Oxygen desaturation and breathlessness during corridor walking in chronic obstructive pulmonary disease: effect of oxitropium bromide

D P S Spence, J G Hay, J Carter, M G Pearson, P M A Calverley

Abstract

Background—Although exercise induced desaturation can occur in patients with chronic obstructive pulmonary disease (COPD), little is known about its frequency during everyday exercise, or how it relates to dyspnoea or prior drug treatment.

Methods—The effects of 200 µg inhaled oxitropium bromide, an anticholinergic bronchodilator drug, on spirometric values, dyspnoea score, and oxygen saturation during corridor walking and cycle ergometry were studied in a double blind, randomised, placebo controlled study.

Results—Oxitropium produced a small increase in forced expired volume in one second (FEV₁) from 0.76 (0.28) l to 0.93 (0.69) l and in six minute walking distance from 311 (93) m to 332 (86) m, but did not change progressive cycle exercise duration. Resting and end exercise breathlessness levels were reduced in both forms of exercise after oxitropium. Resting oxygen saturation fell significantly after active bronchodilator from 92.9% (3.7%) to 92.0% (4.1%) but the nadir saturation during exercise was unchanged. The patients desaturated more during corridor walking than cycle ergometry [walking 7.8% (4.4%), cycle ergometry 2.1% (2.1%)]. Baseline walking distance was related to FVC, resting breathlessness and resting oxygen saturation (multiple $r^2 = 0.46$) but only resting saturation correlated with end exercise breathlessness ($r^2 = -0.25$). Improvements in symptoms or exercise performance after oxitropium could not be predicted by changes in spirometric indices or oxygen saturation.

Conclusions—In patients with COPD arterial oxygen desaturation during self-paced walking is common, of greater severity than that during cycle ergometry, but is unaffected by inhaled oxitropium bromide. The factors that predict initial performance are not appropriate markers of functional improvement after an active bronchodilator drug.

Exertional breathlessness and reduced exercise tolerance are important features of chronic obstructive pulmonary disease (COPD) and are usually attributed to a reduced ventilatory capacity.^{1,2} Arterial oxygen desaturation can occur in these patients³⁻⁶ but its frequency and severity during everyday exercise is controversial as is its relationship to breathlessness.⁷ Most data have come from cycle ergometer or treadmill exercise tests which may not be directly relevant to usual exercise patterns.⁸

Resting oxygen saturation can be affected by adrenergic bronchodilators such as isoprenaline or orciprenaline, whether intravenous or inhaled, which cause small but significant falls in resting PaO₂ in obstructive lung disease. The one anticholinergic drug so far studied, however, did not.⁹⁻¹¹ Anticholinergic drugs can reduce dyspnoea and improve exercise performance even in patients who do not meet the usual criteria of bronchodilator reversibility.¹² This might be due to improvements in exercise related oxygen desaturation as exercise with supplementary oxygen is known to reduce breathlessness and increase exercise performance in normoxic patients with COPD.¹³

The advent of relatively portable and accurate pulse oximeters¹⁴ has meant that the relation of oxygen desaturation to everyday exercise such as self-paced corridor walking can be investigated. We have used the opportunities provided by a double blind randomised crossover trial of the anticholinergic agent oxitropium bromide to investigate: (1) how frequently oxygen desaturation occurs during corridor walking and whether it differs in severity from that during cycle ergometry; (2) whether short term bronchodilatation in patients with COPD influences resting and exercise induced desaturations; and (3) whether spirometric indices, oxygen saturation, and gas transfer factor singly or in combination predict walking distance or intensity of breathlessness, and whether changes in these variables can predict subsequent improvements in exercise performance and symptoms after the anticholinergic drug.

Methods

PATIENTS

Forty eight patients with severe but stable COPD as defined by the American Thoracic Society¹⁵ were recruited from the outpatient

Aintree Chest Centre,
Fazakerley Hospital,
Longmoor Lane,
Liverpool L9 7AL

D P S Spence

J G Hay

J Carter

M G Pearson

P M A Calverley

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Dr P M A Calverley

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clinic. All patients had a history of slowly progressive breathlessness on exertion for at least one year. All used an inhaled sympathomimetic, 32 an inhaled anticholinergic, 14 theophylline preparations, and 26 an inhaled steroid. Patients were instructed to refrain from inhaled β agonists for six hours, inhaled anticholinergics for 12 hours, and from oral bronchodilators for 24 hours before each laboratory visit. Sixteen participated in an earlier study of the effects of oxitropium bromide on corridor walking distance and symptoms.¹²

The study was approved by the hospital ethical committee and all subjects gave informed consent.

MEASUREMENTS

All spirometry measurements were made on the same dry rolling seal spirometer (PK Morgan, Kent) as the best FEV₁ and FVC from three acceptable traces. Gas transfer (TLCO) was measured by the single breath method (PK Morgan Ltd, Kent) within three months of the walking tests. Oxygen saturation at rest and during exercise was measured from the ear probe of a Biox 3700 pulse oximeter (Ohmeda, UK) which was carried by a technician who followed the patient during the six minute walks. Breathlessness was assessed using a modified Borg category scale by asking the question. "How breathless do you feel now?"

A standard self-paced exercise protocol¹⁶ was used in a quiet hospital corridor 20 m in length. No encouragement was given during the walk but it was stressed that the aim of the test was to walk as far as possible in six minutes, stopping if necessary. Oxygen saturation and pulse rate were recorded each minute during the walk and for one minute afterwards.

Cycle ergometry was performed with an electronically braked cycle ergometer (Elema Schonander). After three minutes sitting to acclimatise to the equipment, mouthpiece and nose clip, a symptom limited progressive exercise test was performed using 10 W power increments. Ventilation, oxygen uptake, CO₂ production, and ECG were recorded using a computerised exercise system (PK Morgan, Kent).

PROTOCOL

Patients attended on four consecutive days. On the first two visits baseline spirometric measurements were performed and practice six minute walks were carried out to familiarise the patients with the tests and symptom

scoring. On days 3 and 4 a double blind, randomised, placebo controlled crossover study was performed. Spirometric values, breathlessness, and oxygen saturation were recorded at rest, and then the subjects performed a six minute walk with an assessment of breathlessness immediately after the test. The times of any stops during the walk were recorded, together with the oxygen saturation at the time of the stop. Either 200 μ g oxitropium bromide or an identical placebo was then inhaled and, after resting for one hour, the walking study was repeated. A progressive cycle exercise test was performed on the first 16 patients 15 minutes after the final walk on days 3 and 4. Measurements of heart rate, ventilation, SaO₂ and dyspnoea were recorded at rest at each minute through the test.

STATISTICAL ANALYSIS

Data are expressed as mean (SD) unless otherwise stated. The modified Borg category scale linearises the scoring of sensation within an individual and thus theoretically parametric statistics may be employed in its analysis. When comparing breathlessness data between subject groups we have used non-parametric methods but retained parametric statistics for the construction of regression equations. Mean (SD) of breathlessness scores are quoted only to give an indication of the spread of the data. Breathlessness and breathing pattern at equivalent levels of ventilation were compared at 50%, 75%, and 100% of the maximum level of ventilation achieved on the placebo day of the study. Comparisons of walking distance, breathlessness, and oxygen saturations were made using Student's *t* tests or Wilcoxon signed rank tests as appropriate.

To examine the relation between walking distance, spirometric measurements, SaO₂ and TLCO a stepwise multiple linear regression was constructed with six minute distance as the dependent variable. A similar procedure was used to relate resting dyspnoea to spirometric values, SaO₂, and TLCO. Since these relationships may be altered by the bronchodilator, further equations were constructed to relate the change in walking distance and change in dyspnoea to the changes in these variables.

Results

There was a practice effect on six minute walking distance (6MD) between days 1 and 2, but thereafter the baseline 6MD, symptom scores and resting SaO₂ did not differ between study days (table 1). The subgroup in whom

Table 1 Effect of inhaled oxitropium bromide and placebo on spirometric indices, six minute walking distance, breathlessness scores, and on resting and nadir oxygen saturations (SaO₂) in 48 patients. Borg scores refer to the levels of perceived dyspnoea. Data are expressed as mean (SD)

	FEV ₁ (l)	FVC (l)	Six minute distance (m)	Resting Borg score	End of exercise Borg score	Resting SaO ₂ (%)	Nadir SaO ₂ (%)
Before placebo	0.77 (0.29)	1.93 (0.69)	318 (93)	1.8 (1.4)	3.9 (2.3)	93.2 (2.8)	86.8 (7.2)
After placebo	0.76 (0.30)	1.84 (0.72)	310 (102)	2.4 (1.9)	4.1 (2.3)	92.9 (3.4)	86.5 (8.1)
Before oxitropium	0.76 (0.28)	1.95 (0.72)	311 (93)	1.9 (1.7)	3.7 (2.0)	92.9 (3.7)	86.8 (8.8)
After oxitropium	0.93 (0.69)	2.32 (0.84)	332 (86)*	1.6 (1.3)**	3.2 (2.0)**	92.0 (4.1)	86.5 (8.0)

FEV₁—forced expiratory volume in one second; FVC—forced vital capacity; SaO₂—arterial oxygen saturation.

*p < 0.02, **p < 0.05 compared with values after placebo.

Figure 1 Changes in arterial oxygen saturation during the corridor walking in relation to the resting oxygen saturation (n = 48, some points are overlapping). In general the lower the SaO₂ at rest, the greater the subsequent desaturation on exercise.

cycle ergometry was performed was similar to the parent group with regard to spirometric values, resting saturation, and symptoms. Thirty three patients managed to complete all the six minute walks without stopping. The remaining 15 patients stopped at least once during one of the walks. Those patients who paused to rest during the six minute walk had worse airflow obstruction than those who did not: baseline FEV₁ 0.53 (0.14) l and 0.77 (0.29) l respectively (p < 0.001), but did not differ in terms of TLCO 17.9 (9.1) ml/min/mm Hg and 18.8 (8) ml/min/mm Hg respectively.

OXYGEN SATURATION DURING CORRIDOR WALKING AND CYCLE ERGOMETRY

The level of oxygen saturation at rest before the first walk was correlated with resting FEV₁ (r = 0.4, p < 0.005) and with the walking distance achieved (r = 0.48, p < 0.001). In contrast, FEV₁ and FVC correlated with walking distance less strongly (r = 0.32 and 0.31 respectively, p < 0.05). The resting saturation in the group who had to stop was less than in those who completed the walk without stopping (92.1% (3.7%) v 93.6% (2.1%), p < 0.05).

During the walk oxygen desaturation occurred in 42 of the 48 subjects. The largest desaturations occurred in those patients with the lowest resting oxygen saturation (who also had the worst spirometric measurements) (fig 1). In the 33 patients who walked continuously oxygen saturation declined steadily during the first three minutes of the six minute walk (fig 2A and B) but remained stable thereafter. In those subjects who needed a stop the saturation at the time of the first stop was not significantly different from

Figure 2 Changes in oxygen saturation before and after (A) placebo and (B) oxitropium bromide in the 33 patients who walked continuously. Open symbols refer to the premedication values and closed symbols to those after drug. Data are expressed as mean (SE) at each time point. Although the resting SaO₂ fell significantly after oxitropium bromide, oxygen desaturation during continuous exercise did not differ in its severity in these patients.

the lowest saturation reached during the walk in patients who exercised continuously (86.3% (4.6%) v 87.2% (8.2%)). Oxygen saturation values returned to pre-exercise levels during the one minute rest at the end of the walk.

The 16 patients who performed cycle ergometry achieved 87% of their predicted maximum voluntary ventilation and 75% of their predicted maximum heart rate (table 2). The duration of exercise did not correlate with the resting oxygen saturation. The degree of desaturation during the cycle exercise (2.1% (2.1%)) was significantly less (p < 0.001) than that during corridor walking (7.8% (4.4%)) (fig 3), while the breathlessness scores at the cycle ergometry were greater than those at the walking test (p < 0.001).

ANTICHOLINERGIC BRONCHODILATATION AND EXERCISE DESATURATION

Oxitropium bromide increased FEV₁ and FVC (FEV₁ before oxitropium 0.76 (0.28) l, after oxitropium 0.93 (0.69) l, p < 0.001). There was a modest but significant improvement in six minute walking distance of 29.4

Table 2 Mean (SD) spirometric indices, maximum ventilation (V̇Emax), oxygen uptake (V̇O₂max), carbon dioxide production (V̇CO₂max), breathlessness scores (Borg), and oxygen saturation (SaO₂) after oxitropium bromide or placebo in the 16 patients who performed cycle ergometry

	FEV ₁ (l)	FVC (l)	V̇Emax (l/min)	V̇O ₂ max (ml/min)	V̇CO ₂ max (ml/min)	Resting Borg score	End of exercise Borg score	Resting SaO ₂ (%)	Nadir SaO ₂ (%)
After placebo	0.75 (0.36)	1.84 (0.84)	22 (8)	762 (352)	627 (354)	1.9 (2.4)	5.3 (1.9)	92.6 (3.0)	90.4 (4.3)
After oxitropium	0.88 (0.44)	2.26 (0.96)	25 (9)*	876 (317)**	697 (309)	1.2 (1.1)**	4.0 (1.5)*	93.3 (1.8)	89.7 (4.8)

FEV₁—forced expiratory volume in one second; FVC—forced vital capacity; V̇Emax—maximum expiratory flow; V̇O₂max—maximum oxygen consumption; V̇CO₂max—maximum carbon dioxide production; SaO₂—arterial oxygen saturation. *p < 0.02, **p < 0.05 compared with values after placebo.

Figure 3 Maximum falls in oxygen saturation from resting levels during cycle exercise and corridor walking after either placebo or oxitropium ($n = 16$). Open circles are group mean (SE) for that study. Oxygen desaturation was greater during corridor walking but this was less consistent after oxitropium.

(57.8) m after oxitropium ($p < 0.001$). Both resting and end of walk breathlessness were significantly less after active bronchodilator ($p < 0.002$ and < 0.001 respectively) (table 2).

The resting saturation for the whole group fell slightly but consistently after oxitropium bromide from 92.9% (3.7%) to 92.0% (4.1%) ($p < 0.005$). These changes were not related to the degree of bronchodilation. Arterial desaturation during the walk was not affected by oxitropium despite the lower post-bronchodilator resting saturations and the greater walking distance achieved.

In those patients who stopped during the walk, neither the time to the first stop nor the saturation at the time of the first stop were affected by the bronchodilator. There were no differences in the peak heart rates during the walks before or after active drug.

The duration of cycle exercise was unaffected by oxitropium bromide compared with placebo (3.8 (2.1) min *v* 4.1 (2.2) min). However, maximum oxygen consumption ($\dot{V}O_2$) and minute ventilation ($\dot{V}E$) increased significantly after bronchodilator, whilst the end of exercise breathlessness score fell ($p < 0.002$) (table 2). When breathlessness was calculated at equivalent levels of ventilation, the changes after oxitropium were most marked at the highest levels of ventilation with significant reductions in both breathlessness and respiratory frequency in these conditions. However oxygen desaturation was no different (table 2). The mean maximum fall in SAO_2 during cycle exercise was not significantly altered by bronchodilator, but the scatter did increase with six patients falling by 4% or more after active drug compared with four before it.

PHYSIOLOGICAL PREDICTORS OF CORRIDOR EXERCISE AND DYSPNOEA

Inclusion of FEV_1 and FVC both as absolute values and percentage predicted, resting SAO_2 , $TLCO$, and resting breathlessness in a stepwise multiple regression showed that only resting saturation, resting breathlessness, and FVC were significant predictors of six minute distance (6MD) producing the regression equation:

$$6MD = -673 + (11 \times SAO_2) - (30 \times \text{resting Borg score}) + (30 \times FVC)$$

This equation explained 46% of the residual variance of walking distance.

The same variables, together with nadir oxygen saturation, were included in further stepwise regression analyses using either resting or end of walk breathlessness as dependent variables. No factor predicted resting breathlessness, while only resting oxygen saturation was a significant predictor of end of walk dyspnoea ($r = -0.5$, $p < 0.001$). The improvements in walking distance, resting and end of walk breathlessness after the bronchodilator were unrelated to changes in either FEV_1 , FVC, resting, or nadir saturations.

Discussion

Falls in oxygen tension during exercise in patients with COPD have been described many times,^{3-7 17 18} but the best predictors of such changes and their relationship to exercise performance and symptoms remain controversial.^{5 6 17 18} Our data extend these earlier observations to a larger and more homogenous group of clinically stable patients with COPD and show that significant falls in SAO_2 occur frequently and reproducibly during everyday exercise in most patients with severe COPD. Such changes were little influenced by anticholinergic bronchodilation and did not explain the improvement in walking distance or dyspnoea seen after these drugs.

Almost all of our patients (88%) exhibited rapid and reproducible oxygen desaturations during the corridor walking tests with only small between and within day coefficients of variation in nadir SAO_2 (3% in both cases). Desaturation is most likely to occur and become severe in those patients with the lowest resting SAO_2 , but the sigmoid nature of the haemoglobin dissociation curve means that changes in oxygen tension are likely to be similar. In contrast, oxygen desaturation during cycle ergometry before the active drug was infrequent, despite the greater effort involved as judged by dyspnoea scoring. Previous studies comparing treadmill exercise and cycle ergometry at similar workloads show that desaturation was greater during treadmill walking,¹⁹ but this is the first demonstration of the effect during self-paced corridor exercise.

Previous studies in patients with severe COPD suggest that increases in venous admixture and relative hypoventilation during exercise are the major causes of desaturation.^{8 20} The relation we saw between resting SAO_2 and the severity of the subsequent desaturation during walking is in keeping with such a mechanism, as is the rapid resaturation at the end of exercise. We could not measure ventilation directly during the self-paced walks and differences between the tests may be explained by differences in metabolic load and the breathing pattern adopted. Lactate production is higher during treadmill walking at the same workload than during cycle ergometry, while there are differences in the pattern of recruitment of accessory muscles between the two settings.^{21 22} Whatever

the mechanism, our data show that cycle ergometry will consistently underestimate the severity of desaturation during less intense but more prolonged self-paced exercise.

Oxitropium bromide is an inhaled anticholinergic drug similar to ipratropium bromide but with a somewhat longer duration of action.²³ The present study extends our earlier observation that oxitropium increases corridor walking distance and reduces resting and exercise breathlessness when compared with placebo.¹² In neither study were these changes related to the changes in spirometric indices recorded at rest, and in this report we found similar symptomatic benefit from oxitropium during cycle ergometry. A previous study using atropine methonitrate¹¹ reported similar changes in ventilation and oxygen consumption during cycle exercise to those we saw after oxitropium, but this earlier study did not include an assessment of symptoms. We found a proportionately larger effect of the active drug on symptoms than on other measured physiological variables. This may reflect a lack of proportionality in the Borg scale, although this has not been reported in earlier validation studies.^{24,25}

Arterial oxygen desaturation after bronchodilator drugs has been reported previously,^{9,10} but principally in patients with asthma and after adrenergic bronchodilation. In a study of 12 modestly hypoxaemic COPD patients Gross and Bankwala found that resting PaO_2 fell by 0.7 kPa after orciprenaline and by 0.2 kPa after atropine methonitrate, and that these changes lasted for up to 30 minutes.¹¹ Our group of patients was less hypoxic, but nonetheless we saw a small fall in oxygen saturation of 1% after oxitropium in both normoxic and hypoxaemic patients. Despite this change in resting SaO_2 we found no difference in the nadir and plateau SaO_2 levels between the active and placebo groups, suggesting that the factors influencing resting saturation are not necessarily the major determinants of exercise induced desaturation.

Several simple predictors of exercise performance have been identified and, as in earlier studies, vital capacity was the best spirometric correlate explaining 32% of the variance in walking distance. The residual variance was further reduced, however, when resting SaO_2 and dyspnoea were included in the equation. TLCO has been reported by Mak *et al*⁶ to be well correlated with six minute walking distance and with oxygen desaturation during both corridor walking and cycle ergometry. We did not find such a correlation in our patients, but Mak *et al* did not include patients with chronic asthma and their patients had a lower mean FEV₁ (0.77 l v 1.3 l).

Like Mak *et al* we failed to find a relation between exercise duration and resting breathlessness.⁶ Resting SaO_2 was the only factor predictive of end exercise dyspnoea but this relation is not necessarily causal. While some groups believe that hypoxia is an independent stimulus to dyspnoea,⁷ there is good evidence

that abolishing hypoxia improves breathlessness simply by reducing the minute ventilation²⁶ and our post-bronchodilator data support this. After oxitropium resting SaO_2 fell but so did resting breathlessness, while the improvement in 6MD was unrelated to changes in resting or exercise induced desaturation. During cycle exercise after oxitropium more subjects desaturated, but dyspnoea at equivalent ventilations was less and the respiratory rate was slower, implying that mechanical rather than gas exchange factors were the most important ones.

Our data show that patients with stable severe COPD experience large and normally unsuspected periods of hypoxaemia, the duration of which will vary with the amount of exercise taken. This hypoxic burden may contribute to complications such as secondary polycythaemia seen in COPD.²⁷ Bicycle ergometry can provide useful information about the metabolic response to exercise and maximum performance but underestimates the desaturations seen during self-paced exercise. The addition of pulse oximetry to corridor walking tests should provide a more accurate estimate of the everyday physiological problems of these patients.

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Adventitia

A Research Fellowship at the Brompton: 21 years later

Three months into a research fellowship in London in 1972 I took a week off to attend a Cardiothoracic Institute Advanced Medicine Course. At one of the social events a charming gentleman (John Plant), probing my interests and aspirations, detected some dissatisfaction with my research environment. My enthusiastic response to his questioning whether I would like to work at the Brompton prompted an introduction to the "new professor" and his suggestion to her that I might be offered the opportunity to relocate. Three months later I was graciously and warmly welcomed to the Brompton where I embarked on research under the wise and friendly guidance of Tim Clark, Margaret Turner-Warwick and Simon Godfrey, with active support from Mac Cochrane, Ron Logan-Sinclair and others.

Eighteen months at the Brompton with a year generously sponsored by the Board of Governors provided a transforming experience in my career. Building a "Heath Robinson" pressure constant volume plethysmograph for my research projects and running the Brompton's routine lung function laboratory taught me the need for much patience, ingenuity, diplomacy and dogged persistence in the research endeavour itself (and all the related activities associated with its presentation and ultimate publication), and in the "marketing" of a (then sometimes unwanted) lung function service. Meeting, working and socialising with many outstanding and dedicated clinicians/investigators opened my mind to new ways of thinking and a future indelibly stamped by their influence. Other young investigators from South Africa who were subsequently welcomed and similarly graciously supported at the Brompton have returned home to make innovative contributions to respiratory medicine.

The privilege of retaining highly valued friendships with coregistrars who have become prominent in British thoracic medicine, with SHOs who certainly kept one on one's toes and other generous mentors on the consultant staff, played a sustaining role during subsequent decades of work in the difficult, complex and transforming South African environment.

The political arguments for the need to isolate South Africa in the battle against apartheid received widespread support. The lack of any adequate moral basis for the intellectual impoverishment which accompanied the academic boycott led to the concept of selective support as an appropriate means of openly declaring against apartheid and all its abhorrent effects, without succumbing to intimidating and coercive forces implicit in academic boycott inimical to intellectual and professional pursuits.

As South Africa lurchingly gropes its way into a better future in which dignity will hopefully be restored to all its citizens, we shall rely heavily on our internal personal resources (contributed to by our constructively critical and yet supportive colleagues) and on intellectual and material support from the industrialised world. Tuberculosis, smoking related lung diseases, AIDS, asthma, occupational lung disease, and lung cancer are all major and growing problems in Africa. Collaborative, scientific and social research at many levels could offer mutual benefits.

Our dilemmas—a microcosm of issues underlying global instability—represent the opportunity to show that the wide disparities produced by generations of greed, exploitation, and denegation of other cultures can be addressed and reversed through rational, empathetic and peaceful means.

S R BENATAR