Long-term Oxygen Treatment in Chronic Obstructive Pulmonary Disease: Recommendations for Future Research

An NHLBI Workshop Report

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Long-term oxygen treatment (LTOT) prolongs life in patients with chronic obstructive pulmonary disease (COPD) and severe resting hypoxemia. Although this benefit is proven by clinical trials, scientific research has not provided definitive guidance regarding who should receive LTOT and how it should be delivered. Deficiencies in knowledge and in current research activity related to LTOT are especially striking in comparison to the importance of LTOT in the management of COPD and the associated costs. The National Heart, Lung, and Blood Institute, in collaboration with the Centers for Medicare and Medicaid Services, convened a working group to discuss research on LTOT. Participants in this meeting identified specific areas in which further investigation would likely lead to improvements in the care of patients with COPD or reductions in the cost of their care. The group recommended four clinical trials in subjects with COPD: (1) efficacy of ambulatory O₂ supplementation in subjects who experience oxyhemoglobin desaturation during physical activity but are not severely hypoxemic at rest; (2) efficacy of LTOT in subjects with severe COPD and only moderate hypoxemia; (3) efficacy of nocturnal O₂ supplementation in subjects who show episodic desaturation during sleep that is not attributable to obstructive sleep apnea; and (4) effectiveness of an activity-dependent prescription for O₂ flow rate that is based on clinical tests performed at rest, during exercise, and during sleep.

Keywords: chronic bronchitis; hypoxia, therapy; lung diseases, obstructive; oxygen inhalation therapy; pulmonary emphysema

Chronic obstructive pulmonary disease (COPD) kills approximately 120,000 Americans each year (1). Disease prevention by smoking cessation is critical for the control of COPD because there is no cure for established disease. Nonetheless, there are four interventions that likely prolong the survival of patients with serious COPD. Retrospective studies suggest that pneumococcal and influenza vaccinations reduce mortality (2, 3). Intensive management of those hospitalized for acute exacerbations of COPD probably averts death in many gravely ill patients. In particular, there is apparent benefit from noninvasive positive-pressure ventilation in those with respiratory failure (4). Lung volume reduction surgery improves survival in selected patients

with severe emphysema (5). Finally, long-term oxygen treatment (LTOT) significantly reduces mortality in patients with COPD and severe resting arterial hypoxemia (6, 7). Of these interventions, LTOT has the greatest proven impact on public health. Prospective studies of immunizations are lacking, intensive care during hospitalization does nothing to diminish future risk of exacerbation, and lung volume reduction surgery is indicated for only a small minority of patients with COPD and is available at only a limited number of centers. On the other hand, LTOT is indicated for many patients with severe disease, yields robust effects on survival, and is widely available through a national network of suppliers and a Medicare coverage policy that is consistent with existing clinical trial data.

Despite the importance of LTOT in the management of COPD, there are many deficits in our knowledge regarding its mechanisms of action, indications for prescription, and effects on patient outcomes. For the most part, clinical decision making and insurance coverage policies today are both based on research performed in the 1970s. Little has been done in the past 20 to 25 years to refine or extend the results of early clinical trials, and there is remarkably little current research in this area. Recognizing the possibility that additional research may be needed to inform clinical decision making and insurance coverage policies, the National Heart, Lung, and Blood Institute (NHLBI) convened a working group entitled "Long-term Oxygen Treatment in COPD" in Bethesda, Maryland, May 10–11, 2004. Two other components of the Department of Health and Human Services cooperated with the NHLBI in planning this meeting: the Centers for Medicare and Medicaid Services (CMS) and the Agency for Healthcare Research and Quality (AHRQ). The CMS also commissioned the AHRQ to perform a technical review of prior research. The working group was charged with evaluating the current state of knowledge regarding LTOT, identifying research questions of clinical importance, and discussing technical issues that might influence the feasibility and design of LTOT trials. This report contains an overview of the discussions held during this meeting and gives specific recommendations that were made by these experts regarding needs and opportunities for future research.

CURRENT STATE OF KNOWLEDGE

Reasons for Patients with COPD to Receive LTOT

Clinical trials showing efficacy. Two carefully conducted, randomized, controlled clinical trials demonstrated beneficial effects of LTOT on survival in subjects with COPD and severe resting hypoxemia (6, 7). Similar inclusion criteria were used by both

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the Nocturnal Oxygen Therapy Trial (NOTT) and the Medical Research Council (MRC) study; and considered together, the results of these trials indicate a relationship between survival and the average daily duration of oxygen use. Median survival in those using O₂ for 18 hours/day was approximately twofold longer than in those receiving no O₂. Survival curves for O₂-treated subjects in subsequent uncontrolled studies have generally produced results that are consistent with the data from similarly treated groups of the NOTT and MRC studies (8–13).

Biological rationale. The use of O₂ in severe COPD makes sense. The main function of the lungs is exchange of respiratory gases. COPD primarily affects the lungs and can eventually impair the transfer of O₂ from the atmosphere to the blood. Hence, enhancement of blood oxygenation by increasing the fraction of O₂ in inspired air compensates for a major pathophysiologic consequence of late-stage disease. Although this logic is undoubtedly relevant, it may understate the biological advantages of LTOT in COPD. O₂ controls ventilation, regulates pulmonary blood flow, and modulates gene expression and cellular phenotype throughout the body (14–16). These diverse actions suggest that the benefits of LTOT may exceed the simple metabolic effects of improved O₂ delivery. Reductions in alveolar–arterial oxygen gradient (17) and pulmonary artery pressure (18) observed in severely hypoxemic patients with COPD who received chronic oxygen treatments suggest that oxygen may have a “drug effect” that involves remodeling or repair of the lung.

Potential for improvements in function and well-being. Although indications for LTOT are largely based on mortality data, some prior studies have also suggested improvements in other outcome measures, including depression, cognitive function, quality of life, exercise capability, and frequency of hospitalizations (19–27). The possibility of functional and clinical improvements in patients with COPD provides an additional, important motivation for the use of LTOT.

Reasons for Patients with COPD Not to Receive LTOT

Clinical trials showing no survival benefit. In contrast to the NOTT and MRC studies, trials reported by Górecka and colleagues and Chaouat and colleagues found no effect of LTOT on survival (28, 29). The important difference in these studies appears to be the inclusion of subjects with moderate, rather than severe, resting hypoxemia (typically meaning a resting arterial oxygen concentration between 56–60 and 65–69 mm Hg). Although neither study was powered to prove the absence of a meaningful effect on survival statistically, the striking similarity of results between treated and untreated groups strongly suggests that individuals with less severe COPD do not, as a group, derive any survival benefit from LTOT.

Theoretical possibility of toxicity. There is no evidence that LTOT, as normally administered, has any adverse effects in patients with COPD. Nonetheless, there are related observations that justify continued surveillance for possible adverse effects of LTOT, especially when it is considered for those with less severe disease. First, hyperoxia and fluctuations in inhaled oxygen content can produce severe retinopathy in preterm infants and newborn rodents (30, 31). Second, stepped increases in inhaled oxygen concentration produce acute increases in exhaled biomarkers of oxidative stress (32–34) and in a marker of airway inflammation (34). Third, there is growing appreciation that oxidative stress may contribute to the progression of COPD through stimulation of many molecular pathways that are believed to be involved in COPD pathogenesis (35). Collectively, these observations suggest that future studies should not ignore the possibility that toxic effects of O₂ may develop in some subjects. Toxic effects might be limited to individuals who have impaired capa-

bility of up-regulating antioxidant defense mechanisms or to those who use oxygen sporadically.

Cost. Total Medicare reimbursements for costs related to O₂ exceed \$2 billion/year and are increasing at an annual rate of 12 to 13% (unpublished data, CMS). This figure is a reasonable estimate of the cost of LTOT for patients with COPD in the United States, although it does not include all COPD-related use and does include some use of O₂ for other diseases. In a given year, approximately 1 million patients receive LTOT through the Medicare program (unpublished data, CMS). Despite the apparent absence of adverse effects, the high overall cost of LTOT argues that it should be prescribed only for patients in whom there is a reasonable expectation of clinical benefit. It is possible that research that refines the medical indications for LTOT could lead to substantial cost savings without compromising patient survival or well-being (36). Alternatively, further research might identify additional groups in which LTOT is beneficial, leading to increases in the costs of health care.

Inconvenience and embarrassment. Although many patients with COPD may not be swayed by negative reports in the scientific literature, theories of oxidative stress in COPD pathogenesis, or expenditures that comprise less than 1% of the total Medicare budget, most likely are influenced by the real inconveniences associated with LTOT. Nasal prongs are uncomfortable. Patients receiving O₂ from a stationary source are tethered to it, and this in itself may limit their activities of daily living. Many ambulatory sources are bulky and heavy, discouraging, if not preventing, ambulation by elderly patients and others with impaired strength and endurance. Although lighter, portable sources that use conserver technologies are becoming available, many patients do not have access to these more expensive devices and not all patients can be adequately oxygenated during exercise using devices that use conserver technology. Whether treatment using lightweight ambulatory oxygen supplies yields better patient outcomes than are obtained with heavier sources is an important issue that is currently being investigated by the COPD Clinical Research Network of the NHLBI. Finally, many patients may limit their use of ambulatory O₂ because of embarrassment, not wanting to be seen publicly with the recognizable stigma of smoking-related lung disease. In actual practice, these issues may limit the use of O₂ by those for whom it is prescribed, and thereby decrease the effectiveness of LTOT.

Reasons for Uncertainty regarding Prescription of LTOT to Particular Patients

Arbitrary nature of clinical guidelines. The NOTT and MRC studies are the only randomized trials to show a survival advantage in those receiving LTOT (6, 7). Those oxygen trial data have translated into clinical practice and Medicare coverage policies (Table 1) as a presumption that everyone who meets the inclusion criteria for NOTT will benefit from LTOT and that everyone who fails to meet those inclusion criteria will not benefit. In fact, the cut-offs for arterial oxygen concentration at 55 and 59 mm Hg originate from reasonable, prospective choices made during design of the NOTT and MRC trials and not from the analysis of data from these trials. Hence, the precision and detail of guidelines based on these inclusion criteria overstate their scientific basis. In addition, there are potentially significant differences between the subject population selected for the NOTT and patients eligible for LTOT under current CMS coverage policies. The NOTT protocol required prospective participants to meet the arterial oxygen criterion at least twice during a 3-week stabilization period before randomization. The number of subjects actually enrolled was only slightly greater than the number of potential subjects who were not randomized because of their repeat arterial oxygen measurement. Finally, a focus

TABLE 1. SUMMARY OF THE AVAILABILITY OF COVERAGE FOR LONG-TERM HOME OXYGEN TREATMENT UNDER MEDICARE

Measurement		Condition for Testing ¹		
Arterial O ₂ (mm Hg)	O ₂ Saturation (%)	At Rest	During Exercise	During Sleep
≤ 55	≤ 88	Available	Available ²	Available ³
56–59	89	<i>Available for dependent edema, pulmonary hypertension, or hematocrit > 56</i>		
≥ 60	≥ 90	Coverage available only by special approval		
Devices Covered		Stationary ± Ambulatory	Ambulatory ± Stationary	Stationary Only

Data from Reference 37. Data in *italics* represent conditions similar to the entry criteria of the NOTT and MRC studies, which showed effects of long-term oxygen treatment on survival in subjects with chronic obstructive pulmonary disease.

¹ While breathing room air in a chronic stable state or no earlier than 2 days prior to hospital discharge.

² Requires demonstration that supplemental O₂ improves the exercise-associated hypoxemia.

³ Also available for subjects who show a greater than normal fall in Arterial O₂ (> 10 mm Hg) or arterial O₂ Saturation (> 5%) during sleep with associated symptoms or signs reasonably attributable to hypoxemia.

on arterial oxygen concentration as the primary indication for LTOT, while intuitive, also reflects an *a priori* choice by NOTT and MRC investigators during study design. The usefulness of other measures of disease severity for predicting who will and will not benefit from LTOT has not been systematically addressed in clinical trials.

Paucity, size, and age of existing studies. Only four randomized controlled trials have measured effects of LTOT on mortality in patients with COPD (6, 7, 28, 29). These trials involved a total of only 501 subjects, and few participants were women. No positive results have been reported since 1981. Despite the thoughtful design, careful execution, and statistical significance of the NOTT and MRC studies, it is remarkable that millions of patients have been treated with LTOT, and billions of dollars are spent each year for that treatment, on the basis of data derived decades ago from only a few hundred subjects. The cohorts of the NOTT and MRC studies are unlikely to represent all patients, given the great heterogeneity of the COPD population.

Lack of knowledge regarding requirements for duration and timing of O₂ use. In the NOTT and MRC studies, the effects of LTOT on survival appeared to depend on the daily duration of treatment, with better outcome among subjects who received O₂ for more hours per day. There are several possible explanations for this finding. The total time that O₂ was inspired may be the important variable, in which case O₂ should perhaps be used around the clock, 24/7. Alternatively, longer use of O₂ may have prevented deleterious periods of desaturation during physical activity or sleep, and similar benefits might be obtained by providing supplemental O₂ for less total time but during intervals of greater demand. Another possibility is that greater availability of O₂ enabled more physical activity, and that exercise and conditioning were important mediators of enhanced survival. More complete information on the relationship between timing of LTOT and outcomes would assist clinicians in choosing how many hours per day, and perhaps which hours of the day, to prescribe oxygen. Optimization of hourly use could potentially maximize the therapeutic benefit and reduce the costs of LTOT.

Availability of a range of devices for O₂ administration. LTOT can be provided through stationary sources, portable sources such as an E-cylinder on a wheeled cart, or ambulatory sources that weigh less than 10 lb and can be carried. Although these alternative sources are not distinguished by Medicare reimbursement rates, they differ notably with regard to cost to the provider

and restrictions on mobility and activities of the patients. Few scientific data are available to guide physician recommendations regarding the manner of O₂ delivery.

IMPORTANT ISSUES FOR FUTURE RESEARCH

LTOT Efficacy in Patients with Moderate Resting Hypoxemia

Patients with COPD who demonstrate reduced PaO₂ when awake at rest but in whom hypoxemia is not severe enough to meet the entry criteria of the NOTT comprise a population that might benefit from LTOT. Three questions regarding this group have not been adequately addressed by prior research. First, would use of O₂ for times approaching 24 hours/day produce a survival benefit? The study of Górecka and colleagues (28), which found no effect on survival, involved an average O₂ use of only 13.5 hours/day. This duration of treatment may be inadequate, because patients with COPD who were acclimated to supplemental oxygen showed potentially adverse physiologic responses, including an increase in pulmonary vascular resistance, when switched to room air for as little as 3 hours (38). Second, would LTOT yield therapeutic benefits other than increased survival in this population? Possible benefits include decreased frequency of exacerbations and improved exercise capability, quality of life, and neuropsychologic function. Third, are there subgroups of patients with moderate resting hypoxemia who would benefit from LTOT? Subgroups might be identified by the presence of other characteristics associated with early mortality, such as pulmonary hypertension, low body mass index, poor exercise capability, frequent exacerbations, or comorbid cardiac disease.

Efficacy of LTOT in Patients Who Are Normoxic at Rest but Who Desaturate during Physical Activity

Another group of patients with COPD that might benefit from LTOT consists of those who are normoxic or only moderately hypoxemic at rest but who show substantial desaturation during physical activity. Many patients with COPD desaturate with minimal activity, and there are two possible rationales for O₂ use in these patients. The first is that episodic hypoxemia may in itself have adverse health consequences. Although data in COPD are lacking, it is known that exercise desaturation in normoxic subjects with interstitial lung disease is associated with shorter survival (39). A second rationale is that dyspnea associated with arterial hypoxemia during activity may discourage exercise, promote deconditioning, and thereby diminish quality and length of life. Although chronic studies have not been performed, it has

been shown that acute administration of supplemental oxygen improves ventilatory function and exercise endurance in subjects with advanced COPD (40). Neither rationale favors use of oxygen by these patients at rest, but this distinction may have little practical meaning in those with severe lung disease who desaturate with minimal physical activity, such as talking, eating, and grooming.

Efficacy of LTOT in Patients Who Are Normoxic when Awake and at Rest but Who Desaturate during Sleep

Patients with COPD who show substantial desaturation during sleep comprise another group in which LTOT might provide clinical benefit. Supplemental oxygen prevents transient arterial hypoxemia in a majority of subjects with COPD and nocturnal oxyhemoglobin desaturation (41), and data from one observational study suggest that there may be a survival benefit (42). Prevention of desaturations during sleep with nocturnal O₂ supplementation might reduce all-cause mortality by decreasing the physiologic stresses of repeated hypoxemia in seriously ill patients. Additional benefits might accrue from improved quantity and quality of sleep. It should be noted that this rationale for nocturnal O₂ supplementation applies only to those in whom desaturation results from the compounding effects of ventilatory deficits due to COPD and ventilatory depression as normally occurs during sleep. The rationale does not apply to patients with COPD and coexisting sleep apnea syndrome in whom other therapeutic approaches, such as continuous positive airway pressure ventilatory support, are indicated.

Optimal Timing and Dosage of Oxygen Supplementation

Prior studies have not addressed the optimal timing for O₂ use or the possibility of prescribed adjustments in flow rate. Although the combined data of the NOTT and MRC studies suggest that longer use of O₂ is beneficial, it is not known if use of O₂ for 24 hours/day would provide added benefit over use for 18 hours/day. Alternatively, if the benefit of LTOT in those with severe resting hypoxemia results not from the amelioration of resting hypoxemia but from prevention of further desaturation during physical activity and sleep, similar benefit might be achieved with episodic O₂ use. A logical generalization of episodic use would be to adjust O₂ flow rates according to what the patient is doing. With technological advances in pulse oximetry and accelerometry and electronic regulation of O₂ delivery, automated regulation of O₂ flow rates with time of day, subject activity, and O₂ saturation may soon be feasible. The benefit of an activity-dependent O₂ prescription has not been investigated.

Mechanisms of Action

Questions of who should get O₂ and how it should be delivered could be answered more readily if there were better understanding of why this therapy is beneficial. Very little is known regarding the relevant mechanisms of O₂ action. Many effects are possible, including prevention of hypoxic insult to critical organs, physiologic effects on perfusion, modulation of ventilation via neural pathways, suppression of pathogenetic processes in the lung, enhancement of host defense mechanisms, reduction of oxidative stress induced by hypoxia, and activation of repair and remodeling by structural cells of the lung. Studies of how various effects of supplemental O₂ improve health would aid research on the clinical use of LTOT and also improve general knowledge regarding the pathogenesis of COPD.

Clinical and Biochemical Predictors of Responsiveness to LTOT

Given the complexity of COPD, it is possible that patient characteristics other than PaO₂ may predict who will or will not benefit

from LTOT. Such characteristics might identify individuals for whom LTOT is currently indicated but who are unlikely to benefit. Complementary characteristics might identify individuals not eligible for LTOT by NOTT inclusion criteria who would benefit from LTOT. Measures that might be informative regarding LTOT efficacy include clinical characteristics and biomarkers related to the risk of mortality, pulmonary hemodynamics, acute responses to O₂ inhalation, biomarkers of oxidant-sensitive molecular pathways involved in COPD pathogenesis, and genetic factors that regulate endogenous antioxidant mechanisms.

Methods for Enhancing Adherence to LTOT

Average hours of daily O₂ use by subjects are typically less than is prescribed by their physicians or study investigators (6, 28, 43). Poor adherence to LTOT prescriptions may result from associated discomfort, inconvenience, embarrassment, mental confusion, or misunderstanding of the correct prescription. Given the apparent relationship between hours of O₂ use per day and survival, there is concern that voluntary underuse of O₂ by patients may limit the effectiveness of LTOT. Hence, worthwhile goals for future research include the development of better strategies for patient education and more tolerable methods for O₂ delivery, together with testing of these approaches to verify their effectiveness in improving the outcomes of patients receiving LTOT.

RECOMMENDED STUDIES

The working group identified four trials that are needed to inform clinical decision making with regard to LTOT.

Study 1: Oxygen Supplementation during Ambulation (Very High Priority)

A randomized, double-blinded efficacy trial is recommended to test the hypothesis that clinical outcomes are better in those who receive oxygen supplementation during ambulation in comparison to those who do not receive O₂ (air control). This study will include as subjects patients with COPD who are not severely hypoxemic when awake at rest (e.g., PaO₂ > 59 mm Hg) but show significant oxyhemoglobin desaturation (by transcutaneous oximetry) during controlled exercise. Oxygen or air will be provided during physical activity via a lightweight, portable supply. Possible key outcomes include quality of life, level of activity, and hours of oxygen use.

Study 2: Continuous Oxygen Supplementation in Patients with Moderate Hypoxemia (Very High Priority)

This unblinded efficacy trial will study patients with severe COPD who show evidence of hypoxemia at rest or during exercise but who do not meet the entry criteria of the NOTT trial (see Table 1) because their hypoxemia is sporadic or not sufficiently severe. Inclusion will be limited to subjects with a high risk of mortality (e.g., with severe airflow limitation or low body weight) and with clinical characteristics that are potentially responsive to oxygen treatment, such as severe dyspnea and diminished exercise capability. The hypothesis to be tested is that survival and quality of life differ between groups of subjects randomized to receive LTOT or usual care with regular monitoring of arterial oxygenation. LTOT will be initiated during the course of the trial in subjects of the latter group who develop consistent, severe hypoxemia.

Study 3: Nocturnal Oxygen Treatment of Desaturation during Sleep (High Priority)

A randomized, double-blinded efficacy trial is recommended in patients with COPD who are not severely hypoxemic when

awake at rest (e.g., $\text{PaO}_2 > 59$ mm Hg) but show oxyhemoglobin desaturation during sleep that is of significant degree and duration and is not due to obstructive sleep apnea. The hypothesis to be tested is that clinical outcomes are better in those who receive O_2 supplementation during sleep than in those who receive air in a similar manner.

Study 4: Detailed, Individualized Prescriptions for Long-term Oxygen Supplementation (High Priority)

This randomized, nonblinded effectiveness trial will test the hypothesis that clinical outcomes are better in subjects whose O_2 prescriptions (flow rates) are based on periodic clinical testing at rest, during physical activity, and when asleep in comparison to those whose O_2 prescriptions are based on testing that is performed only when the subjects are awake and at rest. The study population will consist of patients with COPD who qualify for LTOT by standard criteria.

METHODOLOGIC ISSUES

Outcome Measures

Given the widespread biological actions of O_2 , it is reasonable to hypothesize that LTOT may benefit patients with COPD in many different ways, including improvements in exercise capability, mood, cognitive function, quality of life, rate of exacerbations, sleep quality, and health care utilization, as well as survival. In general, to ensure a full appreciation of the effects of O_2 supplementation on patients with this disease, trials of LTOT should include as outcome measures a variety of tests of disease severity and physiologic and neurocognitive function. Measurements of biomarkers related to inflammation may also be of importance for understanding LTOT mechanisms of action. Hemodynamic measures are of considerable interest, but may be impractical in larger studies. Standard measures of COPD severity, such as spirometry and lung imaging, are potentially useful predictors of responsiveness, but are likely to remain unchanged by LTOT despite substantial treatment benefits by other measures.

Staged Approaches

Clinical research of LTOT should ultimately evaluate the effects of the treatment on mortality, either to quantify the survival benefit or to prove that other benefits (e.g., improved cognition, exercise capability, or quality of life) are not offset by a large decrease in survival due to some toxic effect of O_2 . However, the use of mortality as the primary endpoint in a clinical trial may require a larger number of subjects and a longer follow-up period than would a study of other outcome measures. Because of this, a staged approach may be most economical for evaluating many research questions regarding LTOT. An initial study that measures physical activity, exercise ability, cognitive function, quality of life, and O_2 utilization might be used to validate methods, demonstrate functional benefits, and obtain the data needed to estimate the sample sizes required for subsequent studies. A second, larger study could include mortality as the primary endpoint in a controlled test of the efficacy of the intervention. A third stage, of importance for LTOT, is an effectiveness trial that is conducted under conditions approximating the prescription habits for LTOT by primary care physicians. Subsequent effectiveness trials may be needed for Studies 1 and 3, recommended above.

Phenotyping

Because of the great heterogeneity of the population with COPD, extensive phenotyping is advisable in most clinical stud-

ies of this disease. Characteristics related to O_2 transport are especially relevant in studies of LTOT. These include such parameters as spirometric volumes, diffusing capacity of the lung for carbon monoxide (DL_{CO}), hematocrit, arterial blood gas concentrations, oxyhemoglobin saturation by pulse oximetry, and body mass. Ventilatory and blood gas parameters vary with time and activity in these subjects, and, in fact, values obtained during exercise and sleep may be most revealing of need for LTOT. Because of their poor lung function and increased work of breathing, oxygen levels in subjects with severe COPD may be highly responsive to activity and hence very sensitive to the methods used for clinical testing. LTOT investigators should take special care to develop detailed standardized procedures for exercise and sleep examinations, to define precise rules for their interpretation, to train laboratory personnel, and to control and ensure data quality.

Monitoring of Oxygen Use

Because of the apparent relationship between survival and the daily duration of O_2 use, it is of interest to quantify the actual hours that subjects use O_2 in clinical trials. Previously used methods, such as counting the number of O_2 tanks depleted, are prone to errors. Fortunately, recent advances in sensor technology (as used in O_2 -conserving supplies) and in data-logging circuits may allow more precise, long-term monitoring of actual O_2 usage by subjects. Such methods may prove of value in trials of LTOT.

Inclusion of Smokers

Many patients with severe COPD continue to smoke, and it is important to know whether LTOT is efficacious for continuing smokers. The question of including current smokers in trials of LTOT involves competing ethical concerns: although publicly funded research studies should not arbitrarily exclude any subgroup of the population, there are risks of burns to research subjects if they smoke while using O_2 due to oxygen's ability to enhance the combustion of an existing fire (44). Balancing these concerns is difficult. Most reports of burns are anecdotal, and quantitative risk estimates are not available. Subject education in "how to light a cigarette" might reduce the risk of serious burns, but such training could be construed as encouragement to continue smoking. Study designers should obtain ethical guidance at the local level on this issue.

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