Benefits of Supplemental Oxygen in Exercise Training in Nonhypoxemic Chronic Obstructive Pulmonary Disease Patients

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Supplemental oxygen improves exercise tolerance of normoxemic and hypoxemic chronic obstructive pulmonary disease (COPD) patients. We determined whether nonhypoxemic COPD patients undergoing exercise training while breathing supplemental oxygen achieve higher intensity and therefore improve exercise capacity more than patients breathing air. A double-blinded trial was performed involving 29 nonhypoxemic patients (67 years, exercise $Sa_{O_2} > 88\%$) with COPD ($FEV_1 = 36\%$ predicted). All exercised on cycle ergometers for 45 minutes, 3 times per week for 7 weeks at high-intensity targets. During exercise, they received oxygen (3 L/minute) (n = 14) or compressed air (3 L/minute) (n = 15). Both groups had a higher exercise tolerance after training and when breathing oxygen. However, the oxygen-trained group increased the training work rate more rapidly than the air-trained group. The mean ± SD work rate during the last week was 62 ± 19 W (oxygen-trained group) and 52 ± 22 W (air-trained group) ($p < 0.01$). After training, endurance in constant work rate tests increased more in the oxygen-trained group (14.5 minutes) than in the air-trained group (10.5 minutes) ($p < 0.05$). At isotime, the breathing rate decreased four breaths per minute in the oxygen-trained group and one breath per minute in the air-trained group ($p = 0.001$). We conclude that supplemental oxygen provided during high-intensity training yields higher training intensity and evidence of gains in exercise tolerance in laboratory testing.

Keywords: chronic obstructive pulmonary disease; pulmonary rehabilitation; dyspnea

Exercise intolerance is often the chief complaint in persons with chronic obstructive pulmonary disease (COPD). A multidisciplinary pulmonary rehabilitation program, including exercise training, is a safe and effective measure that yields substantially improved exercise tolerance (1–10), increased health-related quality of life (4, 5, 11, 12), increased activities of daily living (13), and decreased use of health services (14).

Patients with both severe disease and mild disease are able to improve exercise capacity and quality of life through participation in a training program (3, 15, 16). Moreover, high-intensity training is tolerated by most patients with COPD (2, 8, 15). Although both low-intensity and high-intensity aerobic training have been shown to yield improvements in quality of life and reduce symptoms (8, 11, 14), high-intensity training has been shown to be more effective in achieving physiologic improvements in the ability to exercise (2). This finding has led to a search for strategies to facilitate higher exercise intensities during training programs as a means to improve their effectiveness.

Oxygen supplementation has been consistently demonstrated to be an ergogenic aid for patients with COPD. Oxygen supplementation during exercise in patients with resting mild hypoxemia results in improved exercise endurance and breathlessness (17–20). In COPD patients without resting hypoxemia who desaturate (pulse oximetry oxygen saturation [Sp_{O_2}] < 90%) during exercise, oxygen supplementation during exercise also results in increased exercise performance (21, 22). Supplemental oxygen also substantially improves exercise tolerance in patients who are normoxemic or only slightly hypoxemic during exercise (23, 24). The mechanism of this benefit has been shown to be related to slowing of the respiratory rate and consequent reduction in hyperinflation (24).

Although a few studies have previously compared the effects of training with supplemental oxygen to training with air (17, 18, 25, 26), none has discerned that supplemental oxygen improved the training results to a greater extent. However, features of the experimental design of these studies might have contributed to negative results (e.g., failure to pursue a high-intensity training program) (17, 18, 26) (*see* DISCUSSION).

We hypothesized that administration of supplemental oxygen during a high-intensity exercise program would enable patients with COPD to achieve higher training work rates. If so, treatment with supplemental oxygen might induce an enhanced physiologic training effect on the peripheral muscles. As a result, training with supplemental oxygen might enhance exercise performance, which would be manifest both while breathing room air and while breathing supplemental oxygen. Some of the results of this study have been previously reported in the form of an abstract (27).

METHODS

See the online supplement for additional details on the methods used.

Patients

We enrolled 30 physically inactive COPD patients (19 men) aged 45–85 years. Entry criteria included FEV_1 less than 50% predicted, resting Pa_{O_2} greater than 55 mm Hg, and $Sp_{O_2} \geq 88\%$ during a constant work rate test (*see* Table 1 for subject descriptors). Written informed consent was obtained.

Exercise Program

The study was randomized and double blinded. Patients were allocated to a 7-week training program in which they received supplemental compressed air (n = 15) or oxygen (n = 15).

Endurance training was on calibrated cycle ergometers three times per week. Sessions included 5 minutes of low-resistance cycling, 35 minutes of high-intensity training, and 5 minutes of no resistance pedaling. During training sessions, gas was delivered at 3 L/minute via nasal can-

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TABLE 1. ANTHROPOMETRIC DATA, RESTING PULMONARY FUNCTION, AND RESTING ARTERIAL BLOOD GASES BEFORE AND AFTER 7 WEEKS OF EXERCISE TRAINING IN THE OXYGEN- AND AIR-TRAINED GROUPS

	Oxygen-trained Group		Air-trained Group	
	Before Training (*n = 14*)	After Training (*n = 14*)	Before Training (*n = 15*)	After Training (*n = 15*)
Age, yr	66 (7)		67 (10)	
Gender, female/male	6/8		5/10	
Height, cm	172 (9)		167 (7)	
Weight, kg	69 (15)		71 (12)	
BMI, kg/m^2	24 (4)		26.5 (6.5)	
FEV_1, L	1.01 (0.33)	1.12 (0.37)	1.01 (0.27)	1.13 (0.30)*
FEV_1, % predicted	35 (10)	39 (14)	38 (8)	42 (10)*
FEV_1/FVC, %	37 (8)	39 (10)	41 (10)	43 (11)
FVC, L	2.7 (0.8)	2.9 (0.8)	2.58 (0.7)	2.74 (0.9)
FVC, % predicted	74 (18)	78 (16)	74 (16)	78 (16)*
TLC, L	7.2 (1.6)	7.3 (1.6)	7.3 (1.2)	7.3 (1.4)
TLC, % predicted	122 (18)	124 (16)	130 (24)	129 (19)
RV, L	4.1 (0.9)	4.1 (0.9)	4.6 (1.3)	4.2 (1.2)
RV, % predicted	189 (35)	186 (36)	212 (70)	194 (60)
D_{LCO}, ml/min/mm Hg	10.9 (3.5)	11.5 (3.6)	11.4 (4.4)	13.1 (5)*
D_{LCO}, % predicted	45 (14)	47 (16)	49 (17)	56 (24)*
pHa	7.43 (0.02)	7.43 (0.02)	7.43 (0.02)	7.42 (0.02)
Pa_{CO_2}, mm Hg	40.6 (5.05)	40.7 (4.2)	41.3 (3.8)	42.3 (3.2)
Pa_{O_2}, mm Hg	71.6 (8.4)	74.9 (8.7)	73.5 (7.8)	73.8 (6.2)
SBC, mmol/L	27.2 (1.9)	27.2 (1.5)	27.7 (1.5)	27.3 (1.1)
Hemoglobin, mg/dL	14.5 (1.2)	14.1 (0.9)	14.1 (1.1)	14.1 (1.2)

Definition of abbreviations: BMI = body mass index; D_{LCO} = diffusing capacity of the lung for carbon monoxide; pHa = arterial pH; RV = residual volume; SBC = standard bicarbonate; TLC = total lung capacity.

* $p < 0.05$ within groups between start and end of the 7 weeks of training.

Predicted values for FEV_1 and FVC, TLC and RV, and D_{LCO} are those of Knudson and colleagues (28), Goldman and Becklake (29), and Crapo and Morris (30), respectively. Values are mean ± SD.

nula. The nasal cannula tubing was connected to the appropriate tank (compressed air or oxygen) by an unblinded investigator. Patient and staff did not know which gas mixture the patient received.

During the first week, exercise intensity was low. Intensity target for the 2nd week was 75% of the peak work rate in the room air-breathing incremental test. Exercise intensity was subsequently adjusted, considering the subject's dyspnea and fatigue sensations, by blinded therapists.

Patients trained in groups of four to six. Work rate, heart rate, blood pressure, breathlessness, and leg fatigue (Borg scale) were recorded several times per session. An unblinded investigator measured oxygen saturation periodically; the findings were never reported to the patients or therapists. During weeks 2–7, arterialized venous blood was sampled weekly toward the end of an exercise session and assayed for plasma lactate. Patients were offered educational sessions during the first 3 training weeks. On average, patients attended six sessions.

Outcome Measures

Exercise testing was performed on an electrically braked cycle ergometer. Ventilation and gas exchange were measured with a computerized breath-by-breath system. Equipment was calibrated before each test with a 3-L syringe and precision gas mixtures and daily using a gas exchange simulator (31).

Incremental and constant work rate tests were performed inhaling either compressed air or 30% oxygen (four tests). Subject were blinded to the inhaled mixture and breathed through mouthpiece and low-resistance valve with a noseclip in place. Heart rate, oxygen saturation, and blood pressure were recorded by electrocardiography, pulse oximetry, and sphygmomanometry, respectively. End-exercise leg effort and breathlessness were scored by Borg ratio scale.

The incremental test used a 5 or 10 W/minute increment. The same increment rate was used for pretraining and post-training evaluations for a given patient. The constant work rate test was performed to tolerance at 75% of peak work rate in the air-breathing preintervention incremental test. Tests were terminated at 30 minutes if tolerance had not been reached.

Before and after training, spirometry, plethysmographic lung volumes, and carbon monoxide diffusing capacity were assessed. Arterial blood gases were measured from radial artery samples at rest breathing air. Health status was assessed by the disease-specific Chronic Respiratory Disease Questionnaire (32) and the general Medical Outcomes Survey Short Form 36 questionnaire (33).

Statistical Analysis

Laboratory exercise results on air and oxygen were compared using the paired *t* test or the Wilcoxon test. Unpaired *t* tests identified differences between groups. Relationship between variables was determined using Pearson's correlation coefficient. χ^2 tests detected differences between proportions. Results are presented as mean ± SD in the text and mean ± SEM in figures. As we hypothesized that oxygen breathing during training enhances exercise tolerance, one-tailed tests were used when comparing group responses; significance was accepted if p was less than 0.05 (34).

RESULTS

See the online supplement for additional details on the results.

Characteristics of Patients and Compliance with Intervention

Patients were randomized to exercising while breathing supplemental oxygen (oxygen trained group, n = 15) or while breathing compressed air (air trained group, n = 15). One patient from the oxygen-trained group was excluded because of illness during the postintervention testing period. Thus, data from 29 patients are presented. Missed training sessions were rescheduled or (for two subjects) added at the end of the program. All patients performed the 21 planned exercise sessions, except for two subjects, who performed 20 sessions. The pretraining physical characteristics of each group are presented in Table 1, columns 1 and 3. There were no significant differences in any of these characteristics between study groups at the start of the training program.

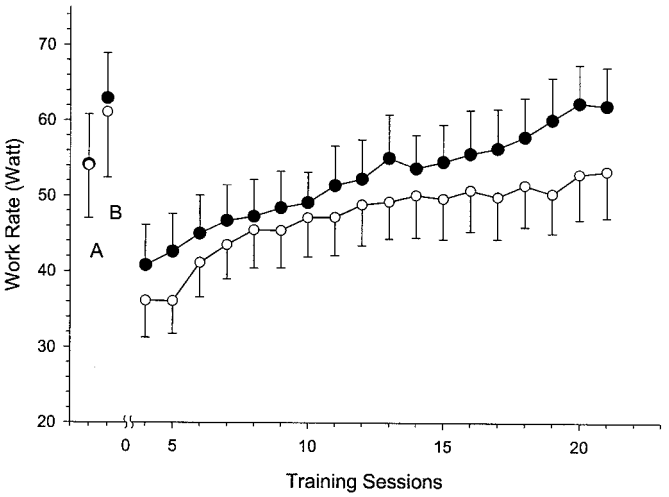

Figure 1. Training work rate (watts) achieved during the last 6 weeks of training. (*Closed circles*) The oxygen training group; (*open circles*) the air training group. *A* and *B* represent the peak work rate in the pretraining incremental exercise test breathing air (*A*) (the same peak work rate for both groups) and 30% oxygen (*B*). Values and error bars represent the mean and SEM. Despite nearly identical pretraining exercise tolerance, the oxygen-training group was able to exercise at a higher work rate throughout the training program, and the work rate increased more rapidly than in the air-training group (discussed in the text).

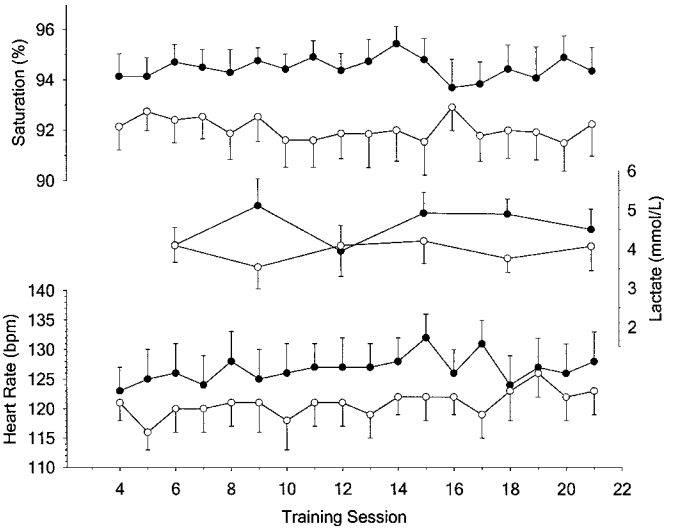

Figure 2. Responses recorded during training sessions in the air breathing (*open circles*) and oxygen breathing (*closed circles*) training groups. (*Upper tracings*) Arterial oxygen saturation, estimated by pulse oximetry recorded during training session during the last 6 weeks of training. The values recorded represent the lowest saturation of the three to five recorded during any given session. Note that oxygen supplementation results in higher O_2 saturation, although neither group exhibits clinically significant desaturation during the training sessions. (*Middle tracings*) Blood lactate from arterialized venous samples drawn weekly during training sessions. (*Lower tracings*) Heart rate recorded during training sessions during the last 6 weeks of training. Note that training session lactate levels and heart rates are both similar to peak exercise values (Table 2), documenting the high-intensity nature of the training program. Note also that neither training lactate levels nor heart rate increases over the course of the training program despite substantial increases in training work rate (Figure 1), consistent with a physiologic training effect. Values and error bars represent the mean and SEM.

Effects of Training on Pulmonary Function

On initial testing, on average, patients had severe airflow obstruction, hyperinflation, and reduced diffusing capacity (Table 1). Small improvements in spirometric variables were observed post-training (e.g., an FEV_1 increase of 11% in the oxygen-trained group and 12% in the air-trained group), but these increases did not differ significantly between groups. The improvement in FEV_1 was not significantly correlated with the improvement in endurance capacity ($r = 0.2$ in the oxygen-trained group, $p = 0.4$; $r = 0.1$ in the air-trained group, $p = 0.6$; $r = 0.2$ in the total group, $p = 0.3$).

Training Program Characteristics

Although both groups increased training intensity significantly over the course of the training program ($p < 0.001$), the training work rate was able to be increased more rapidly over the 18 high-intensity sessions in the oxygen-trained group than in the air-trained group (Figure 1). During the first half of the training period, both groups increased training intensity significantly ($p < 0.001$), whereas only the oxygen-trained group continued to increase training intensity significantly during the second half of the training period. The mean target work rate (75% of the pretraining peak work rate in the incremental test breathing air) was achieved during the 1st high-intensity week in the oxygen-trained group and during the 2nd week in the air-trained group. The mean work rate during the last week of training was 62 ± 19 W (138% of pretraining peak work rate) in the oxygen-trained group and 52 ± 22 W (96% of peak work rate) in the air-trained group ($p < 0.01$). Pulse oximeter O_2 saturation was measured at rest, breathing room air before each training session. The mean saturation was 96 ± 1% in oxygen-trained group and 95 ± 1% in the air-trained group. During the training sessions, saturation was measured three to four times; the lowest saturation value measured in each session averaged 95 ± 1% in the oxygen-trained group and 92 ± 1% in the air-trained group ($p < 0.001$) (Figure 2), demonstrating that supplemental oxygen succeeded in raising oxygen saturation. Dyspnea and leg fatigue were scored on a Borg category scale (0–10) during the last 5 minutes of cycling in each exercise session. Averaged over all sessions, the mean dyspnea was 5.1 ± 0.5 in the oxygen-trained group and 4.2 ± 0.5 in the air-trained group ($p < 0.001$), and dyspnea ratings did not increase over the course of training sessions despite substantial increases in work rate. Also of importance is that dyspnea ratings during training were only mildly lower than those elicited during the maximal exercise tests (Table 2). The mean leg fatigue over all sessions was 4.8 ± 0.4 in the oxygen-trained group and 4.4 ± 0.6 in the air-trained group ($p = 0.2$). These values were also only mildly lower than those measured during the maximal exercise tests (Table 2). Blood lactate was measured during exercise sessions 6, 9, 12, 15, 18, and 21. The mean values for these six occasions were 4.6 ± 0.2 mEq/L in the oxygen-trained group and 4.0 ± 0.1 mEq/L in the air-trained group ($p = 0.07$) (Figure 2), demonstrating that both groups exercised at high exercise intensity. The fact that blood lactate values remained at a constant level despite substantial work rate increase over the course of the training program is evidence of a physiologic training effect in both groups.

Heart rate was measured during all exercise sessions (Figure 2). The oxygen-trained group was able to exercise at a slightly higher heart rate than the air-trained group, but this did not reach statistical significance. During the high-intensity sessions, the mean heart rate remained virtually unchanged despite a sub-

TABLE 2. EFFECT OF TRAINING ON THE PEAK RESPONSES IN INCREMENTAL EXERCISE TESTS IN WHICH AIR WAS RESPIRED

	Oxygen-training Group		Air-training Group	
	Before Training	After Training	Before Training	After Training
Work rate, W	54 (25)	67 (24)*	54 (27)	64 (29)*
SBP, torr	197 (23)	188 (26)*	187 (25)	187 (31)
DBP, torr	94 (10)	92 (8)*	92 (14)	87 (12)
Heart rate, beats/min	125 (22)	128 (22)	125 (16)	130 (19)
$\dot{V}O_2$, L/min	0.89 (0.22)	0.93 (0.27)	0.91 (0.36)	0.97 (0.32)
VCO_2, L/min	0.90 (0.28)	0.95 (0.30)	0.90 (0.39)	0.98 (0.32)
$\dot{V}E$, L/min	34 (8)	39 (10)*	36 (11)	39 (11)*
VT, L	1.06 (0.21)	1.21 (0.32)	1.11 (0.30)	1.18 (0.36)
f, breaths/min	30.9 (4.1)	32.6 (5.0)	32.2 (7.3)	33.8 (10.0)
Breathlessness	6.3 (2.5)	6.7 (2.1)	5.8 (1.8)	5.9 (1.5)
Leg fatigue	5.4 (2.4)	4.6 (2.7)	5.3 (2.2)	4.0 (2.4)
Lactate, mmol/L	4.2 (2.8)	4.8 (2.3)	3.8 (1.8)	4.6 (2.2)
Sa_{O_2}, %	94 (3)	93 (4)	93 (4)	93 (3)

Definition of abbreviations: DBP = diastolic blood pressure; f = respiratory rate; SBP = systolic blood pressure; $\dot{V}E$ = ventilation; $\dot{V}O_2$ = O_2 uptake.

Breathlessness and leg fatigue are measured on Borg scales (0–10), with higher scores denoting more severe symptoms. Values are mean ± SD.

*$p < 0.05$ pre–post training.

stantial increase in work rate as the training program progressed. This may also be taken as a sign of a physiologic training effect.

Laboratory Exercise Testing

Responses to air breathing tests are presented in Tables 2–5. Responses to oxygen breathing tests are shown in the online supplement (Tables E1–E4).

Effects of Training on Constant Work Rate Test Endurance

Endurance capacity, measured as an increase in the exercise time in the constant work rate tests, improved significantly in both groups (Table 3) but significantly more in the oxygen-trained group. The increase in duration in the oxygen-trained group (considering both tests on air and on 30% oxygen) was 14.5 ± 6.2 minutes, and in the air-trained group, it was 10.5 ± 6.0 minutes ($p < 0.05$) (Figure 3). Therefore, on average, endurance gain was 40% greater in the oxygen-trained group than in the air-trained group. The difference between the groups was likely underestimated because tests were stopped at 30 minutes. After training, 16 tests in the oxygen-trained group versus only 7 tests in the air-trained group were terminated at 30 minutes ($p < 0.01$). This was mostly due to differences in the air breathing tests, in which seven oxygen-trained group patients, but only two air-trained group patients were stopped at 30 minutes ($p < 0.05$). Breathlessness at exercise termination (rated on the Borg scale) was lower after the training period than before, despite increased exercise duration (Table 3). The mean Borg breathlessness score decrease in all tests (breathing air or oxygen) tended to be greater in the oxygen-trained group (1.8) than in the air-trained group (0.7) ($p = 0.2$), despite the greater duration of exercise in the former group. Similarly, for all tests, the average end-exercise leg fatigue (rated on the Borg scale) decreased more in the oxygen-trained group (1.6) than in the air-trained group (0.8), but this too failed to achieve statistical significance ($p = 0.4$). There was a significant correlation ($r = 0.5$, $p < 0.01$) between improvement in endurance time with added oxygen, as compared with room air tests, and improvements in exercise capacity (in the room air tests) post-training, indicating that

TABLE 3. EFFECT OF TRAINING ON THE END-EXERCISE RESPONSES TO CONSTANT WORK RATE EXERCISE IN WHICH AIR WAS RESPIRED

	Oxygen-training Group		Air-training Group	
	Before Training	After Training	Before Training	After Training
Work rate, W	40 (18)		41 (19)	
Time, min	6.6 (3.0)	21.4 (10.1)*	5.8 (2.4)	16.7 (8.0)*
SBP, torr	197 (24)	179 (25)*	182 (36)	187 (28)
DBP, torr	92 (9)	83 (12)	93 (19)	88 (18)
Heart rate, beats/min	122 (22)	120 (19)	125 (18)	120 (14)
$\dot{V}O_2$, L/min	0.89 (0.22)	0.84 (0.21)	0.93 (0.34)	0.93 (0.30)
VCO_2, L/min	0.86 (0.26)	0.81 (0.24)	0.90 (0.36)	0.88 (0.30)
$\dot{V}E$, L/min	33 (7)	34 (8)	33 (10)	34 (10)
VT, L	1.1 (0.3)	1.2 (0.3)	1.1 (0.3)	1.2 (0.3)
f, breaths/min	30.1 (3.9)	28.9 (3.3)	29.7 (7.0)	29.0 (5.6)
Breathlessness	7.9 (1.4)	5.3 (2.3)*	6.0 (2.0)	5.3 (2.5)
Leg fatigue	5.6 (2.3)	3.6 (2.4)	4.8 (2.5)	4.2 (2.7)
Sa_{O_2}, %	94 (3)	93 (4)	94 (3)	94 (2)

For definition of abbreviations, *see* Table 2.

*$p < 0.05$ pre–post training.

Values are means ± SD.

TABLE 4. EFFECT OF TRAINING ON THE RESPONSES TO CONSTANT WORK RATE AT IDENTICAL WORK RATE AND EXERCISE DURATION (ISOTIME) IN TESTS IN WHICH AIR WAS RESPIRED

	Oxygen-training Group		Air-training Group	
	Before Training	After Training	Before Training	After Training
Work rate, W	40 (18)		42 (20)	
Exercise duration, min	6.4 (3.1)		5.8 (2.4)	
SBP, torr	195 (23)	177 (25)*	187 (34)	177 (33)
DBP, torr	91 (8)	80 (11)*	96 (18)	84 (9)*
Heart rate, beats/min	122 (21)	111 (18)*	126 (18)	115 (17)*
$\dot{V}O_2$, L/min	0.89 (0.22)	0.77 (0.19)*	0.93 (0.36)	0.87 (0.31)*
VCO_2, L/min	0.87 (0.26)	0.73 (0.21)*	0.91 (0.38)	0.81 (0.31)*
$\dot{V}E$, L/min	33 (7)	30 (7)*	33 (10)	31 (9)*
VT, L	1.12 (0.31)	1.20 (0.28)*	1.15 (0.32)	1.20 (0.35)
f, breaths/min	30 (4)	26 (4)*	29 (5)	26 (5)*
Sa_{O_2} (%)	94 (3)	94 (4)	95 (2)	94 (3)

For definition of abbreviations, *see* Table 2.
* $p < 0.05$ identical exercise durations.
Values are mean ± SD.

patients found to improve exercise tolerance when breathing supplemental oxygen are more likely to benefit from supplemental oxygen during exercise training.

Effects of Training on Exercise Tolerance in Incremental Exercise Testing

Peak exercise tolerance increased significantly in both groups (Table 2). In the oxygen-trained group, the increase in peak work rate was 13 ± 13 W (24%) in the air test ($p < 0.05$) and 11 ± 11 W (17%) in the 30% oxygen test ($p < 0.05$). The corresponding values in the air-trained group were 10 ± 9 W (19%) ($p < 0.05$) and 9 ± 8 W (15%) ($p < 0.05$). However, although the increase in peak work rate was roughly 24% greater in the oxygen-trained group than in the air-trained group, this difference failed to achieve statistical significance. The peak ventilation ($\dot{V}E$) increase in the oxygen-trained group was 5 L/minute in the air test ($p < 0.05$) and 4 L/minute in the test on oxygen ($p < 0.05$). In the air-trained group, the values were 3 ($p < 0.05$) and 4 L/minute ($p < 0.05$); the difference between groups was not significant. Peak $\dot{V}O_2$ increased slightly but insignificantly in both groups. End-exercise breathlessness and leg fatigue values (Borg scale) did not differ significantly between inhalates or between groups and did not change significantly with the intervention (Table 2). Similarly, there were no significant differences in end-exercise lactate values between inhalates or groups or as a result of the exercise program.

Effects of Training on the Responses to Identical Exercise Tasks (Isotime)

Responses to identical exercise durations at identical work rates (isotime) before and after the exercise program are shown in Table 4 (constant work rate tests) and in Table 5 (ramp tests). Comparisons were made at the time equal to the shorter of the pretraining or post-training test (almost always the pretraining test). Appreciable changes in the respiratory pattern and in the overall ventilation were seen. In the constant work rate tests, the respiratory rate decreased 15% in the air test ($p < 0.001$) and 13% in the oxygen test ($p < 0.01$) in the oxygen-trained group and 8% in the air test ($p < 0.01$) and 3% in the oxygen test (p = NS) in the air-trained group (Figure 4) (p = 0.003 between groups). VT increased 7% in the air test ($p < 0.05$) and 9% in the oxygen test (p = NS) in the oxygen-trained group. In the air-trained group, VT increased 9% in the air test (p = NS) but decreased 8% in the oxygen test ($p < 0.05$) (p = 0.02 between groups). $\dot{V}E$ decreased 8% in both air tests ($p < 0.05$) and oxygen tests ($p < 0.05$) in the oxygen-trained group and 5% in the air test ($p < 0.05$) and 9% in the oxygen test ($p < 0.05$) in the air-trained group (p = NS between groups).

In the ramp tests, improvements similar to those seen in the constant work rate tests were observed. Both isotime respiratory rate and VT changed significantly more in the oxygen-trained group than in the air-trained group. The respiratory rate de-

TABLE 5. EFFECT OF TRAINING ON THE RESPONSES TO INCREMENTAL EXERCISE AT IDENTICAL WORK RATE AND DURATION (ISOTIME) IN TEST IN WHICH AIR WAS RESPIRED

	Oxygen-trained Group		Air-trained Group	
	Before	After	Before	After
Work rate, W	54 (24)		54 (28)	
SBP, torr	192 (25)	170 (21)*	185 (27)	171 (27)*
DBP, torr	92 (10)	82 (11)*	92 (14)	85 (10)*
Heart rate, beats/min	124 (22)	114 (20)*	125 (16)	121 (15)
$\dot{V}O_2$, L/min	0.88 (0.21)	0.78 (0.19)*	0.91 (0.36)	0.88 (0.29)
VCO_2, L/min	0.88 (0.28)	0.76 (0.22)*	0.90 (0.39)	0.85 (0.28)
$\dot{V}E$, L/min	34 (8)	32 (8)	36 (11)	34 (9)
VT, L	1.12 (0.29)	1.21 (0.30)*	1.13 (0.30)	1.16 (0.38)
f, breaths/min	31 (4)	27 (4)*	32 (8)	31 (10)
Sa_{O_2}, %	94 (3)	94 (3)	93 (5)	94 (2)

For definition of abbreviations, *see* Table 2.
* $p < 0.05$ identical exercise work rates.
Values are means ± SD.

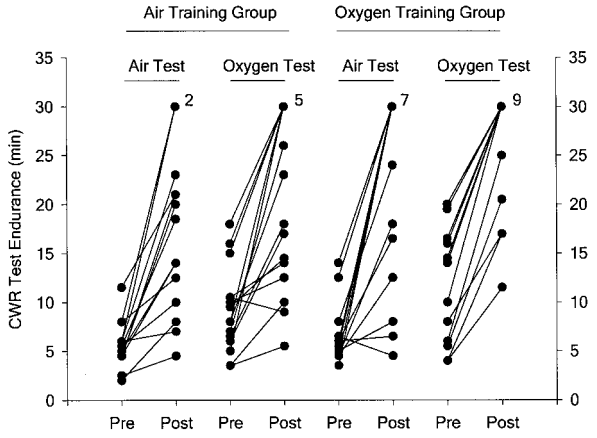

Figure 3. Endurance time in the constant work rate (CWR) tests while breathing air (air test) and 30% oxygen (oxygen test) before (*pre*) and after (*post*) the exercise program. The number of patients who performed 30 minutes (cut off time) in these tests is marked at 30 minutes. Note that both oxygen breathing and training substantially increase exercise endurance. The oxygen-training group manifests a larger increase in constant work rate duration for both air and oxygen tests and a higher fraction of group members reach the 30-minute cutoff time as compared with the air training group (discussed in the text).

creased 12% in the air test ($p < 0.01$) and 14% in the oxygen test ($p < 0.02$) in the oxygen-trained group, whereas the decreases were 3% in the air test (p = NS) and 1% in the oxygen test (p = NS) in the air-trained group ($p < 0.02$ between groups in the two tests). V_T increased 8% in the air test ($p < 0.02$) and 8% in the oxygen test (p = NS) in the oxygen-trained group, whereas the increases were 3% in the air test (p = NS) and 0% in the oxygen test (p = NS) in the air-trained group ($p < 0.03$ between groups in the two tests). In addition, for the identical exercise task, the heart rate decreased significantly more in the oxygen-trained group ($p < 0.01$). Thus, a slower and deeper ventilatory pattern was seen after training, and the magnitude of the change was greater in patients who had trained with supplemental oxygen.

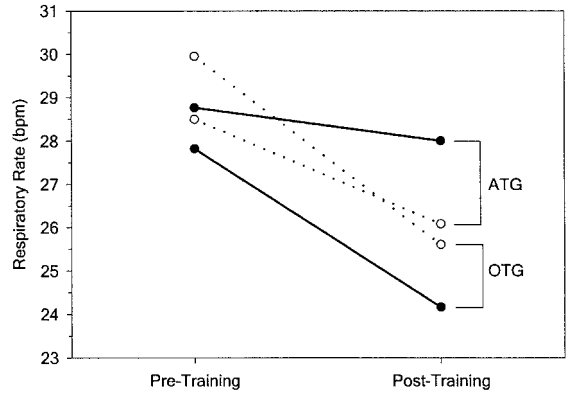

Figure 4. Respiratory rate at identical work rate and exercise durations (isotime) in the constant work rate tests before (pretraining) and after (post-training) the exercise program in the oxygen-training group (OTG) and air-training group (ATG) in tests in which room 30% oxygen (*closed circles, solid line*) and room air (*open circles, dotted line*) are respired. Note that the breathing rate slows more in the OTG than in the ATG, evidence of a superior physiologic training effect.

Acute Effects of Oxygen on the Constant Work Rate and Incremental Tests

In the oxygen-trained group, the endurance time in the constant work rate test was 5.2 minutes longer on oxygen than on air ($p < 0.05$) pretraining and 4.4 minutes longer ($p < 0.05$) post-training. The corresponding values in the air-trained group were 3.3 ($p < 0.05$) and 3.3 minutes (p = 0.1). In the incremental exercise test in the oxygen-trained group, the peak work rate was 9 W higher ($p < 0.05$) (pretraining) and 7 W higher ($p < 0.05$) (post-training) in the tests in which 30% oxygen was respired. The corresponding increases in the air-trained group were 7 W ($p < 0.05$) and 6 W ($p < 0.05$). In the oxygen-trained group peak $\dot{V}O_2$ was higher while breathing 30% oxygen by 0.12 L/minute ($p < 0.05$) before training and by 0.19 L/minute ($p < 0.05$) after training. In the air-trained group, the corresponding values were 0.12 L/minute ($p < 0.05$) and 0.14 L/minute ($p < 0.05$).

Effects of Training on Health-related Quality of Life

Quality of life, measured with the disease-specific questionnaire, the Chronic Respiratory Disease Questionnaire, increased significantly in both groups, in total score and in all subscores ($p < 0.05$). The increases in the oxygen-trained group were 24 (total score), 7 (dyspnea), 7 (emotional functioning), 5 (fatigue) and 5 (mastery). The corresponding increases in the air-trained group were 20, 7, 5, 4, and 4. Only in mastery was a statistically significantly greater improvement detected in the oxygen-trained group ($p < 0.05$). These improvements in the Chronic Respiratory Disease Questionnaire can be seen to be clinically significant, as a change of 0.5 within each domain has been suggested as a threshold for clinical significance (35). In the generic instrument, the Short Form-36, the oxygen-trained group improved significantly in general health (11-point increase), vitality (14-point increase), physical functioning (7-point increase), and role physical (23-point increase) ($p < 0.05$), whereas the air-trained group only improved significantly in vitality (13 points increase). Between groups, a significant difference was seen in general health ($p < 0.05$).

DISCUSSION

Several studies have now shown that exercise-training programs can achieve a physiologic training effect and ameliorate muscle dysfunction in COPD patients (2, 3, 16). However, not all training programs are equally effective. In particular, it has been demonstrated that high-intensity training is more effective than moderate-intensity training in COPD patients with both moderate and severe disease (36, 37).

It is therefore of interest to identify methods to allow COPD patients to exercise at higher intensity during training programs. Oxygen supplementation seems a promising candidate, as it has been demonstrated to increase exercise tolerance and reduce breathlessness in COPD patients with mild resting hypoxemia and in patients who desaturate during exercise (17–20). Moreover, supplemental oxygen increases exercise tolerance substantially even in COPD patients who do not desaturate with exercise (23, 24, 38). Interestingly, the improvement in exercise capacity has been shown to be greater in patients with moderate and severe airflow limitation (FEV_1 percentage predicted < 50), but independent of the level of oxygen saturation (38). Somfay and colleagues (24) showed during high-intensity constant work rate tests in normoxic patients with severe airflow limitation (average FEV_1 = 31% predicted) a dose-dependant increase in exercise endurance. A fraction of 30% oxygen yielded substantial improvement in exercise tolerance, with a further increase if 50% oxygen was used. Higher fractions did not further improve exercise tolerance.

Oxygen has three beneficial effects that might promote reduced ventilatory response to a given level of exercise and, thereby, improve exercise tolerance: (*1*) Increased Pa_{O_2} directly inhibits carotid body stimulation (39). (*2*) Increased arterial oxygen content promotes better muscle oxygenation, thus reducing lactic acid production and thereby decreasing carotid body stimulation. (*3*) Pulmonary vasodilation induced by oxygen increases cardiac output and muscle oxygen delivery, also reducing lactic acid production and decreasing carotid body stimulation (38). The study of Somfay and colleagues (39) suggested that direct carotid body inhibition is the most important factor. An important mechanism linking reduced carotid body stimulation and improved exercise tolerance in COPD is the prolongation of the time for exhalation, which yields less hyperinflation and reduced elastic work of breathing (23, 24).

In COPD patients with resting hypoxemia, long-term oxygen therapy is a routine practice leading to increased survival and quality of life (40, 41). In the United States, patients who are normoxemic at rest but are hypoxemic during exercise (Sa_{O_2} = 88%) often receive supplemental oxygen during exercise if their dyspnea or exercise tolerance is improved with oxygen therapy (42). A review of published reports of rehabilitative exercise training showed that in a minority of programs oxygen was supplied to all COPD patients irrespective of whether they did or did not desaturate during exercise (43).

Although supplemental oxygen in COPD patients improves exercise capacity and alleviates dyspnea, only a few randomized trials have evaluated the benefit of supplemental oxygen during pulmonary rehabilitation (17, 18, 25, 26). These studies showed virtually no benefits for patients assigned to breathing supplemental oxygen compared with those breathing air during exercise. However, on examination, these studies used substantially different experimental designs from the one we employed, which may explain the differences in results. Key to our experimental approach was that (*1*) a double-blinded design was employed, (*2*) sufficient supplemental oxygen was given during training to raise arterial oxygen saturation, (*3*) subjects were urged to maximize their training work rates so that any increase in exercise tolerance produced by oxygen breathing would result in higher exercise intensity, and (*4*) both effort-dependent and effort-independent measures of exercise tolerance were used to detect the magnitude of the training effect. Examining these four features in previous studies:

- None of these studies employed a double-blinded design (17, 18, 25, 26).
- Either oxygen saturation during the training sessions was not reported (17, 25, 26) or a significant increase in the oxygen group was not achieved (18).
- Training intensity was not assessed objectively in three studies (17, 18, 26). In the study of Rooyackers and colleagues, the oxygen-trained group achieved a higher training intensity, but exercise was stopped if Sp_{O_2} dropped below 90% (25).
- Measures of improvement in exercise tolerance consisted of a 6-minute walk distance (17, 26), shuttle walk testing (18), or peak incremental exercise tolerance and constant work rate test duration (25). None of these tests assessed effort-independent outcomes (e.g., isotime responses).

This study showed that the oxygen-trained group could exercise at a higher intensity and improve exercise capacity significantly more than the air-trained group. The results are strengthened by the double-blinded design, as both the patients and the investigators were unaware of gas type. That high training intensities were employed is confirmed by the high blood lactate values (2) and high ratings of dyspnea and leg fatigue during training sessions. Despite a substantial increase in work rate during the training course heart rate, blood lactate, dyspnea, and leg fatigue remained approximately constant, showing a physiologic training effect in both groups. Exercise oxygen saturation was significantly higher in the oxygen-trained group (95%) than in the air-trained group (92%), likely a reason for the higher training intensity in the oxygen-trained group and, consequently, increased exercise capacity.

This high-intensity exercise program resulted in a substantial improvement in exercise capacity in both training groups, confirming the findings of others (1–3, 7, 8, 15). However, the increase in endurance time in the constant work rate test (averaging 14.5 minutes in oxygen-trained group vs. 10.5 minutes in air-trained group) and the increase in peak work rate in the incremental test (21% in oxygen-trained group vs. 17% in air-trained group) are appreciably greater than those reported by most previous studies employing high-intensity strategies, suggesting that we may have been more successful in achieving high-intensity training than in previous studies. During the 1st week of high-intensity training, several patients in the air-trained group had to divide the sessions in two or three parts to be able to sustain the 45-minute training session. Training intensity generally started at levels below the target level and increased as tolerated by symptom limits. Our experience indicates that high-intensity exercise is both safe and well tolerated in patients with severe COPD. By the end of the study, most patients were exercising for the entire training session at work rates higher than their preprogram peak work rate.

We observed small but significant improvements in spirometry in our study participants. In the past, training studies have occasionally reported improvements in resting pulmonary function, although most have not (43). In our study, the improvement in FEV_1 was not correlated to the improvement in endurance capacity. Furthermore, average improvement in FEV_1 in the two study groups was virtually identical; spirometry improvements cannot explain the differences in exercise tolerance gains between the oxygen- and air-trained groups. A plausible explanation for spirometry improvement might be better technique in taking bronchodilators as a result of the educational part of the program. There were no changes in medication during the study.

Although patients in this study were not clinically hypoxemic, both training groups manifested substantial acute effects of supplemental oxygen during constant work rate tests (20, 23–25, 38) and incremental tests (25). Despite similar end-exercise values of lactate, respiratory rate, and ventilation at the end of the incremental tests, patients were able to sustain significantly higher work rates when respiring 30% oxygen. Fujimoto and coworkers (38) recently showed that patients with a mild degree of COPD ($FEV_1 > 50\%$ predicted) did not improve exercise capacity to as great an extent as did patients with a moderate or severe disease, indicating that oxygen supplementation during exercise might be useful only in patients with a moderate or severe disease.

Comparing results at identical levels of exercise on a cycle ergometer provides an effort-independent measure of physiologic training responses. Both training groups showed significant isotime changes, as others have demonstrated (3, 16, 44). When comparing the two training groups, we observed only modest differences in isotime changes in cardiovascular parameters (heart rate, blood pressure). However, pattern of breathing changed significantly more in the oxygen-trained group, yielding a slower, deeper pattern of breathing that has been shown to be associated with greater ventilatory efficiency (i.e., lower V_D/V_T) (3) decreased hyperinflation (24) and prolonged exercise tolerance.

This rehabilitative exercise program affected health-related quality of life in both patient groups. The improvements in the disease-specific Chronic Respiratory Disease Questionnaire were both statistically and clinically significant (12, 45). There was a positive correlation between the improvement in total score and the improvement in constant work rate endurance ($r = 0.4$, $p < 0.04$), supporting the linkage between improvements in exercise tolerance and health status. In the general Short Form-36 instrument, only the oxygen-trained group improved substantially ($p = 0.05$). There were trends for most of the subscales of these instruments to improve more for the oxygen-trained group than for the air-trained group. Statistical significance was achieved for the improvements in the mastery scale of the Chronic Respiratory Disease Questionnaire and the vitality scale of the Short Form-36, but the improvement did not correlate with the improvement in constant work rate endurance ($r = 0.06$, $p = 0.8$). Thus, although there were trends for oxygen supplementation to engender superior quality-of-life improvement, this benefit cannot be clearly established. To be considered is that individual variability in response to these instruments renders differences difficult to detect when the study population is small.

We considered whether it might be possible to identify a subset of COPD patients who would be more likely to benefit from oxygen supplementation during exercise training. We found a significant correlation between the improvement in endurance time induced by oxygen supplementation in the pretraining tests and the training-induced improvements in exercise capacity in the room air test ($r = 0.5$, $p < 0.01$). Thus, patients found to improve exercise tolerance when given supplemental oxygen would tend to benefit more from oxygen supplementation during rehabilitative exercise training. However, the correlation is not sufficiently high to allow accurate prediction for individual subjects. Given the modest costs of oxygen supplementation over the course of a rehabilitation program (which we estimate as roughly $5, if oxygen is supplied from H-cylinders), in many settings, it may be practical to give supplemental oxygen to all patients.

Limitations of this study include a failure to delineate clearly the mechanism by which oxygen supplementation improves exercise tolerance. Furthermore, because of the small sample size, we were unable to define with certainty patient characteristics that predict the effectiveness of oxygen supplementation during exercise training. Finally, we have not specifically determined whether the benefits obtained in cycle ergometer performance extend to other kinds of physical tasks, although the trends for improvement in health-related quality of life measures provide indirect evidence for a more general benefit.

In summary, we have shown in moderate and severe COPD patients who do not experience appreciable desaturation during exercise that providing supplemental oxygen during high-intensity endurance training adds to the benefits of training. Training intensity could be kept at a higher level, and apparently as a result, endurance capacity and breathing pattern improved significantly more in patients using supplemental oxygen. In pulmonary rehabilitation, when starting a high-intensity exercise program, supplemental oxygen may be considered for COPD patients with a moderate or severe degree of airflow obstruction.

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