

## Bronchodilator reversibility, exercise performance and breathlessness in stable chronic obstructive pulmonary disease

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**ABSTRACT:** Partial bronchodilator reversibility can be demonstrated in many patients with stable chronic obstructive pulmonary disease (COPD), but its relevance to exercise capacity and symptoms is uncertain. Previous data suggest that anticholinergic bronchodilators do not improve exercise tolerance in such patients.

We studied 32 patients with stable COPD, mean age 65 yrs, in a double-blind, placebo-controlled, cross-over trial of the inhaled anticholinergic drug, oxitropium bromide. From the within and between day placebo spirometry, we derived the spontaneous variation in forced expiratory volume in one second (FEV<sub>1</sub>) and forced vital capacity (FVC) of this population (FEV<sub>1</sub> 140 ml; FVC 390 ml) and considered responses beyond this to be significant.

Oxitropium bromide increased baseline FEV<sub>1</sub> from 0.70 (0.28) l (mean (SD)) to 0.88 (0.36) l. The 6 min walking distance increased by 7% compared with placebo, whilst resting breathlessness scores fell from 2.0 to 1.23 at rest and 4.09 to 3.28 at the end of exercise after the active drug.

Improvements in walking distances and symptoms were unrelated to changes in either FEV<sub>1</sub> or FVC, indicating that routine reversibility testing is not a good predictor of symptomatic benefit in these patients.

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Many patients with stable chronic obstructive pulmonary disease (COPD) show some reversibility of their airflow limitation on testing with beta-adrenergic or anticholinergic drugs [1-3], and some of these respond to corticosteroids [4-6]. Whilst the benefits of treatment associated with large changes in pulmonary function are clear in asthmatic patients [7], the smaller changes seen with partial reversibility in COPD are harder to evaluate. In particular, we do not know whether the improvements in breathlessness or exercise tolerance are confined to patients whose bronchodilator response exceeds the normal between measurement variability.

Inhaled anticholinergic bronchodilators appear to be more effective in older patients with less labile airflow limitation [2, 8, 9] but, unlike salbutamol, they did not improve corridor walking distance in a previous study [10]. We have investigated this unexpected finding in a double-blind, placebo-controlled, cross-over study of the effects of the anticholinergic drug, oxitropium bromide, on corridor walking distance and symptoms. In addition, we have established the spontaneous variability of forced expiratory volume in one second (FEV<sub>1</sub>) and forced vital capacity (FVC) in these

patients, and using the data have examined the relationship between short-term bronchodilator response and changes in both exercise performance and dyspnoea, using different reversibility criteria.

### Methods

We studied 32 patients in two centres. Chronic obstructive pulmonary disease was defined as a history of continuous breathlessness for more than 12 months together with an FEV<sub>1</sub> of  $\leq 1.2$  l. Patients with known cardiac or other respiratory disorders were excluded, as were those with exacerbations in the last two months and those taking oral corticosteroids. All subjects had been shown to have a >15% improvement in FEV<sub>1</sub> after inhaled salbutamol at sometime in the preceding six months and no change was made in their normal drug therapy during the study. No patient was receiving oral prednisolone. The mean age (SD) of the group was 65 (8) yrs, 17 were female, 7 were current smokers, 21 ex-smokers and 4 nonsmokers. Informed consent was obtained in all cases and the study protocol was approved by the District Ethics Committees of both hospitals.

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Each patient attended on four occasions, at the same time of day, and at least 6 h after any inhaled bronchodilator treatment, (oral bronchodilators were discontinued seven days before entry to the study). All spirometric measurements were made with the dry spirometer (Vitalograph UK Ltd) recording the best FEV<sub>1</sub> and best FVC of three acceptable traces. Breathlessness was assessed by asking the patients "how breathless do you feel?" and recording the response on a modified Borg category scale [11]. Six minute walks (6MD) were performed as described by BUTLAND *et al.* [12] with a standardized encouragement during the walk. On the first two visits, spirometry was measured before and 15 min after salbutamol 200 µg or 45 min after ipratropium bromide 40 µg, both given by metered dose inhaler under supervision. Two practice 6 min walks were performed with 60 min rest between each walk. Breathlessness was assessed before and immediately after each walk (end-exercise). On visits 3 and 4, baseline spirometry was recorded and patients performed a walking test, as previously. Then, patients received either oxitropium bromide 200 µg or placebo from a metered dose inhaler in a randomized, double-blind fashion and, after 45 min, spirometry and the 6 min walk were repeated.

In assessing reversibility, we considered that significant change after a bronchodilator was likely when the spirometric variable (either FEV<sub>1</sub> or FVC) increased by 15% from its baseline value and this change exceeded the 95% confidence intervals for the variable in this population. Four patterns of response were possible - an isolated improvement in FEV<sub>1</sub> but not FVC, in FVC but not FEV<sub>1</sub>, in both or in neither. We derived the spirometric confidence intervals for the population using the method described by TWEEDALE *et al.* [13]. Results are expressed as mean and standard deviation unless otherwise stated. Comparisons between treatments have been made using the paired Student's *t*-test as part of a general linear model analysis programme; *p*=0.02 being taken as the lower limit of significance [14]. The modified Borg scale linearizes the relationship between sensation and other physical variables within an individual [15]. Changes within individuals have been compared using both parametric and non-parametric tests (Wilcoxon signed rank) and no difference was seen between them. Statistical comparisons of Borg scale data between the subjects have been made using only non-parametric tests.

## Results

There were no differences attributable to either the centre in which the study was conducted or to treatment order for any of the variables assessed. Mean walking distance increased significantly from 370 (82) to 401 (75) m between practice days 1 and 2 (*p*<0.001), but there was no further increase in baseline walking distance after day 2. Data describing the natural variability of these variables is presented for days 3 and 4 only, in order to exclude any practice effects.

### Spontaneous measurement variation

The group mean baseline FEV<sub>1</sub> were very similar on days 3 and 4 (0.70 (0.28) l and 0.72 (0.28) l, respectively). Likewise, baseline FVC was stable at 1.74 (0.60) l and 1.72 (0.72) l on each day. Data describing the within and between day variability in spirometry, walking distance and breathlessness scoring were derived from measurements on the placebo day, before and after drug administration as appropriate. In this population a change of 140 ml in FEV<sub>1</sub> and 390 ml in FVC was required to exceed the within day 95% confidence intervals for these measurements. These values exceeded 15% of the baseline FEV<sub>1</sub> in these patients.

Likewise, baseline walking distance and resting breathlessness scores did not differ between the study days. The within day variation in walking distance was 53 m with a between day variability of 78 m. The non-parametric nature of the breathlessness scoring across the population makes a similar analysis for these variables inappropriate but there was no change in the group mean breathlessness score before and after placebo walks.

### Bronchodilator effects

Group mean spirometry before and after salbutamol, ipratropium bromide and oxitropium bromide is reported in table 1, with the individual data interrelationships shown in figure 1. All three drugs produced a statistically significant bronchodilatation for the group as a whole but there was considerable variation in the size of these responses between subjects and across the different drugs. Oxitropium bromide increased group mean 6MD by 27 m, reduced breathlessness at rest scores from 2.02 to 1.23 and end-exercise scoring from 4.09 to 3.28 (*p*<0.01 in all cases compared with pre-drug values and placebo data (fig. 2)). However, the absolute increase in breathlessness scored during the walks before and after oxitropium bromide was not different.

In table 2 the characteristics of patients showing different patterns of bronchodilatation to oxitropium bromide are summarized. Approximately one third of the group showed no response spirometrically, one third responded with changes in both FEV<sub>1</sub> and FVC and one third with one or the other. Non-responders had a lower initial FEV<sub>1</sub>, higher level of resting breathlessness and shorter baseline 6MD than complete responders. Statistically significant improvements in walking distance and reductions in breathlessness scores were seen in all three groups, with a similar absolute change in these variables occurring in the non-responder and complete responder subgroups. The absolute change in walking distance was not dependent on the size of the increase in FEV<sub>1</sub> but was inversely correlated with the change in resting breathlessness score, so that the greater the reduction in dyspnoea, the further the patient walked (*r*=-0.44, *p*<0.01).

Table 1. - Changes in group mean (sd) spirometric variables after placebo and the three inhaled bronchodilator drugs; each drug was administered on a different day

	FEV <sub>1</sub> l		FVC l	
	Before	After	Before	After
Placebo	0.72 (0.28)	0.73 (0.31)	1.74 (0.67)	1.69 (0.72)
Salbutamol	0.69 (0.27)	0.90 (0.34)*	1.62 (0.67)	2.10 (0.80)*
Ipratropium	0.71 (0.27)	0.88 (0.35)*	1.71 (0.69)	2.09 (0.86)*
Oxotripium	0.70 (0.28)	0.88 (0.36)*	1.72 (0.71)	2.13 (0.81)*

\*: statistically significant difference at the p<0.001 level. FEV<sub>1</sub>: forced expiratory volume in one second; FVC: forced vital capacity.

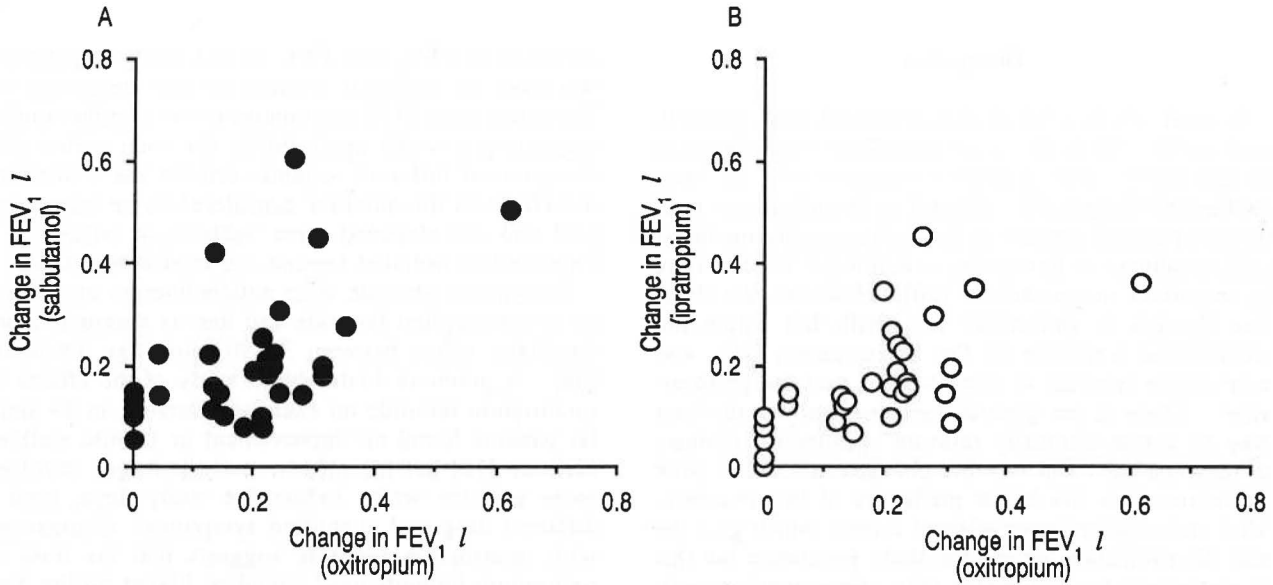


Fig. 1. - Individual data showing the interrelationship between the bronchodilator response to oxitropium with: A) 200 µg salbutamol; and B) 40 µg ipratropium bromide, and the variability of the response with three drugs.

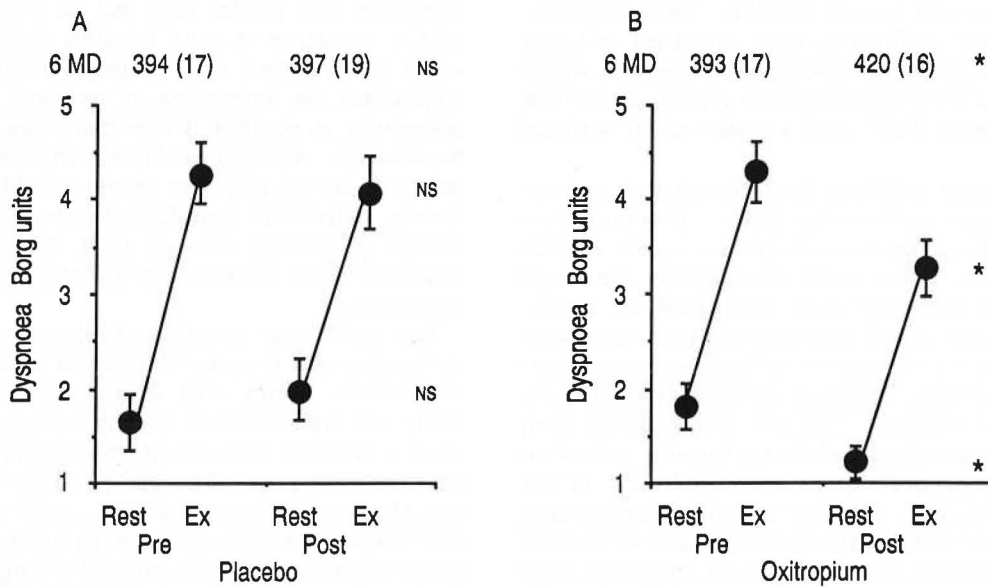


Fig. 2. - The effect of oxitropium bromide (B) on 6 min walking distance (6MD) and breathlessness scores compared with placebo (A). Data expressed as group mean (SEM). Error bars are included with breathlessness scores as a measure of variability and do not reflect the statistical treatment of the data. \*: significantly different at the 1% level in the paired comparisons of walking distance, rest and exercise dyspnoea before and after drug. Ex: end-exercise.

Table 2. - Relationship of the bronchodilator response to walking distance and symptoms

Response Criterion	n	Baseline		After bronchodilator				
		FEV <sub>1</sub> l	6MD m	ΔFEV <sub>1</sub> l	ΔFVC l	Δ6MD m	Δ Dyspnoea Rest End-exercise	
FEV <sub>1</sub> + FVC	10	0.80 (0.33)	441 (101)	0.30 (0.12)	0.76 (0.36)	26 (37)	-0.6	-1.0
FEV <sub>1</sub> only	6	0.74 (0.29)	417 (52)	0.24 (0.02)	0.26 (0.15)	19 (16)	-0.6	-1.1
FVC only	3	0.57 (0.12)	348 (58)	0.14 (0.01)	0.44 (0.02)	15 (48)	-0.2	-0.7
Neither	13	0.60 (0.16)	358 (100)	0.06 (0.07)	0.19 (0.13)	33 (32)	-0.7	-1.1

Response criteria are defined by a change ( $\Delta$ ) in spirometry which exceeds the 95% confidence intervals for short-term variation in the measure. Responder groups are separated by the presence or absence of changes in FEV<sub>1</sub> and/or FVC. Data for the mean (SD) baseline FEV<sub>1</sub> (l) and 6 min walking distance (6MD, m) are given for each responder group, as are the mean changes in these variables and breathlessness scores after oxitropium bromide. FEV<sub>1</sub>: forced expiratory volume in one second; FVC: forced vital capacity.

### Discussion

Several studies have demonstrated that patients with stable COPD can show significant improvements in spirometry after inhaled  $\beta_2$ -agonists [16] or anticholinergic drugs [17]. Control of bronchomotor tone in such patients appears to be cholinergically mediated [18], is subject to day-to-day variation [3, 19] and may be important prognostically [20]. However, the absolute changes in spirometry are small, fall within the spontaneous variation of the measurement [13], and may not be relevant to symptoms or exercise performance. There is no general agreement about the best way to define clinically relevant spirometric changes in these patients and whether changes in FVC or peak expiratory flow are better predictors of improvement. Most investigators have selected criteria which give the best discrimination among the study population but this is not necessarily associated with symptomatic benefit [5, 6, 21]. We found that patients with stable COPD show small but significant improvements in breathlessness and corridor walking distance after inhaled oxitropium bromide but not placebo. These improvements were not confined to those classified as being reversible on spirometric criteria, but patients in whom both FEV<sub>1</sub> and FVC improved after bronchodilator had a higher baseline FEV<sub>1</sub> and a better initial walking distance.

Methodological problems limit the clinical application of the tests used in this study. Familiarization with the walking test is an important aspect of trial design [22] but unlike some other groups we found that after two pre-study visits there were no significant differences in the pre-drug walking distances. Quantification of respiratory sensations using visual analogue or category scaling is increasingly used in the assessment of treatment [23] and the modified Borg scale has the advantage of being linearly related to objective physiological measurements [14, 24]. In this study, breathlessness provided a complimentary endpoint and some individuals (n=11) walked for a similar distance but to a lower level of dyspnoea after active drug, whilst others (n=5) increased their 6MD and end-exercise level of breathlessness.

In defining a bronchodilator response, we were able to use our placebo data to establish the spontaneous

variation of FEV<sub>1</sub> and FVC in our study population. We used an identical method to that described by TWEEDALE *et al.* [13] and obtained very similar results, suggesting a wider applicability for such values [5]. Adoption of different response criteria has a substantial effect on the numbers considered to be responsive [25] and we observed three subjects in whom FVC improved in isolation beyond our confidence limits.

Oxitropium bromide is an anticholinergic drug similar to ipratropium bromide and has its maximal bronchodilator effect between 30–90 min after inhalation [26]. A previous double-blind study of the effects of ipratropium bromide on exercise tolerance in 24 similar patients found no improvement in 12 min walking distance [10] but the present study is larger, involved more practice walks before the study days, used a different drug and quantified symptoms. Comparison with ipratropium bromide suggests that the dose of oxitropium bromide used would be higher on the dose response curve [26] and this may explain the somewhat greater increases in walking distance that we found. However, the impact of the active drug on symptoms was greater than that on walking distance with a reduction in both baseline and end-exercise levels of dyspnoea after oxitropium bromide. This emphasizes the importance of assessing symptoms as objectively as possible if important drug effects are to be detected. Although within the short-term reproducibility of this measure the change in 6MD was, nonetheless, statistically significant for the group. A small change in walking distance alone is of doubtful significance unless accompanied by parallel reductions in symptoms.

The rapid onset of action of inhaled adrenergic and anticholinergic bronchodilators has made short-term reversibility testing with spirometry practical in the clinic and the laboratory, but the interpretation of such tests is difficult because of spontaneous variation in baseline FEV<sub>1</sub> [3]. Although, all of the study patients had shown reversibility in FEV<sub>1</sub> prior to entry, only half would have been classified as having such reversibility when studied with our active drug. We did not find a relationship between baseline FEV<sub>1</sub> and 6MD, nor was the change in FEV<sub>1</sub> predictive of improvement in walking distance after oxitropium bromide. Reversibility status, however defined, had no effect on the

small but statistically significant increases in walking distance and reduction in breathlessness which occurred in these patients. This suggests that the FEV<sub>1</sub> response behaves as a continuous variable and that for these purposes the separation into "reversible" and "irreversible" patients is not helpful. These findings with anticholinergic blockade are similar to those reported in smaller studies, where patients were selected for lack of reversibility to  $\beta_2$ -agonists [27], and to a study which shows reduction in breathlessness at rest after bronchodilator in similar COPD patients [28]. Whether such changes would be present in patients who do not respond on repeated reversibility testing is not known.

Why these effects occur is unclear. The small degree of bronchodilatation produced by oxitropium bromide in the central airways [29-31] may be sufficient to permit better lung emptying during exercise. Alternatively, improvement may also affect small airway calibre, which might improve exercise tolerance, as has been suggested with other drugs, in similarly disabled patients [32]. Such an effect may influence the degree of hyperinflation at rest, reducing the inspiratory threshold load imposed by positive end-expiratory pressure (PEEPi), and hence diminish the perception of breathlessness. The mechanisms underlying this have recently been reviewed [33-35]. Anticholinergics might affect afferent information from intrapulmonary stretch receptors but the evidence for an important role for such a sensation in the perception of breathlessness in man, is presently lacking.

Whatever the mechanism, these data show that anticholinergic therapy can improve symptoms and exercise tolerance in COPD, even when the changes in spirometry fall within the expected variability of the measurement. Whilst tests of bronchodilator reversibility may help to categorize the patients and select a group more likely to be steroid responsive [5], failure to show a "reversible" response should not preclude a trial of symptomatic bronchodilator treatment.

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