Oxygen May Improve Dyspnea and Endurance in Patients with Chronic Obstructive Pulmonary Disease and only Mild Hypoxemia[1,2]

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SUMMARY Oxygen (O_2) has been reported to improve exercise tolerance in some patients with chronic obstructive pulmonary disease (COPD) despite only mild resting hypoxemia (Pa_{O_2} > 60 mm Hg). To confirm these prior studies and evaluate potential mechanisms of benefit, we measured dyspnea scores by numeric rating scale during cycle ergometry endurance testing and correlated the severity of dyspnea with right ventricular systolic pressure (RVSP) measured by Doppler echocardiography during a separate supine incremental exercise test. Both sets of exercise were performed according to a randomized double-blind crossover protocol in which patients breathed compressed air or 40% O_2. We studied 12 patients with severe COPD (FEV_1 0.89 ± 0.09 L [mean ± SEM], FEV_1/FVC 37 ± 2%, D_{LCO} 9.8 ± 1.5 ml/min/mm Hg [47% of predicted], Pa_{O_2} 71 ± 2.6 mm Hg). With endurance testing on compressed air, Pa_{O_2} did not change significantly in the group as whole (postexercise Pa_{O_2} 63 ± 5.1 mm Hg, p = NS), but did fall to less than 55 mm Hg in four patients from this group. Duration of exercise increased on 40% O_2 from 10.3 ± 1.6 to 14.2 ± 1.5 min (p = 0.005), and the rise in dyspnea scores was delayed. Oxygen delayed the rise in RVSP with incremental exercise in all patients and lowered the mean RVSP at maximum exercise from 71 ± 8 to 64 ± 7 mm Hg (p < 0.03). Improvement in duration of exercise correlated with decrease in dyspnea (r^2 = 0.66, p = 0.001) but not with decreases in heart rate, minute ventilation, or RVSP. Four patients more than doubled their duration of exercise on 40% O_2, but only two of these four desaturated while exercising on compressed air. We conclude that supplemental O_2 improves dyspnea and exercise tolerance in patients with COPD who have only mild hypoxemia at rest, and that the improvement may be dramatic even in the absence of exercise-induced oxyhemoglobin desaturation.

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Introduction

Supplemental oxygen (O_2) has been shown to improve exercise tolerance (1-3) and prolong life (4, 5) in patients with severely hypoxemic chronic obstructive pulmonary disease (COPD). Its role in COPD patients without severe hypoxemia (Pa_{O_2} > 55 mm Hg) has been less clear, although one group of investigators has shown that supplemental O_2 may acutely improve dyspnea and exercise tolerance in such patients (6). The mechanisms of this response were not investigated in that study (6), but others have shown that O_2 may decrease ventilatory drive (7), minute ventilation (V_E) (8, 9), ventilatory muscle fatigue (10), and direct central perception of dyspnea during exercise (11, 12).

We undertook this study to corroborate the previously reported benefit of O_2 in COPD patients who would not be candidates for supplemental O_2 under current guidelines, to identify predictors of this clinical response, and to identify some of the mechanisms involved. We compared dyspnea, exercise tolerance, and ventilatory and hemodynamic parameters in exercising patients with severe COPD while they breathed compressed air (CA) or 40% O_2 in a double blind crossover study.

Methods

Patients

We recruited patients with severe airways obstruction and a clinical diagnosis of emphysema or chronic bronchitis from the Chest Clinic and from the Pulmonary Function Laboratory at the San Francisco Veterans Affairs Medical Center Hospital. Entry criteria included age >50 yr, D_{LCO} < 80% predicted, extensive smoking history, and resting Pa_{O_2} > 55 mm Hg. The criterion of a reduced D_{LCO} was used to exclude patients with asthma as the primary cause of airways obstruction. We also excluded patients with active coronary artery disease, congestive heart failure, and vascular, orthopedic, or neurologic problems that would interfere with cycling. Patients were studied when clinically stable; evaluations were rescheduled when clinical exacerbations of symptoms had occurred within the previous 4 wk. The study protocol was approved by the Committee for Human Research, University of California, San Francisco.

Measurement of Pulmonary Function, Dyspnea, and Exercise Testing

Spirometry was performed according to American Thoracic Society standards (13) (Gould model 5000; Sensormedics, Anaheim, CA). We calculated maximum voluntary ventilation (MVV) by measuring the volume expired in 12 s while the resting patient breathed as rapidly and deeply as possible. We multiplied by five the largest volume of two attempts. Lung volumes were calculated by breath nitrogen washout (4). Diffusing capacity was measured by the single breath technique and corrected for hemoglobin (15).

Incremental and endurance exercise studies were performed with the patients in a sitting position on an electronically braked cycle ergometer (Gould model 9000; Sensormedics, Anaheim, CA). Expired $\%O_2$, $\%CO_2$ and end-tidal CO_2, ventilatory rate, expired tidal volume (dry rolling seal spirometer), and temperature of expired gas were directly measured every 20 s during exercise. On the mornings of exercise testing, patients ate a light breakfast and took their usual prescribed medications including inhaled bronchodilators. The patients were asked to continue exercise until they could go no further, whether limited by dyspnea, fatigue or muscular complaints. Verbal encouragement was given at least every 2 min during exercise.

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Oxyhemoglobin saturation (Nellcor, Hayward, CA) was measured transcutaneously during all studies. Oxygen consumption was measured only during the incremental study because of technical difficulty in measurement while patients are breathing 40% O_2. Arterial blood gases were drawn from an indwelling radial arterial line during the endurance studies only. The arterial line failed in one patient, so complete arterial blood gas data are available in only 11 of the 12 patients.

The incremental studies were performed on room air beginning at a workload of 10 W, with increases of 10 to 20 W every 2 min to a symptom limited maximum. On the following day, using a randomized, double-blind, crossover protocol, two endurance studies were performed while the patients breathed 40% O_2 or CA. The endurance study workload was set at 80% of the maximum workload achieved during the prior incremental study. Oxygen and CA were delivered to the mouthpiece by a high flow mixing device (Veriflow, Richmond, CA), with sufficient tubing reservoir to prevent entrainment of room air. The high flow mixing device was screened from the patient and supervising physician to preserve blinding. Prior to each exercise test, a technician set the O_2 at either 40% or 21%, with the order being determined by a coin flip. Oximetry values were not available to the patient or supervising physician during endurance testing to preserve blinding. Exercise was not begun until expired O_2 and CO_2 measurements had stabilized. Arterial blood gases were determined prior to initiation of exercise, every 2 min during exercise, and 2, 5, and 10 min after cessation of exercise. Heart rate and V_E were measured every 20 s. Dyspnea was measured every 2 min using a numerical rating scale, a modified Borg scale numbered 1–10 for which the two extremes were "none" and "extremely severe" (16, 17). Patients reported their dyspnea by touching an 8 × 11 reproduction of the numerical rating scale, with the physician conducting the study recording the scores on a flow sheet to the nearest half unit.

Each patient came to the Echocardiography Laboratory at Moffitt Hospital, University of California, San Francisco, on a separate day for Doppler echocardiography at rest and during supine cycling on a variable-load bicycle ergometer (Engineering Dynamics Corporation Model 8420, Lowell, MA). Measurements of right ventricular systolic pressure (RVSP) were made at rest and during exercise as previously described, with the ergometer table tilted 20° to the left (18). In brief, the saline-enhanced, maximum trans-tricuspid gradient is added to the right atrial pressure estimated by the respiratory behavior of the inferior vena cava diameter to derive RVSP. Agitated saline was injected intravenously at each stage of exercise to enhance the Doppler tricuspid insufficiency envelope and to detect right-to-left intracardiac shunting. Patients pedaled at a constant speed beginning at a workload of 10 W and increasing by 10 W every 2 min until limited by symptoms. Patients were tested on CA and on 40% O_2 by tight-fitting mask according to a randomized crossover double-blind design with 1 h of rest between studies. Doppler measurement of maximum RVSP was recorded at rest, at each stage of exercise, and after 4 min of recovery. Invasively obtained data in patients with COPD performing cycle ergometry while sitting is similar to data obtained using this method (18–20).

Statistics

Group data are presented as the mean value ± SEM. Data were analyzed by Student's *t* test for paired samples, and by least squares linear regression. Correlations are reported as the coefficient of determination, r^2. The level of statistical significance was defined as $p < 0.05$.

Results

Fourteen patients meeting the entry criteria volunteered to participate in this study. Two were excluded from further study after undergoing the incremental exercise study. One of these two patients developed supraventricular tachycardia and chest pain during exercise, and the other was limited to 4 min of exercise because of hip pain. The study group therefore consisted of 12 male patients who had smoked cigarettes for 30 to 100 pack-years. Results of static pulmonary function testing are shown in table 1. The mean FEV_1 was 0.89 ± 0.09 L, FEV_1/FVC was 37 ± 2%, TLC was 101 ± 3.6% of predicted, and D_{LCO} was 9.8 ± 1.5 $ml \cdot min^{-1} \cdot mm$ Hg (47% of predicted).

Ventilatory limitation to exercise was found in each of the study patients during incremental testing. Maximum O_2 consumption ($\dot{V}O_2max$) was 49% of predicted (21) (range 35 to 71%), and maximum exercise ventilation ranged from 79 to 141% of measured MVV. Dyspnea was the primary limiting symptom in each patient. The maximum heart rate during exercise was 79 ± 3% of predicted, with two patients having a heart rate reserve of less than 15 beats per min (91 and 93% of predicted heart rate). During incremental testing, the duration of exercise was 10.8 ± 1.4 min, and the maximum work rate was 50 ± 6 W.

During endurance testing on CA, Pa_{O_2} decreased slightly from 71 ± 2.6 to 63 ± 5.1 mm Hg (p = NS), but did fall to less than 55 mm Hg in four individual patients (table 1). In the patient in whom the arterial line failed, the O_2 saturation remained 95% or greater throughout exercise. During 40% O_2 breathing, Pa_{O_2} remained above 100 mm Hg in all patients, and mean duration of exercise increased from 10.3 ± 1.6 to 14.2 ± 1.5 min ($p < 0.01$). Four patients increased their duration of exercise by 100% or more, and only one patient failed to show an increase with O_2 breathing (figure 1). There was no significant correlation between resting Pa_{O_2} and increase in duration of exercise with supplemental O_2 ($r^2 = 0.26$, p = 0.09). The correlation between oxyhemoglobin saturation at end exercise and increased duration of

TABLE 1

PATIENT DATA AT REST AND DURING EXERCISE

Patient	FEV_1	FVC	D_{LCO}*	Pa_{O_2} Rest†	Pa_{O_2} End Exercise†	Exercise Duration‡ (%) CA	Exercise Duration‡ (%) O_2	ΔDyspnea§
1	0.78	2.75	35	65	51	14	18 (29)	−1
2	0.48	1.56	9	78	§	3.3	7 (112)	−5
3	0.99	2.28	74	75	80	6	8 (33)	−1.5
4	0.66	1.88	34	80	71	22	24 (9)	2
5	1.23	3.79	62	70	77	6	12 (100)	−4
6	0.51	1.90	25	60	40	6	10 (67)	−1.5
7	0.78	1.91	65	68	66	8	11 (38)	−1
8	1.55	2.90	57	79	86	18	14 (−22)	−1
9	0.63	1.43	43	57	40	10	22 (120)	−3
10	1.10	2.59	71	72	81	14	16 (14)	−2
11	1.11	2.85	12	63	46	6	14 (133)	−5
12	0.81	2.65	44	87	56	10	14 (40)	−2
Group	0.89 ± 0.09	2.37 ± 0.20	47 ± 6	71 ± 2.6	63 ± 5.1	(56 ± 14)		−2.1 ± 0.6

FEV_1 and FVC are reported in liters.

* % of predicted value.

† On compressed air, mm Hg.

‡ Duration of exercise in minutes (% change).

§ Difference between endurance exercise on 40% O_2 and compressed air at the "Isotime." A negative value means there was less dyspnea while breathing O_2.

Data not available (see methods). By pulse oximetry, saturation 98% was at rest and 95% at end exercise.

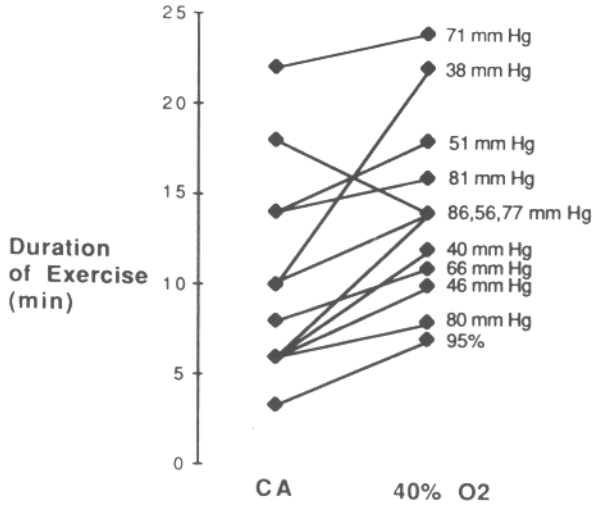

Fig. 1. Duration of steady state exercise while breathing compressed air versus 40% oxygen is compared in individual patients. The Pa_{O_2} in mm Hg at the end of exercise while breathing compressed air is reported to the right of each line. The patient for whom only oxygen saturation is available has this reported as a percentage. Mean duration of exercise increased from 10.3 min on compressed air to 14.3 min on 40% oxygen ($p < 0.01$).

exercise did not reach statistical significance ($r^2 = 0.29$, $p = 0.07$). However, end exercise Pa_{O_2} (excluding patient 2) did correlate with increased duration of exercise ($r^2 = 0.43$, $p = 0.03$). Of the four patients whose duration of exercise increased by ⩾ 100%, only two had substantial oxyhemoglobin desaturation on CA (table 1).

At the time point equivalent to end exercise on CA (which we refer to as "Isotime"), dyspnea scores, V_E, and heart rate while breathing 40% O_2 were all significantly reduced relative to exercise on CA (table 2). Dyspnea scores at Isotime were 6.5 ± 0.5 ± on 40% O_2 versus 8.5 ± 0.3 on CA ($p = 0.005$). At end exercise, however, there were no significant differences in V_E, heart rate, or dyspnea scores between exercise on CA versus 40% O_2. Improvement in duration of exercise correlated with decrease in dyspnea at the Isotime ($r^2 = 0.66$, $p = 0.001$; figure 2). No significant correlations were present between increased duration of exercise and decrease in Isotime V_E ($r^2 = 0.04$, $p = 0.56$) or decrease in Isotime heart rate ($r^2 = 0.20$, $p = 0.17$). There were no significant correlations between increased duration of exercise on 40% O_2 and any resting pulmonary function, blood gas, or echocardiographic or clinical parameter.

Inhalation of 40% O_2 resulted in slight rises in Pa_{CO_2} at rest as mean Pa_{CO_2} increased from 40.6 ± 1.9 mm Hg on CA to 42.5 ± 2.5 mm Hg ($p = 0.01$), and at the end of exercise, it increased from 46.4 ± 3.7 mm Hg on CA to 49.9 ± 3.8 mm Hg on 40% O_2 ($p = 0.01$). The mean pH did not differ between the CA and 40% O_2 studies at any point in time.

Right ventricular systolic pressures measured at rest in the supine position were 38 ± 4 mm Hg on CA and 36 ± 3 mm Hg on 40% O_2 (p = NS). Seven of the patients had a resting RVSP more than two standard deviations above the laboratory normal value of 23 mm Hg (18). With exercise, RVSP on CA increased to 71 ± 8 mm Hg, and every patient had an RVSP more than two standard deviations above the normal peak exercise value of 30 mm Hg (18). Oxygen delayed the rise in RVSP with incremental exercise (Isotime RVSP 60 ± 5 mm Hg compared with 71 ± 8 mm Hg) and lowered the peak RVSP from 71 ± 8 to 64 ± 7 mm Hg ($p = 0.01$). However, there was no significant correlation between oxygen-induced changes in RVSP and duration of endurance exercise ($r^2 = 0.17$, $p = 0.21$).

TABLE 2

RESULTS OF EXERCISE TESTING ON AIR AND 40% OXYGEN

	Compressed Air at End Exercise	40% Oxygen	
		Isotime*	End Exercise
Duration, min	10.3 ± 1.6	10.3 ± 1.6	14.2 ± 1.5†
Dyspnea score, 0–10	8.5 ± 0.3	6.5 ± 0.5†	8.6 ± 0.4
Ventilation, L/min	36 ± 4.0	33 ± 3.8‡	36 ± 3.7
Blood gases			
Pa_{O_2}, mm Hg	63 ± 5.1	168 ± 10.2†	172 ± 9.8†
Pa_{CO_2}, mm Hg	46 ± 3.8	49 ± 3.5†	50 ± 3.8†
pH	7.34 ± 0.02	7.34 ± 0.02	7.34 ± 0.02
Heart rate	127 ± 5.6	117 ± 4.8‡	120 ± 4.5

All comparisons versus compressed air.
* Isotime = at the time equivalent to the end of exercise on compressed air.
† $p < 0.01$.
‡ $p < 0.05$.

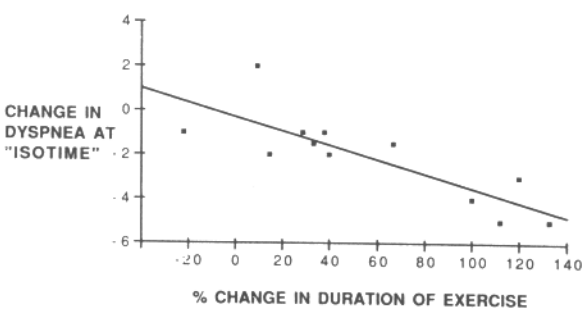

Fig. 2. Decreased dyspnea at the time point equal to end exercise on compressed air (Isotime) correlated with increased duration of exercise, $r^2 = 0.66$, $p = 0.001$.

Discussion

Dyspnea is the sensation that breathing is uncomfortable, distressing, or requires greater than normal effort. Dyspnea in patients with chronic lung disease is usually most bothersome with exertion, limiting the patient's ability to perform normal activities. Treatment of dyspnea depends primarily on treatment of the underlying disease. However, even after such treatment has been exhausted, dyspnea may remain a major management problem (17). A variety of approaches, including pulmonary rehabilitation, O_2 therapy, ventilatory muscle training, pursed lip breathing, psychotherapy, biofeedback, opiates, and carotid body surgery, have been used to relieve this frightening symptom (6, 17, 22–25). Though O_2 supplementation increases longevity in severely hypoxemic patients with COPD (4, 5), its role in the treatment of dyspnea per se is not established, and most studies of O_2 therapy have not addressed this issue. By clinical experience, the response of dyspnea to O_2 is variable among individuals. The utility of O_2 therapy for dyspnea in the patient with mild or borderline resting hypoxemia (Pa_{O_2} >

60) is particularly controversial (26), and this form of therapy is generally not covered by third-party payers (2).

To help clarify the role of oxygen therapy in the treatment of the symptom of dyspnea per se, we measured the response to a moderate level of supplemental oxygen (40%) during exercise in 12 patients with severe COPD (mean $FEV_1 = 0.89$) and only mild resting hypoxemia (mean $Pa_{O_2} = 71$). Supplemental O_2 prevented desaturation, increased endurance exercise time by 38%, and delayed the rise in dyspnea. (Dyspnea score at Isotime fell by 25%.) Ventilation at Isotime decreased from 36 to 33 L/min ($p < 0.05$), possibly explaining part of the decrease in dyspnea, though the correlations between improvement in endurance and decrease in ventilation did not reach statistical significance. Changes in Isotime heart rate and RVSP were also small, although statistically significant. The importance of the small fall in RVSP is unclear. While we suspect it was due to a beneficial effect of oxygen on either pulmonary vascular resistance or cardiac output, it could conceivably have been due to the depressive effect of oxygen on minute ventilation resulting in less dynamic hyperinflation. Improvement in exercise duration correlated with decrease in dyspnea ($r^2 = 0.66$, $p = 0.001$) but not with decreases in heart rate, ventilation, or RVSP. The beneficial response to O_2 could not be predicted from resting pulmonary function, or echocardiographic or clinical parameters. Four patients had > 100% increase in duration of exercise with O_2, but only two of these four desaturated while exercising on room air. These data will add to the controversy about the utility of oxygen treatment for dyspnea apart from the benefit of oxygen for the physiologic dysfunction associated with severe chronic lung disease.

The potential of oxygen supplementation to improve exercise performance has been recognized for some time. Cotes and Gilson (1) showed in 1956 that administration of supplemental O_2 (30, 50, or 100%) improved walking time on a treadmill more than 100% in 22 of their 29 patients with severe pneumoconiosis. They found that 30% O_2 was nearly as effective as 50% or 100%. Subsequently, other uncontrolled studies reported improvement in level of function with supplemental O_2 (27). However, these studies were all performed in very hypoxemic patients for whom there would now be no question about the need for O_2 (4, 5). Results in less hypoxemic patients have not been as clear. Longo and colleagues (26) reported lack of response to O_2 in 27 mildly hypoxemic patients (mean $Pa_{O_2} = 64$ mm Hg) studied on the treadmill (incremental) with CA or O_2 (either 2 or 4 L/min. They found no changes in respiratory rate, heart rate, or blood pressure, and stated (without reporting the data) that exercise tolerance and dyspnea were unaffected by either level of O_2. Only 6 of these 27 patients desaturated with exercise, and there was a nonsignificant tendency for this subgroup to do better with supplemental O_2. In contrast, Vyas and coworkers (8) reported a similar group of patients with even higher mean Pa_{O_2} (72 mm Hg) but showed that administration of 40% O_2 in a double-blind protocol (cycle ergometer) resulted in increased duration of exercise, maximal work rate, and O_2 consumption and decreased V_E and ventilatory rate at equal work loads. Bradley and colleagues (28) also looked at a group of only mildly hypoxemic patients (mean $Pa_{O_2} = 69$ mm Hg), most of whom desaturated with exercise (mean $Pa_{O_2} = 59$ mm Hg). They found that 5 L/min of O_2 given by nasal prongs did not affect maximum work rate on the treadmill (grade increased 2% every minute until exhaustion) but that endurance at a submaximal work load increased approximately 50% while breathing O_2 compared with CA. None of these authors specifically measured dyspnea.

In contrast to these studies, Woodcock and coworkers (6) actually measured changes in dyspnea as well as exercise tolerance in response to oxygen supplementation. Woodcock and colleagues studied "pink puffer" patients with mild hypoxemia. They measured not only the distance walked to exhaustion on the treadmill but also asked patients to grade the severity of their dyspnea each minute on a 10-cm visual analog scale. Although their patients desaturated only mildly with exercise (mean decrease in Pa_{O_2} was from 73 to 63 mm Hg), supplemental O_2 at 4 L/min by nasal cannulae produced a variable, clinically modest but statistically significant improvement in both dyspnea and distance walked. Unfortunately, they did not relate the amount of improvement to the degree of desaturation that occurred during exercise on room air. However, in their earlier study, Bradley and coworkers found no correlation between degree of desaturation on room air exercise and subsequent response to supplemental O_2 in 26 patients with COPD measured by improvement in endurance (28).

Stein and coworkers (9) looked at the impact of 30% O_2 on treadmill exercise in a group of nine mildly hypoxemic COPD patients (mean $Pa_{O_2} = 63$ mm Hg, though two patients had $Pa_{O_2} < 56$) and found that O_2 significantly improved exercise performance, whether measured by length of time on the treadmill or by improvement in $\dot{V}O_2$max (up 34%). They felt that the improvement in exercise was due to delay in the rise of V_E to the "maximum" level that had been found at end exercise on room air. In their study, ventilation correlated weakly but significantly with O_2 saturation, and the authors thought that the delay in reaching this level of ventilation was due to decrease in respiratory drive induced by breathing O_2. There was also a reduction in V_{CO_2} and blood lactate, and these findings also could have contributed to a reduction in respiratory drive. Unfortunately, these authors did not measure dyspnea.

While hypoxemia can be a major stimulus for dyspnea, it is often absent in dyspneic patients (6). Variability of hypoxic drive and sensitivity of the carotid bodies explain part of the variability in the symptom of dyspnea, though recent work has shown that the ability of O_2 to improve exercise performance does not correlate with the level of hypoxic drive (29, 30). Oxygen supplementation might affect the sensation of dyspnea in several ways. As peripheral chemoreceptor stimulation by hypoxemia may directly elicit dyspnea in normals (11, 12), hyperoxemia might decrease dyspnea by directly decreasing chemoreceptor activity. Even normal levels of arterial oxygenation probably elicit signals from the carotid bodies that might contribute to dyspnea, as it has been shown that increasing F_{IO_2} above 0.21 in normal subjects may dramatically prolong breath-holding (31). With 100% O_2, normal subjects were able to breathhold as long as those with no carotid body function. Adams and colleagues (12) showed that the onset of dyspnea precedes increased V_E-associated with breathing hypoxic gas mixtures while exercising. There is also evidence that O_2 supplementation improves respiratory muscle function and delays the onset of respiratory muscle fatigue; both of these changes would decrease the sensation of effort (i.e., dyspnea) from the respiratory muscles (10). This effect of O_2 could be due in part to the decrease in the total ventilation required before reaching a "limiting" exercise ventilation (9). On the other hand, if O_2 changes the perception of respiratory discomfort (perhaps mediated in part through signals from the carotid body), a major benefit of O_2 would

be to decrease the level of dyspnea experienced at each workload without any change in ventilation.

Our study supports the concept that inhibiting signals from the carotid bodies with supplemental oxygen may decrease dyspnea as well as decrease ventilatory demand and thereby improve exercise performance. This response to supplemental O_2 is highly variable and appears to be identifiable only with exercise testing. Simply looking at exercise-induced desaturation is insufficient. In our study, the correlations between end exercise Pa_{O_2} or oxyhemoglobin saturation and differences in endurance were weak. All but one patient improved when breathing 40% O_2, but only two of the four patients with 100% or greater improvement in endurance had oxyhemoglobin desaturation while exercising on CA. Also, in our study, measurements of dyspnea correlated more closely with the increase in endurance time than changes in V_E, heart rate, oxyhemoglobin saturation, or RVSP. These findings suggest that oxygen-induced reduction in direct "dyspnogenic" signals to the CNS may be important apart from the effect of O_2 on ventilatory and hemodynamic responses to exercise. Thus, improvement in breathlessness with O_2 supplementation may be more dramatic than improvement in parameters more commonly measured during standard pulmonary exercise tests. The findings of our study indicate the potential importance of measuring dyspnea as well as the usual physiologic parameters during exercise testing.

It is not yet clear which patients with COPD should be offered supplemental O_2 with exercise if they do not meet the standard NOTT (4) criteria. The response to O_2 in such patients can be dramatic during laboratory exercise testing, though the significance of this for home use has not been established. If a patient's exercise tolerance is severely limited by dyspnea, it is worth considering endurance testing to determine in a blinded fashion whether supplemental O_2 substantially (e.g., by more than 50%) improves exercise tolerance and/or the symptoms limiting exercise (2). Such an exercise study allows the patient and his or her physician to determine whether endurance and dyspnea really are improved by O_2 and whether a home trial of this expensive and inconvenient treatment is indicated. Results from such studies may also help the treating physician justify the use of supplemental O_2 to third-party payors. Although this justification is easiest if exercise-induced hypoxemia develops, the results may be sufficient to allow reimbursement for O_2 even in its absence. Further research is needed to determine whether patients who respond to supplemental O_2 in the exercise laboratory actually benefit clinically from long-term supplemental O_2 therapy.

References

1. Cotes JE, Gilson JS. Effect of oxygen on exercise ability in chronic respiratory insufficiency; the use of portable apparatus. Lancet 1956; 1:872–6.
2. Anthonisen NR. Long-term oxygen therapy. Ann Intern Med 1983; 99:519–27.
3. Brown HV, Wasserman K. Exercise performance in chronic obstructive pulmonary diseases. Med Clinic North Am 1981; 65:525–47.
4. Nocturnal Oxygen Therapy Trial Group. Continuous or nocturnal oxygen therapy in hypoxemic chronic obstructive lung disease: a clinical trial. Ann Intern Med 1980; 93:391–8.
5. Medical Research Council Working Party. Long term domiciliary oxygen therapy in chronic hypoxic cor pulmonale complicating chronic bronchitis and emphysema. Lancet 1981; i:681–6.
6. Woodcock AA, Gross ER, Geddec DM. Oxygen relieves breathlessness in "pink puffers." Lancet 1981; 1:907–9.
7. Scano G, Van Meerhaeghe A, Willeput R, Vachaudez JP, Sergysels R. Effect of oxygen on breathing during exercise in patients with chronic obstructive lung disease. Eur J Respir Dis 1982; 63:23–30.
8. Vyas MN, Banister EW, Morton JW, Grzybowski S. Response to exercise in patients with chronic airway obstruction. II. Effects of breathing 40 percent oxygen. Am Rev Respir Dis 1971; 103:401–12.
9. Stein DA, Bradley BL, Miller W. Mechanisms of oxygen effects on exercise patients with chronic obstructive pulmonary disease. Chest 1982; 81:6–10.
10. Bye PTP, Esau SA, Levy RD, *et al.* Ventilatory muscle function during exercise in air and oxygen in patients with chronic air-flow limitation. Am Rev Respir Dis 1985; 132:236–40.
11. Guz A, Adams L, Minty K, Murphy K. Breathlessness and the ventilatory drives of exercise, hypercapnoea and hypoxia. Clin Sci 1981; 60:17–8P.
12. Adams L, Chronos N, Guz A. The dyspnogenic effect of hypoxia—dissociation from ventilatory response. Clin Sci 1982; 63:17P.
13. American Thoracic Society. Statement on standardization of spirometry. Am Rev Respir Dis 1987; 136:1285–98.
14. Darling RC, Cournand A, Richards DW Jr. Studies on the intrapulmonary mixture of gases:III. An open circuit method for measuring residual air. J Clin Invest 1940; 19:609–18.
15. Burrows B, Kaski JE, Niden AH. Clinical usefulness of the single breath diffusing capacity test. Am Rev Respir Dis 1961; 84:789–806
16. Borg GAV. Psychophysical bases of perceived exertion. Medicine and science in sports and exercise. 1982; 14:377–81.
17. Carrieri VK, Janson-Bjerklie S, Jacobs S. The sensation of dyspnea: a review. Heart Lung 1984; 13:436–47.
18. Himelman RB, Stulbarg MS, Kircher B, *et al.* Noninvasive evaluation of pulmonary pressure with exercise by Doppler echocardiography in chronic pulmonary disease. Circulation 1989; 79:863–71.
19. Timms RM, Khaja FU, Williams GW, and the Nocturnal Oxygen Study Group. Hemodynamic response to oxygen therapy in chronic obstructive pulmonary disease. Ann Intern Med 1985; 102:29–36.
20. Light RW, Mintz HM, Linden GS, Brown SE. Hemodynamics of patients with severe chronic obstructive pulmonary disease during progressive upright exercise. Am Rev Respir Dis 1984; 130:391–5.
21. Jones NL, Campbell EJM. Clinical exercise testing. Philadelphia, WB Saunders, 1982; 249.
22. Belman MJ, Mittman C. Ventilatory muscle training improves exercise capacity in chronic obstructive pulmonary disease patients. Am Rev Respir Dis 1980; 121:273–80.
23. Mahler DA, Matthay RA, Snyder PE, Wells CK, Loke J. Sustained-release theophylline reduces dyspnea in nonreversible obstructive airway disease. Am Rev Respir Dis 1985; 131:22–5.
24. Stulbarg MS, Winn WR. Bilateral carotid body resection for relief of dyspnea in chronic obstructive pulmonary disease. Chest 1989; 95:1123–8.
25. Woodcock AA, Gross ER, Gellert A, Shah S, Johnson M, Geddes DM. Effects of dihydrocodeine, alcohol and caffeine on breathlessness and exercise tolerance in patients with chronic obstructive lung disease and normal blood gases. N Engl J Med 1981; 305:1611–6.
26. Longo AM, Moser KM, Luchsinger PC. The role of oxygen therapy in the rehabilitation of patients with chronic obstructive pulmonary disease. Am Rev Respir Dis 1971; 103:690–7.
27. Pierce AK, Paez PM, Miller WF. Exercise training with the aid of a portable oxygen supply in patients with emphysema. Am Rev Respir Dis 1965; 91:653–9.
28. Bradley BL, Garner AE, Billiu D, Mestas JM, Forma J. Oxygen-assisted exercise in chronic obstructive lung disease: the effect on exercise capacity and arterial blood gas tensions. Am Rev Respir Dis 1978; 118:239–43.
29. Light RW, Mahutte CK, Stansbury DW, Fischer CE, Brown SE. Relationship between improvement in exercise performance with supplemental oxygen and hypoxic ventilatory drive in patients with chronic airflow obstruction. Chest 1989; 95:751–6.
30. Robinson DP, White DP, Zwillich CW. Occlusion pressure (p. 1) responses to hypoxia and hypercapnia do not explain dyspnea or exercise limitation in severe COPD. Am Rev Respir Dis 1986; 133:A61.
31. Davidson JT, Whipp BJ, Wasserman K, Koyal SN, Lugliani R. Role of the carotid bodies in breatholding. N Engl J Med 1974; 290:819–22.