Original articles

Supplemental oxygen during pulmonary rehabilitation in patients with COPD with exercise hypoxaemia

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Abstract
Background—**Supplemental oxygen in patients with chronic obstructive pulmonary disease (COPD) and exercise hypoxaemia improves exercise capacity and dyspnoea. However, the benefit of oxygen during pulmonary rehabilitation in these patients is still unknown.**
Methods—**Twenty five patients with stable COPD (mean (SD) forced expiratory volume in one second (FEV_1) 0.76 (0.29) l and 30.0 (9.89)% predicted, arterial oxygen tension (Pao_2) 8.46 (1.22) kPa, arterial carbon dioxide tension ($Paco_2$) 6.32 (1.01) kPa) and significant arterial desaturation on exercise (82.0 (10.4)%) were entered onto a pulmonary rehabilitation programme. Patients were randomised to train whilst breathing oxygen (OT) (n = 13) or air (AT) (n = 12), both at 4 l/min. Assessments included exercise tolerance and associated dyspnoea using the shuttle walk test (SWT) and Borg dyspnoea score, health status, mood state, and performance during daily activities.**
Results—**The OT group showed a significant reduction in dyspnoea after rehabilitation compared with the AT group (Borg mean difference –1.46 (95% CI –2.72 to –0.19)) but there were no differences in other outcome measures: SWT difference –23.6 m (95% CI –70.7 to 23.5), Chronic Respiratory Disease Questionnaire 3.67 (95% CI –7.70 to 15.1), Hospital Anxiety and Depression Scale 1.73 (95% CI –2.32 to 5.78), and London Chest Activity of Daily Living Scale –2.18 (95% CI –7.15 to 2.79). At baseline oxygen significantly improved SWT (mean difference 27.3 m (95% CI 14.7 to 39.8) and dyspnoea (–0.68 (95% CI –1.05 to –0.31)) compared with placebo air.**
Conclusions—**This study suggests that supplemental oxygen during training does little to enhance exercise tolerance although there is a small benefit in terms of dyspnoea. Patients with severe disabling dyspnoea may find symptomatic relief with supplemental oxygen.**
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Keywords: chronic obstructive pulmonary disease; exercise induced dyspnoea; rehabilitation; oxygen

Physical training as part of a pulmonary rehabilitation programme can improve exercise tolerance and health status in patients with chronic obstructive pulmonary disease (COPD).[1–3] However, patients with more severe COPD are prone to arterial hypoxaemia during exercise and routine activities.[4–6] In these patients exercise hypoxaemia may offset improvements in exercise tolerance, thereby limiting benefits of rehabilitation.[3] Supplemental oxygen in patients with COPD and exercise hypoxaemia results in acute improvements in exercise tolerance and dyspnoea[7–9] whilst, in patients without hypoxaemia, there is little reported benefit.[10] Ambulatory oxygen during exercise may increase training endurance in these patients with arterial desaturation. Only one study has previously investigated the role of ambulatory oxygen during an exercise programme in patients with COPD.[13] This study found no benefit of oxygen therapy on physiological training effects after a 10 week exercise programme. However, patients were instructed to stop exercising before arterial saturation (Sao_2) fell below 90% so the true extent of exercise hypoxaemia is not known. Also, the lack of a matched placebo in the control group may have influenced findings.[8 14]

This study tests the hypothesis that the addition of oxygen during a training programme in patients with exercise hypoxaemia will lead to greater improvements in exercise tolerance and health status than training alone. Our primary outcome measure was exercise tolerance and associated breathlessness with secondary outcome measures of quality of life and ability to perform daily activities. This randomised, placebo controlled study is therefore designed to investigate the effects of supplemental oxygen administered during a rehabilitation programme.

Methods

PATIENTS

Figure 1 shows the study design and experimental protocol. Twenty six patients (19 men) with stable severe COPD (median age 70 years (range 52–84)) were recruited from the outpatient clinics of the London Chest Hospital. Patients had had no exacerbations in the previous six weeks. Of the 26 patients approached,

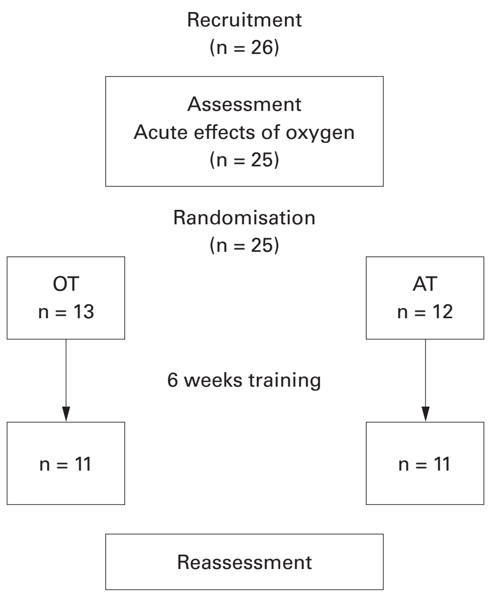

Figure 1 Study design and experimental protocol. OT = oxygen trained group; AT = air trained group

one declined, one was admitted to hospital after the initial assessment, and two were unable to attend follow up due to admission to hospital with exacerbation of COPD.

The study was approved by the ethics committee of the East London and City Health Authority with all patients providing written informed consent. Patients included in the study had a history of severe COPD with forced expiratory volume in one second (FEV_1) of less than 40% predicted with less than 15% reversibility to inhaled salbutamol (400 µg). All patients had limited exercise tolerance due to dyspnoea and all had a fall in arterial saturation of at least 4% from baseline to 90% or below on exercise testing.[11] Patients were excluded from the study if they had unstable angina, intermittent claudication, or other mobility limiting conditions. Eleven of the 25 patients were receiving long term oxygen therapy at home.

ASSESSMENTS

The following baseline assessments were made:

Lung function and exercise tolerance

Resting blood gas tensions were obtained from ear lobe samples while breathing room air at rest for at least 20 minutes and analysed on a Ciba-Corning 278 Blood Gas Analyser (Medfield, Massachusetts, USA).[15] Spirometric tests were performed using a rolling seal spirometer (PK Morgan Ltd, Rainham, UK). Exercise capacity was assessed using the shuttle walk test (SWT) which is a maximal externally paced incremental exercise test.[16]

All patients performed three walking tests with a rest of at least 20 minutes between each walk. A baseline walk was performed whilst breathing room air with the next two walks determined in a random order. Patients were tested whilst breathing either compressed air from a small portable cylinder of weight 2.5 kg or oxygen from an identical cylinder; both gases were given at 4 l/min via nasal cannulae. SaO_2 was monitored throughout the walk using a pulse oximeter (Minolta Pulsox 7, AVL Instruments, Schaffhausen, Switzerland) and the lowest SaO_2 was recorded. Patients were blinded as to whether they were breathing oxygen or air but it was not possible to blind the investigator. The patients were asked to indicate their level of breathlessness using the Borg dyspnoea score before and immediately after each walk.[17]

Health status assessment

The Chronic Respiratory Disease Questionnaire (CRDQ) measures health status and was designed for the assessment of change in individuals.[18] It comprises four component scores (Dyspnoea, Fatigue, Emotional Function, and Mastery) measured on a seven point Likert scale. The dyspnoea component of the questionnaire is individualised to five activities which cause dyspnoea and are assessed in order of importance and severity to the patient. The higher the score the better the health status.

Mood state

The Hospital Anxiety and Depression Scale (HAD) assesses anxiety and depression; it consists of 14 items and is scored from 0–21 with a score of more than 10 in either anxiety or depression representing symptoms of clinical significance.[19]

Activity of daily living assessment

The London Chest Activity of Daily Living Scale (LCADL) is a 15 item questionnaire designed to measure dyspnoea during routine daily activities in patients with COPD. It consists of four components (Self Care, Domestic, Physical, and Leisure). Patients score from 0 ("I wouldn't do it anyway") to 5 ("Someone else does this for me (or helps)"), with higher scores representing maximal disability. Development and validation of the questionnaire has been reported previously.[20]

RANDOMISATION

After assessment the patients were randomised into two groups using sealed envelopes: oxygen trained (OT) (n =13) or air trained (AT) (n = 12). Of the 11 patients receiving long term oxygen therapy, five were randomised to the air trained group and six to the oxygen trained group. Patients in the OT group performed physical training whilst breathing supplemental oxygen at 4 l/min and patients in the AT group attended an identical exercise programme whilst breathing compressed air at 4 l/min. Patients in the OT group received supplemental oxygen through a 2.5 kg cylinder fitted with an oxygen conserving device which we have previously shown to be adequate in maintaining arterial saturation during exercise.[21] All patients were blinded to the gas mixture throughout the course of the programme.

REHABILITATION PROGRAMME

The rehabilitation programmes were performed in groups of 6–8. All patients carried their own cylinders whilst performing the exercises. The exercise programme consisted of upper and lower limb training three times a week for six weeks, each session lasting one hour. Arm exercises were performed using dumb bells of 1 kg weight, whilst lower limb

Table 1 Baseline physiological parameters

	Oxygen trained group (OT) (n = 13)	*Air trained group (AT) (n = 12)*
Age, range (years)	64.3 (54–77)	71.6 (52–81)
FEV_1 (l)	0.77 (0.26)	0.84 (0.26)
FEV_1 (% predicted)	28.5 (10.0)	35.0 (10.2)
FVC (l)	2.30 (0.81)	2.14 (0.68)
Pao_2 (kPa)	8.50 (1.40)	8.48 (1.22)
$Paco_2$ (kPa)	6.47 (0.91)	6.14 (1.48)
Baseline Sao_2 (%)	92.0 (3.16)	93.1 (3.09)
End SWT Sao_2 (%)	80.2 (10.4)	85.2 (4.82)
SWT (m)	160 (89.1)	131 (103)
Post SWT Borg score	4.53 (1.12)	3.83 (1.27)
CRDQ (Total score)	84.4 (21.2)	77.9 (24.4)
HAD (Total score)	13.5 (7.76)	15.2 (9.90)
LCADL (Total score)	36.3 (12.6)	36.6 (14..4)

FVC = forced vital capacity; FEV_1 = forced expiratory volume in one second; Pao_2, $Paco_2$ = arterial oxygen and carbon dioxide tensions; SWT = Shuttle Walk Test; HAD = Hospital Anxiety and Depression Scale (higher score reflects worse symptoms); LCADL = London Chest Activity of Daily Living Scale (higher score reflects greater disability); CRDQ = Chronic Respiratory Disease Questionnaire (higher score reflects better quality of life).
There were no significant difference between the groups at baseline.

Table 2 Acute effects of oxygen on exercise tolerance and dyspnoea at baseline (data presented as mean values with 95% confidence intervals, n = 25)

	Air cylinder	*Oxygen cylinder*	*Difference (95% CI)*	*p value*
SWT (m)	149.1	176.4	27.3 (14.7 to 39.8)	<0.001
Borg score	4.20	3.52	–0.68 (–1.05 to –0.31)	<0.001

p value represents difference between oxygen and placebo air walk.
SWT = Shuttle Walk Test.

exercises were performed without resistance. The aerobic component of the exercise programme involved fast walking over a distance of 10 metres; walking intensity was determined on an individual basis and set by the physiotherapist at 80% maximum oxygen consumption from the results of the initial SWT.[22] Patients also performed unloaded cycling on a cycle ergometer. They exercised for as long as they could and used the Borg breathlessness score to monitor intensity.[23] The actual time spent cycling and walking for each patient per session was measured and Sao_2 at the end of the walk and cycle was recorded. The patients were instructed to exercise only at the three supervised sessions in order to monitor and standardise all exercise performed. The education programme was standardised for both the AT and OT groups and lasted approximately 45 minutes, covering medical management of COPD, relaxation, chest clearance and breathing techniques, signs and symptoms of infection, energy conservation, stress management, the benefits of exercise, and smoking cessation.

Table 3 Changes in mean outcome measures after six week rehabilitation programme in both groups

	Oxygen group (n = 11)	*Air group (n = 11)*	*Mean (95% CI) difference in changes between groups*	*p value*
Δ SWT on air (m)	20.0	43.63	–23.6 (–70.7 to 23.5)	0.19
Δ Borg Score	–1.00	0.46	–1.46 (–2.72 to –0.19)	0.02*
Δ CRDQ (Total)	9.27	5.60	3.67 (–7.70 to 15.1)	0.50
Δ Dyspnoea	2.18	0.50	1.68 (–1.04 to 4.40)	0.21
Δ Fatigue	1.27	0.37	0.90 (–2.53 to 4.35)	0.58
Δ Emotion	4.27	2.55	1.73 (–3.18 to 6.64)	0.47
Δ Mastery	1.54	1.27	0.27 (–2.11 to 2.65)	0.81
Δ HAD (Total)	–1.46	–3.18	1.73 (–2.32 to 5.78)	0.38
Δ Anxiety	–0.09	–1.81	1.72 (–0.59 to 4.05)	0.13
Δ Depression	–1.36	–1.36	0.00 (–2.90 to 2.90)	0.49
Δ LCADL (Total)	–6.82	–4.64	–2.18 (–7.15 to 2.79)	0. 37
Δ Self care	–2.09	–0.73	–1.36 (–3.46 to 0.73)	0.19
Δ Domestic	–2.18	–2.27	0.09 (–3.89 to 4.06)	0.96
Δ Physical	–1.00	–0.27	–0.73 (–1.96 to 0.50)	0.23
Δ Leisure	–1.54	–1.36	–0.18 (–1.87 to 1.49)	0.82

p values and 95% confidence intervals represent differences between groups.
SWT = Shuttle Walk Test; LCADL = London Chest Activity of Daily living Scale (minus value represents reduction in symptoms); HAD = Hospital Anxiety and Depression Scale (minus value represents reduction in symptoms); CRDQ = Chronic Respiratory Disease Questionnaire.

STATISTICAL ANALYSIS

The continuous variables were normally distributed. Differences between the groups in response to rehabilitation were identified using the unpaired Student's *t* test, whilst changes within groups were measured using the paired Student's *t* test. Results are presented as mean (SD) with the 95% confidence intervals shown. Relationships between the continuous variables were identified using Pearson's correlation coefficient. Baseline data are presented on 25 patients and rehabilitation data on 22 patients.

Results

BASELINE CHARACTERISTICS

Table 1 shows the baseline characteristics of all the patients; there were no significant differences between the groups at the start of rehabilitation. The patients had severe COPD with mean (SD) FEV_1 0.76 (0.29) l and FEV_1 % predicted 30.0 (9.89). They showed significant arterial desaturation on exercise from mean (SD) 92.3 (3.60)% at baseline to 82.0 (10.4)% at exercise. Eleven patients were receiving long term oxygen therapy. The mean arterial desaturation observed on a baseline walk was similar to those patients not receiving oxygen at home (mean desaturation (SD) 12.5 (11.5)% and 8.23 (16.5)%, respectively (p = 0.21). There was no difference between these individuals and the rest of the group in baseline FEV_1 (p = 0.29) or baseline arterial oxygen levels (p = 0.71).

ACUTE EFFECTS OF OXYGEN ON SWT AND DYSPNOEA

Comparison of the SWT in patients on air and on oxygen showed a significant effect of oxygen on exercise tolerance prior to rehabilitation (mean difference 27.3 m (95% CI 14.7 to 39.8)). Supplemental oxygen also showed an acute benefit on dyspnoea when compared with placebo (mean difference –0.68 (95% CI –1.05 to –0.31)); table 2).

CHANGE IN OUTCOME MEASURES IN OT AND AT GROUPS

Table 3 shows the difference in the outcome measures after rehabilitation for the AT and OT groups separately. There was no significant difference in the change in SWT (p = 0.30) (fig 2), CRDQ (p = 0.50), HAD (p = 0.38), and LCADL (p = 0.37) after rehabilitation between the two groups although there was a different effect on dyspnoea. Only the OT patients showed a significant reduction in dyspnoea after training (mean difference –1.00 (95% CI 0.20 to 1.79) for the OT group and –0.46 (95% CI –1.55 to 0.64) for the AT group (p = 0.02)). There was no difference in Sao_2 between the two groups during the training programme with mean Sao_2 at the end of the training walk of 89.4 (5.63)% in the AT patients and 92.0 (3.89)% in the OT patients. The duration of the walking component of the programme was also similar between the two groups (mean 5.27 (3.95) min and 7.18 (4.09) min, respectively, in

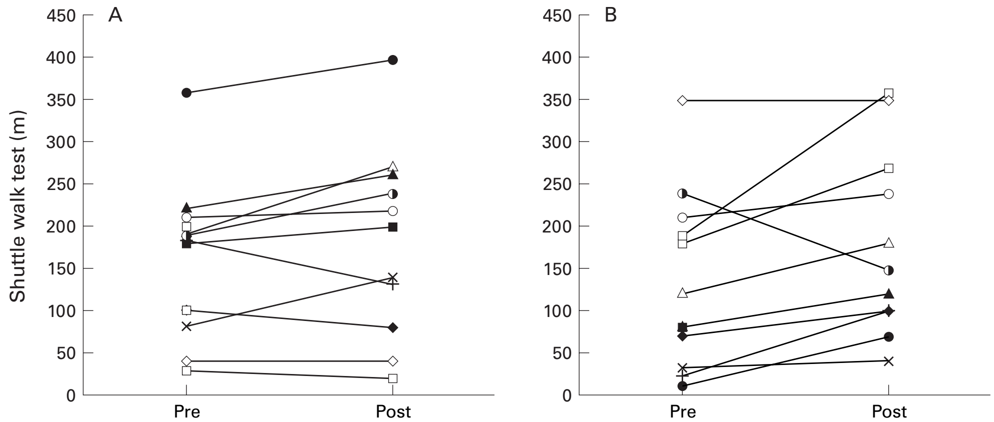

Figure 2 Change in shuttle walk test in (A) the oxygen trained and (B) the air trained groups before and after rehabilitation.

the AT and OT groups). After cycling, Sa_{O_2} reached a mean of 85.8 (6.52)% and 89.8 (5.78)% in the AT and OT groups while on oxygen. The mean time spent cycling was 8.85 (7.16) min and 8.81 (3.84) min in the AT and OT groups, respectively.

EFFECTS OF REHABILITATION ON ACTIVITIES OF DAILY LIVING (ADL)

In the group as a whole there was a significant improvement in dyspnoea during ADL represented by a reduction in scores for all components of the LCADL (Self Care, mean difference 1.42 (95% CI 0.34 to 2.47); Domestic, mean difference 2.30 (95% CI 0.29 to 4.16); Physical, mean difference 0.64 (95% CI 0.16 to 1.26); Leisure, mean difference 1.46 (95% CI 0.64 to 2.27); Total Score, mean difference 5.70 (95% CI 3.26 to 8.19).

There were significant correlations between the baseline LCADL scores and baseline SWT ($r = -0.41$, p = 0.04), dyspnoea ($r = 0.39$, p = 0.04), and FEV_1 % predicted ($r = -0.48$, p = 0.01), but the changes in SWT did not correlate with the changes in LCADL.

Discussion

This study investigated the effects of supplemental oxygen during a training programme and found no additional benefit of oxygen on exercise tolerance or health status. However, the oxygen trained group had a greater reduction in dyspnoea on exertion measured with the Borg scale compared with the air trained group. In a previous study which showed no benefit of supplemental oxygen, patients were instructed to stop exercising before the Sa_{O_2} fell below 90%.[13] Muscle hypoxia may act as a stimulus to training in individuals and thus avoidance of hypoxia may have minimised any differences between the two groups.[24] Unlike the study by Rooyakers and colleagues,[13] our patients were not instructed to stop exercising if arterial saturation fell below 90% and thus intensity of training was not limited. Our patient groups displayed marked falls in Sa_{O_2} during exercise, emphasising the severe disability present. Patients were blinded as to their gas mixture and carried a cylinder during all walks, thus negating any differences that may have occurred as a result of the extra weight of an oxygen cylinder.[8]

Oxygen improves exercise capacity through a variety of mechanisms including reduction of ventilation and associated respiratory rate,[25 26] a delay in the onset of diaphragmatic muscle fatigue,[27] and improved oxygen delivery leading to reduction in metabolic acidosis during exercise.[26 28 29] Physiological effects of training are greater in those patients who are able to train at a higher intensity.[30] However, many patients with severe disease are unable to train to such high intensities and are less likely to show reductions in lactate levels after training.[31 32] One possibility for the lack of effect of supplemental oxygen on exercise capacity may be that ventilatory impairment prevented our patients training at an intensity sufficient to reach anaerobic threshold. Although patients were trained at 80% of their maximum oxygen consumption according to the results of baseline SWT, more severe patients may display ventilatory limitation during exercise, making a true maximum oxygen consumption unattainable.[22] Training effects are a result of duration and intensity and it was expected that patients who trained on oxygen would train for a longer duration per session. However, walking time did not differ between the two groups, even though dyspnoea was reduced in the oxygen treated group. In the patients who trained with oxygen the mean Sa_{O_2} levels were lower than expected, which suggests that avoidance of exercise desaturation may be difficult in these patients.

The mechanism by which oxygen affects dyspnoea is complex and there is little evidence of a relationship between change in exercise tolerance and change in dyspnoea.[7 11] In this study the reduction in dyspnoea after training was greater in the OT group than in the AT group. Although dyspnoea was significantly reduced in the OT patients after training, the AT patients walked further than at baseline without worsening dyspnoea, suggesting that desensitisation also occurred.[34]

The rehabilitation programme was held three times a week for six weeks and was effective in showing improvements in health status and exercise tolerance in the group as a whole.

The programme was standardised for both groups and fully supervised by an experienced physiotherapist. Patients were asked to exercise only during the outpatient programmes in order to standardise the training. Other programmes might expect greater improvements with a combination of supervised and home training. The use of oxygen conserving devices throughout the programme was a pragmatic measure to ensure that oxygen lasted through the session, though patients were unaware of the reason for the use of this device.

In this study we used a new measure designed specifically to assess dyspnoea during activities of daily living in patients with severe disease.[20] We showed significant improvements in daily activities in both groups, suggesting that rehabilitation programmes are successful in treating functional limitation in these patients. The changes in exercise tolerance were smaller in this population than in previous outpatient programmes[2 3 34] which may be a reflection of the severity of the disease or the relatively short duration of the study. It is interesting to note that the degree of improvement in exercise tolerance after training is similar to the magnitude of change with ambulatory oxygen, reinforcing the clinical importance of physical training.

This study has shown a reduction in dyspnoea in COPD patients with exercise hypoxaemia who use oxygen during a training programme compared with training on air. The difference in dyspnoea did not translate into additional exercise capacity or improved activities of daily living. However, the minimal clinical difference of the CRDQ has been identified as a change of 4 points in the total score. The change in CRDQ in the OT group was greater at 9.27 compared with 5.60 in the AT group, although this did not reach statistical significance.[35] We cannot rule out the possibility that we failed to detect a significant difference in health status between the groups due to the low power of the study.

The results of this study suggest that the additive effect of oxygen during training is marginal; however, a small benefit in terms of dyspnoea appears to exist. Patients with particularly disabling dyspnoea may benefit from supplemental oxygen during their training programmes.

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