodilator was 160–500 ml in group A, 160–850 ml in group B, and 160–950 ml in group C; but single patients in groups B and C accounted for the extreme responses (figure). When the Wilcoxon signed rank test [7] was applied to the median increases the response in FEV_1 after the bronchodilator was found to be similar in the three groups. In those defined as PC responders the range of response after the bronchodilator was 10–48% in group A, 10–42% in group B, and 10–24% in group C. The percentage response was significantly smaller in group C than in group A.

Discussion

This study of patients referred for bronchodilator tests was carried out prospectively under routine laboratory conditions. The range of natural variability observed is therefore likely to be representative of that encountered in patients with airflow obstruction in normal clinical practice.

We have examined the interaction of natural variability with different selection criteria of the types used in clinical trials based on response to bronchodilators. When absolute change in FEV_1 is used to

define response, similar numbers of patients are selected at each FEV_1 level, with most patients in the lowest FEV_1 range (group A) failing to show a significant response (table 2). If the criteria are widened to include absolute change in VC, the number of AC responders increases, with the additional patients coming from the lower FEV_1 ranges (groups A and B).

Use of a 15% change to define response in FEV_1 selects a greater proportion of more severely than of less severely impaired patients. Overall, fewer patients are defined as responders (table 2). Use of a 10% criterion again selects a greater proportion of more severely impaired patients, but it yields the greatest number of responders overall. It should be noted, however, that many of the increases in FEV_1 in those defined as responders by percentage criteria (particularly when 10% is used) fall in the range that is statistically indistinguishable from natural variability. The validity of this type of selection is thereby diminished.

In this study, in contrast to the previous one, no relationship was found between pretest activity and natural variability. The pattern of pretest activity, however, was very different in the two studies, only one patient with airway obstruction having taken moderate exercise before the test. More work is required to resolve this point.

This study does not attempt to examine the clinical importance of the recorded changes in FEV_1 and VC. This issue is of particular relevance in two groups of patients. The first group comprises those with an FEV_1 of less than 1 litre who show increases lying within the range of natural variability, which could therefore have occurred by chance. In such patients any increase may be thought by the clinician to be of some clinical value and the failure to achieve statistical significance tends to be disregarded. The second group comprises patients with a higher FEV_1 who achieve changes of statistical significance that may be disregarded because they are not considered to be of clinical importance. If response is to be defined by percentage changes that do not have statistical validity, other evidence must be put forward to justify these assertions. Until this evidence is forthcoming, our study emphasises the need for critical appraisal of whatever criterion is chosen to define response to bronchodilators.

References

1 Tweeddale PM, Merchant S, Leslie M, Alexander F, McHardy GJR. Short term variability in FEV_1: relation to pretest activity, level of FEV_1, and smoking habits. *Thorax* 1984;**39**:928–32.

2 American Thoracic Society. ATS statement—Snowbird Workshop on Standardisation of Spirometry. *Am Rev Respir Dis* 1979;**119**:831–8.

3 Hall AM, Heywood C, Cotes JE. Lung function in healthy British women. *Thorax* 1979;**34**:359–65.

4 Crapo RO, Morris AH, Gardner RM. Reference spirometric values using techniques and equipment that meet ATS recommendations. *Am Rev Respir Dis* 1981;**123**:659–64.

5 European Community for Coal and Steel. Standardised lung function testing. *Bull Eur Physiopathol Respir* 1983:19(suppl 5)**26**:45–51.

6 Brown MB, Forsythe AB. Robust tests for the equality of variances. *Journal of the American Statistical Association* 1974;**69**:364–7.

7 Wilcoxon F. Individual comparisons by ranking methods. *Biometrics Bulletin* 1945;**1**:80–3.