

Assessment of reversibility of airway obstruction in patients with chronic obstructive airways disease

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Abstract

Spirometry before and after an inhaled beta agonist or a course of oral prednisolone is widely used to detect reversible airflow limitation in patients with chronic obstructive lung disease. How many of these patients have a response and how the response to beta agonists relates to the response to corticosteroids is not clear. In 127 outpatients (mean (SD) FEV₁ 0.92 (0.38) l) who had a clinical diagnosis of chronic obstructive lung disease (continuous breathlessness for more than six months and an FEV₁/forced vital capacity (FVC) ratio < 60%) and who appeared to be stable, the change in FEV₁ was measured after salbutamol 200 µg from a metered dose inhaler and 5 mg from a nebuliser. Symptoms and spirometric values were recorded before and after two weeks of oral prednisolone 30 mg. Reversibility was defined as a response in FEV₁ of 15% or more from baseline alone and as a 15% change and a minimum increase of at least 200 ml. The latter gave results that showed greater internal consistency between the drug regimens. On the basis of this criterion 56 patients (44%) had no response to salbutamol or prednisolone, 71 responded to salbutamol (including all 27 steroid responders), and 25 patients had a response to salbutamol 5 mg but not to 200 µg. In general, the largest increase in FEV₁ after salbutamol occurred in the subjects with greatest improvement after prednisolone. Subjects showing a response in FEV₁ after two weeks' prednisolone had a fall in total symptom score, unlike those who had no response to any treatment or a response to salbutamol only. These data show that reversibility in response to beta agonists is common in patients diagnosed on clinical grounds as having stable chronic obstructive lung disease, that it can be substantial, and that it is best detected by using a larger dose of salbutamol. Salbutamol responders were those most likely to improve after a trial of oral prednisolone. Allowance should be made for the variability of FEV₁ in the calculation of the percentage response at low baseline values (less than 1 litre).

to the chest physician but there is a shortage of firm data on which to base rational diagnosis and management. Airflow limitation is improved in many patients by bronchodilator drugs^{1,2} and less frequently by oral corticosteroids.^{3,4} Some physicians test for reversibility of airflow obstruction by measuring FEV₁ before and after 200 µg salbutamol; others strongly advocate a trial of oral corticosteroids for all patients diagnosed as having chronic obstructive lung disease. There is similar uncertainty about the appropriateness of defining reversibility as an increase in FEV₁ after treatment, particularly in patients with a low FEV₁.^{5,6}

We have tried to resolve some of this uncertainty by studying a consecutive series of stable outpatients diagnosed as having chronic obstructive lung disease and presenting to a single hospital. We addressed the following questions: (1) How often do such patients have an FEV₁ response to inhaled salbutamol and how does the response to 200 µg compare with the response to 5 mg? (2) Do the same patients respond to corticosteroids and salbutamol? (3) Are the spirometric changes related to symptomatic improvement?

Methods

All outpatients referred with a history of progressive continuous breathlessness of more than six months' duration and with spirometric evidence of limitation (FEV₁/forced vital capacity (FVC) < 60%) were considered for the study. Patients were excluded if they had had a recent exacerbation of a chest illness or had any coexisting cardiovascular or lung disorder. Patients with previously documented asthma and patients taking oral corticosteroids were also excluded.

We assessed 127 consecutive patients who met the above criteria. The 78 patients taking bronchodilators and the 43 taking oral theophylline were asked to stop the drugs for at least six hours and for 24 hours respectively before the tests. All patients gave their informed consent to the study protocol, which formalised our existing clinical practice. All the spirometric measurements were made with a wet spirometer (PK Morgan). In each case the best FEV₁ and FVC from three tracings were recorded.

On the first visit patients completed a respiratory questionnaire that included questions on the presence or absence of wheeze, cough, sputum, and dyspnoea. Clinical stability was confirmed. Patients then performed baseline

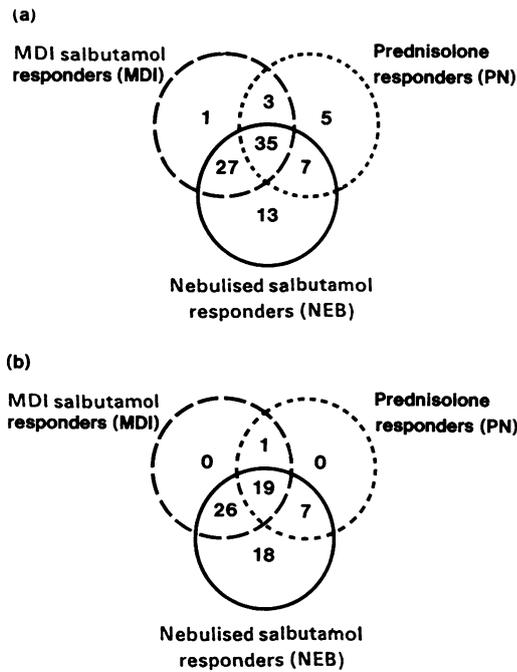
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Chronic obstructive pulmonary disease is one of the commonest clinical problems presenting

Figure 1 Venn diagram to show the distribution of responders among the three test modalities:
 (a) criterion 1: increase in FEV₁ of ≥ 15%;
 (b) criterion 2: increase in FEV₁ of ≥ 15% and ≥ 200 ml.



spirometric tests, and after being shown how to use a placebo metered dose inhaler they inhaled two puffs of salbutamol (200 µg total) one minute apart under supervision. Spirometry was repeated at 15 minutes. The patients then inhaled 5 mg salbutamol via a System 22 nebuliser (5 l/min) and spirometry was repeated after a further 15 minutes. Lastly, each patient was prescribed oral prednisolone 30 mg daily for two weeks. Spirometry was repeated and the respiratory questionnaires administered at the end of the two weeks. The response to each treatment was assessed by comparing the postbronchodilator FEV₁ with the baseline value.

We examined two separate criteria for deciding if a response was greater than that expected by the random variation of the measurement:

criterion 1: a rise in FEV₁ of at least 15% from the baseline value; criterion 2: a rise in FEV₁ of at least 15% from the baseline value in addition to an absolute increase in FEV₁ of at least 200 ml (to exclude errors due to the known coefficient of variation of spirometry^{6,7}).

Data are expressed as means with standard variations in parentheses and comparisons within groups were made by Student's unpaired *t* test.

Results

Of the 127 patients, 81 (64%) were male and 118 (93%) were cigarette smokers (mean 36 pack years). Forty four (35%) were current smokers. Ninety nine (78%) gave a history of regular cough and sputum production. Mean FEV₁ was 0.92 (0.38) l (43% of predicted) and mean FVC 2.13 (0.73) l. Almost two thirds (63%) of the patients had an FEV₁ of less than 1 litre.

On the basis of criterion 1, 91 patients (72%) responded to one or more of the three treatments but the distribution of responses between treatments showed no clear pattern (fig 1a). Fifty patients responded to prednisolone, of whom five had no response to either form of salbutamol. Among the salbutamol responders four patients responded to 200 µg but not to 5 mg. Such "unexpected" results were always associated with small absolute volume changes.

When criterion 2 was applied a different and simpler pattern emerged (fig 1b). Seventy one patients were responders but only one of these responded to 200 µg salbutamol by metered dose inhaler and not to 5 mg by nebuliser. This patient showed a fall of 0.3 l in FEV₁ after nebulised salbutamol. All the subjects who responded to oral prednisolone showed a response to inhaled salbutamol 200 µg or 5 mg. The response to salbutamol 200 µg by metered dose inhaler identified only 46 responders. The

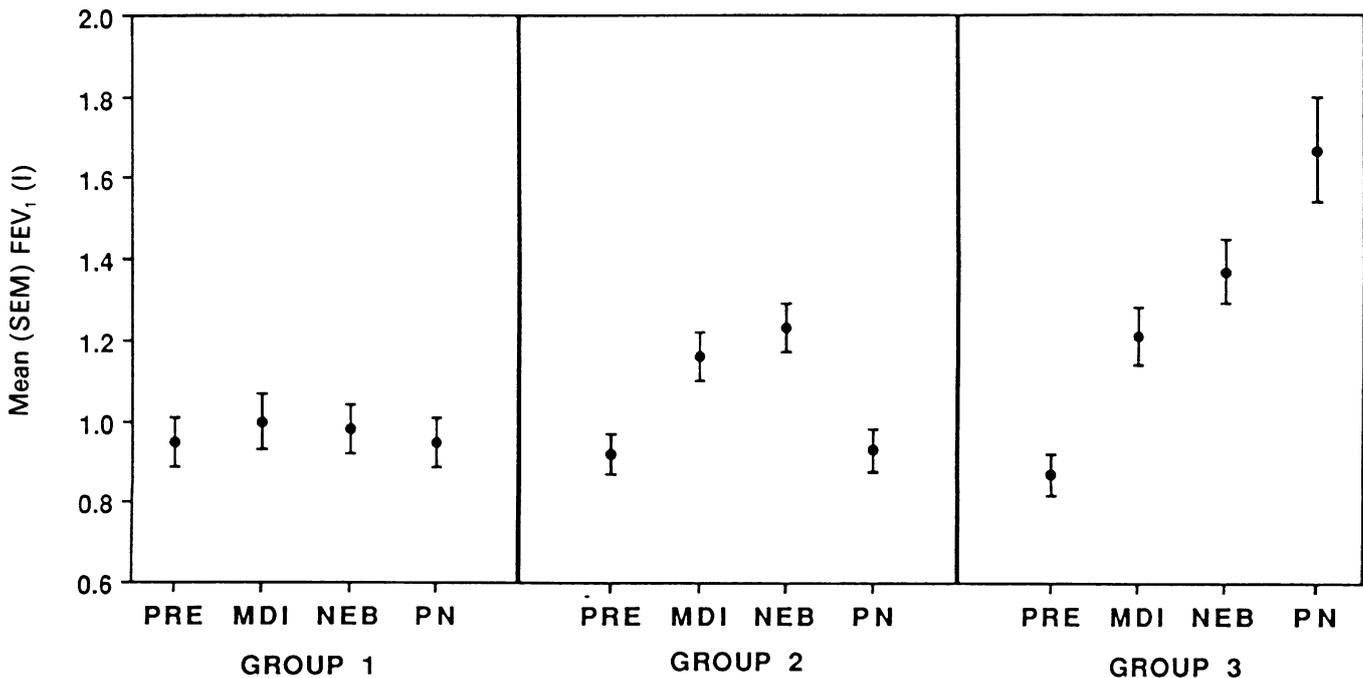


Figure 2 Mean (SEM) FEV₁ (l) before and after salbutamol (MDI—200 µg by metered dose inhaler; NEB—5 mg by nebuliser) and oral prednisolone (PN—30 mg daily for two weeks) in the three groups.

Table 1 Clinical characteristics, eosinophil count, and spirometric values of the three groups* of patients

	Group 1 (n = 56)	Group 2 (n = 44)	Group 3 (n = 27)
Mean (SD) age (y)	61.5 (8.1)	59.8 (8.0)	62.5 (7.5)
No (%) male	31 (55)	30 (68)	20 (74)
Mean (SD) pack years	37 (25)	36 (26)	31 (22)
No (%) atopic	19 (34)	13 (30)	11 (41)
No (%) with chronic bronchitis	36 (64)	28 (64)	17 (63)
Mean (SD) eosinophil count ($\times 10^{-6}$)	134 (153)	190 (264)	451 (486)
Mean (SD) baseline FEV ₁ (l)	0.95 (0.46)	0.92 (0.35)	0.87 (0.25)
Mean (SD) baseline (l) forced vital capacity	2.02 (0.76)	2.28 (0.78)	2.09 (0.56)

*See under "Methods."

addition of a steroid trial would have identified a further seven responders, whereas the use of nebulised salbutamol caused a further 25 patients to be detected.

On the basis of criterion 2 (fig 1b), the patients' responses can be divided into three groups. The first group (group 1) comprises 56 patients who failed to respond to any treatment. Group 2 includes 44 patients who responded only to beta agonists. Group 3 contains 27 patients who responded to both beta agonists and oral prednisolone. There was no difference in mean age, sex, smoking habits, or baseline FEV₁ values between the three groups; the eosinophil count was significantly higher in subjects in group 3 ($p < 0.001$; table 1). Figure 2 shows the mean change in FEV₁ with the three treatments for the three groups. In group 1 the mean changes in FEV₁ were close to zero for each treatment and the standard deviation was 160 ml. As mean FEV₁ was unchanged the standard deviation is a measure of the reproducibility of the FEV₁ in these patients. In groups 2 and 3 nebulised salbutamol 5 mg produced a greater increase in FEV₁ than did 200 μ g salbutamol administered by metered dose inhaler ($p < 0.05$). In group 2 despite substantial increases in FEV₁ after salbutamol (up to 0.6 l) there was not even a trend towards an increase in baseline FEV₁ after two weeks of oral prednisolone. Group 3 patients showed larger changes in FEV₁ after both doses of salbutamol than patients in group 2 ($p < 0.01$) and the increase after prednisolone was even

greater. The substantial increase in FEV₁ in group 3 is partly due to three subjects whose FEV₁ improved by more than 1 litre. These three subjects could not be separated from either of the other two groups on the basis of symptoms or initial lung function. Although the response to steroids was broadly related to that after nebulised salbutamol (fig 3), the scatter of the data is too large for the magnitude of one to be predicted from a knowledge of the other.

The percentage of patients with particular symptoms and the mean breathlessness score and FEV₁ before and after the steroid trial for the three groups are shown in table 2. There was no improvement in symptoms after the steroid trial for patients in groups 1 and 2 who also had no change in FEV₁; and group 3 patients had less cough, sputum, wheeze, and breathlessness after treatment in conjunction with the improvement in FEV₁.

Discussion

With the recognition that the degree of airflow limitation rather than symptoms of chronic bronchitis is the important factor in determining outcome in patients with chronic obstructive lung disease,⁸ more attention is being paid to the detection and improvement of airflow limitation. The definition of chronic obstructive lung disease adopted in this study is a clinical one that can be readily applied in any chest clinic. The requirement for a history of persistent progressive breathlessness excludes patients with classical asthma and the reduced FEV₁/FVC ratio ensures that airflow obstruction is present. We excluded patients with other cardiorespiratory conditions in order not to confuse the data. The tests of reversibility were chosen to represent those commonly used in clinical practice in the United Kingdom.

The American Thoracic Society recommends that a 15% increase in FEV₁ above baseline (criterion 1) should be considered as a positive response to a bronchodilator⁵ and this definition is widely used in pharmaceutical trials. Many patients with chronic obstructive

Figure 3 Change in FEV₁ (l) in response to oral prednisolone and nebulised salbutamol in patients responding to both agents.

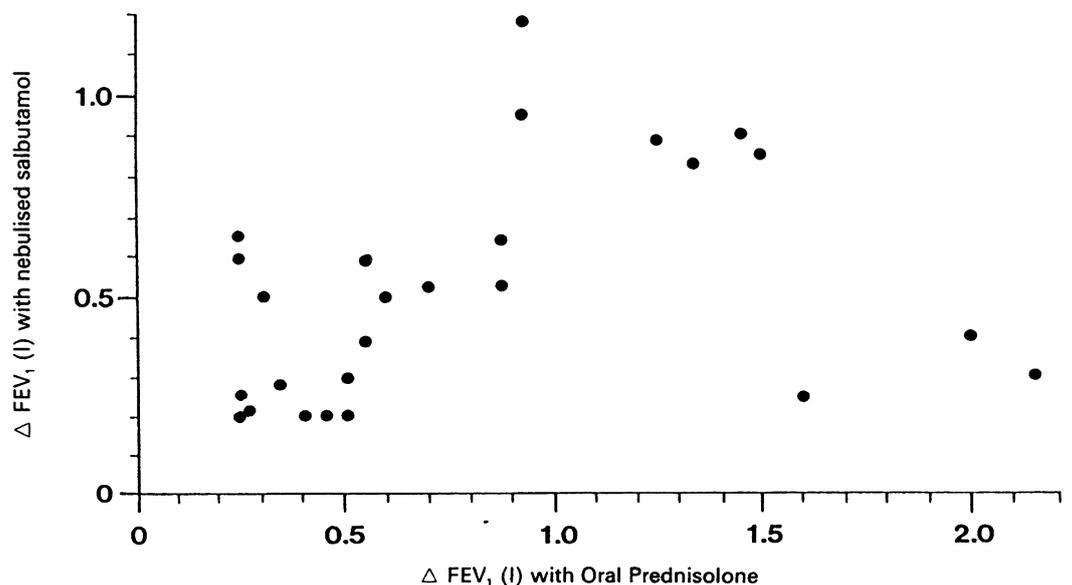


Table 2 Symptoms and spirometric values before and after prednisolone in the three groups* of patients

	Group 1 (n = 56)		Group 2 (n = 44)		Group 3 (n = 27)	
	Before	After	Before	After	Before	After
No (%) with:						
cough (%)	42 (75)	31 (56)	33 (75)	30 (68)	22 (81)	14 (52)**
wheeze (%)	46 (82)	34 (60)	35 (80)	34 (77)	25 (93)	15 (56)**
sputum (%)	39 (70)	31 (56)	36 (82)	30 (69)	24 (89)	13 (48)**
Mean (SD) dyspnoea score*	3.5 (1.3)	3.1 (1.5)	3.7 (1.3)	3.3 (1.3)	3.7 (1.3)	2.7 (1.4)**
Mean (SD) FEV ₁ (l)	0.95 (0.45)	0.95 (0.45)	0.92 (0.35)	0.93 (0.34)	0.87 (0.25)	1.67 (0.67)**

*See under "Methods."

**p < 0.01.

lung disease, however, have an FEV₁ of a litre or less; a 15% change in FEV₁ is then less than the coefficient of reproducibility of FEV₁ measurement as shown by Tweedale and McHardy^{6,7} and confirmed in our data for patients of group 1. When criterion 1 was used to determine whether the patient had had a response to treatment 70% of the patients were identified as responders. It is difficult to understand, however, why some patients should respond to 200 µg salbutamol but not to 5 mg. If these inconsistent results were due to poor reproducibility of measurements in patients with a low FEV₁, the addition of an absolute volume criterion would be expected to reduce such anomalies. Our data show that adopting criterion 2 did exactly that. Twenty of the patients with low volume changes were then labelled as non-responders and three clear response patterns emerged: no response, response to nebulised bronchodilator but not prednisolone, and response to both nebulised salbutamol and prednisolone. With this definition of responder only one patient showed an inconsistent response. He was the only patient in whom the FEV₁ fell (by 0.3 litre) after nebulised salbutamol, which suggests that he might have had a bronchoconstrictor response to the preservative in the nebuliser solution (he has not been rechallenged).

The choice of the absolute volume to be used in criterion 2 is clearly arbitrary but ours has the advantage of simplicity and, moreover, does exceed the coefficient of reproducibility of the FEV₁ measurement that has been reported.^{1,6} If criterion 2 were too harsh, then the non-responding patients (group 1) should show a trend towards a positive response. This did not occur for either FEV₁ or symptoms after the trial of prednisolone and thus provides indirect evidence for the appropriateness of this response criterion. Moreover, the only group to show significant improvement in symptoms after oral prednisolone was the one in which the spirometric improvement met our criterion 2 (table 2).

Giving 200 µg salbutamol via a metered dose inhaler produced smaller increments in FEV₁ in fewer patients than nebulised salbutamol (5 mg) despite carefully supervised administration of the dose. Use of this dose would have missed 35% of patients identified as responders with the higher dose by nebuliser and also some patients who were later shown to be steroid responsive. Nebulisers are now widely available and circumvent the problem of poor

compliance with treatment by metered dose inhaler.⁹ Moreover, a single 5 mg dose of salbutamol is safe and using this dose for reversibility testing seems logical.

The role of the steroid trial has been extensively studied^{3,4,10} but there is disagreement about the dose and the test to be used,¹⁰ and even whether it is relevant.¹¹ Prednisolone 30 mg daily, as used in this study, is in the mid range of prednisolone doses used previously. The 21% of patients identified as steroid responders on the basis of criterion 2 is similar to the percentage found in previous studies¹²; there are data that support the claim that increasing either the dose¹⁰ or the length of a steroid trial will increase the number of responders. Among the steroid non-responders, however, there was not even a trend towards a response by two weeks. This makes it unlikely that the numbers would have changed substantially had different steroid regimens been adopted.

The failure of 200 µg salbutamol to detect a response in seven of the 27 patients who subsequently responded to steroids has provided the rationale for empirical trials of steroids in all patients with chronic obstructive lung disease. Our observation that 96% of the steroid responders had a response to nebulised salbutamol may make it possible to reduce the number of steroid trials with a negative outcome.

The use of change in FEV₁ to assess the response to two weeks' oral prednisolone is supported by the clear symptomatic improvements that occurred in steroid responders, in contrast to the lack of any change in symptoms in non-responders. FEV₁ changes appear therefore to reflect variables important to the patient. The addition of a minimum absolute volume criterion helped to clarify an otherwise confusing scatter of data.

The existence of patients not responsive to steroids who nevertheless show bronchodilation with beta agonists has received little attention. They formed 30% of the study population and included 10 patients who had a greater than 0.4 litre increase in FEV₁. Whether the mechanism underlying airways obstruction in these patients is different cannot be answered here. Possibly steroid responders have an "asthmatic" component that is responding to the relief of airways inflammation, whereas those who respond only to bronchodilators are benefiting from the removal of resting bronchomotor tone.

The use of the term reversibility of airways obstruction is fraught with difficulty. In common usage it implies a complete abolition of the physiological impairment seen in asthmatic patients. It is also used, however, to signify an improvement in pulmonary function greater than could be predicted by the random variation of the measurement. Our data show that reversibility in the second sense occurs frequently in patients with moderate to severe airflow limitation, at least with acute testing. By including a simple volume criterion to recognise the limitations of the measurement anomalous results can be avoided. High dose nebulised beta agonists can identify a subgroup who are more likely to respond to prednisolone and who have the greatest responses in absolute terms. The relation between short term responses and subsequent symptomatic and physiological progress with long term treatment is unknown. Whether testing during a single visit to the laboratory is reliable enough to help determine appropriate long term treatment has yet to be determined.

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