PHYSICAL TRAINING WITH AND WITHOUT OXYGEN IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE AND EXERCISE-INDUCED HYPOXAEMIA

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A randomized, controlled, single-blind study was performed on 20 patients with chronic obstructive pulmonary disease and exercise-induced hypoxaemia. Ten patients each were randomly assigned to one of two groups, one training with air and the other training with oxygen. There were no significant differences between the groups regarding values measured prior to the study. The patients trained 3 times per week for 30 minutes each time for a duration of 8 weeks. The training consisted of interval walking on a treadmill (intensity set according to Borg ratings) with either air or oxygen administered through a nasal cannula at a rate of 5 l/min. Training significantly improved the 6-minute walking distance by 20% and 14% in the air and oxygen group, respectively, when the patients were tested on air. In the same test the air group significantly decreased Borg ratings for perceived exertion. Borg ratings for dyspnoea and perceived exertion significantly decreased in the oxygen group when they were tested on oxygen. It was concluded that oxygen supplementation did not further improve the training effect, compared with training with air, in patients with chronic obstructive pulmonary disease and exercise-induced hypoxaemia.

Key words: chronic obstructive pulmonary disease, exercise training, hypoxaemia, oxygen, 6MWD, walking, Borg.

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is an increasing problem in the society. It is now ranked third for men and fourth for women as the cause of death in the USA, and both morbidity and mortality from COPD continue to increase (1, 2). Dyspnoea is the most common symptom causing patients with COPD to consult a doctor (3).

Rehabilitation of patients with COPD is well established (1, 2, 4–6). The primary goal of rehabilitation is to restore the patient to the highest possible level of independent function. Physical training is often included in the rehabilitation programmes, and studies have shown that general exercise training, treadmill, cycle ergometer or simple walking programmes will improve exercise performance for patients with COPD (4–11).

In several studies, oxygen administered during physical exercise was shown to improve exercise performance in patients with COPD (12–20). These positive short-term effects of oxygen have been observed in patients who are hypoxaemic both at rest (14, 16, 19) and during exercise (12, 13, 15, 17, 18, 20).

Only a few studies have examined the long-term effect of oxygen used during longer training periods, and the results from these studies differ. One study found that training with oxygen in COPD patients that desaturate during exercise had positive effects on exercise capacity after the training period (5). However, the effect of oxygen supplementation vs no supplementation was not evaluated in that study. Compared with breathing room air, supplemental oxygen used during daily activities at home by patients with COPD and mild hypoxaemia was found to be of limited benefit regarding exercise performance (21). Recently, a controlled study on 10-weeks pulmonary rehabilitation for inpatients showed that supplementation of oxygen during the training did not add to the effects of training on room air (22). In contrast, another study showed that oxygen-supplemented exercise training increased maximum exercise test workload compared with training with room air (23). Due to the varying results and designs in previous studies there are no clear conclusions regarding the benefit of oxygen supplementation during exercise training in patients with COPD who do not have chronic respiratory insufficiency.

The purpose of this study was to investigate if exercise training with oxygen supplementation, compared with training with air, increased walking distance and/or decreased subjective experience of dyspnoea and perceived exertion during physical activity in COPD patients who became hypoxaemic during exercise. It was also investigated how training with oxygen compared with training with air affected lactic acidosis and the pCO_2-levels during exercise.

METHODS

Patients

Twenty-two patients with stable COPD, according to the European Respiratory Society (ERS) (24), were selected for the study. Twenty of the patients completed the training programme. The subjects were recruited from previously diagnosed outpatients who had been treated at the Department of Respiratory Medicine and Allergy at the University

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Table I. *Baseline data for patients randomized for training with air (AG) and those training with oxygen (OG). Values are presented as median (min–max)*

	AG (n = 10)	OG (n = 10)
Age	69 (60–72)	65 (52–73)
FEV_1 (% pred)	51.6 (24.0–65.7)	39.3 (23.3–59.1)
VC (% pred)	91.9 (81.5–139.0)	92.6 (73.1–131.0)
FEV_1/VC (% pred)	49.1 (30.1–71.4)	44.7 (22.9–59.8)
RV (% pred)	164.0 (78.1–202.0)	151.0 (95.0–240.0)
TLC (% pred)	123.0 (82.6–133.0)	127.0 (79.0–143.0)
TLCO (% pred)	60.1 (31.1–85.6)	48.6 (27.0–99.0)
Arterial paO_2 at rest (kPa)[a]	9.3 (7.9–11.4)	9.5 (8.6–11.6)
Arterial $paCO_2$ at rest (kPa)[a]	5.3 (4.5–6.3)	5.4 (4.5–5.8)
SaO_2 at rest (%)[a]	94.6 (90.7–97.2)	95.2 (92.9–97.3)
Weight (kg)[a]	75 (52–109)	66 (57–101)
Height (cm)[a]	170 (156–180)	167 (157–183)
BMI (kg/m^2)[a]	25.1 (19.9–38.9)	24.3 (18.4–30.2)

[a] These data were collected the first testing day after the patients were selected.
Methods used: SaO_2, paO_2, $paCO_2$: analysed from arterial blood samples in "IRMA Blood analysis system", St Paul, USA or "ABL 520" Radiometer, Copenhagen, Denmark.
FEV_1, VC, FEV_1/VC, RV, TLCO: Master Lab, Erich Jaeger, Wuerzburg, Germany.
TLC: Bodyplethysmograph, Master Lab, Erich Jaeger, Wuerzburg, Germany.

Hospital in Umeå, Sweden. The patients were asked to participate and were included if they accepted and fulfilled the following inclusion criteria: were under the age of 75, had stopped smoking at least 6 months before entering the study, presented hypoxaemia during exercise ($SaO_2 \leq 92\%$ in 6MWD (6-minute walking distance test) performed in corridor), had $FEV_1 < 70\%$ of predicted value, had $PaO_2 \geq 8$ kPa at rest, had no infection the last 3 weeks and had no change in medical treatment the last month before entering the study. Patients were excluded if they had any past or present major illness, such as cardiac, orthopaedic, or neurological disease that might have interfered with exercise performance. Before entering the study all patients performed pulmonary function tests and exercise electrocardiogram (ECG). All patients gave informed consent prior to the study. The study was approved by the Ethics Committee of Umeå University in Sweden.

Ten men and 12 women composed the original study group. Two women (one from each training group) were excluded after the start of the study due to airway infection. The baseline data for the twenty patients, randomized to training with either supplemental air (air group—AG) or supplemental oxygen (oxygen group—OG) are shown in Table I. Each group consisted of five men and five women. The differences between the groups at baseline were not statistically significant.

Study design

The study was designed as a controlled, randomized, single-blind trial. The included patients were randomly allocated (randomization by blocks, men and women were randomized separately) to train either with air (AG) or with oxygen (OG).

Training procedures

After randomization, the patients started the training programme with air or oxygen at a flow rate of 5 l/min through a dual-prong nasal cannula (19). The training programme consisted of walking on a treadmill for 30 minutes, 3 times per week for 8 weeks. The subjects were allowed to be absent for a maximum of three training sessions.

During the 30-minute training sessions, the patients exercised on a motorized treadmill (Rodby RL 1500 E, Enhörna, Sweden). The programme was designed as interval training, comprised of 5 minutes warming up, 2–3 minutes higher speed alternated with 2–3 minutes lower speed, and ending with 2–5 minutes cooling down. Normally one session consisted of five intervals with higher speed. A physiotherapist adjusted the speed, and slowed down or stopped the treadmill on request from the patients. SaO_2 and heart rate were continuously monitored with a pulse oximeter using a finger probe or a forehead probe (Omeda Biox 3700e, Louisville, USA or Nellcor N-20, Pleasanton, USA). The patients rated their perceived dyspnoea according to Borg CR10 (scale 0–10), and perceived exertion according to Borg RPE (scale 6–20) (25) every 5th minute and after every speed interval. The intensity of the sessions was individualised with respect to the patients' saturation and their subjective ratings of dyspnoea and perceived exertion (26). Target dyspnoea was set to 7/10 and target perceived exertion was set to 17/20. The treadmill was stopped if the patients rated 7/17 (respectively) or more on the Borg scales and/or if the patients' SaO_2 fell below 90%. The treadmill was started again when SaO_2 rose above 90% and/or when the ratings lowered. When the walking speed of patients had to be increased above 6.0 km/hour, the treadmill was inclined instead of further increasing speed. In these cases some of the higher-speed-intervals included an inclined treadmill during weeks 2–7 (not the first and last training week). The inclination varied between 1.0 and 5.0 degrees. The distance walked was noted after every session.

Test procedures

Before and after the training period, the subjects performed two 6-minute walking distance tests (6MWD), one with air (Test A) and one with oxygen (Test B), with 1-hour rest in between. The order in which the patients walked with air and oxygen was randomized, and the tests were performed at the same time of day for pre- and post-training to account for diurnal variation. A non-motorized treadmill (Skip Sport Walker 2000, Tyresö, Sweden) was used during the tests. The treadmill was driven by the patients' own walking which made it possible for them to decide speed and stops independently (disregarding the test leader). The test procedure was first demonstrated to the patients who then practised walking on the treadmill for 1–2 minutes before the test. The instruction before the tests was to walk as far as possible during 6 minutes. The test leader was not supposed to intervene during the tests. The patients were unaware as to whether they were breathing air or oxygen. The flow rate was set at 5 litres/minute and administered through a dual-prong nasal cannula for both tests.

Measurements during the tests

Oxygen saturation (SaO_2) and heart rate were continuously measured during the tests with a pulse oximeter (Omeda Biox 3700e, Louisville, USA) using a finger probe. Transcutaneous Carbon dioxide ($TcpCO_2$) was continuously measured with a $TcpCO_2$-meter ("Tina TCM 3" Radiometer, Copenhagen, Denmark). The probe was connected to the 3rd rib or to the temple of the patient. The pulse oximeter and the $TcpCO_2$-meter were connected to a recorder (Yokogawa LR 4200, Tokyo, Japan) that continuously printed the levels. The time below 90% in SaO_2 was registered. Arterial blood gases were taken from arteria radialis at rest, and again directly after the test. The samples were analysed in an arterial blood gas analyser (IRMA Blood analysis system, St Paul, USA or "ABL 520" Radiometer, Copenhagen, Denmark). The pCO_2-values from the arterial blood gas tests were used to calibrate the $TcpCO_2$-meter. Venous blood samples to determine the lactate levels were taken from a venous catheter on three occasions—at rest, directly after the test, and 3 minutes after the test. The samples were analysed in a YSI 1500 Sport L-Lactate Analyzer (Yellow Springs, USA). Subjective experience of dyspnoea and perceived exertion were scored by showing the Borg CR10 and Borg RPE (25) to the patients at rest, after 3 minutes walk, immediately following the test, and 2 minutes after test completion. Frequency of breathing was measured by counting the frequency for 15 seconds, at rest and immediately following the test. The reason for using a treadmill for the 6MWD was to simplify continuous registrations of $TcpCO_2$, SaO_2, and heart rate and to simplify the blood sampling from the patients. In our laboratory the test-retest variation for the non-motorized treadmill used during tests was 3.0%.

Statistical analysis

The data were analysed using SPSS (version 7.5). Non-parametric

Table II. *Distance walked and heart rate during Test A (with air) and Test B (with oxygen), before and after training. Values are presented as median (min–max)*

	Training groups	Pre-training	Post-training	% change
Test A (air)				
6MWD (m)	AG	230 (110–280)	270 (130–390)	19.8**
	OG	210 (90–360)	245 (140–380)	14.0**
Max heart rate (bpm)	AG	137 (102–162)	144 (113–155)	5.4
	OG	128 (104–142)	128 (102–140)	4.9
Test B (oxygen)				
6MWD (m)	AG	235 (160–310)	290 (180–360)	21.3**
	OG	245 (130–400)	275 (170–350)	9.9
Max heart rate (bpm)	AG	130 (110–152)	137 (113–162)	4.3
	OG	122 (102–142)	127 (102–150)	2.1

** Significant difference between pre- and post-training tests at $p \leq 0.01$.
6MWD—6 minute walking distance, AG—patients training with air, OG—patients training with oxygen. % change is the change post-training compared with pre-training.

methods were used and the data presented as medians along with the minimum and maximum values. Changes within the training groups were compared with the Wilcoxon matched-pairs signed-ranks test. Differences between the groups were compared with the Mann-Whitney U test. The level of statistical significance was defined as $p < 0.05$.

RESULTS

Both groups significantly increased their 6MWD after training when tested on air (Test A, Table II). When tested on oxygen (Test B, Table II), the AG showed a significant increase in distance walked, but the OG did not change the distance walked. No significance was found when comparing the two groups regarding change in walking distance in either of the tests.

The short-term effect of exercising with oxygen was evaluated by comparing 6MWD with air (A) and with oxygen (B) before training. The patients (not separated in groups) improved the distance walked with 30 meters (−30–60) when walking with oxygen (B) compared with walking with air (A) ($p < 0.01$). When evaluating the short-term effect of oxygen after the training period it was found that the patients (not separated in groups) walked 25 meters (−90–60) longer when tested with oxygen (B) compared with the test with air (A) ($p < 0.05$). There were no significant differences regarding these short-term effects before and after training, within or between the groups.

The sum of distance walked during the first training week and the last week (a total of 90 minutes walking each week) is shown in Fig. 1. The AG increased the total distance walked, between the first and the last training week by 1952 meters (843–3003) (50%), and the OG increased the distance by 2173 meters (1405–2895) (43%). The increase for each group was statistically significant ($p < 0.01$). No difference was found between groups.

The perceived exertion (Borg RPE) was significantly lower after training compared to before training for the AG during Test A (with air). The OG showed no significant changes and the difference between the groups was not significant (Table III). The results were opposite in Test B (with oxygen) with the OG reporting a significantly lower dyspnoea and perceived exertion after training (Table III). In Test B there was a significant difference between the AG and OG regarding change in dyspnoea ratings (Borg CR10) before and after training ($p < 0.05$).

The OG showed a significantly larger increase in lactate levels during exercise (difference between pre- and post-test) in the test with air (Test A) after compared with before training. The increase was 1.51 mMol/l (0.77–4.89) after the training period compared with an increase of 0.98 mMol/l (0.30–2.37) before training ($p < 0.01$) (Fig. 2). No significant changes were found for the AG in any of the tests or for the OG in test with oxygen (Test B) (Fig. 2).

There was no statistically significant change in pCO_2 in any of the tests.

The total time during which the patients desaturated below 90% was significantly longer after training in the OG when tested on air (Test A). The time below 90% in SaO_2 was 174 seconds (0–291) before training and 251 seconds (0–288) after training ($p < 0.05$). In the AG there was no significant change. Regarding heart rate (Table II), the lowest level of SaO_2 and breathing frequency, no significant changes were found between the tests before and after training either within or between groups.

DISCUSSION

Although a number of studies have investigated the short-term effects of oxygen on exercise performance (12–20), only a few studies exists, the present study included, that have investigated the long-term effect of oxygen used during longer training periods.

In our study both groups increased the distance walked after training in the test with air, which indicates a positive training effect. In addition, the AG rated lower perceived exertion (Borg RPE) and displayed an unchanged increase in lactate during exercise after training. The OG increased the distance walked in this test but did not decrease their Borg ratings. They also

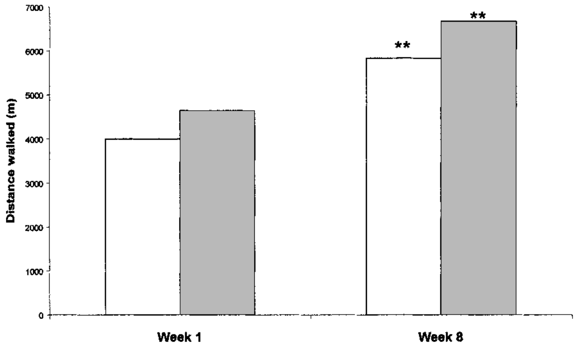

Fig. 1. Total distance walked during the first and last weeks of training (constituting of 90 minutes of walking) for the group training with air (AG, open bars) and the group training with oxygen (OG, grey bars). Values presented as median. Min–max for the first and last week respectively for AG (2112–5761), (3247–7371) and OG (2625–5194), (4924–7270). ** Significant increase in distance walked in both groups at $p \leq 0.01$.

displayed a higher increase in lactate during exercise after training. Also, an increase in time during which the patients were below 90% in SaO_2 during the test was found for the OG group.

One possible explanation why the patients in the OG did not have the same positive training effect as those in the AG, could be that they were too well oxygenated during training. Training with a slight hypoxaemia gives physiologic stress, which is required for improvements in physical capacity. During training sessions the OG performed better than the AG but when tested on air the OG did not show the same improvements as the AG. These results imply that training of patients with COPD and exercise-induced hypoxaemia can be conducted without supplemental oxygen.

In the test with oxygen only the AG increased the distance walked. However, this group showed no decrease in subjective ratings, while the OG did. These findings suggest that the patients preferred to walk with the supplementation that they had trained with. Other studies have also shown that general exercise training leads to improved ratings regarding dyspnoea (5, 9, 27). Oxygen supplementation during training has also been shown to lower the ratings of dyspnoea during exercise (15, 22).

Previous studies show contrasting results regarding long-term effects after training with oxygen. Zack & Palange (23) found that training with oxygen supplementation increased work performance. However, they did not have a control group training with air. No differences between training with oxygen and air have been shown in previous studies using various designs. McDonald et al. (21) assessed the effects of supplemental air and oxygen on exercise performance during activities that normally caused dyspnoea. They found no difference in exercise tests (6MWD or steps achieved) when comparing oxygen and air. In the study by Rooyackers et al. (22), no difference in training effects when training with air or oxygen was found, although the patients in the study were not blinded as to which treatment they received. Patessio et al. (28) found similar results in a single-blind controlled study, but their COPD patients did not desaturate during exercise.

In agreement with previous exercise studies (12–20) we found that supplemental oxygen led to an immediate increase in 6MWD compared with walking with air during the tests. The patients in the OG walked longer distance during the training sessions than the AG group, and this difference persisted during the whole period (Fig. 1). It appears then that the acute positive effect of oxygen prevails during and after training. According to this it is important to differ between the positive acute effects and the actual training effects of supplemental oxygen.

Previous studies have shown that exercise training for patients with COPD leads to a less pronounced increase in the level of lactate after training (8, 10, 27). One study, examining COPD patients training with either air or oxygen, found similar results for both training groups (28). The results in our study, which differ in relation to other studies, may be explained by us having used a different study design. In other studies (8, 10, 27, 28) the patients performed the tests at the same intensity level before

Table III. *Borg ratings during Test A (with air) and Test B (with oxygen) before and after training. Values are presented as median (min–max). Borg CR10 and Borg RPE measure dyspnoea and perceived exertion, respectively*

	Training groups	Pre-training at rest	Pre-training after test	Post-training at rest	Post-training after test	% change
Test A (air)						
Borg CR10 (0–10)	AG	1.5 (0–3)	6.5 (4–9)	1 (0–3)	6 (1–7)	0
	OG	0 (0–3)	6.5 (3–10)	0 (0–2)	4.5 (3–9)	−5.0
Borg RPE (6–20)	AG	7.5 (6–11)	16.5 (13–19)	9 (6–11)	15 (12–17)	−15.5*
	OG	6 (6–13)	15 (9–19)	6 (6–11)	15 (10–17)	5.5
Test B (oxygen)						
Borg CR10 (0–10)	AG	0.5 (0–3)	4.5 (3–7)	1 (0–2)	5 (3–6)	12.5
	OG	0 (0–3)	6.5 (3–8)	0 (0–3)	3.5 (2–7)	−34.0**†
Borg RPE (6–20)	AG	7.5 (6–11)	15 (11–17)	8 (6–10)	15 (12–17)	0
	OG	6 (6–13)	15.5 (11–17)	6 (6–12)	13.5 (9–17)	−17.5*

* $p < 0.05$ and ** $p < 0.01$ when comparing pro- and post-training tests.
† Significant difference in relative change pre- and post-training between training groups at $p \leq 0.05$.
AG—patients training with air, OG—patients training with oxygen. % change is the change in difference between the rest rating and the rating after test post-training compared with pre-training.

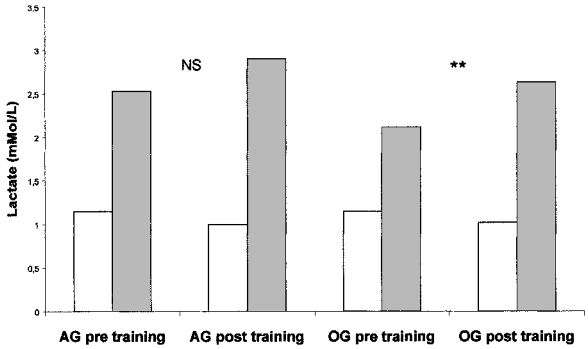

Fig. 2. Blood lactate levels during Test A, with air. Open bars, sample taken at rest; grey bars, sample taken directly after test. Both groups before and after training. Values presented as median. ** Significant difference in lactate increase between pre- and post-training tests at $p \leq 0.01$.

and after training. Our patients worked at a greater intensity in tests after training. We used lactate measurement as a complement to provide a more objective assessment of the stress of the patient during the test. Unchanged lactate levels in combination with increased walking distance indicated that the aerobic physical capacity had increased.

In patients with COPD there are difficulties in deciding the exercise intensity because of the limited possibility in using heart rate as a target. Since the respiration, and not the cardiovascular system, is often the limiting factor, we chose to use the subjective ratings of dyspnoea and perceived exertion in addition to the saturation as targets during training. In the OG the saturation could not be used because for this group the value never reached low enough, although according to the subjective ratings the two groups trained at the same intensity level. In a recent study on COPD patients (26), dyspnoea ratings were found to be reliable as a target to produce an expected exercise intensity. When comparing the heart rate and breathing frequency during the tests before and after training in this study there was no difference in any of the groups, which agrees with most previous studies (7, 10, 17, 18).

When patients with COPD and hypoxaemia are treated with oxygen there is always a risk of retention of CO_2. We therefore examined the pCO_2-levels when the patients were walking with supplemental oxygen during tests. The pCO_2-level tended to be higher than when walking with air but there was no significant increase during or after the test with oxygen. Additionally, when the patients were lying down after the test while still breathing oxygen, the pCO_2-level did not differ from when tested with air. Thus, it does not seem to be a risk of CO_2-retention during walking with oxygen in patients with COPD and exercise-induced hypoxaemia despite the relatively high oxygen flow.

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