Long-term Oxygen Therapy*

Robert H. Groves, Jr., M.D.;† William C. Bailey, M.D., F.C.C.P.;‡ and Scott E. Buchalter, M.D., F.C.C.P.§

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COT = continuous oxygen therapy; DME = durable medical equipment; CPaO₂ = ground level PaO₂; HAST = hypoxia-altitude simulation test; HCFA = Health Care Financing Administration; LTOT = long-term oxygen therapy; NOTT = Nocturnal Oxygen Therapy Trial Group

Long-term oxygen therapy (LTOT) is an important adjunct in the treatment of many hypoxemic patients. Appropriate prescription by the physician requires knowledge of the rationale for oxygen therapy, the indications for its use, and the appropriate delivery system for individual patients. Recommendations for use of LTOT should be guided by clear data, clinical judgment, and the consensus recommendations of many experts.

Recent emphasis on cost containment and new data regarding the benefits of oxygen therapy have prompted a reappraisal of oxygen utilization criteria. The following case will provide an appropriate clinical framework for the discussion of the foundations for and evolution of current utilization criteria.

Case Report

Dr. Buchalter: A 65-year-old woman presented to our institution complaining of worsening shortness of breath for one week in the setting of a five-year history of progressive shortness of breath and dyspnea on exertion.

She had been generally healthy as a child and young adult, with no history of respiratory problems or major medical illnesses. She related a 50-pack-year smoking history, and noted that approximately five years prior to hospital admission, she began to experience dyspnea on exertion, which, over time, progressed to dyspnea on walking approximately two blocks and eventually with any exertion. She denied chest pain, wheezing, cough, or sputum production, and had no peripheral edema.

One week prior to hospital admission, she developed symptoms of an upper respiratory tract infection, and she had a temperature of 37.7°C orally. A cough was productive of small amounts of yellow sputum. Over the ensuing week, she noted progressive shortness of breath, eventually at rest, and was referred for further evaluation.

Her medical history was pertinent for a history of successfully treated Graves' disease and there was a family history of coronary artery disease. She claimed no allergies and was receiving no medications.

On physical examination, she was awake, alert, oriented, and in moderate respiratory distress. Vital signs were as follows: blood pressure (BP), 110/40 mm Hg; pulse, 100 beats per minute and regular; and respiratory rate (RR), 22/minute with a prolonged expiratory phase. She was afebrile. Chest examination revealed moderate hyperinflation with diminished breath sounds in the bases, with some expiratory rhonchi. Cardiac examination revealed a slight accentuation of the pulmonary component of the second heart sound. Results of the remainder of her examination were unremarkable.

Laboratory evaluation revealed normal serum electrolytes, renal function, glucose, liver function tests, and thyroid function tests. Her complete blood cell count (CBC) was normal, except for a hematocrit of 49. Chest roentgenogram demonstrated marked hyperinflation with flattened hemidiaphragms, an increase in retrosternal air, and reduced vascular markings, all compatible with chronic obstructive pulmonary disease (COPD). Her ECG demonstrated P pulmonale.

Pulmonary functions test results were abnormal with an FEV₁ of 0.75 L, an FEV₁/FVC ratio of 56, and severe air trapping. Dco, corrected for alveolar volume, was 53 percent of predicted. Arterial blood gases, obtained during room air breathing, demonstrated a pH of 7.41, PaO₂ of 39 mm Hg, and PaCO₂ of 50 mm Hg.

Discussion

Rationale and Indications for LTOT

Dr. Groves: As early as 1798, oxygen was used to treat a variety of maladies in England. In the 1920s, Alvan Barach established the first routine use of oxygen in the United States, and he was also the first to design portable oxygen cylinders for ambulatory use. However, it was not until the late 1960s and 1970s that the benefits of low-flow oxygen therapy began to be widely appreciated, based on both clinical experience and a developing body of literature. In 1967, Levine et al. were among the first to examine the effects of LTOT. A small, uncontrolled study reported improved clinical status, increased exercise tolerance, reduction in secondary erythrocytosis, and a fall in pulmonary vascular resistance in patients with hypoxemic chronic airway obstruction.

In 1968, Abraham et al. reported a reduction in
pulmonary artery pressure, pulmonary vascular resistance, and hematocrit in six patients with hypoxemic COPD treated with one to four weeks of continuous ambulatory oxygen. In 1970, Neff and Petty expanded on the work of Levine et al by showing reduced mortality in hypoxemic patients with COPD and cor pulmonale when these patients were compared with historical controls.

These data suggested a direct relationship between hypoxemia, altered pulmonary hemodynamics, and subsequent poor survival. This hypothesis gained further support when Burrows et al published the results of a seven-year longitudinal study of patients with COPD, demonstrating an inverse relationship between pulmonary vascular resistance and survival.

In 1977, the American Thoracic Society Council approved a statement on oxygen administration in the home. It suggested that although there was no conclusive evidence that LTOT could prolong life, its potential benefit outweighed the potential hazards in patients with persistent evidence of arterial or tissue hypoxia.

These early studies and recommendations set the stage for two landmark studies. In 1980, the Nocturnal Oxygen Therapy Trial Group (NOTT) reported the results of a six-center randomized trial, comparing nocturnal oxygen therapy (NOT) with continuous oxygen therapy (COT) in 206 hypoxemic patients with COPD with a PaO2 of less than or equal to 55 mm Hg, or a PaO2 of less than or equal to 59 mm Hg with clinical evidence of secondary erythrocytosis or cor pulmonale. Patients with prior oxygen use or other complicating illnesses were excluded. At a mean follow-up of 19.3 months, mortality of patients with only nocturnal oxygen (approximately 12 h/day) was significantly higher (1.94/1.0) than that of patients with continuous oxygen (approximately 19 h/day).

Despite investigating a number of other issues prospectively, no clear factors could be identified to explain the mechanism for reduced mortality in the continuous oxygen group. Specifically, although the researchers showed small but significant decreases in pulmonary vascular resistance and hematocrit in the patients receiving COT as compared with the patients receiving NOT, comparisons between these two groups showed that matched patients without these beneficial effects also experienced similar improvement in survival. Nevertheless, this study demonstrated conclusively that in hypoxemic patients with COPD who met the study criteria, COT was associated with a significant reduction in mortality when compared with NOT.

A multicenter British Medical Research Council (BMRC) study was ongoing at the time of the NOTT report, and the results of their trial were subsequently reported in the Lancet in early 1981. The BMRC trial was a prospective, randomized study, evaluating 87 patients with chronic bronchitis or emphysema who, in addition to hypoxemia, demonstrated CO2 retention and/or a history of congestive heart failure (CHF), and thus, differed slightly from the patient group in the NOTT study. These patients were randomly assigned to receive standard therapy, and either 15 hours of nocturnal oxygen or no oxygen therapy. Over a three-year period, the no oxygen group had a mortality more than twice that of the oxygen-treated group.

These two studies established the efficacy of oxygen therapy in hypoxemic COPD. Since both studies involved similar patients, many researchers have created cumulative percentage survival curves using data from both studies (Fig 1). In sum, they suggest that NOT (12 to 15 h/day) is superior to no oxygen therapy, but that COT (approximately 19 h/day based on compliance data) provides an additional survival benefit.

Current guidelines for the use of LTOT are based primarily on these two landmark studies, and in the United States, hypoxia is defined by the same blood gas criteria as in the NOTT study (Table 1). In the patient under discussion, the initiation of oxygen therapy would be appropriate based on these criteria, and oxygen was prescribed for this patient continuously at the minimum liter flow to correct her PaO2 to at least 60 mm Hg.

**Figure 1:** Cumulative percentage survival data from both the NHLBI NOTT and British MRC studies of long-term oxygen therapy for hypoxemic COPD. Survival was improved with nocturnal oxygen for 12 to 15 h/day but not with nearly continuous oxygen therapy. (Adapted from Flenley DC, Petty TL [eds]. Recent advances in respiratory medicine, 4th ed. London: Churchill Livingstone; 1986; 218; with permission.) Dotted line = NOTT/COT; dashed line = NOTT/NOT; solid line = BMRC/oxygen; and dot-dash line = BMRC/controls.
Table 1—Guidelines for Prescribing Long-term Oxygen Therapy

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<td>A. The patient has underlying disease of the lungs, airways, or thoracic cage resulting in severe chronic hypoxemia not responsive to appropriate medical therapy.</td>
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<td>B. One of the following criteria has been met:*</td>
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<td>1. PaO₂ ≤55 mm Hg while breathing room air</td>
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<tr>
<td>2. PaO₂ of 56 to 59 mm Hg while breathing room air with clinical evidence of secondary tissue hypoxia such as cor pulmonale or erythrocytosis</td>
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*Selected patients without resting hypoxemia but in whom desaturation is documented during exercise or sleep may also require oxygen for these specific activities (see text).

Oxygen Storage and Delivery Systems

**Dr. Bailey:** For the prescribing physician, three oxygen delivery systems are currently available: compressed gas, liquid oxygen, and the oxygen concentrator. Indications and advantages for each system have been recently reviewed by Petty and Nolte. Compressed gas is probably the most widely available delivery system today. Cost is relatively low for stationary use. Its primary disadvantage is its weight and limited capacity. The typical standard E-cylinder weighs about 7.0 kg and stores only enough oxygen to last about 5 h at 2 L/min flow. This system is considered portable (by stroller) but is not truly best for ambulatory use. It must also be serviced frequently because of its limited capacity, and because transferring a smaller cylinder from a larger H- or K-cylinder is considered too dangerous and difficult for patients to accomplish.

In the liquid oxygen system, liquid oxygen is stored in a type of thermos flask at extremely cold temperatures. As a result, much less volume is required for a given amount of gas. A typical liquid oxygen container weighs about 4.0 kg and lasts about 8 h at 2 L/min flow. These containers can be easily filled from stationary units that weigh approximately 60 kg and that store enough O₂ to last about one week with flows of 2 L/min. The liquid system is truly ambulatory, since most patients are able to carry the device in a shoulder bag. The disadvantages are that liquid oxygen has limited availability, is more expensive, and patients who travel may find that their ambulatory reservoir cannot be filled through a different supplier source. Nevertheless, liquid oxygen is considered the system of choice for patients who pursue vigorous pulmonary rehabilitation or for any patient who is willing and able to be active and mobile outside the home. 

Oxygen concentrators work by separating oxygen from room air, usually by means of a molecular sieve. They require an electric current to operate, and as of yet, no lightweight, truly ambulatory system has been designed. A typical oxygen concentrator weighs about 15 kg and can be adapted to a 12-V current for automobile and hotel room use. Because of their reduced cost of operation, they have become quite popular, particularly with durable medical equipment (DME) suppliers. However, because they depend on electricity, a back-up system must always be available, and because they are not yet practical for ambulatory patients, any patient who must ambulate beyond about 15 meters should be provided with another system that will allow more mobility.

The patient presented remained active and ambulatory outside the home. Therefore, the lighter-weight, longer-lasting liquid oxygen system is the most appropriate method of delivery in her case.

**Clinical Course**

**Dr. Buchalter:** The patient was begun on a regimen of oral theophylline, ampicillin, and albuterol, and ipratropium by metered dose inhalers. Additionally, she was placed on a regimen of 2 L of oxygen via nasal cannula, which resulted in arterial blood gas levels of pH 7.43; PCO₂, 41 mm Hg; and PO₂, 72 mm Hg. She was strongly advised to discontinue smoking, which she successfully accomplished.

Eight weeks after presentation, she was clinically back to her baseline and pulse oximetry without oxygen demonstrated a saturation of >90 percent. Subsequent arterial blood gases obtained on room air demonstrated a pH of 7.42, PCO₂ of 37 mm Hg, and PO₂ of 68 mm Hg. Bronchodilator therapy was continued, but home oxygen therapy was stopped. She demonstrated continued stability of gas exchange over the ensuing six months.

**Stabilization and Follow-up**

**Dr. Groves:** At an eight-week follow-up evaluation, oximetry demonstrated a significant improvement in resting saturation, and based on this finding and confirmatory arterial blood gases, COT was withdrawn. It is important to establish when a follow-up evaluation should take place, and what criteria should prompt withdrawal of COT.

Both the NOTT study and a recent study by Levi-Valensi et al have demonstrated that a substantial number of patients (up to 45 percent) will no longer require oxygen therapy, based on previously outlined criteria, when tested approximately one to three months after initiation. This suggests that many patients improve gradually with aggressive therapy.

Although most experts agree that significant hypoxemia should be treated even in patients in whom further recovery is expected, it is advisable to document the continued need for oxygen between one and three months after therapy has begun. If the patient no longer meets the utilization criteria at this point, most experts also agree that COT can be stopped, assuming the patient is clinically stable and has no
other complicating illnesses. This same logic may not necessarily apply if the patient is tested more than three months after initiation of oxygen therapy. Some authors suggest that in this situation, improvement in oxygenation may be related to the reparative effects of prolonged oxygen therapy.\textsuperscript{11} Currently, no data exist to support or refute continuation of oxygen therapy in this situation.

Dr. Bailey: The issue of the appropriateness of oximetry in lieu of arterial blood gases in the re-evaluation process must also be addressed. It is the current expert consensus that a saturation of 88 percent or less corresponds best to a PaO\textsubscript{2} of 55 mm Hg or less.\textsuperscript{14,15}

Most experts maintain that oximetry alone is not accurate enough to establish the initial need for LTOT. Its use, however, may be appropriate in follow-up evaluations, as well as for the less clear situations of hypoxemia related to exercise or sleep.\textsuperscript{16,17}

In our case discussion, pulse oximetry demonstrating a saturation of >90 percent at the eight-week follow-up suggested that COT could be stopped, but since the discontinuance of oxygen therapy was a major decision (as is initiation of therapy), the clinician confirmed improvement with arterial blood gases.

Questions from the Audience

Question 1: The studies you have reviewed are clear with regard to the use of supplemental oxygen for patients with COPD, such as the one presented, who have hypoxemia at rest, but many hypoxemic patients in clinical practice will not fall into this specific category. Under what circumstances should oxygen be used other than continuously or in patients with diagnoses other than COPD?

Dr. Groves: It is true that the most convincing data on LTOT is specific to patients with COPD. However, oxygen delivery is a complex process, and the detrimental effects of chronic arterial or tissue hypoxia are unlikely to be specific to a given underlying illness. Furthermore, the mechanism leading to improved survival in the BMRC and NOTT studies is unclear. Therefore, most experts suggest that we apply the same criteria for prescription of oxygen to other causes of chronic arterial or tissue hypoxia, such as interstitial lung disease or abnormalities of the chest bellows such as kyphoscoliosis.\textsuperscript{9,14,18,19}

There are also some instances in which LTOT may be appropriate in patients with normal oxygen saturation at rest, but these issues remain somewhat controversial, particularly outside the United States. We will consider briefly three such situations: transient hypoxemia during sleep (but not obstructive sleep apnea syndrome or OSAS); hypoxemia during exercise; and hypoxemia during air travel.

Sleep desaturation not due to OSAS has been shown to occur in COPD, even in patients without daytime hypoxemia.\textsuperscript{30-33} A number of adverse consequences have been reported, including increases in pulmonary artery pressures, electrocardiographic abnormalities, and evidence of end-organ hypoxia.\textsuperscript{32,34}

Current postulates are that nocturnal desaturation may lead to irreversible pulmonary arterial hypertension and cor pulmonale.\textsuperscript{36,37} Based in part on these assumptions, most clinicians in the United States prescribe supplemental oxygen to relieve nocturnal desaturations, assuming the patient is optimally treated otherwise.\textsuperscript{19,26}

Exercise desaturation is another area of interest and controversy. Several authors have shown improved exercise performance with supplemental oxygen in patients with chronic respiratory diseases.\textsuperscript{2,28-31} These and other studies suggest that oxygen administration during exercise will lower pulmonary artery pressure and pulmonary vascular resistance, and reduce ECG abnormalities. These data and the recent emphasis on pulmonary rehabilitation to improve patient mobility and quality of life have led many experts to suggest that oxygen should be supplemented for most patients with documented exercise desaturation to 88 percent or less.\textsuperscript{14,18}

Dr. Bailey: As an additional consequence of the recent emphasis on patient rehabilitation and mobility, physicians may be asked to advise patients with COPD on the relative safety of air travel. Although modern commercial airplanes are pressurized, routine air travel may involve altitude exposures that are the equivalent of over 8,000 feet, and this may subject many chronically hypoxemic patients to transient hypobaric hypoxemia.\textsuperscript{32}

Traditional contraindications to air travel have included vital capacity less than 50 percent predicted; maximum voluntary ventilation less than 40 L/min, respiratory acidosis, or a PaO\textsubscript{2} of less than 50 mm Hg.\textsuperscript{33} Recent clinical studies, summarized below, have added to the clinician’s ability to advise patients with chronic hypoxemia on the safety of air travel.

In 1978, Graham and Houston\textsuperscript{34} demonstrated that a few patients with mild to moderate COPD tolerated an altitude of 6,300 feet for four days reasonably well. Baseline resting PaO\textsubscript{2} decreased from 66 to 54 mm Hg. No severe adverse consequences were reported.

In 1984, Gong et al\textsuperscript{35} studied 22 patients with COPD and developed a hypoxia-altitude simulation test (HAST) by administering hypoxic gas mixtures equivalent to P\textsubscript{1O}2 at 5,000, 8,000, and 10,000 feet. They found that the best predictor of altitude PaO\textsubscript{2} was ground level PaO\textsubscript{2} (GPaO\textsubscript{2}). GPaO\textsubscript{2} of 68 and 72 mm Hg predicted >90 percent of patients with an altitude PaO\textsubscript{2} of greater than 55 mm Hg at 5,000 feet of >50 mm Hg at 8,000 feet, respectively. From their
HYPOXIA-ALTITUDE SIMULATION TEST

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FIGURE 2: Nomogram for predicting altitude PaO_2 (5,000 to 10,000 feet) in normocapnic patients with COPD at sea level. A straight line connecting sea level PaO_2 and the anticipated altitude will intersect the altitude PaO_2 at the appropriate value. (From Gong et al.74 with permission.)

data, they also developed a nomogram for the prediction of PaO_2 at altitudes of 5,000 to 10,000 feet (Fig 2).

Dillard et al.16 recently added to these data by using a hypobaric chamber to expose patients with COPD for 45 minutes to a simulated altitude equivalent of 8,000 feet. Their findings suggested an additional benefit in predicting altitude PaO_2 by including the preflight FEV_1 in their predictive equation. Both Dillard and Gong caution that their results apply only to nonexercising, nonhypercapnic patients with COPD, without other underlying diseases.

A recent editorial suggests that predictions of altitude PaO_2, based on GPaO_2 alone or GPaO_2 and FEV_1, are primarily screening procedures, and that patients with complicating illnesses, borderline GPaO_2, or those with diseases other than COPD, should undergo an altitude stress test, in either a pulmonary function laboratory or hypobaric chamber. Further, although the clinical consequences of hypobaric hypoxia as they apply to air travel are unknown, Gong77 states that the minimum desirable in-flight PaO_2 should be 50 mm Hg.

Practically speaking, arrangement for in-flight supplemental O_2 is not simple. Most carriers will not allow patients to carry their own oxygen aboard, and airline-supplied delivery systems differ within the industry. Arrangements must be made well in advance, and often according to different guidelines for each airline carrier.

Question 2: In keeping with the recent emphasis on cost containment, how will Medicare and third-party reimbursement practices affect our decisions with regard to prescribing LTOT?

Dr. Buchalter: This is certainly an important question, and one that deserves the attention of every physician involved in the care of chronically hypoxemic patients. The Health Care Financing Administration (HCFA) classifies home oxygen therapy as durable medical equipment (DME). This definition allows reimbursement by Medicare. Reimbursement policies have generally paralleled recommendations of experts in the field.

In 1984, a panel of 28 expert participants convened for the first ACCP-NHLBI Conference on Oxygen Therapy, during which issues related to home oxygen therapy were addressed.6 In a subsequent consensus conference at the Webb-Waring Lung Institute in 1986, investigators and clinicians addressed the specific issue of home oxygen therapy and problems related to the Medicare guidelines in place at that time.14

The recommendations of a follow-up consensus conference were reported in 1988,14 and many of these recommendations have since been adopted, although several problem areas remain, particularly in DME supplier reimbursement practices.

At the present time, oxygen is reimbursed on a flat rate basis by Medicare, regardless of the type of system or the prescribed liter flow; as long as it falls between 1 and 4 L/min. For liter flows greater than 4, or less than 1 L/min, a 50 percent increase or reduction in reimbursement is allowed, respectively. Only a small add-on is allowed for portable systems. Thus, the DME supplier is penalized for providing the more expensive ambulatory oxygen systems.

In addition, inconsistency in adherence by physicians to guidelines for prescribing oxygen therapy has created some problems. Recent government audits have estimated that perhaps one third of patients with home oxygen either did not meet standard criteria or did not require oxygen to the extent billed.3 Some physicians allowed DME suppliers to assume the responsibility for documenting medical necessity and the type of delivery system needed. As a result of these findings, further HCFA recommendations have been made that will increase both the complexity of the prescription form and physician accountability for signatures on Certificates of Medical Necessity.

The decision to provide LTOT should be based on physical, psychological, social, and regional factors, as well as cost. This is especially important since current DME supplier reimbursement policies provide a powerful incentive to prescribe the least expensive delivery method available.

The Third Oxygen Consensus Conference held recently in Washington, DC, addressed these reimbursement problems and further recommendations.
were made.11 This conference emphasized that since third-party payers are increasing the complexity of reimbursement requirements, and since reimbursement policies are not always in the patient’s best interest, it is incumbent on the medical profession to educate physicians about the rational use of LTOT. We must remain active advocates for quality patient care and maintain control of prescribing authority so that it is based on sound clinical judgment and not on reimbursement policies. Proper evaluation, documentation, and follow-up will be required of all prescribing physicians if we are to meet this goal.

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