Training with supplemental oxygen in patients with COPD and hypoxaemia at peak exercise

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Training with supplemental oxygen in patients with COPD and hypoxaemia at peak exercise. J.M. Rooyackers, P.N.R. Dekhuijzen, C.L.A. Van Herwaarden, H.T.M. Folgering. ©ERS Journals Ltd 1997.

ABSTRACT: Supplemental oxygen has acute beneficial effects on exercise performance in patients with chronic obstructive pulmonary disease (COPD). The purpose of this study was to investigate whether oxygen-supplemented training enhances the effects of training while breathing room air in patients with severe COPD.

A randomized controlled trial was performed in 24 patients with severe COPD who developed hypoxaemia during incremental cycle exercise (arterial oxygen saturation (S_{a,O_2}) <90% at peak exercise). All patients participated in an in-patient pulmonary rehabilitation programme of 10 weeks duration. They were assigned either to general exercise training while breathing room air (GET/RA group: forced expiratory volume in one second (FEV1) 38% of predicted; arterial oxygen tension (P_{a,O_2}) 10.5 kPa at rest; P_{a,O_2} 7.3 kPa at peak exercise), or to GET while breathing supplemental oxygen (GET/O_2 group: FEV1 29% pred; P_{a,O_2} 10.2 kPa at rest; P_{a,O_2} 7.2 kPa at peak exercise). S_{a,O_2} was not allowed to fall below 90% during the training. The effects on exercise performance while breathing air and oxygen, and on quality of life were compared.

Maximum workload (W_{max}) significantly increased in the GET/RA group (mean (SD) 17 (15) W, p<0.01), but not in the GET/O_2 group (7 (25) W). Six minute walking distance (6MWD), stair-climbing, weight-lifting exercise (all while breathing room air) and quality of life significantly increased in both groups. Acute administration of oxygen improved exercise performance before and after training. Training significantly increased W_{max}, peak carbon dioxide production (V'_{CO_2}) and 6MWD while breathing oxygen in both groups. Differences between groups were not significant.

Pulmonary rehabilitation improved exercise performance and quality of life in both groups. Supplementation of oxygen during the training did not add to the effects of training on room air.
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Hypoxaemia may occur during exercise in patients with chronic obstructive pulmonary disease (COPD). This is caused by alveolar hypoventilation, diffusion limitation, shunt, ventilation-perfusion inhomogeneity and a low mixed venous oxygen tension ($P_{\bar{v},O_2}$) (low cardiac output) [1]. Exercise-induced hypoxaemia will raise the pulmonary artery pressure during exertion, and may contribute to the decreased exercise tolerance in these patients [2].

Acute administration of oxygen has been shown to improve exercise performance in patients with COPD [3–6]. These acute effects of oxygen have been observed both in normoxic patients and in patients who are hypoxaemic at rest or during exercise. Several mechanisms may be involved, including reduction in ventilatory response to exercise (reduced ventilatory equivalent for carbon dioxide (V'_E/V'_{CO_2})) [6], ventilatory muscle recruitment [7] and delayed ventilatory muscle fatigue [8, 9], improved aerobic capacity of the working muscles [10] and a reduction in breathlessness [11].

As a consequence, patients with COPD would be expected to benefit from supplemental oxygen during the training. Indeed, recent guidelines recommend the administration of oxygen during exercise training in patients with exercise-induced hypoxaemia [12]. Whether this approach results in a further improvement in exercise performance as compared to training on room air has not been fully clarified. Many studies have investigated the effects of training in patients with COPD. Some of these studies included a small number of patients who developed hypoxaemia during exercise and received supplemental oxygen during the training, whereas patients who did not desaturate trained on room air [13–15]. Other, uncontrolled, studies have shown that oxygen-supplemented exercise training increased exercise performance [16–17]. However, in these studies no comparison was made with a control training group breathing room air.

We hypothesized that the administration of oxygen enables patients with COPD who develop hypoxaemia during exercise to achieve higher exercise intensities

during the training. If so, this treatment might induce an additional physiological training effect on the cardiocirculatory system and the peripheral muscles in terms of increased oxygen delivery, peripheral oxygen extraction and muscle oxygen utilization. As a result, training with oxygen might also enhance exercise performance on room air. To test this hypothesis, we performed a controlled study to compare the effects of training with and without supplemental oxygen on exercise performance and quality of life in patients with severe COPD and hypoxaemia at peak exercise due to a diffusion-perfusion limitation.

Methods

Study design and patients

Twenty four patients with stable COPD [18] entered the study; all were referred to our hospital for pulmonary rehabilitation. They met the following inclusion criteria: hypoxaemia (arterial oxygen saturation (Sa,O_2) <90%) at maximum exercise, and an increase in alveolar-arterial difference in oxygen tension (P(A-a)O_2) of at least 2 kPa from rest to maximum exercise during maximal incremental cycle exercise. Patients were excluded if they had a resting Pa,O_2 of less than 8.5 kPa, a mean nocturnal Sa,O_2 of less than 90%, a mean pulmonary artery pressure ($\bar{P}$pa) of more than 25 mmHg measured at rest by Doppler echocardiography [19], and if they had neuromuscular or cardiovascular disease.

All patients were ex-smokers. Their medication was not changed during the study. They were familiar with the procedures of exercise testing. The patients were randomly allocated either to general exercise training while breathing room air (GET/RA), or GET while breathing supplemental oxygen (GET/O_2) at a flow rate of 4 L·min^{-1} through a dual-prong nasal cannula. Informed consent was obtained from each patient. The study was approved by the Hospital Ethics Committee.

Pulmonary rehabilitation programme

All patients participated in a multidisciplinary in-patient programme for 10 weeks, which consisted of physical training, breathing retraining, physical therapy (relaxation and mobilization exercises), education and psychosocial support.

General exercise training (GET). Training consisted of dynamic and isometric strength training and specific training of daily life activities. Training sessions were held 5 days per week and had a mean duration of 80 min, including periods of rest [20]. GET comprised the following exercises: interval cycling (2 min of exercise alternated with 2 min of rest for 20 min); rowing (5 min); dynamic exercises for the muscles of the arm and shoulder girdle using a pulley (5 min), and for the muscles of the back and abdomen by lifting the upper body and the legs, respectively, from the supine position (5 min); isometric strength training of the arms, shoulder girdles and legs (3 min); stair-climbing (3 min); sitting down and getting up from a chair alternating with slalom walking (5 min); and arm exercise by moving a weight of 1–2 kg between racks at 20 cm above and below shoulder level (5 min).

All sessions were supervised by a physiotherapist. Sa,O_2 during exercise was monitored with a pulse oximeter using a finger probe (Oxyshuttle, Sensor Medics, Bilthoven, The Netherlands). Exercise training was started at low workloads. After the first week, the exercise intensity was gradually increased as tolerated by the patients [21]. In both groups, the work rate was not allowed to exceed the level at which Sa,O_2 fell below 90%.

Outcome measures

Pulmonary function tests. Spirometry and transfer coefficient for carbon monoxide (KCO, single-breath) were performed according to European Respiratory Society (ERS) standards [22]. All tests, including measurement of $\bar{P}$pa at rest, were repeated at the end of the training period.

Maximal incremental cycle exercise test. The patients cycled on an electrically-braked cycle ergometer (Lode, Groningen, The Netherlands) at a pedalling rate of 60 revolutions per minute (rpm), breathing room air. The work rate was increased each minute by 10% of the estimated maximal workload (Wmax) until exhaustion [23]. Arterial blood samples were drawn from an indwelling catheter in the brachial artery. Minute ventilation (V'E), oxygen consumption ($V'O_2$) and carbon dioxide production ($V'CO_2$) were measured every 30 s by a mixing chamber ergospirometry unit (Oxycon IV, Mijnhardt, Maarsen, The Netherlands). Breathlessness was scored every 3 min, and at the end of exercise, on a modified Borg scale [24]. V'Emax was related to predicted maximum exercise values (V'Emax predicted= 37.5 × forced expiratory volume in one second (FEV1)) [25].

Single-stage cycle exercise test. After 1 min of unloaded pedalling, exercise was performed at a constant workload of 65% of the actual Wmax. Endurance cycling time was measured. The test was terminated when the patient could not sustain exercise any longer, or after a maximum of 15 min. The same measurements were made as during the maximal incremental test, except for blood gas analysis.

Activities of daily life. After 3 practice tests, the 6 min walking distance (6MWD) was measured in a gymnasium, while standardized encouragement was given [26, 27]. Sa,O_2 was measured continuously and breathlessness was scored at the end of the test.

Stair-climbing was performed on an exercise staircase with a hand-rail, which had four steps for going up, a plateau, and three steps for going down. The number of rounds during 5 min of exercise were counted.

During weight-lifting the patients held a weight of 2 kg in the dominant hand and moved it between racks at 20 cm above and below shoulder level. The number of lifts to both levels during 3 min was counted [28].

Acute effects of supplemental oxygen on exercise performance. The maximal incremental cycle exercise test, the single-stage exercise test and the 6MWD were repeated while oxygen was supplied at a flow rate of 4 L·min^{-1}. Resting periods between tests lasted at least 4

h. During oxygen breathing, it was not possible to measure V'_{O_2}, and blood gas analysis was not performed.

Quality of life. Quality of life was assessed by means of the Chronic Respiratory Disease Questionnaire (CRDQ) [29]. The questionnaire examines the dimensions: dyspnoea, fatigue, emotional function and mastery. Altogether, 20 items are scored on a 7-point scale (maximum score 140 points; a higher score indicates a better quality of life). The test was administered at the start of the study and 6 weeks after completion of the pulmonary rehabilitation programme.

Statistical analysis. The data were analysed with the Statistical Analysis System (SAS) package (SAS Institute Inc., Cary, NC, USA). The results were expressed as mean±SD. Changes within the training groups were compared with the Wilcoxon test for paired samples. Differences between the groups were compared with the Kruskal Wallis test (Chi-squared approximation). The correlation between various parameters was tested with the Spearman correlation coefficient. Since multiple comparisons were performed, the level of significance was set at a p-value less than 0.01.

Results

Pulmonary function tests

The patients had severe airway obstruction and emphysema, as suggested by hyperinflation. They had a reduced K_{CO} and an elevated resting $P_{(A-a)O_2}$, but they were normoxic at rest. Anthropometrics and resting pulmonary function remained unchanged after pulmonary rehabilitation. No significant differences were present between groups (table 1).

Table 1. – Anthropometrics and resting pulmonary function before and after pulmonary rehabilitation

	GET/RA Before	GET/RA After	GET/O_2 Before	GET/O_2 After
Patients n	12		12	
Sex M/F	10/12		10/12	
Age yrs	59±13		63±5	
BMI kg·m^{-2}	23.2±1.6	23.0±1.6	22.5±2.2	22.1±2.0
TLC % pred	114±20	110±11	109±17	110±22
IVC % pred	93±19	95±17	87±16	98±23
FEV1 L	1.2±0.5	1.2±0.5	0.9±0.3	1.0±0.4
% pred	38±11	38±12	29±7	33±9
K_{CO} % pred	37±14	40±15	30±14	30±15
$\bar{P}$pa mmHg	13±3	16±7	17±7	15±5
P_{a,O_2} kPa	10.5±1.1	10.2±1.3	10.2±1.6	9.5±2.0
P_{a,CO_2} kPa	5.0±0.8	4.9±0.6	5.1±1.1	5.3±1.1
$P_{(A-a),O_2}$ kPa	4.4±0.9	5.2±1.6	4.6±1.9	5.5±1.3

Values are presented as mean±SD. GET/RA: general exercise training/room air; GET/O_2: general exercise training/supplemental oxygen; M: male; F: female; BMI: body mass index; TLC: total lung capacity (He-dilution); IVC: inspiratory vital capacity; K_{CO}: transfer coefficient for carbon monoxide (single-breath); $\bar{P}$pa: mean pulmonary artery pressure; P_{a,O_2}: arterial oxygen tension; P_{a,CO_2}: arterial carbon dioxide tension; $P_{(A-a),O_2}$: alveolar-arterial difference in oxygen tension; % pred: percentage of predicted value. No significant differences were present between groups.

Cycle exercise intensity during the training

During the last 6 weeks of pulmonary rehabilitation, the mean (SD) workload achieved during interval cycle exercise training in the GET/RA and the GET/O_2, group was 114 (32) and 124 (43)%, respectively, of W_{max} during maximal incremental cycle exercise at the start of the study (GET/RA *versus* GET/O_2; p=0.12).

Exercise testing on room air

During maximal incremental cycle exercise before training, V'_E approached or exceeded predicted maximal values. P_{a,CO_2} increased by less than 1 kPa, while P_{a,O_2} decreased and $P_{(A-a)O_2}$ increased by approximately 3 kPa in both groups (table 2). Training increased W_{max} by 17 (15) W (p<0.01) in the GET/RA group, and by 7 (25) W (p=0.1) in the GET/O_2, group. Peak V'_E, V'_{O_2}, V'_{CO_2} and the change in base excess (Δbase excess) were similar after training in both groups. P_{a,O_2} at Wmax showed a further decrease after training in both groups, which was significant in the GET/O_2 group. Exercise efficiency (W/V'_{O_2}) at peak exercise on room air increased by 13 (23) W/(L·min^{-1}) in the GET/RA group (p<0.01), and by 10 (25) W/(L·min^{-1}) in the GET/O_2 group (p=0.1). In both groups, the reduction in dyspnoea score was about 1.3 points (p=NS).

The variability between patients in cycling time during single-stage exercise was large. At the start of the study, only three patients were able to cycle at least 10 min, whereas 14 patients stopped within 5 min of exercise. Training did not improve cycling time in the GET/RA group. In the GET/O_2 group, the increase in cycling time (2.2 (4.2) min) was not significant (p=0.1) (table 3).

The 6MWD increased significantly by 123 (77) m in the GET/RA group and by 86 (77) m in the GET/O_2 group. This was achieved at a higher cardiac frequency (f_C) in both groups, which was significant only in the GET/O_2, group (table 3).

Table 2. – Maximal incremental cycle exercise test breathing room air before and after pulmonary rehabilitation

	GET/RA Before	GET/RA After	GET/O_2 Before	GET/O_2 After
W_{max} W	70±51	87±58**	58±33	65±39
f_C beats·min^{-1}	133±21	132±23	126±17	126±19
V'_E L·min^{-1}	43±21	43±21	35±15	37±17
% pred	96±23	95±18	101±23	92±13
V'_{O_2} L·min^{-1}	1.2±0.5	1.2±0.6	1.0±0.3	1.0±0.3
V'_{CO_2} L·min^{-1}	1.2±0.5	1.2±0.6	1.0±0.4	1.0±0.4
P_{a,O_2} kPa	7.3±0.7	6.9±0.7	7.2±1.0	6.7±1.0**
P_{a,CO_2} kPa	5.7±1.1	5.7±0.8	5.9±1.2	5.8±1.3
Δbase excess mmol·L^{-1}	-5.3±2.8	-5.7±2.8	-4.8±3.3	-5.4±3.4
$P_{(A-a),O_2}$ kPa	7.7±1.3	8.2±1.5	7.4±1.3	8.1±1.5
Dyspnoea Borg scale	7.3±2.4	5.8±1.9	6.6±2.1	5.3±1.2

Values are presented as mean±SD. Wmax: maximum workload; f_C: cardiac frequency; V'_E: minute ventilation; V'_{O_2}: oxygen consumption; V'_{CO_2}: carbon dioxide production; Δbase excess: base excess after-before the test. For further definitions see legend to table 1. **: p<0.01, within-group comparison before *versus* after rehabilitation.

Table 3. – Single-stage exercise test and activities of daily life breathing room air before and after pulmonary rehabilitation

	GET/RA		GET/O$_2$	
	Before	After	Before	After
Single-stage cycle exercise test				
Cycling time min	6.5±4.4	6.5±4.4	4.5±2.5	6.7±3.7
fC beats·min^{-1}	124±22	125±19	116±21	126±21
V'E L·min^{-1}	39±15	40±21	32±14	36±15
V'CO$_2$ L·min^{-1}	1.0±0.4	1.1±0.5	0.8±0.3	1.0±0.4
Sa,O$_2$ %	86±4	83±6	86±4	83±6
Dyspnoea Borg scale	5.8±0.9	6.2±1.7	6.1±1.8	5.8±1.7
6MWD m	487±191	610±166**	389±140	475±180**
fC beats·min^{-1}	118±10	126±11	110±23	124±19**
Sa,O$_2$ %	84±5	82±5	85±6	83±6
Dyspnoea Borg scale	4.8±1.2	5.1±1.6	4.5±1.1	4.8±1.6
Stair-climbing n	29±12	41±18**	22±10	30±14**
Weight-lifting n	36±14	52±18**	37±9	46±7**

Values are presented as mean±SD. For exercise testing protocols for stair-climbing and weight-lifting see text. Sa,O$_2$: oxygen saturation (pulse oximeter); 6MWD: 6 min walking distance. For further definitions see legends to tables 1 and 2. **: p<0.01, within-group comparison before *versus* after rehabilitation.

The performance during stair-climbing and weight-lifting increased significantly by 20–40% in both groups (table 3).

No significant differences were observed in exercise performance, responses to exercise and effects of training between the two groups.

Oxygen-supplemented exercise testing

Supplemental oxygen had acute effects on exercise performance before and after training. The effects did not differ between the two training groups. Before training, oxygen improved Wmax during maximal incremental cycle exercise in the GET/RA group by 12 (19) W (p=0.04), and in the GET/O$_2$ group by 4 (19)

Table 4. – Oxygen supplemented exercise testing before and after pulmonary rehabilitation

	GET/RA		GET/O$_2$	
	Before	After	Before	After
Maximal incremental cycle exercise test				
Wmax W	82±53	104±68$^{+\#}$	62±27	79±40$^{+\#}$
fC beats·min^{-1}	132±21	139±30	123±19	129±21
V'E L·min^{-1}	41±20	45±23	35±14	39±17
V'CO$_2$ L·min^{-1}	1.2±0.6	1.4±0.7$^{+\#}$	1.0±0.4	1.2±0.5$^{+\#}$
Sa,O$_2$ %	94±3	94±4	93±5	93±6
Dyspnoea Borg scale	5.8±1.5	6.3±1.4	6.4±2.3	5.8±1.9
Single-stage cycle exercise test				
Cycling time min	11.4±4.7$^{\#}$	9.4±5.2$^{\#}$	11.0±4.5$^{\#}$	12.2±4.4$^{\#}$
fC beats·min^{-1}	129±18	125±20	121±18	127±25
V'E L·min^{-1}	38±15	39±21	34±15	36±14
V'CO$_2$ L·min^{-1}	1.1±0.4	1.1±0.5	0.9±0.3	1.0±0.3
Sa,O$_2$ %	95±2	95±2	95±2	95±2
Dyspnoea Borg scale	6.0±1.5	5.7±2.2	6.3±2.1	5.0±1.5
6MWD m	529±193$^{\#}$	637±221^{+}	436±162$^{\#}$	504±164^{+}
fC beats·min^{-1}	121±11	125±15	111±24	121±22^{+}
Sa,O$_2$ %	90±5	87±8	92±3	91±3
Dyspnoea Borg scale	4.8±1.5	4.7±1.5	4.8±2.6	4.3±1.4

Values are presented as mean±SD. For definitions see legends to tables 1–3. $^{+}$: p<0.01, within-group comparison before *versus* after rehabilitation; $^{\#}$: p<0.01, oxygen-supplemented exercise test *versus* exercise test on room air.

W (p=0.15). After training, oxygen significantly increased Wmax in both groups by 17 (15) and 13 (11) W, respectively (fig. 1a).

Supplemental oxygen significantly increased cycling time during single-stage exercise before training by 4.8 (4.8) in the GET/RA group and by 6.5 (3.9) min in the GET/O$_2$ group, and after training by 2.9 (4.3) and 5.5 (3.9) min, respectively (fig. 1b).

Before training, supplemental oxygen significantly increased 6MWD by 42 (30) in the GET/RA group and by 47 (63) m in the GET/O$_2$ group (fig. 1c). The acute effect of oxygen on 6MWD was lost after training.
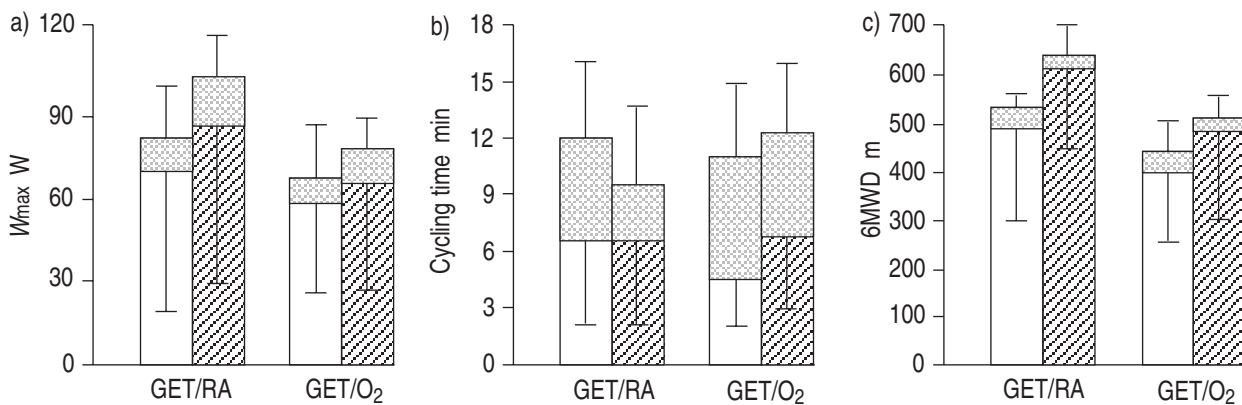

Fig. 1. – Exercise performance on room air before (□) and after (▨) general exercise training while breathing room air (GET/RA; n=12) and supplemental oxygen (GET/O$_2$; n=12). The acute effects of supplemental oxygen are depicted in the closed bars (▩). Error bars indicate standard deviation. a) Training significantly increased maximal workload (Wmax) on room air in the GET/RA group (p<0.01), but not in the GET/O$_2$ group. Supplemental oxygen increased Wmax before and after training in both groups, but these improvements were significant only after training (p<0.01). b) Training did not improve cycling time during single-stage exercise on room air at a constant workload of 65% of Wmax in both groups. Supplemental oxygen significantly increased cycling time both before and after training in both groups (p<0.01). c) Training significantly increased 6 min walking distance (6MWD) on room air in both groups (p<0.01). Supplemental oxygen significantly increased 6MWD before training in both groups (p<0.01). After training, no further improvement in 6MWD was observed. Differences between groups were not significant.

Table 5. – Quality of life (CRDQ) before and after pulmonary rehabilitation

| | GET/RA | | GET/O$_2$ | |
	Before	After	Before	After
Dyspnoea	14.9±5.8	21.6±4.5**	15.9±5.3	21.6±5.5**
Fatigue	17.4±4.8	20.0±4.5	15.5±4.3	18.8±3.9
Emotional function	32.0±6.9	35.2±8.5	29.5±7.1	35.3±6.3**
Mastery	20.4±4.1	22.8±3.7**	18.0±5.5	22.1±3.3**
Total score	85±16	100±17**	79±18	98±16**

Values are presented as mean±SD. CRDQ: Chronic Respiratory Disease Questionnaire. **: $p<0.01$, within-group comparison before *versus* after rehabilitation.

The acute effects of oxygen on Wmax, cycling time and 6MWD before training did not differ significantly from those after training.

Training significantly increased Wmax, peak V'CO$_2$ and 6MWD while breathing oxygen, to a similar extent in both groups (table 4). The increase in 6MWD was achieved at a higher fC in the GET/O$_2$ group, while the fC did not change in the GET/RA group. Differences between groups were not significant.

Quality of life

Before rehabilitation, CRDQ scores were similar in both groups. Rehabilitation significantly increased total CRDQ score by 15 (7) points in the GET/RA group and by 19 (14) points in the GET/O$_2$ group. The improvements were equally distributed among the four dimensions, but were not significant for the dimension "fatigue" in both groups and for "emotional function" in the GET/RA group (table 5).

Discussion

In this study, we investigated whether patients with severe COPD and hypoxaemia at peak exercise might benefit from supplemental oxygen during training. Exercise training, both on air and oxygen, improved exercise performance and quality of life. Although supplemental oxygen had acute beneficial effects on exercise performance, oxygen-supplemented exercise training did not add to the effects of training while breathing room air.

The diffusion capacity below 50% of predicted [30], the elevated P(A-a)O$_2$ at rest and the increase in P(A-a)O$_2$ by more than 3 kPa during exercise [31] indicate that a diffusion-perfusion limitation, rather than hypoventilation, was the cause of the hypoxaemia at peak exercise in these patients [1, 32].

Pulmonary rehabilitation in patients with severe COPD

Several studies have reported beneficial effects of pulmonary rehabilitation in patients with moderate-to-severe COPD, some of whom were hypoxaemic at rest or during exercise [13–15, 33, 34]. These studies showed improvements in maximal workload [14, 15], endurance exercise capacity [13–15, 34], walking distance [13], perceived breathlessness [14, 15], and quality of life [13]. A physiological training effect in terms of an increase in peak V'O$_2$, and reduction in fC, blood lactate levels and ventilation at identical work rates after training, has been reported in some studies [14, 15, 34], but was not found by others [13, 33]. The effects in patients who developed hypoxaemia during the training were not described separately.

The patients in the present study were normoxic at rest and hypoxaemic at peak exercise. During the training they desaturated, but Sa,O$_2$ was not allowed to fall below 90%. Training did not increase aerobic capacity while breathing room air. The improvement in exercise performance was achieved in part by an improvement in exercise efficiency (W/V'O$_2$). Since the Borg score at peak exercise tended to decrease after training, both desensitization to dyspnoea and motivation may have played a role in patients in whom training proportionally improved Wmax and peak V'O$_2$.

Acute effects of supplemental oxygen on exercise performance

In patients with COPD, the acute administration of supplemental oxygen has been shown to improve exercise performance [3–6]. Breathing supplemental oxygen increased Wmax during cycle exercise by 10% [6], endurance cycling and walking time by 88 and 59%, respectively, and 6MWD by 17% [5] in comparison with room air. We found similar results in the present patients. Since the ventilatory equivalent for V'O$_2$ is higher for walking than for cycling, and 6MWD is a submaximal exercise test, diffusion-perfusion may be less important as a factor limiting 6MWD. Hence, the acute effect of supplemental oxygen on 6MWD was small as compared to performance during cycling at high exercise intensities. After training, this difference became even more clear, as breathing oxygen did not improve 6MWD further in comparison with room air. This was caused, in part, by the effect of training on 6MWD, which far exceeded the acute effect of oxygen.

Effects of oxygen-supplemented exercise training

Few studies have investigated the effects of training with supplemental oxygen in patients with COPD. In the study by ZACK and PALANGE [17], oxygen-supplemented training significantly increased Wmax while breathing oxygen, whereas Wmax and peak V'O$_2$ on room air did not improve. Endurance cycling time and 12 min walking distance significantly improved both on air and oxygen [17]. DEGRE *et al.* [16] reported an increase in peak V'O$_2$ by 10% after training with supplemental oxygen (3–4 L·min^{-1}), which was related to the oxygen tension during exercise [16]. Maximal cardiac output and stroke volume did not change [16]. In these studies, however, no comparison was made with a control group breathing room air.

In the present study, training with supplemental oxygen did not add to the effects of training on room air. Recently, similar results have been reported in patients who did not desaturate during exercise [35]. Comparing exercise tests on oxygen, however, our study showed that training improved Wmax and peak V'CO$_2$, (V'O$_2$ could not be measured under these conditions) in both groups.

This implies a physiological training effect, regardless of the use of oxygen during the training. These training effects were not observed during exercise testing on room air, possibly because hypoxaemia limited exercise performance.

In contrast to previous studies, training with or without supplemental oxygen did not improve endurance cycling time on air and oxygen in the present patients [13–15, 17, 34]. Furthermore, endurance work (constant workload × endurance cycling time) did not improve in either group. Study population and test design may explain the results in our study. Hypoxaemia and the high constant workload, which was adjusted to the actual Wmax after training, may have contributed to the poor performance during the single-stage exercise test on room air. Indeed, endurance cycling time increased considerably when oxygen was administered. However, the single-stage test was limited to 15 min, which may have concealed some of the effects of training.

Many factors may account for the absence of an additional effect of training with supplemental oxygen, as observed in the present study. Firstly, the contribution of hypoxaemia to the exercise limitation is still uncertain, and the mechanisms by which oxygen affects exercise performance are complex [6–11]. The present study confirmed previous reports showing that the acute effects of oxygen, as well as the effects of training, correlated poorly with lung function parameters or blood gas values at rest or during exercise [5, 6, 17]. Furthermore, in the present study, the acute effects of oxygen did not predict the effects of training in individual subjects. Hence, patients with a poor response to oxygen are not necessarily poor candidates for training. These findings suggest that oxygen and training may influence exercise performance by different mechanisms.

Secondly, in spite of the acute effects of oxygen, the GET/O_2 group did not achieve higher work rates during cycle exercise training than the GET/RA group. Thus, the total amount of work performed during the training was equal in both groups. This was due to the training regimen, which consisted of interval training with bouts of exercise of 3 min or less. Endurance exercise was not performed during the training. Thus, the GET/RA group could keep Sa,O_2 above 90% at relatively high work rates. As a result, during exercise training, the patients in both groups were similarly limited by their ventilatory impairment and by breathlessness rather than by hypoxaemia.

Thirdly, increased blood lactate levels during exercise have been shown to enhance the effects of training in patients with COPD [34]. In healthy subjects and in patients with peripheral vascular disease, muscle ischaemia is a potent stimulus for improving endurance exercise [36]. Since supplemental oxygen abolishes the desaturation and reduces lactate levels during exercise [4, 37], it might also have reduced the training stimulus in these patients.

Finally, in addition to the diffusion-perfusion limitation in the lungs, a diffusion limitation at the level of the skeletal muscles may be present [38, 39]. In healthy subjects under hypoxaemic conditions, muscle diffusion capacity was an important factor limiting maximal V'O$_2$, especially in deconditioned muscles [39]. Supplemental oxygen may, thus, fail to enhance muscle oxygen utilization during the training in patients with COPD in whom peripheral muscle weakness may exist [40].

Clinical implications and conclusions

Supplemental oxygen attenuates the increase in Ppa during exercise in patients with COPD [41]. However, it is not known whether this may prevent the development of pulmonary hypertension. In the present study, training did not change resting $\bar{P}$pa. Thus, training both on air and oxygen may be safe, as long as Sa,O_2 is kept above 90% during exercise.

This study shows that pulmonary rehabilitation improves functional capacity and quality of life in patients with severe chronic obstructive pulmonary disease and hypoxaemia at peak exercise. The increase in quality of life scores after pulmonary rehabilitation is considered clinically relevant [42], and is in agreement with previous studies [43]. Breathing supplemental oxygen during the training had no advantage over training while breathing room air.

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