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The effect of bronchodilators and oxygen alone and in combination on self-paced exercise performance in stable COPD

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KEYWORDS

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Summary

Both oxygen therapy and bronchodilators reduce exertional breathlessness and improve exercise tolerance in patients with stable chronic obstructive pulmonary disease (COPD). However their relative effectiveness and the value of their combined use on exercise performance has not been assessed.

The effects of 5 mg of salbutamol plus 500 µg ipratropium bromide nebulisation followed by a 6-min walking test while breathing O₂ were studied in a randomised, single-blind, placebo controlled, crossover trial in 28 patients with severe or very severe COPD, breathless on exertion and with oxygen saturation ≤ 89% at rest or on exercise. Bronchodilator reversibility was minimal. The 6-min walking distance increased from 356 (128) m to 377 (117) m after the bronchodilator ($P < 0.05$), to 406 (109) m after supplementary oxygen but without bronchodilators ($P < 0.011$ versus bronchodilators/air and 0.001 versus placebo/air), and to 430 (109) m after the combination of oxygen and the bronchodilators ($P < 0.0001$ versus placebo/air and bronchodilators/air; $P = 0.014$ versus placebo/oxygen). End-exercise dyspnea only fell significantly when oxygen and bronchodilator were combined.

In severe or very severe COPD patients with relatively fixed airway obstruction bronchodilators enhance exercise performance obtained with oxygen. Clinically relevant improvement is possible when therapies with a different mechanism of action are combined.

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Abbreviations: COPD, chronic obstructive pulmonary disease; SaO₂, oxygen saturation; ATS/ERS, American Thoracic Society/European Respiratory Society; DL_{CO}, single breath diffusing capacity for carbon monoxide; 6MWD, 6-min walking distance

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Introduction

Breathlessness and reduced exercise capacity are the most disabling symptoms in patients with chronic obstructive pulmonary disease (COPD)¹ and a major goal of treatment is to reduce dyspnoea, improve exercise tolerance and decrease handicap. Several studies have shown that short-acting bronchodilator drugs can reduce dyspnoea and increase self-paced exercise performance,^{2–4} mainly by reducing dynamic hyperinflation which is thought to occur secondary to tidal expiratory flow limitation.⁵ Increasing the inspired oxygen concentration during exercise also improves exercise capacity^{6,7} probably through the combination of reductions in dynamic hyperinflation due to a diminished ventilatory requirement,⁸ and better systemic oxygen delivery.⁹ These different and commonly used treatments appear to act through different physiological mechanisms. To date, no study has directly compared their relative benefit singly or in combination in the same individual.

Laboratory exercise protocols where the workload is fixed or allowed to rise in intensity have provided insights into the mechanisms by which treatment improves exercise performance in COPD.^{10–12} However, these tests do not necessarily correspond to the way patients behave in everyday life and for this reason so-called 'field' tests of exercise performance such as the self-paced 6-min walking distance (6MWD) have been developed.^{13,14} Although relatively simple to perform, standardised results require attention to detail, particularly in terms of prior familiarisation¹⁵ and encouragement.¹⁶ When this is done it has been shown that self-paced walking produces a progressive increment in oxygen consumption which approaches the peak oxygen consumption measured during conventional laboratory exercise.¹⁷ Walking tests have proven sensitive to a range of interventions noted above as well as pulmonary rehabilitation.¹⁸ They are also prognostically useful which has led to their incorporation in multistage clinical scoring systems.¹⁹

This study was designed to evaluate the short-term impact of oxygen alone or in combination with bronchodilators on exercise capacity and breathlessness in patients with relatively advanced but clinically stable COPD who themselves would be suitable for the prescription of ambulatory oxygen. We hypothesised that the effect of both interventions would be greater than the placebo and that each intervention would itself be additive in its effect. To test this we conducted a randomised single blind placebo controlled cross-over trial comparing either high-dose nebulised ipratropium bromide together with salbutamol or a saline placebo given before first walking test of the study day and oxygen or air randomly administered during a subsequent walking test.

Methods

Subjects

Patients aged 40–80 years with clinically stable COPD were studied as outpatients at the pulmonary division of the University of Sao Paulo Medical School Hospital. COPD was defined using the ATS/ERS criteria²⁰ and all patients had breathlessness on exertion, a history of smoking of at least

25 years, a pre-bronchodilator forced expiratory volume in 1 s (FEV₁) of less than 60% predicted with an FEV₁/ forced vital capacity (FVC) ratio of <70% and exhibited resting and/or exercise induced arterial oxygen desaturation with an oxygen saturation (SaO₂) of <90%. Patients were excluded if they gave a history of an exacerbation of COPD in the preceding month, had significant cardiovascular disease, musculoskeletal problems, peripheral vascular disease or other disabling conditions which would interfere with their ability to exercise. All patients were taking short-acting bronchodilators as symptom reliever and the following medication as maintenance therapy: inhaled corticosteroids (58%), long-acting β 2 agonists (42%) and theophylline preparations (38%). None were receiving long-acting inhaled anticholinergics. The study protocol was approved by the local Research Ethics committee and informed consent was obtained in all cases.

Pulmonary function testing

Pulmonary function was tested in accordance with recommended methodologies²¹ and included spirometry, static lung volumes determined in a constant volume plethysmograph, single breath diffusing capacity for carbon monoxide (DL_{co}) (Collins/GS, Warren E Collins Inc., USA) and arterial blood gas tensions breathing air at rest. On the study days, spirometry was recorded before exercise using a hand held spirometer (Micro Spirometer, Micro Medical Ltd., Kent, UK) to confirm clinical stability.

Exercise testing

The 6MWD was measured as previously described with standardised encouragement during each walk.²² Continuous arterial oxygen saturation (SpO₂) and heart rate was measured with a finger oximeter (Palco Labs model 120 pulse oximeter, Palco Labs Inc, Santa Cruz, CA, USA). Dyspnoea was assessed using a modified Borg scale in response to the question 'How breathless do you feel?' and leg fatigue by the question 'How tired do your legs feel?'. Patients were familiarised with these questions before testing. They were asked to point to the Borg score corresponding to their current sense of intensity at rest, during exercise and during recovery. All tests were performed by the same investigator who used the same form of encouragement in the same way, irrespective of the treatment given.

Study design

The study protocol is presented in Fig. 1. Patients attended on three occasions at a same time of day and at least 6 or 24 h after taking short-acting bronchodilators or long-acting bronchodilators as appropriate. At the first visit, pulmonary function tests were obtained as described above, arterial blood was drawn while breathing air at rest and two practice 6-min walks were performed with a 60 min rest period between each test. At visits two and three, in a single blind cross-over fashion (to bronchodilators and the respective gas mixtures), baseline spirometry was recorded before and 30 min after inhalation of nebulised saline. Next, a walking

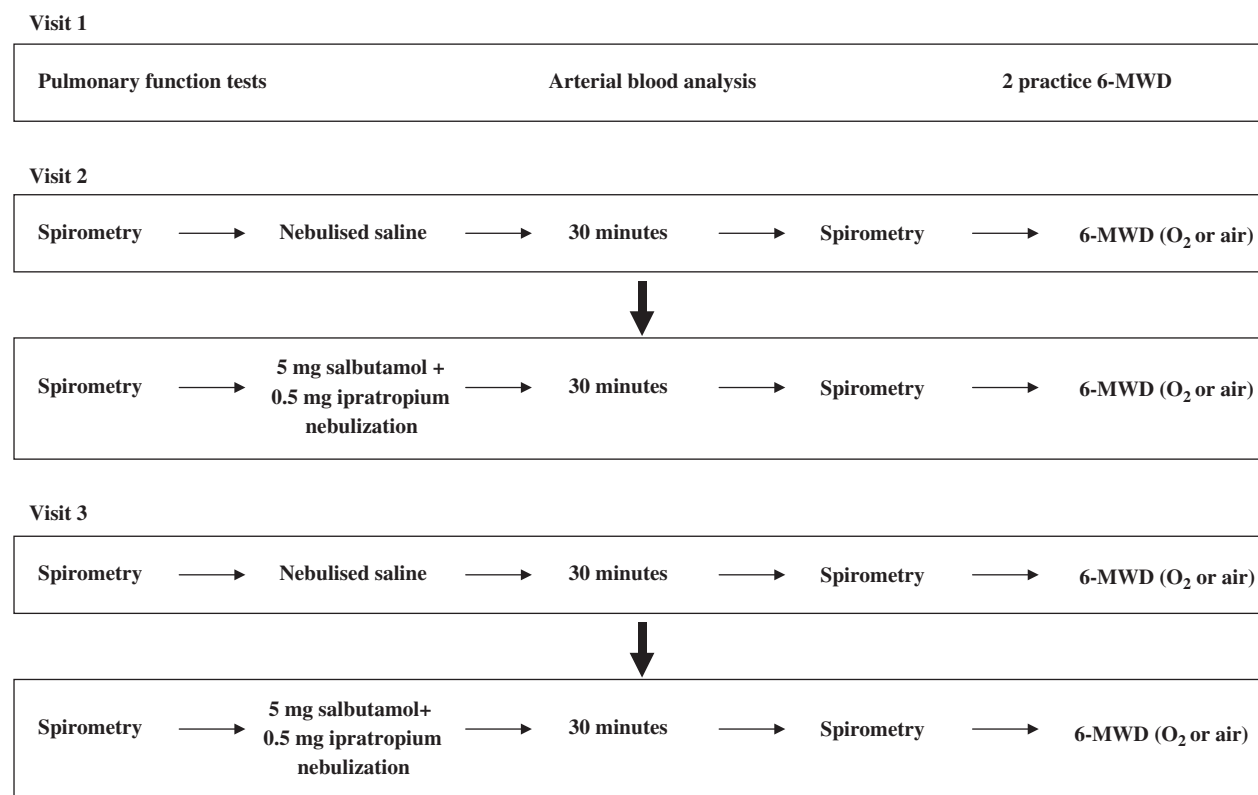


Figure 1 Schematic presentation of study design to show the sequence of aerosol administration, timing of spirometry and 6-min walking test (6MWD).

test was performed with the patient breathing compressed air or supplemental oxygen by nasal prongs at 3l/min according to randomisation. Subsequently, the patients rested for 1 h, repeated their spirometry and then received salbutamol 5 mg together with ipratropium bromide 0.5 mg via an identical nebuliser. After this, spirometry was repeated as was the 6MWD breathing either compressed or supplemental oxygen according to the randomisation schedule.

Statistical analysis

Results are expressed as mean and standard deviation when describing populations and as standard error of the mean for group comparisons. The order of the visits was randomised in each patient, so the patients received either compressed air or supplemental oxygen for each walking test at the first visit with cross-over at the second visit. The study was powered on the assumption that the combination of oxygen and the bronchodilators would produce a difference of 54 m in the walking distance. A study of 12 patients would have a 90% power to detect such a difference. To permit comparison with other endpoints e.g. placebo and each active therapy, the sample size recruited was doubled with allowance for possible study drop out. Comparison between treatments were made using analysis of variance of repeated measures with a *P* value of <0.05 being accepted as the lower limit of significance. Pearson correlation was used to establish association between the performance

during the acclimatisation walk and the walk breathing air after placebo.

Results

The demographic characteristics of the patients entering the study are shown in Table 1. They were an elderly group, predominantly male and had severe airflow obstruction with significant resting hyperinflation as seen by the increased residual volume and total lung capacity as a percent of predicted. Although gas transfer was significantly reduced they did not have marked resting hypoxaemia, the lowest PaO₂ being 52 mmHg. All were significantly limited by breathlessness as indicated by the low baseline dyspnea index across the group. They showed minimal bronchodilator reversibility, only six of the 28 increasing their FEV₁ by 12% of baseline and 200 ml after the nebulised bronchodilators. The 6MWD on the air study day varied between patients ranging from 72 to 581 m while mean end-exercise breathlessness was 4.0. The 6MWD and breathlessness scores breathing air were reproducible, the mean distance after the acclimatisation walk being 335 m compared with the mean distance breathing air after placebo of 355 m (intraclass correlation coefficient 0.91). Desaturation breathing air occurred in all cases, the mean change in oxygen saturation being 9.4%. In six patients the saturation was ≤89% at rest (minimum, 85.7%; maximum, 95.5%).

Data summarising the effect of the bronchodilators and oxygen on spirometry and oxygen saturation, respectively, are shown in Table 2. Similarly data about the walking

distance and breathlessness in the different conditions are presented in Fig. 2. After the bronchodilator the 6MWD breathing air showed a small statistically significant improvement of 22 (10)m but only five subjects (18%) improved by 54 m or more, the minimum clinically important difference suggested for this test.²³ Breathing supplementary oxygen without extra bronchodilators increased the minimum SpO₂ during exercise relative to the placebo-air

walk in all cases and in 22 patients minimum SpO₂ was >89%. With this comparison we saw an increase of 51 (14) m in 6MWD which was significant ($P = 0.001$). This improvement was also significantly greater than the walking distance breathing air after the bronchodilator alone, altogether 13 patients (46%) increasing their walking distance by more than 54m. The combination of oxygen and the bronchodilators increased SpO₂ >89% in 19 patients and produced the greatest increase in walking distance relative to air and this was also significantly greater than either component alone with 19/28 (68%) improving the walking distance by 54 m or more.

Subjects exercised to a similar intensity of breathlessness after both bronchodilator and oxygen treatment, although in each case the distance covered was greater. When using the combination of the bronchodilators and oxygen the subjects still did not report such severe breathlessness when they stopped as was the case in the other treatment conditions. The rate of increase of breathlessness per metre walked differed with the treatments (Fig. 3). There was no statistically significant difference in the rate of change of breathlessness after the bronchodilator; however, breathlessness appeared to increase more slowly during the oxygen alone walk with a value, which approached but this trend did not reach statistical significance ($P = 0.06$). There was a significant change in the rate of increase of breathlessness when oxygen and bronchodilator treatment were combined ($P = 0.03$). The increase in Borg score for leg fatigue at end-exercise was less pronounced than breathlessness score and there was no statistically significant difference between the treatments (mean (SE): placebo/air 0.89 (0.29); bronchodilators/air 1.05 (0.29); placebo/oxygen 0.89 (0.26); bronchodilators/oxygen 1.14 (0.31). There was no statistically significant difference in end-exercise heart rate (mean (SE): placebo/air 112.0 (2.4) bpm; bronchodilators/air 116.4 (2.3) bpm; placebo/oxygen 113.4 (2.0) bpm; bronchodilators/oxygen 115.1 (2.3) bpm). There was no difference in the time taken to return to the initial breathlessness score after the end of exercise between any of the four treatment conditions (mean (SE): placebo/air 2.88 (0.16) min; bronchodilators/air 2.94 (0.19) min; placebo/oxygen 3.10 (0.19) min; bronchodilators/oxygen 2.83 (0.16) min).

The degree of oxygen desaturation during exercise breathing air and placebo varied from 73% to 89% and was

Table 1 Baseline anthropometric and resting lung function data.

No. of patients	28
Sex (M:F)	20:8
Age (years)	66.8 (9.0)
BMI (kg/m ²)	23.7 (4.5)
FEV ₁ (l)	0.81 (0.25)
FEV ₁ (% predicted)	34.61 (10.35)
FVC (l)	2.11 (0.64)
FVC (% predicted)	65.54 (16.72)
FEV ₁ /FVC (%)	0.39 (0.07)
IC (l)	1.58 (0.46)
IC (% predicted)	72.04 (16.99)
SVC (l)	2.28 (0.66)
TLC (l)	7.09 (1.89)
TLC (% predicted)	134.39 (25.87)
RV (l)	4.79 (1.64)
RV (% predicted)	240.04 (78.68)
DL _{co} (% predicted)	43.04 (23.16)
pH	7.40 (0.02)
PaO ₂ (mmHg)	61.49 (5.94)
SaO ₂ (%)	90.9 (2.3)
PaCO ₂ (mmHg)	40.71 (4.56)
Resting Borg breathlessness score	1.23 (1.12)
Resting Borg leg score	0.21 (0.62)
Baseline dyspnoea index	4.2 (2.2)

Values given are mean (SD).

BMI, body mass index; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; IC, inspiratory capacity; SVC, slow vital capacity; TLC, total lung capacity; RV, residual volume; DL_{co}, diffusing capacity; PaO₂, arterial oxygen tension; SaO₂, arterial oxygen saturation; PaCO₂, arterial carbon dioxide tension.

Table 2 Effect of inhaled salbutamol+ipratropium and placebo on spirometric indices, and of oxygen and air on oxygen saturation in 28 patients.

	FEV ₁		FVC		SpO ₂	
	Before inhalation	After inhalation	Before inhalation	After inhalation	Resting	End-exercise
Placebo inhalation/air walk	0.76 (0.05)	0.80 (0.05)	1.72 (0.12)	1.89 (0.11)**	91.3 (0.5)	81.9 (1.0)
Placebo inhalation/O ₂ walk	0.72 (0.05)	0.76(0.06)	1.56 (0.11)	1.77 (0.14)***	91.0 (0.4)	92.3 (0.9)****
BD inhalation/air walk	0.78 (0.06)	0.91 (0.06) *	1.84 (0.13)	2.11 (0.13)*	90.8 (0.5)	82.0 (1.0)
BD inhalation/O ₂ walk	0.78 (0.05)	0.90 (0.06) *	1.87 (0.12)	2.10 (0.13)*	91.0 (0.4)	90.4 (1.4)****

Data are expressed as mean (SE).

FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; SpO₂, oxygen saturation; BD, bronchodilators. * $P \leq 0.001$ compared with pre inhalation values. ** $P = 0.01$ compared with pre-inhalation values. *** $P = 0.007$ compared with pre-inhalation values. **** $P < 0.001$ compared with placebo inhalation/air walk and BD inhalation/air walk.

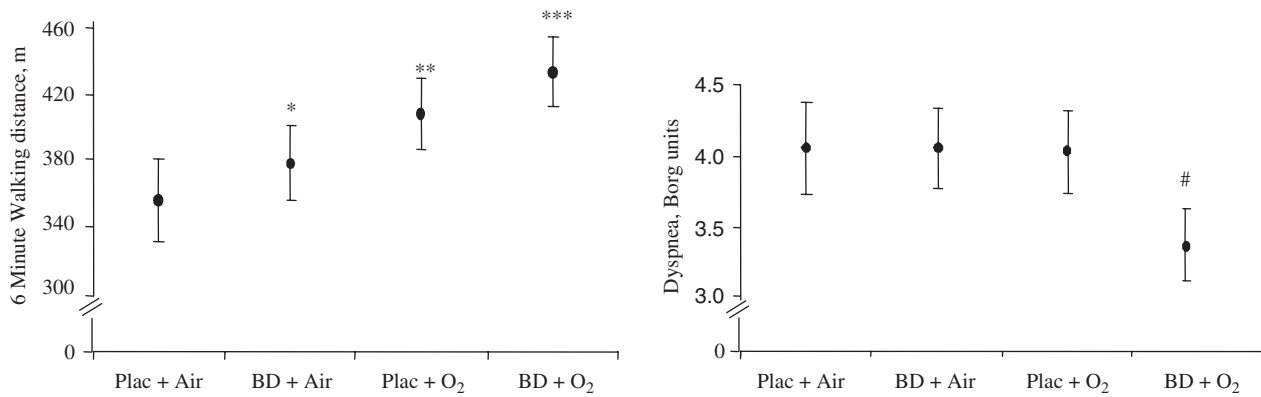


Figure 2 The effect of ipratropium plus salbutamol (BD) and oxygen on 6-min walking distance (6MWD) and dyspnoea scores at end exercise. Values given are mean (SEM). Plac+air: placebo nebulisation and walk on compressed air; BD+air: bronchodilators nebulisation and walk on compressed air; Plac+O₂: placebo nebulisation and walk on oxygen; BD+O₂: bronchodilators nebulisation and walk on oxygen. *Significant difference with Plac+air ($P = 0.047$); **Significant difference with Plac+air ($P = 0.001$) and BD+air ($P = 0.011$); ***Significant difference with Plac+air ($P < 0.0001$), BD+air ($P < 0.0001$) and Plac+O₂ ($P = 0.014$); #Significant difference with Plac+air ($P = 0.027$), BD+Air ($P = 0.029$) and Plac+O₂ ($P = 0.028$).

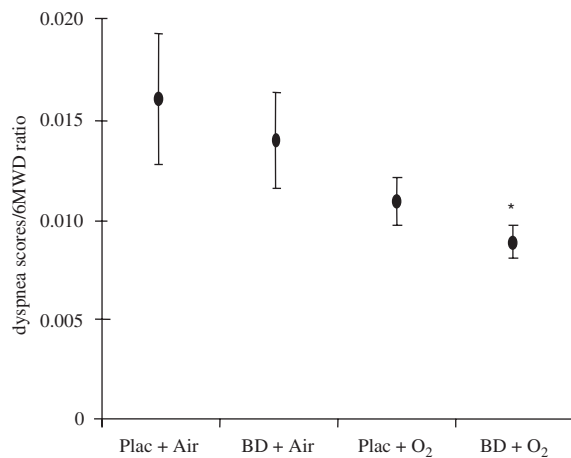


Figure 3 The effect of ipratropium plus salbutamol (BD) and oxygen on dyspnoea scores/6 min walking distance (6MWD) ratio at end exercise. Values given are mean (SEM). Plac+air: placebo nebulisation and walk on compressed air; BD+air: bronchodilators nebulisation and walk on compressed air; Plac+O₂: placebo nebulisation and walk on oxygen; BD+O₂: bronchodilators nebulisation and walk on oxygen. *Significant difference with Plac+air ($P = 0.008$), BD+air ($P = 0.010$) and Plac+O₂ ($P = 0.003$).

not related to the distance walked. The minimum saturation during exercise was lower with the bronchodilator drug compared to placebo, irrespective of whether the patient was breathing oxygen or air but this difference was not statistically significant. Oxygen breathing failed to prevent desaturation below 90% in six subjects who received he saline nebulisation and in nine who received bronchodilator. However, these patients did not differ significantly in their response to treatment to those where desaturation was less severe.

No pre-exercise variable, whether clinical or physiological, identified a different pattern of response to any treatment and specifically, the initial FEV₁, inspiratory

capacity, residual volume and total lung capacity and the magnitude of increase in FEV₁ after the bronchodilators were all unhelpful. Neither was the degree of oxygen desaturation at rest or during exercise a predictor of either the initial walking distance breathing air or of the change in walking distance in the regimes where oxygen was administered. However the initial walking distance breathing air without bronchodilators was inversely related to the subsequent improve in distance walked (Fig. 4). This relationship was relatively weak for the bronchodilators alone but was stronger for walk tests where oxygen was administered where an effect on exercise performance was evident even in patients with higher initial walking distances, something not seen in the bronchodilator-air walks.

Discussion

It is now accepted that exercise tolerance in patients with significant COPD can be improved by treatment even when spirometry is unaffected.^{2,24} A range of short- and long-acting bronchodilator drugs increase the duration of endurance exercise mainly by reducing end-expiratory lung volume at any given time during exercise.^{10,11,24,25} The same appears to be true for patients treated with oxygen, although the rate of increase of end-expiratory lung volume for any externally imposed load is less, reflecting a reduction in ventilatory demand, which is thought to be mediated by chemoreceptor suppression.⁹ These effects of treatment, which have been demonstrated using cycle ergometry and with self-paced walking tests, appear to occur independently of the degree of oxygen desaturation.²⁶ However the relative magnitude of these effects has not previously been assessed in the same patients under conditions in which the treatment would be administered. The present trial was not designed to assess the mechanisms by which these treatments might interact but has focussed on whether worthwhile improvements in exercise capacity are possible in the type of patients in whom these

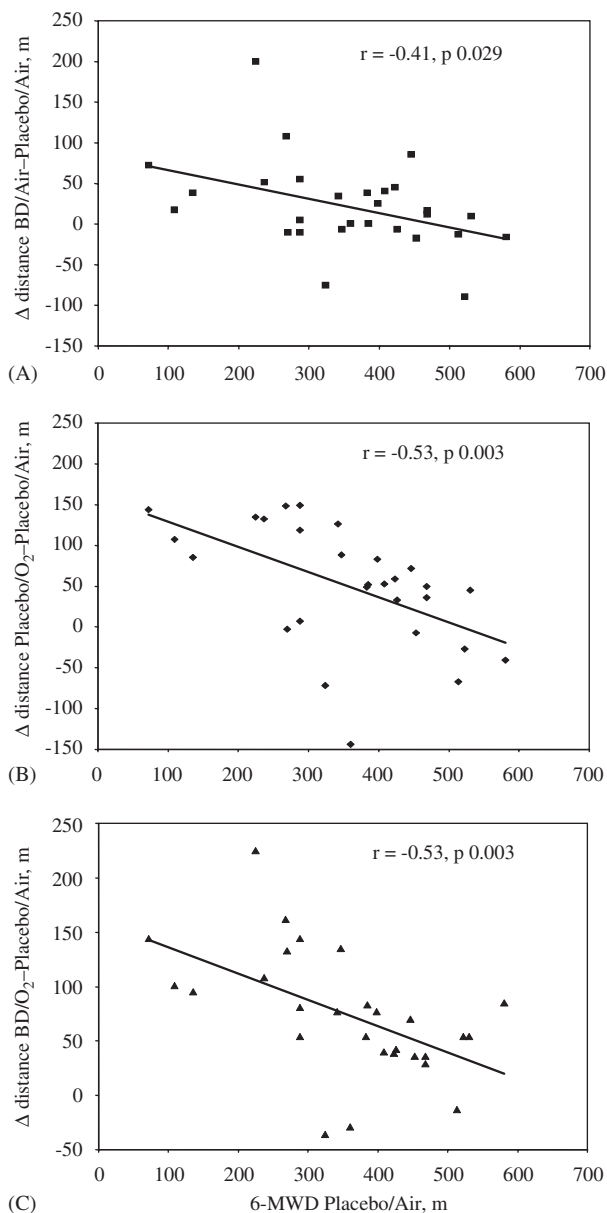


Figure 4 Relationship between initial walking distance and the change in distance walked with treatment relative to that initial distance breathing air only. Data are shown for tests breathing air after bronchodilator (A), breathing oxygen without bronchodilation (B) and for the combination of the two conditions (C).

treatments would be used. Our data suggest that treatment with different modalities of therapy is not mutually exclusive, even in poorly reversible COPD and worthwhile improvements in the walking distance and reductions in the intensity of breathlessness at end-exercise are possible.

Our patients had severe to very severe COPD as currently defined²⁰ and their daily activities were significantly impaired as judged by a mean BDI score of four. Most would be considered to be 'irreversible' on acute bronchodilator testing, although the value of this has been questioned in both severe and milder COPD.^{27,28} Despite this all the treatments tested produced a statistically significant improvement in exercise performance when the air breathing

walking test was compared to that after the bronchodilator with five individuals showing a change that by itself would be recognised as clinically important.²³ Oxygen was more effective in these short-term tests than high-dose nebulised bronchodilators with a larger number of subjects exceeding the minimum clinically important distance in walking distance as compared with bronchodilator treatment alone. However, like the bronchodilator therapy the intensity of breathlessness reported at the end of exercise was similar to that breathing air. When the treatments were combined walking distance showed a further significant improvement that was now accompanied by a reduction in the intensity of breathlessness at the end of exercise. On this occasion two thirds of the patients exceeded the minimal clinically important difference in walking distance. Treatment effectiveness could not be predicted from resting measurements but patients who walked less initially showed the greatest benefit. Some patients walked less far after bronchodilators, a change which may have a physiological basis.²⁵ In contrast oxygen alone or in combination improved walking distance consistently with the greatest absolute increase again being found in the most limited patients. This may reflect a relative ceiling effect of the 6MWD test and requires further testing using other endurance exercise protocols.

If anything, this is likely to be an under-estimate of the true improvement possible in these patients since the most effective treatment in terms of increased exercise performance was associated with less breathlessness and presumably, a greater capacity to increase exercise further. A composite endpoint of breathlessness per metre walked has been reported in pharmacological trials^{29,30} and this endpoint also distinguished between patients receiving the different treatments. However, it was no better than reporting only walking distance in our patients.

The use of a field test like 6MWD restricted the physiological data that could be collected. Nonetheless, the rate of increase of breathlessness per metre walked was unaffected by the bronchodilator but approached a significant reduction when oxygen and air breathing were compared ($P = 0.06$), in keeping with the known physiological effect of supplementary oxygen. The significant reduction in the rate of increase of breathlessness per metre walked seen with the combination of bronchodilator and oxygen supports the idea that each therapy is operating through an independent mechanism to improve exercise performance. The maximum heart rate achieved was similar at the end of each walking test irrespective of therapy suggesting that treatment was acting by improving ventilatory limitation and that patients were achieving a similar cardiovascular stress on each occasion. These changes were seen irrespective of the degree of resting or exercise oxygen desaturation while breathing air or oxygen, in keeping with previous data.²⁶ We failed to prevent desaturation during exercise in a number of cases but could see no consistent differences in treatment response between these patients and those where desaturation was prevented. Higher concentrations of inspired oxygen can improve exercise duration in the laboratory setting^{7,8} but delivering such high flows is not possible with the nasal prongs usually used in ambulatory therapy, which was the comparator system we used in this study.

The randomised order of testing was selected because of practical constraints on the number of tests we could perform in these relatively unwell patients. We saw no evidence of any order affected in our data although the fact that the post-bronchodilator or post-nebulised saline test was always second might have limited the improvements seen due to patient fatigue. However, the greatest improvement was seen after both bronchodilator and oxygen, which was the second test to be conducted in randomised order so we do not think that this is likely to be a significant limitation of our results. We noted that in some individuals, the greatest distance walked occurred on the placebo nebulisation and air test which may reflect the modest between day variability we established when comparing the post-practice and placebo air walks. Thus, some caution is needed in interpreting the results of a single or coupled walking test with regard to the individual patient. Our study was powered statistically to show a difference between the post-bronchodilator and oxygen combination and the other treatments, which it did. However, we were not fully powered to establish a difference between the oxygen alone and the bronchodilator alone treatment. Although such a difference is not likely to be large, other studies specifically designed to address this would be needed before any definitive conclusion could be established. The dose of bronchodilator chosen was high on the known dose response relationship³¹ the change in walking distance after the bronchodilator breathing air being comparable to that seen previously after large doses of salbutamol,³² and is similar to that reported when significant changes in resting inspiratory capacity were observed with the same drug combination.³³

Our data have practical implications. We have shown that clinically relevant improvement in exercise performance is possible when therapies with a different mechanism of action are combined in the way in which they would be used in clinical practice. This is analogous to other studies where a positive interaction between drug therapy and rehabilitation³⁴ has been demonstrated. Moreover, these benefits were most evident in patients who had the worst walking distance when breathing room air. Treating patients like these with oxygen and bronchodilators should produce noticeable improvements in exercise capacity in most cases and may improve compliance with ambulatory oxygen therapy, although this requires formal testing.

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