CHEST Recent Advances in Chest Medicine

Oxygen Therapy for Patients With COPD

Current Evidence and the Long-Term Oxygen Treatment Trial

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Long-term use of supplemental oxygen improves survival in patients with COPD and severe resting hypoxemia. However, the role of oxygen in symptomatic patients with COPD and more moderate hypoxemia at rest and desaturation with activity is unclear. The few long-term reports of supplemental oxygen in this group have been of small size and insufficient to demonstrate a survival benefit. Short-term trials have suggested beneficial effects other than survival in patients with COPD and moderate hypoxemia at rest. In addition, supplemental oxygen appeared to improve exercise performance in small short-term investigations of patients with COPD and moderate hypoxemia at rest and desaturation with exercise, but long-term trials evaluating patient-reported outcomes are lacking. This article reviews the evidence for long-term use of supplemental oxygen therapy and provides a rationale for the National Heart, Lung, and Blood Institute Long-term Oxygen Treatment Trial. The trial plans to enroll subjects with COPD with moderate hypoxemia at rest or desaturation with exercise and compare tailored oxygen therapy to no oxygen therapy. ***CHEST 2010; 138(1):179–187***

Abbreviations: LOTT = Long-term Oxygen Treatment Trial; LTOT = long-term oxygen therapy; MRC = Medical Research Council; NOD = nocturnal oxygen desaturation; NOTT = Nocturnal Oxygen Therapy Trial; PA = pulmonary artery; PVC = premature ventricular contraction; Sa_{O_2} = arterial oxygen saturation; Sp_{O_2} = oxygen saturation by pulse oximetry

Use of supplemental long-term oxygen therapy (LTOT) by patients with COPD is common, with more than 1 million Medicare recipients using oxygen at an annual cost of more than $2 billion.[1,2] Although current indications for LTOT are based on the results of older randomized trials,[3,4] a recent conference identified uncertainties regarding LTOT in COPD, including its efficacy in patients with more moderate hypoxemia.[1]

This article reviews the available evidence regarding the efficacy of LTOT for individuals with COPD

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and frames current clinical research needs. We review the evidence regarding use of LTOT for patients with severe hypoxemia at rest, moderate hypoxemia at rest, hypoxemia only during activity, and desaturation only at night. We analyzed articles from a Medline search of published literature in the English language on oxygen therapy in patients with COPD. Because the number of randomized controlled trials are limited for subjects with less severe hypoxemia, we also reviewed nonrandomized trials. Finally, we introduce a recently launched multicenter National Heart, Lung, and Blood Institute trial (the Long-term Oxygen Treatment Trial [LOTT]) of supplemental oxygen for patients with COPD and moderate hypoxemia at rest or with desaturation only with exercise.

The Role of LTOT in Patients With COPD and Severe Hypoxemia at Rest

Survival

Supplemental oxygen is a well-established therapy with clear evidence for benefit in patients with COPD and severe resting hypoxemia, which is defined as a room air $PaO_2 \leq 55$ mm Hg or ≤ 59 mm Hg with signs of right-sided heart strain or polycythemia. Oxygen was the first treatment shown to prolong life in people with COPD.[3,4] Current recommendations for prescribing LTOT (Table 1) are based on results from two randomized trials in patients with COPD published almost 30 years ago: the Nocturnal Oxygen Therapy Trial (NOTT) and the Medical Research Council (MRC) study (Fig 1).[3,4]

The MRC study was a randomized controlled oxygen therapy trial designed to assess whether use of supplemental oxygen for 15 h/d (including overnight) compared with no supplemental oxygen conferred a survival advantage over ≥ 3 years.[3] Eighty-seven subjects

Table 1—*Current Indications for Continuous Oxygen Use in COPD*

Based on Randomized Controlled Clinical Trials[3,4]	Based on Less Evidence[a]
Continuous oxygen use	Intermittent oxygen use
Resting $PaO_2 \leq 55$ mm Hg	Desaturation ($SpO_2 \leq 88\%$) with activity
Resting PaO_2 of 56-59 mm Hg with any one of the following:	Desaturation ($SpO_2 \leq 88\%$) at night
Dependent edema	
P pulmonale on the electrocardiogram (P wave exceeding 3 mm in standard lead II, III, or aVF)	
Polycythemia (hematocrit, > 56%)	

SpO_2 = oxygen saturation by pulse oximetry.
[a]Reimbursed by the Centers for Medicare & Medicaid Services.

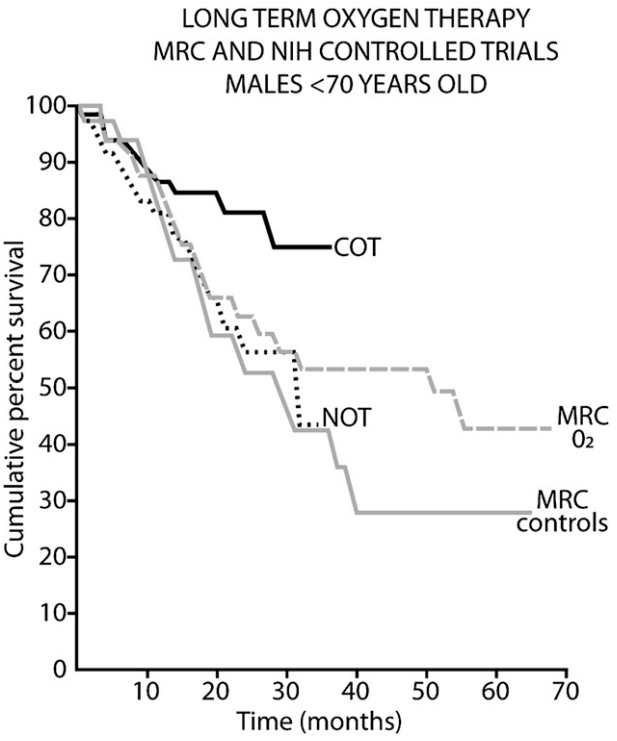

FIGURE 1. Long-term oxygen therapy in Medical Research Council and National Institutes of Health controlled trials in men aged < 70 years, examining the fraction of subjects surviving compared to the time from randomization or duration of treatment. COT = continuous oxygen therapy[3]; MRC = Medical Research Council[4]; NOT = nocturnal oxygen therapy.[3]

with severe airflow limitation (mean FEV_1, 0.58 L), marked hypoxemia (PaO_2, 49-52 mm Hg), hypercapnia (PCO_2, 56-59 mm Hg), and mild pulmonary hypertension were enrolled. Oxygen was delivered at 2 L/min (or higher if needed to achieve a PaO_2 > 60 mm Hg). Results in the 87 subjects showed that supplemental oxygen use improved survival (55% vs 33% in controls; $P < .05$). Secondary outcome measures showed no significant benefit of supplemental oxygen (ie, days spent working, days spent in the hospital for COPD exacerbations, RBC mass, pulmonary hemodynamics). The results of this trial established the survival advantage of nocturnal supplemental oxygen in subjects with COPD and severe resting hypoxemia.

Further evidence of enhanced survival benefit with supplemental oxygen is provided by the National Institutes of Health NOTT.[4] The study assessed whether continuous supplemental oxygen improved survival compared with nocturnal oxygen. Eligible subjects had COPD and severe resting hypoxemia ($PaO_2 \leq 55$ mm Hg or $PaO_2 \leq 59$ mm Hg with either edema, polycythemia [hematocrit, ≥ 55%], or P pulmonale on electrocardiogram). The study enrolled 203 subjects. Over a mean follow-up period of 19.3 months, use of continuous oxygen conferred a significant survival

benefit ($P = .01$), with a relative risk of death of 1.94 (95% CI, 1.17-3.24) with use of nocturnal oxygen compared with continuous oxygen. Among secondary outcome measures, hematocrit fell more in continuous than in nocturnal oxygen users ($P = .008$ at 18 months), and pulmonary vascular resistance fell 11.1% in continuous oxygen users but rose 6.5% in nocturnal oxygen users ($P = .04$ at 6 months). Subjects receiving continuous oxygen therapy averaged (mean ± SD) 17.7 ± 4.8 h/d, and subjects receiving nocturnal oxygen therapy averaged 12.0 ± 2.5 h/d.

Results of the NOTT demonstrated that use of continuous supplemental oxygen enhanced survival compared with use of nocturnal supplemental oxygen. Taken together with the results of the MRC study, the findings suggest that in patients with COPD and resting hypoxemia, some oxygen is better than none, and continuous oxygen is better than nocturnal oxygen.

Pulmonary Hemodynamics

The effects of supplemental oxygen on pulmonary hemodynamics in patients with COPD using LTOT for > 13 h/d also have been investigated.[5,6] Weitzenblum et al[5] evaluated 16 patients with severe COPD (mean FEV_1, 0.89 L) and hypoxemia (mean PaO_2, 59.3 mm Hg) over a mean of 78 months. Pulmonary artery (PA) pressure was measured by right-sided heart catheterization before and twice after initiating supplemental oxygen for > 15 h/d to achieve a PaO_2 ≥ 65 mm Hg. Supplemental oxygen reversed a pretreatment trend toward worsening pulmonary hypertension. Between the baseline measurement and the first post-oxygen catheterization, mean PA pressure rose by 1.47 mm Hg, whereas over the ensuing 31 months, mean PA pressure fell by 2.15 mm Hg.

In the longest hemodynamic study of patients with COPD and hypoxemia (mean PaO_2, 55 mm Hg) receiving supplemental oxygen for a mean of 14.7 h/d, Zieliński et al[6] measured PA pressures serially for up to 6 years. In a subset (39 of 73) of subjects who underwent follow-up right-sided heart catherization at 2 years, mean PA pressure fell slightly from 25 mm Hg to 23 mm Hg. In those who continued supplemental oxygen for 4 years, mean PA pressure remained stable. In 12 subjects who completed 6 years of supplemental oxygen use, mean PA pressure fell from baseline to 2-year follow-up (from 25 mm Hg to 21 mm Hg) but then returned to baseline values thereafter (mean PA pressure, 26 mm Hg at 4- and 6-year follow-up). The authors concluded that supplemental oxygen in patients with COPD and hypoxemia caused a short-term decline in PA pressure followed by subsequent return and stabilization of PA pressures to baseline levels.

The Role of LTOT in Patients With COPD and Moderate Hypoxemia

Mortality

In contrast with the results of the MRC study and NOTT, supplemental oxygen has not been shown to improve survival in patients with COPD and moderate hypoxemia.[7,8] Górecka et al[7] randomly assigned 135 patients with a resting room air PaO_2 of 56 to 65 mm Hg to receive supplemental oxygen for > 17 h/d (to raise PaO_2 to ≥ 65 mm Hg) or no supplemental oxygen. Over a mean observation of 40.9 months, cumulative survival in the treatment and control groups did not differ significantly. Furthermore, no survival difference was observed for patients using supplemental oxygen for more than 15 h/day vs those using it for shorter periods.

Haidl et al[8] randomly assigned 28 patients with COPD (mean FEV_1, 40.8 ± 10.2% predicted) and moderate hypoxemia (mean PaO_2, 66.5 ± 6.3 mm Hg) to supplemental oxygen (2 L/min for > 15 h/d) or no supplemental oxygen for 3 years. At 1 year, cycle ergometry endurance time and end-exercise dyspnea were better in patients who received LTOT. The mortality rate was similar in both groups. Because of the small study population and large number of dropouts, later outcomes could not be assessed.

Analysis of the survival in these two studies in patients with COPD and moderate hypoxemia demonstrates no survival benefit for LTOT (odds ratio, 1.39; 95% CI, 0.74-2.59).[9] However, these studies enrolled small numbers of subjects. As noted later in this article, the LOTT plans to enroll 1,134 subjects and follow them for up to 4½ years to assess a potential benefit in survival or hospitalization rate.

The Role of Supplemental Oxygen in Patients With Hypoxemia During Activity

Definition

Important challenges in ascertaining the effectiveness of supplemental oxygen during activity in patients with COPD are the lack of uniform criteria for defining exertional desaturation and standardized exercise protocols. Threshold values for oxygen desaturation range from 88% to 90%, and relative declines vary from 2% to 5% in published investigations. Some studies require maintenance of the oxygen saturation by pulse oximetry (SpO_2) below a threshold value for a specified interval (usually between 0.5 min and 5 min) (Table 2). The techniques for inducing exertion vary from activities of daily living to incremental maximal cycle ergometry.

Table 2—*Studies of Oxygen Therapy in Subjects With COPD and Exertional Desaturation*

Authors	No.	Subject Characteristics[a]	Design	Benefits of Oxygen
Drummond et al[10]	471	Severe COPD (moderate-severe emphysema; mean FEV_1, 0.73 L [continuous oxygen], 0.77 L [intermittent oxygen], 0.86 L [no oxygen group]) randomized to medical therapy in NETT; $Pao_2 > 60$ mm Hg; desaturation to < 90% during treadmill walk	Retrospective review of patients treated with continuous oxygen, intermittent supplemental oxygen, and no supplemental oxygen	No difference in survival
Stein et al[11]	9	Severe COPD (mean FEV_1, 0.87 L; mean Pao_2, 63 mm Hg; range, 50-78 mm Hg)	Treadmill exercise while breathing 30% oxygen or compressed air	Increased duration of exercise; reduced minute ventilation; reduced tidal volume
McDonald et al[12]	26	Severe COPD (mean FEV_1, 0.9 L; mean Pao_2, 69 mm Hg; mean Sao_2, 94%)	Double-blind randomized crossover study comparing supplemental air or oxygen during 6MW and step tests after using either supplemental air or oxygen with activity for 6 weeks	Increased 6MW distance and steps climbed; no change in Borg dyspnea score
Jolly et al[13]	11	Severe COPD (mean FEV_1, 0.9 L; mean Pao_2, 74 mm Hg; Spo_2 reduction, ≥ 5% and absolute value < 90% during 6MW)	Double-blind, randomized, placebo-controlled trial comparing supplemental oxygen and compressed air during 6MW	Increased 6MW distance; reduced dyspnea
Somfay et al[14]	10	Severe COPD (mean FEV_1, 0.92 L; mean Sao_2 at rest, 95.7%; mean Sao_2 with exercise, 92%)	Single-blind randomized controlled study comparing compressed air and 30%, 50%, 75%, and 100% oxygen during cycle exercise testing at 75% of maximal work rate	Increased exercise duration; reduced dyspnea in dose-dependent manner due to decreased dynamic hyperinflation and respiratory rate
Rooyackers et al[15]	24	Moderate to severe COPD (mean FEV_1, 1.2 L; mean Pao_2, 78.9 mm Hg; exercise Sao_2, < 90%)	Ten-week inpatient pulmonary rehabilitation program with general exercise training breathing either supplemental oxygen or room air	No difference in training effect
Garrod et al[16]	25	Severe COPD (mean FEV_1, 0.76 L; mean Pao_2, 63.6 mm Hg; exercise Sao_2, 82%)	Six-week pulmonary rehabilitation training program using either compressed air or supplemental oxygen	Reduced breathlessness; no effect on exercise tolerance, health status, mood state, or performance of daily activities
Wadell et al[17]	20	COPD (median FEV_1 51.6% predicted [air group], 39.3% predicted [oxygen group]; median Pao_2 69.9 mm Hg [air group], 71.4 mm Hg [oxygen group] exercise Sao_2, ≤ 92%)	Single-blind randomized controlled study comparing supplemental oxygen or air during 8 weeks of exercise training three times/week for 30 min	No difference in training effect; dyspnea less in subjects receiving air
Emtner et al[18]	29	COPD (mean FEV_1, 36% predicted; Pao_2, > 55 mm Hg; exercise Sao_2, ≥ 88%)	Double-blind trial comparing supplemental oxygen and compressed air during 7 weeks of three times/week high-intensity cycle ergometry training	Improved maximal work rate; increased exercise endurance; increased training work rate more rapidly; reduced exercise breathing rate
Eaton et al[19]	41	COPD (mean FEV_1, 25.9% predicted; mean Pao_2, 69 mm Hg; mean exercise Sao_2, 82%)	Twelve-week double-blind randomized crossover trial comparing compressed supplemental air and oxygen during dyspnea-inducing exertion	Improved health-related quality of life

6MW = 6-min walk test; NETT = National Emphysema Treatment Trial; Sao_2 = arterial oxygen saturation. See Table 1 for expansion of other abbreviation.

[a]Pao_2 assessed at rest while breathing room air, unless otherwise noted.

Mortality

Several studies suggested that exertional desaturation may portend a poor prognosis for patients with COPD.[10,20-23] In a retrospective review of 144 patients, Takigawa and coworkers[21] showed that a fall in $Spo_2 \geq 6\%$ during a 6-min walk predicted mortality. Similarly, in a prospective study of 576 patients with stable COPD, Casanova and colleagues[22] demonstrated that desaturation (a decrease in the $Spo_2 \geq 4\%$ or $Spo_2 < 90\%$ on 6-min walk) predicted mortality with a relative risk of 2.63. The Pao_2 slope (rate of change of Pao_2 and oxygen consumption) during incremental cardiopulmonary exercise testing and age were the most significant independent prognostic factors associated with survival in 120 patients with COPD.[24] In a cohort of 64 patients with hypercapnia followed for ≤ 15 years, the decline in arterial oxygen saturation (Sao_2) and increase in $Paco_2$ during exercise

were significantly greater in those who died.[23] A retrospective review of 471 subjects with emphysema, resting normoxemia, and exertional desaturation randomized to medical treatment in the National Emphysema Treatment Trial[10] demonstrated no differences in survival among subjects treated with continuous oxygen, intermittent oxygen, or no supplemental oxygen. Although exertional desaturation in patients with COPD and resting normoxemia appears to predict a poor prognosis, the effect of continuous supplemental oxygen on survival in this group has not been prospectively assessed in a large population.

Dyspnea, Exercise Performance, and Health-Related Quality of Life

In some studies, supplemental oxygen has been shown to enhance exercise performance in patients with COPD who are normoxemic at rest but desaturate with exertion.[11-13] However, these studies only examined the effects of relatively short-term oxygen use.

In 11 patients with COPD and resting normoxemia, the distance walked during 6 min increased from 391 ± 36 m to 450 ± 29 m, and the level of dyspnea decreased with supplemental oxygen but not with room air.[13] Somfay et al[14] examined the mechanism for this improvement and showed that supplemental oxygen increases exercise endurance time and reduces respiratory rate and dynamic hyperinflation during exercise in patients with COPD and mild hypoxemia. In a 12-week double-blind, randomized, crossover study that compared use of supplemental oxygen and air in 26 patients with resting near-normal Sao_2 (94% ± 2.1%), McDonald and colleagues[12] found that supplemental oxygen acutely increased 6-min walk distance and step test duration but did not have any long-term benefit in exercise performance, dyspnea, or quality of life.

Small studies of the short-term effects of supplemental oxygen in patients undergoing pulmonary rehabilitation suggested improvement in exercise performance but inconsistent outcomes on exercise training, an effect possibly related to methodologic variation.[15-18,25] During 7 weeks of high-intensity cycle ergometer exercise in patients with COPD and resting normoxemia, a higher maximal workload and greater endurance were demonstrated in the group treated with supplemental oxygen than in the group treated with compressed air.[17] In 24 patients with exertional desaturation to < 90%, supplemental oxygen did not add to exercise performance or quality of life.[15] During pulmonary rehabilitation in 25 patients with exertional desaturation, supplemental oxygen reduced dyspnea but did not affect exercise tolerance, health status, mood state, or performance of daily activities compared with room air.[16] A meta-analysis of oxygen supplementation during training in patients with COPD concluded that oxygen augmented the benefits of exercise but emphasized the limited numbers of enrolled subjects and varied study design.[26]

An additional study examined health-related quality of life in patients with COPD without concomitant pulmonary rehabilitation and exertional desaturation treated with supplemental oxygen. In 50 patients with COPD (Sao_2, 82% ± 5.4% after 6-min walk), Eaton and coworkers[19] evaluated the effect of 12 weeks of supplemental oxygen on health-related quality of life in a double-blind, randomized, crossover trial. Supplemental oxygen significantly improved respiratory and general health-related quality of life, anxiety, and depression. However, the effect of supplemental oxygen on the 6-min walk distance and the Borg dyspnea scale did not correlate with the patient-reported outcomes, and 41% of the responders elected not to continue supplemental oxygen after the trial.

Other Outcomes

Cerebral Sao_2 decreases during exercise in COPD. Supplemental oxygen reduces deoxyhemoglobin and improves cerebral oxygenation, thereby possibly helping to sustain cerebral function during exertion.[27]

As-Needed or Short-Burst Oxygen Therapy

Short duration, intermittent supplemental oxygen has been used to relieve breathlessness with exercise.[28-30] There is no uniform definition of the amount or duration of oxygen therapy used for short periods of time. Published reports have used oxygen to relieve breathlessness as needed, before exercise, during exercise, or after exercise.

Several early studies suggested that short-burst oxygen immediately before or just after exertion reduces dyspnea and increases 6-min walk distance.[31-33] Subsequent studies failed to demonstrate such benefits.[34,35] Short-burst oxygen either before or after a 6-min walk does not improve the distance walked or the Borg dyspnea scale in patients with COPD and normoxemia at rest and desaturation with exertion.[36] Compared with air, supplemental oxygen after the completion of exercise decreases the time to recovery from dynamic hyperinflation but does not affect the time to return to baseline breathlessness or maximal perception of dyspnea during recovery.[37] Thus, there are few randomized controlled studies of short-term supplemental oxygen use. A metaanalysis of short-burst oxygen therapy concluded that there is no reduction in breathlessness and inconsistent effects on exercise capacity.[38]

It is not clear whether patients with COPD who desaturate during the day with exercise also desaturate at night. Because the mechanisms of desaturation during exercise and during sleep differ, patients who desaturate with activity may not desaturate at night.

The Role of LTOT in Patients With COPD and Nocturnal Desaturation

Definition

Nocturnal oxygen desaturation (NOD) has been reported in patients with COPD with an awake $Pa_{O_2} > 60$ mm Hg.[39-45] The most significant episodes of NOD occur during rapid eye movement sleep, with a reported prevalence of 27%.[46] However, there are no accepted standards for the level or duration of desaturation that define NOD in patients with COPD[45-47] (Table 3).

Mortality

Although retrospective data suggest a decreased survival in patients with NOD,[49] only a few studies examined the impact of nocturnal supplemental oxygen therapy on mortality in patients with COPD and NOD.[7,48,51] In patients with mild to moderate daytime hypoxemia (Pa_{O_2}, 56-69 mm Hg) and associated NOD, no improvement in survival was noted with nocturnal supplemental oxygen therapy at the end of 2 years.[48] A similar lack of improvement in survival was seen in patients with COPD and isolated NOD who were randomized to nocturnal oxygen therapy for 3 years.[51] Therefore, based on limited available data in small numbers of subjects, it is unknown whether continuous supplemental oxygen therapy affects survival in patients with COPD and isolated NOD.

Sleep Quality

Sleep quality is poor in patients with COPD.[39-42,52-54] Subjective complaints include difficulty falling and staying asleep, morning tiredness, early awakenings, and excessive daytime sleepiness.[41,52-54] Objective assessment of sleep quality demonstrates increased sleep latency, decreased total sleep time, increased number of arousals, and a decrease in rapid eye movement sleep.[40,44]

The results of studies investigating the effects of oxygen therapy on sleep quality are limited and conflicting, with one study demonstrating improved sleep quality[40] and another noting no change.[44] Therefore, although sleep quality is known to be poor in patients with COPD, the effects of nocturnal supplemental oxygen therapy are unknown.

Other Outcomes

Premature ventricular contractions (PVCs) occur during the night in 64% of patients with COPD,[55] with a frequency more than twice that during the day.[50] In patients with more significant nocturnal

Table 3—*Studies of Oxygen Therapy in Subjects With COPD and Nocturnal Desaturation*

Authors	No.	Subject Characteristics[a]	Design	Benefits of Oxygen
Górecka et al[7]	135	COPD (mean FEV_1, 0.83 L; mean Pa_{O_2}, 60 mm Hg; range, 56-69 mm Hg)	Randomized study of conventional therapy vs conventional therapy plus continuous oxygen therapy (mean oxygen use, 14 h/d); followed over 3 years	No difference in survival, even in those using oxygen > 15 h/d; survival better with younger age, higher FEV_1, and higher BMI
Chaouat et al[48]	76	COPD (mean FEV_1, 1.08 L in nocturnal oxygen group and 0.98 L in controls; mean Pa_{O_2}, 62.7 mm Hg; range 56-69 mm Hg; mean nocturnal Sp_{O_2}, 88%)	Randomized study of conventional therapy vs conventional therapy plus supplemental nocturnal oxygen therapy; followed over 2 years	No difference in survival and pulmonary hemodynamics; no delay in need for supplemental oxygen (defined as Pa_{O_2} < 55 mm Hg during the day)
Fletcher et al[49]	16	COPD (mean FEV_1, 1.42 L; mean Pa_{O_2}, 76 mm Hg; isolated NOD Sp_{O_2} < 90% for ≥ 5 min; nadir, ≤ 85%)	Randomized to supplemental nocturnal oxygen therapy vs a sham control	No difference in survival at the end of 3 years; small improvement in pulmonary hemodynamics
Calverly et al[40]	6	Severe COPD (mean FEV_1, 0.6 L [all with FEV_1 < 1 L]; mean Pa_{O_2}, 48 mm Hg)	Sleep studies off and on supplemental oxygen	Improved sleep quality compared with control night
Fleetham et al[44]	15	Severe COPD (mean FEV_1, 24% predicted; mean Pa_{O_2}, 52 mm Hg)	Sleep studies off and on supplemental oxygen	No improvement in sleep quality
Flick and Block[50]	10	Severe COPD (mean FEV_1, 0.76 L; mean Sa_{O_2}, 86%)	Continuous 24-h electrocardiogram monitoring with and without supplemental oxygen (2 L/min)	Decrease in the number of nocturnal PVCs

NOD = nocturnal oxygen desaturation; PVCs = premature ventricular contractions. See Tables 1 and 2 legends for expansion of other abbreviations.
[a]Pa_{O_2} assessed at rest while breathing room air, unless otherwise noted.

hypoxemia, there is a >150% increase in the frequency of PVCs.[55] In one study, supplemental oxygen did not decrease the mean number of PVCs in all subjects; however, four of the 10 subjects experienced a 50% decrease in PVC frequency.[56] Although some investigators have reported elevations in PA pressure and pulmonary vascular resistance in patients with NOD,[56] others have not.[47] Similarly, studies of nocturnal supplemental oxygen therapy on pulmonary hemodynamics have shown conflicting results.[48,56] In patients with isolated NOD, Fletcher et al[56] showed a downward trend in PA pressure (−4 mm Hg) with supplemental oxygen therapy compared with an increase (+4 mm Hg) in the control group. Another study found no change in PA pressures in patients with NOD.[48] Overall, whether supplemental oxygen therapy in patients with NOD affects the prevalence of cardiac dysrhythmias and the development of pulmonary hypertension has not been determined.

The LOTT

Based on the evidence and unanswered questions summarized herein and the research needs identified by the Sixth Oxygen Consensus Conference[2] and a workshop report on LTOT,[1] the National Heart, Lung, and Blood Institute and Centers for Medicare & Medicaid Services are sponsoring the LOTT. The LOTT is a multicenter, randomized clinical trial of tailored oxygen therapy (ie, continuous oxygen therapy [24 h/d] for subjects with moderate resting hypoxemia and supplemental oxygen therapy with sleep and activity for subjects with exercise desaturation) vs no supplemental oxygen therapy. The goal is to randomize 1,134 patients over 2½ years, with a maximal follow-up period of 4.5 years (minimum follow-up, 1 year). The primary objective of LOTT is to determine whether continuous supplemental oxygen therapy increases time to the composite outcome of all-cause mortality or all-cause hospitalization as well as deterioration of disease-specific quality of life (St. George Respiratory Questionnaire) and preference-weighted quality of life (Quality of Well-Being Scale).

Eligible subjects are aged ≥40 years, have COPD (postbronchodilator FEV_1, ≤65% predicted; FEV_1/FVC, <0.70), and have a dyspnea rating ≥1 by the modified MRC scale. Subjects will use oxygen delivery devices designed to be wearable and convenient and to deliver adequate, tailored supplemental oxygen according to the protocols (either continuously in those with moderate resting hypoxemia or during activity and sleep in those with exercise desaturation).

It is hoped that LOTT will offer generalizable conclusions with regard to the safety, efficacy, and cost-effectiveness of LTOT in patients with COPD and moderate hypoxemia at rest or desaturation during exercise. Health-care practitioners are encouraged to refer candidates for the LOTT to one of the clinical centers listed at www.jhucct.com/lott/open/centers/centers.htm.

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References

1. Croxton TL, Bailey WC. Long-term oxygen treatment in chronic obstructive pulmonary disease: recommendations for future research: an NHLBI workshop report. *Am J Respir Crit Care Med*. 2006;174(4):373-378.
2. Doherty DE, Petty TL, Bailey W, et al. Recommendations of the 6th long-term oxygen therapy consensus conference. *Respir Care*. 2006;51(5):519-525.
3. Report of the Medical Research Council Working Party. Long term domiciliary oxygen therapy in chronic hypoxic cor pulmonale complicating chronic bronchitis and emphysema. *Lancet*. 1981;1(8222):681-686.
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(3):391-398.
5. Weitzenblum E, Sautegeau A, Ehrhart M, Mammosser M, Pelletier A. Long-term oxygen therapy can reverse the progression of pulmonary hypertension in patients with chronic obstructive pulmonary disease. *Am Rev Respir Dis*. 1985;131(4):493-498.
6. Zieliński J, Tobiasz M, Hawryłkiewicz I, Sliwiński P, Pałasiewicz G. Effects of long-term oxygen therapy on pulmonary hemodynamics in COPD patients: a 6-year prospective study. *Chest*. 1998;113(1):65-70.
7. Górecka D, Gorzelak K, Sliwiński P, Tobiasz M, Zieliński J. Effect of long-term oxygen therapy on survival in patients with chronic obstructive pulmonary disease with moderate hypoxaemia. *Thorax*. 1997;52(8):674-679.
8. Haidl P, Clement C, Wiese C, Dellweg D, Köhler D. Long-term oxygen therapy stops the natural decline of endurance in COPD patients with reversible hypercapnia. *Respiration*. 2004;71(4):342-347.
9. Cranston JM, Crockett AJ, Moss JR, Alpers JH. Domiciliary oxygen for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*. 2005; (4):CD001744.
10. Drummond MB, Blackford AL, Benditt JO, et al; NETT Investigators. Continuous oxygen use in nonhypoxemic emphysema patients identifies a high-risk subset of patients: retrospective analysis of the National Emphysema Treatment Trial. *Chest*. 2008;134(3):497-506.

11. Stein DA, Bradley BL, Miller WC. Mechanisms of oxygen effects on exercise in patients with chronic obstructive pulmonary disease. *Chest*. 1982;81(1):6-10.
12. McDonald CF, Blyth CM, Lazarus MD, Marschner I, Barter CE. Exertional oxygen of limited benefit in patients with chronic obstructive pulmonary disease and mild hypoxemia. *Am J Respir Crit Care Med*. 1995;152(5 Pt 1): 1616-1619.
13. Jolly EC, Di Boscio V, Aguirre L, Luna CM, Berensztein S, Gené RJ. Effects of supplemental oxygen during activity in patients with advanced COPD without severe resting hypoxemia. *Chest*. 2001;120(2):437-443.
14. Somfay A, Porszasz J, Lee SM, Casaburi R. Dose-response effect of oxygen on hyperinflation and exercise endurance in nonhypoxaemic COPD patients. *Eur Respir J*. 2001;18(1): 77-84.
15. Rooyackers JM, Dekhuijzen PN, Van Herwaarden CL, Folgering HT. Training with supplemental oxygen in patients with COPD and hypoxaemia at peak exercise. *Eur Respir J*. 1997;10(6):1278-1284.
16. Garrod R, Mikelsons C, Paul EA, Wedzicha JA. Randomized controlled trial of domiciliary noninvasive positive pressure ventilation and physical training in severe chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2000;162 (4 Pt 1):1335-1341.
17. Wadell K, Henriksson-Larsén K, Lundgren R. Physical training with and without oxygen in patients with chronic obstructive pulmonary disease and exercise-induced hypoxaemia. *J Rehabil Med*. 2001;33(5):200-205.
18. Emtner M, Porszasz J, Burns M, Somfay A, Casaburi R. Benefits of supplemental oxygen in exercise training in nonhypoxemic chronic obstructive pulmonary disease patients. *Am J Respir Crit Care Med*. 2003;168(9):1034-1042.
19. Eaton T, Garrett JE, Young P, et al. Ambulatory oxygen improves quality of life of COPD patients: a randomised controlled study. *Eur Respir J*. 2002;20(2):306-312.
20. Kawakami Y, Terai T, Yamamoto H, Murao M. Exercise and oxygen inhalation in relation to prognosis of chronic obstructive pulmonary disease. *Chest*. 1982;81(2):182-188.
21. Takigawa N, Tada A, Soda R, et al. Distance and oxygen desaturation in 6-min walk test predict prognosis in COPD patients. *Respir Med*. 2007;101(3):561-567.
22. Casanova C, Cote C, Marin JM, et al. Distance and oxygen desaturation during the 6-min walk test as predictors of long-term mortality in patients with COPD. *Chest*. 2008;134(4): 746-752.
23. Vandenbergh E, Clement J, Van de Woestijne KP. Course and prognosis of patients with advanced chronic obstructive pulmonary disease. Evaluation by means of functional indices. *Am J Med*. 1973;55(6):736-746.
24. Hiraga T, Maekura R, Okuda Y, et al. Prognostic predictors for survival in patients with COPD using cardiopulmonary exercise testing. *Clin Physiol Funct Imaging*. 2003;23(6): 324-331.
25. Ries AL, Bauldoff GS, Carlin BW, et al. Pulmonary Rehabilitation: Joint ACCP/AACVPR Evidence-Based Clinical Practice Guidelines. *Chest*. 2007;131(5 suppl):4S-42S.
26. Nonoyama ML, Brooks D, Lacasse Y, Guyatt GH, Goldstein RS. Oxygen therapy during exercise training in chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*. 2007;(2):CD005372.
27. Jensen G, Nielsen HB, Ide K, et al. Cerebral oxygenation during exercise in patients with terminal lung disease. *Chest*. 2002;122(2):445-450.
28. Okubadejo AA, Paul EA, Wedzicha JA. Domiciliary oxygen cylinders: indications, prescription and usage. *Respir Med*. 1994;88(10):777-785.
29. Roberts CM. Short burst oxygen therapy for relief of breathlessness in COPD. *Thorax*. 2004;59(8):638-640.
30. O'Neill B, Bradley JM, Heaney L, O'Neill C, MacMahon J. Short burst oxygen therapy in chronic obstructive pulmonary disease: a patient survey and cost analysis. *Int J Clin Pract*. 2005;59(7):751-753.
31. Woodcock AA, Gross ER, Geddes DM. Oxygen relieves breathlessness in "pink puffers". *Lancet*. 1981;1(8226): 907-909.
32. Evans TW, Waterhouse JC, Carter A, Nicholl JF, Howard P. Short burst oxygen treatment for breathlessness in chronic obstructive airways disease. *Thorax*. 1986;41(8):611-615.
33. Killen JW, Corris PA. A pragmatic assessment of the placement of oxygen when given for exercise induced dyspnoea. *Thorax*. 2000;55(7):544-546.
34. McKeon JL, Murree-Allen K, Saunders NA. Effects of breathing supplemental oxygen before progressive exercise in patients with chronic obstructive lung disease. *Thorax*. 1988;43(1):53-56.
35. Nandi K, Smith AA, Crawford A, et al. Oxygen supplementation before or after submaximal exercise in patients with chronic obstructive pulmonary disease. *Thorax*. 2003;58(8): 670-673.
36. Lewis CA, Eaton TE, Young P, Kolbe J. Short-burst oxygen immediately before and after exercise is ineffective in nonhypoxic COPD patients. *Eur Respir J*. 2003;22(4):584-588.
37. Stevenson NJ, Calverley PM. Effect of oxygen on recovery from maximal exercise in patients with chronic obstructive pulmonary disease. *Thorax*. 2004;59(8):668-672.
38. O'Neill B, Mahon JM, Bradley J. Short-burst oxygen therapy in chronic obstructive pulmonary disease. *Respir Med*. 2006;100(7):1129-1138.
39. Wynne JW, Block AJ, Hemenway J, Hunt LA, Flick MR. Disordered breathing and oxygen desaturation during sleep in patients with chronic obstructive lung disease (COLD). *Am J Med*. 1979;66(4):573-579.
40. Calverley PM, Brezinova V, Douglas NJ, Catterall JR, Flenley DC. The effect of oxygenation on sleep quality in chronic bronchitis and emphysema. *Am Rev Respir Dis*. 1982;126(2): 206-210.
41. Cormick W, Olson LG, Hensley MJ, Saunders NA. Nocturnal hypoxaemia and quality of sleep in patients with chronic obstructive lung disease. *Thorax*. 1986;41(11): 846-854.
42. Krachman SL, Chatila W, Martin UJ, et al; National Emphysema Treatment Trial Research Group. Effects of lung volume reduction surgery on sleep quality and nocturnal gas exchange in patients with severe emphysema. *Chest*. 2005;128(5):3221-3228.
43. Koo KW, Sax DS, Snider GL. Arterial blood gases and pH during sleep in chronic obstructive pulmonary disease. *Am J Med*. 1975;58(5):663-670.
44. Fleetham J, West P, Mezon B, Conway W, Roth T, Kryger M. Sleep, arousals, and oxygen desaturation in chronic obstructive pulmonary disease. The effect of oxygen therapy. *Am Rev Respir Dis*. 1982;126(3):429-433.
45. Bradley TD, Mateika J, Li D, Avendano M, Goldstein RS. Daytime hypercapnia in the development of nocturnal hypoxemia in COPD. *Chest*. 1990;97(2):308-312.
46. Fletcher EC, Miller J, Divine GW, Fletcher JG, Miller T. Nocturnal oxyhemoglobin desaturation in COPD patients with arterial oxygen tensions above 60 mm Hg. *Chest*. 1987; 92(4):604-608.
47. Chaouat A, Weitzenblum E, Kessler R, et al. Sleep-related O2 desaturation and daytime pulmonary haemodynamics in COPD patients with mild hypoxaemia. *Eur Respir J*. 1997; 10(8):1730-1735.

48. Chaouat A, Weitzenblum E, Kessler R, et al. A randomized trial of nocturnal oxygen therapy in chronic obstructive pulmonary disease patients. *Eur Respir J*. 1999;14(5):1002-1008.
49. Fletcher EC, Luckett RA, Goodnight-White S, Miller CC, Qian W, Costarangos-Galarza C. A double-blind trial of nocturnal supplemental oxygen for sleep desaturation in patients with chronic obstructive pulmonary disease and a daytime PaO_2 above 60 mm Hg. *Am Rev Respir Dis*. 1992;145:1070-1076.
50. Flick MR, Block AJ. Nocturnal vs diurnal cardiac arrhythmias in patients with chronic obstructive pulmonary disease. *Chest*. 1979;75(1):8-11.
51. Fletcher EC, Donner CF, Midgren B, et al. Survival in COPD patients with a daytime PaO2 greater than 60 mm Hg with and without nocturnal oxyhemoglobin desaturation. *Chest*. 1992;101(3):649-655.
52. Bellia V, Catalano F, Scichilone N, et al. Sleep disorders in the elderly with and without chronic airflow obstruction: the SARA study. *Sleep*. 2003;26(3):318-323.
53. Klink ME, Dodge R, Quan SF. The relation of sleep complaints to respiratory symptoms in a general population. *Chest*. 1994;105(1):151-154.
54. Dodge R, Cline MG, Quan SF. The natural history of insomnia and its relationship to respiratory symptoms. *Arch Intern Med*. 1995;155(16):1797-1800.
55. Shepard JW Jr, Garrison MW, Grither DA, Evans R, Schweitzer PK. Relationship of ventricular ectopy to nocturnal oxygen desaturation in patients with chronic obstructive pulmonary disease. *Am J Med*. 1985;78(1):28-34.
56. Fletcher EC, Luckett RA, Miller T, Costarangos C, Kutka N, Fletcher JG. Pulmonary vascular hemodynamics in chronic lung disease patients with and without oxyhemoglobin desaturation during sleep. *Chest*. 1989;95(4):757-764.