Oxygen Therapy in COPD

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Long-term oxygen therapy (LTOT) at home has been demonstrated to improve survival in patients with COPD and severe resting hypoxemia. Support for LTOT is based on 2 landmark trials published nearly 4 decades ago. These results form the basis for reimbursement and prescription of LTOT to this day. Recent work has demonstrated no outcome benefit of LTOT in stable COPD patients with moderate desaturation at rest or during activity. Oxygen therapy during activity and exercise has been shown to alleviate symptoms and maintain arterial oxygen saturation, but not improve long-term outcomes. Oxygen therapy in COPD has a number of physiologic, functional, and biologic effects, not all of which are completely understood. Oxygen therapy in exacerbations of COPD can be both helpful and harmful. New guidance on the use of oxygen therapy during pre-hospital care has been published in the United Kingdom. Technology for LTOT represents a challenge for physicians writing prescriptions, durable medical equipment suppliers, caregivers, and patients. New technology for automated control of LTOT shows promise but is hampered by regulatory processes and cost pressures. Recent changes in government reimbursement for home oxygen therapy also present challenges. This paper will review the current evidence regarding LTOT in COPD and the impact on mortality and functional outcomes as well as reviewing technological challenges. *Key words: COPD; long-term oxygen therapy; oxygen concentrator; oxygen; quality of life.* [Respir Care 2018;63(6):734–748.

Introduction

Long-term oxygen therapy (LTOT) is a common pharmacologic treatment for COPD. Estimates from government records suggest that more than one million Medicare recipients receive oxygen at home. Medicare costs for this therapy exceed $2 billion dollars/year in the United States.[1,2] The evidence base for LTOT in COPD is nearly 4 decades old, and data from these initial trials are still used as a basis for prescription and treatment.[3,4] More recent trials are plagued by small numbers and physiologic end points, not outcomes. The use of oxygen in stable COPD with periodic hypoxemia associated with activity has provided the necessary data in defining the role of oxygen in this population.[5] The role of oxygen in COPD exacerbation has the ability to be therapeutic and toxic. Important data, primarily from the United Kingdom, have shed important light on this issue.[6] Technology for oxygen therapy can be confusing for physicians, caregivers, providers, and patients. New technology for LTOT might prove beneficial, but cost constraints and reimbursement have limited innovation.

This paper will review the large trials in support of LTOT in COPD with hypoxemia at rest as well as data from new trials, discuss the physiologic impact of oxygen therapy, evaluate LTOT in exertional hypoxemia, and discuss oxygen use during COPD exacerbation and technological issues related to home oxygen therapy. Emphasis will be placed on new data since the last comprehensive review on this subject by Criner.[7]

LTOT in COPD With Severe Hypoxemia

LTOT in COPD patients with resting hypoxemia, defined at $P_{aO_2} < 55$ mm Hg or < 59 mm Hg with evidence of right heart strain or polycythemia, improves survival. Two classic trials from the 1970s, the Nocturnal Oxygen Treatment Trial (NOTT)[3] and the Medical Research Council (MRC) Trial,[4] form the basis for LTOT. The current qualifications for LTOT used by Medicare are based on these studies. Table 1 provides the current recommendations for continuous delivery of home oxygen.

The NOTT enrolled 203 subjects with COPD and hypoxemia at rest. Subjects were randomized to receive either continuous oxygen therapy or 12 h of nocturnal oxygen therapy. The primary outcome at 12 months was mortality. Additionally, pulmonary vascular pressures, neuropsychological function, and quality of life were determined at 12 months. Mean survival for the entire cohort was a mean of 19.3 months. At the 1-year follow-up, mortality was 11.9% in the continuous oxygen therapy group and 20.6% in the nocturnal oxygen therapy group. At 24 months, the mortality was 22.4% in the continuous oxygen therapy group and 40.8% in the nocturnal oxygen therapy group, nearly a 2-fold difference. The continuous oxygen therapy cohort had a greater reduction in hematocrit and pulmonary vascular resistance at 12 months. Other outcomes measures, including FEV_1, lung volumes, gas exchange, and lung volumes, were not different between groups.[3] A lack of change in lung function indices is consistent with the progressive, irreversible nature of COPD.

The MRC trial[4] was performed in the United Kingdom and enrolled 87 subjects with chronic bronchitis or emphysema with severe hypoxemia at rest and carbon dioxide retention. All subjects had irreversible air-flow obstruction, determined by FEV_1 and evidence of elevated pulmonary artery pressures (cor pulmonale). Subjects were randomized to either no supplemental oxygen (control group) or 2 L/min of nasal oxygen for at least 15 h/d. Mortality rate was 67% (30 of 45) in the control group and 45% (19 of 42) in the oxygen therapy group after 5 years. Mortality was associated with elevated hematocrit and elevated baseline P_{aCO_2}. Additionally, subjects in the oxygen therapy group had slower deterioration in gas exchange and pulmonary vascular pressures.

Although these studies are commonly considered together, there are important differences in the inclusion/exclusion, treatment, and follow-up measures. Subjects in the MRC study had a greater severity of illness along with hypercarbia and/or cor pulmonale. Subjects in the MRC study were also more likely to continue to smoke during the trial. In some respects, the treatment group in the MRC trial (12 h of oxygen/d) was similar to the nocturnal oxygen group in the NOTT trial. Table 2 compares the 2 trials and highlights differences in therapy and outcomes.

Taken together, the NOTT and MRC trials demonstrate that the dose of oxygen is important. Both the nocturnal oxygen treatment group from NOTT and the treatment group in MRC had a shorter duration of oxygen exposure compared with the continuous oxygen group in NOTT. Importantly, only the patients receiving continuous oxygen therapy demonstrated decreases in hematocrit and pulmonary vascular resistance. Comparing the control group of MRC (no oxygen) with the continuous oxygen therapy

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Table 1. Current Medicare Requirements to Qualify for Home Oxygen Therapy

Resting $P_{aO_2} \leq 55$ mm Hg or $S_{aO_2} < 88\%$
Resting or exertional P_{aO_2} 56–59 mm Hg or S_{aO_2} with any of the following: Dependent edema P pulmonale on ECG (P wave exceeding 3 mm in standard lead II, III, or AVF) Polycythemia (hematocrit > 56%)
$P_{aO_2} \leq 55$ mm Hg or $S_{aO_2} \leq 88\%$ during exertion and documented improvement of hypoxemia during exertion with oxygen
When the patient is tested during sleep, if $P_{aO_2} \geq 56$ mm Hg or $S_{aO_2} \geq 89\%$ while awake and additional testing shows P_{aO_2} (55 mm Hg or S_{aO_2} (88% for at least 5 min taken during sleep or decrease in $P_{aO_2} > 10$ mm Hg or a decrease in $S_{aO_2} > 5\%$ from baseline for at least 5 min associated with symptoms or signs reasonably attributed to hypoxemia (eg, impaired cognition, nocturnal restlessness, insomnia) P_{aO_2} 56–59 mm Hg or S_{aO_2} 89% for at least 5 min with any one of the following: dependent edema, P pulmonale on ECG (P wave exceeding 3 mm in standard lead II, III, or AVF), or polycythemia (hematocrit > 56%)

From Reference 71.
ECG = electrocardiogram

group of NOTT, subjects receiving oxygen had a 2-fold increase in median survival.

Further evidence for continuous LTOT comes from work in the 1980s.[9,10] Weitzenblum et al[9] evaluated the impact of continuous oxygen therapy on pulmonary hemodynamics in COPD subjects with resting hypoxemia. They performed 3 right heart catheterizations in 16 subjects at baseline (mean 47 months before start of LTOT), just before the start of LTOT and after an average of 31 months of LTOT. Oxygen was prescribed for 15–18 h/d. They demonstrated that from baseline to the initiation of LTOT, there was a worsening of oxygenation and a rise in pulmonary artery pressures. Following LTOT, pulmonary artery pressures fell as a consequence of a decrease in pulmonary vascular resistance. Without oxygen, pulmonary pressures increased by 1.5 mm Hg/y, whereas during LTOT, pulmonary pressures fell by 2.1 mm Hg/y. These data nicely describe the impact of oxygen therapy on the progression of pulmonary hypertension.[9]

A second study enrolled 90 COPD subjects and performed serial right heart catheterizations for up to 6 y (75 subjects lived 2 y; only 16 were studied at year 6). They reported that LTOT resulted in a reduction in pulmonary artery pressures over the first 2 y, followed by a return to initial values and stabilization over the ensuing 4 y. Importantly, LTOT was associated with a fall in right heart pressures, but gas exchange and air-flow obstruction continued to deteriorate.[10]

Table 2. Comparison of the Nocturnal Oxygen Treatment Trial and the Medical Research Council Trials

Parameters	NOTT 1980[3]	MRC 1981[4]
Age, y	>35	42–69
Subjects, *n*	203	87
Male, %	73–80	76
Baseline FEV_1	29% predicted	0.58–0.75 L
Baseline P_{aO_2}, mm Hg	51	49–52
Baseline P_{aCO_2}, mm Hg	43	55–60
Baseline mean pulmonary artery pressure, mm Hg	30	32–35
Intervention	Nocturnal oxygen vs continuous oxygen	No oxygen vs oxygen >15 h/d including during sleep
Average oxygen use per day, h	12 ± 2.5 vs 17.7 ± 4.8	0 vs 15
Smoking status, %	Not reported	25–52%
Outcomes	Mortality, quality of life, hemodynamics: right atrial pressure, right-ventricular stroke volume index, pulmonary artery pressure, pulmonary vascular resistance pulmonary wedge pressure, cardiac index, stroke volume index	Mortality, 5-y mortality (19 of 42 with oxygen, 30 of 45 without oxygen), FEV_1, FVC, P_{aO_2}, P_{aCO_2}

From Reference 8.
NOTT = Nocturnal Oxygen Treatment Trial
MRC = Medical Research Council

These data, which are the basis for the use of ambulatory oxygen at home demonstrate a reversal of hypoxemia with supplemental oxygen, improved survival, and a salutary effect on pulmonary vasculature resistance. These findings only apply to subjects with COPD and resting hypoxemia and unfortunately are dated. The impact of changes in the care of COPD patients in the last 40 years suggests that perhaps LTOT be revisited. Funding for such a project seems unlikely. At present, however, the data clearly support the use of continuous oxygen therapy over nocturnal oxygen therapy to achieve the desired benefits.

LTOT in COPD With Moderate Hypoxemia

Improvements in outcomes in severe hypoxemia have raised the question of earlier use of LTOT in moderate hypoxemia. This is a common theme in medical practice, earlier intervention of a successful therapeutic option (eg, early steroids or early high-frequency ventilation in ARDS). Two important trials have failed to demonstrate any survival impact of LTOT in moderate hypoxemia. Both of these trials applied LTOT in subjects with $P_{aO_2} > 56$ mm Hg and provided oxygen for an average of 13 h compared with a control group not receiving oxygen. Subjects were followed for 3–7 y.[11,12] Criner[7] has noted that the duration of oxygen delivery in these subjects may have been insufficient to achieve the desired goals compared with the NOTT and MRC trials.

Haidl et al[13] conducted a randomized controlled trial of 2 L/min of oxygen versus no oxygen in a group of COPD subjects with severe lung dysfunction but normoxemia. Subjects received oxygen for 15 h/d. At 12-month follow-up, subjects receiving oxygen had improved exercise endurance and had reduced post-exercise dyspnea, but survival was unchanged. These findings are impacted by the small sample size ($N = 28$) and short period of observation. A meta-analysis of data from these trials demonstrated no improvement in survival in COPD subjects with moderate hypoxemia.[14]

These data do not support the use of LTOT in moderate hypoxemia, but this population is often prescribed home oxygen therapy. Drummond et al[15] analyzed data from the National Emphysema Treatment Trial (NETT) and found that a third of patients with severe disease without resting hypoxemia received home oxygen. In addition, those subjects receiving oxygen despite normoxemia experienced a higher mortality than those who did not receive oxygen. Similar findings were reported in the COPDgene study,[16] where 14% of subjects were prescribed oxygen. This study included 1,060 subjects, 92% of whom did not have resting hypoxemia.[16] These findings demonstrate a disconnect between the evidence supporting LTOT and those subjects likely to be prescribed home oxygen therapy.

Despite the lack of support for LTOT in moderate hypoxemia, clinicians continued to have unanswered questions related to when to use oxygen therapy in the absence of resting hypoxemia. Specifically, did subjects with exertional desaturation or nocturnal desaturation benefit from oxygen therapy? The difference between evidence and practice was the impetus for the Long Term Oxygen Treatment Trial (LOTT).[5]

The LOTT trial was originally designed to enroll subjects with moderate hypoxemia ($S_{pO_2} = 89–93\%$), but poor recruitment led to expanding inclusion criteria to subjects with moderate exercise-induced hypoxemia. Moderate exercise-induced desaturation was defined as an $S_{pO_2} < 90\%$ for ≥ 10 s and $S_{pO_2} \geq 80\%$ for ≥ 5 min during the 6-min walk test. An additional outcome of time to first hospitalization was implemented at this time. Oxygen was titrated at baseline while subjects walked and annually for the duration of the trial. Subjects were randomized to receive either no oxygen or oxygen. Within the oxygen group, subjects with resting desaturation received continuous therapy 24 h/d, and those with exercise-induced desaturation received oxygen during exercise and at night. The primary outcome of LOTT was time to death and all-cause hospitalization. Secondary outcomes included 6-min walk distance, incidence of exacerbations, health-related quality of life measures, and symptom burden.

During the 6-year study, 738 subjects from 42 centers were enrolled. No differences were found between the oxygen and no oxygen groups in time to death or first hospitalization or the rates of hospitalizations or COPD exacerbations. There were also no differences in the 6-min walk distance, lung function, or health-related quality of life measures. The authors concluded that in subjects with stable COPD and resting or exercise-induced oxygen desaturation, LTOT did not provide a mortality benefit or any sustained benefits in other outcomes.

Criticisms of the LOTT trial include concerns related to both selection bias and performance bias. Selection bias may have limited subjects currently using LTOT from participating; presumably, these subjects may have already been benefiting from oxygen therapy. Performance bias may have impacted outcomes, as subjects only used oxygen for an average of 13.6 h/d.[17] This duration of oxygen use was similar to that for the subjects using nocturnal oxygen in the NOTT study.[3] The results of the LOTT trial again put the evidence and clinical practice at odds. Clearly, the response to LTOT is variable among individual patients with respect to symptom relief, beyond measures of mortality.

An accompanying editorial by Ekström[18] provides a practical approach to the use of oxygen therapy in COPD patients with moderate exertional hypoxemia and dyspnea. He suggests that these patients be evaluated using a blinded exercise test while breathing either air or oxygen. If there

is no benefit during the test or in the next few days, then the therapy is discontinued.[19] He also suggests that if benefit is demonstrated, the therapy should be covered by insurance. Finally, he reiterates that LTOT should not be routinely prescribed in patients with mild or moderate hypoxemia at rest or during exercise.[18]

In the short time since the publication of LOTT, a number of authors have made recommendations regarding oxygen therapy in this patient group.[20-22] The concept of the *n* of 1 experiment for COPD subjects with exercise-induced moderate hypoxemia makes sense. However, the cost of these evaluations must be considered against the fact that a short-term improvement in S_{pO_2} may not result in positive changes in quality of life. Hatipoğlu and Stoller[17] suggested that in the group amenable to a trial of oxygen therapy titrated during a walk test, following symptom burden after several months can help identify those who benefit.

LTOT for Exertional Desaturation

Results of the LOTT in part answer the questions related to the use of LTOT for exertional hypoxemia.[5] Similarly, the re-evaluation of the NETT provides supporting evidence that there are no long-term outcome benefits to oxygen therapy for exertional hypoxemia.[15] However, there are several papers that have advocated for oxygen therapy in this setting.[23-26]

McDonald et al[23] evaluated 26 subjects with severe COPD but only mild hypoxemia (mean P_{aO_2} = 69 mm Hg) while receiving either air or oxygen during a 6-min walk test. Subjects had used either air or oxygen during activity for 12 weeks before assessments. In this randomized, blinded trial, oxygen therapy was associated with an increase in 6-min walk distance but no difference in dyspnea or quality of life measures.

Eaton et al[24] studied 41 subjects with COPD, mild hypoxemia, and significant exercise desaturation (S_{aO_2} 82%) in a double-blind randomized trial. Subjects received air or oxygen during exertional dyspnea for 12 weeks. They reported improvements in quality of life scores and reductions in anxiety and depression in the group receiving oxygen. Two additional studies identified increased 6-min walk distance[25] but no changes in quality of life measures[25,26] comparing air with oxygen in a double-blind randomized fashion.

Importantly, oxygen therapy may positively impact both dyspnea and exercise intolerance in COPD.[27-35] These are short-term physiologic effects and may not predict outcomes or need for continuous oxygen therapy. Oxygen therapy may improve exercise tolerance by reducing minute ventilation and therefore air trapping, improving muscle function, by increasing oxygen delivery, reducing pulmonary artery pressures, and alleviating dyspnea.[7] Answers related to the role of oxygen therapy during exercise are obfuscated by variable trial designs, different exercise training regimens, and small numbers of subjects studied. A meta-analysis of oxygen during exercise concluded that COPD patients may exercise longer and at a greater intensity with less shortness of breath when using oxygen therapy. This analysis was limited to 3 small trials and could not identify the characteristics of subjects likely to benefit from oxygen therapy.[25]

LTOT for Nocturnal Desaturation

Nocturnal oxygen desaturation is a common occurrence in COPD patients, occurring in just under half of all patients.[36,37] Nocturnal oxygen desaturation is defined as an $S_{pO_2} < 90\%$ for $> 30\%$ of the time during nocturnal oximetry. Nocturnal oxygen delivery improves oxygenation and may limit cardiac arrhythmias and help prevent elevations in blood pressure.[38,39] These observations are, however, 40 y old and probably should undergo further investigation.

The data on impact of oxygen on sleep quality are mixed.[40,41] It was hypothesized that nocturnal oxygen desaturation was an etiology for progressive increases in pulmonary artery pressures and subsequent cor pulmonale.[42,43] However, data regarding pulmonary artery pressures in COPD refute this initial suspicion. Despite this evidence, the Medicare guidelines for home oxygen therapy include a provision of nocturnal oxygen desaturation.

Studies directly evaluating the impact of oxygen therapy on mortality are few.[11,44-46] Cumulatively, these studies demonstrate no improvement in mortality with up to 3 y of nocturnal oxygen therapy. Studies are mixed with regard to changes in pulmonary artery pressure, showing either no difference or a small decrement compared with air. The paucity of recent data from quality studies has spurred new investigation. Lacasse et al[46] have proposed a double-blind placebo-controlled trial to study the role of oxygen therapy in COPD subjects with nocturnal oxygen desaturation using all cause 3-y mortality as the primary end point (ClinicalTrials.gov registration NCT01044628). The review by Owens[47] covers the role of oxygen during sleep across a range of maladies in great detail and is recommended reading.

Oxygen for COPD Exacerbation

The potential consequences of high-flow oxygen in the presence of COPD were described over 50 years ago by Campbell in a seminal paper in The Lancet.[48] Campbell observed that high levels of inspired oxygen resulted in hypercapnia due to respiratory depression, and although the observation was correct, the mechanism was not fully understood. Work by Milic-Emili and colleagues suggested

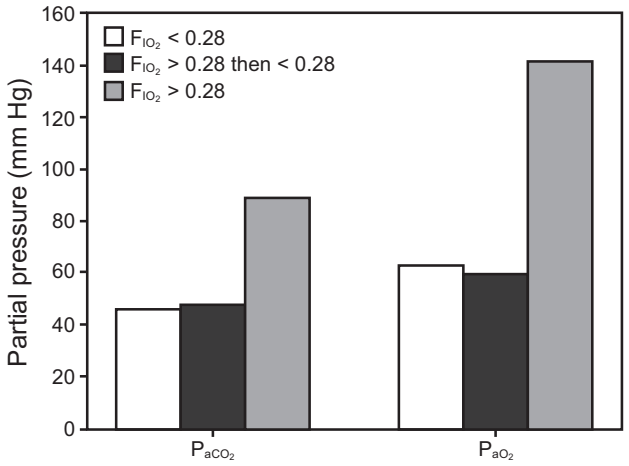

Fig. 1. Changes in P_{aCO_2} and P_{aO_2} during pre-hospital oxygen delivery at $F_{IO_2} \leq 0.28$, initial $F_{IO_2} \geq 0.28$ changed to ≤ 0.28, and $F_{IO_2} \geq 0.28$. From Reference 53.

that alterations in ventilation-perfusion matching resulting from loss of adaptive regulatory mechanisms were responsible for hypercarbia.[49-51] Impressively, over half a century ago, Campbell[48] suggested that patients with acute on chronic respiratory disease should receive oxygen that allows the inspired concentration to be controlled within limits of ± 1% over a range of 24–35%.

A number of trials have evaluated the role of pre-hospital oxygen use in COPD patients. Durrington et al[52] evaluated pre-hospital oxygen delivery in the United Kingdom in rural areas where transport times are commonly longer than 30 min. They hypothesized that with prolonged transport times, the impact of excess oxygen delivery might be fully elucidated. A retrospective review of subjects admitted with COPD exacerbations was undertaken, followed by a second review after training in appropriate oxygen usage. During training, caregivers were instructed to use an air-entrainment oxygen mask at an F_{IO_2} of 0.28 for initial management. Subjects in the initial phase receiving an $F_{IO_2} > 0.28$ had a greater incidence of acidosis, hypercarbia, and hyperoxia (Fig. 1). Subjects receiving higher oxygen flows were more likely to have a complicated hospital course, more likely to receive aminophylline, noninvasive ventilation, and invasive ventilation. The high-flow oxygen group also had a higher mortality rate.

A study of COPD exacerbations admitted to the emergency department from New Zealand showed similar outcomes.[54] They found that hyperoxemia occurred in nearly a quarter of all admissions and that the number of adverse outcomes was significantly greater compared with normal oxygenation (odds ratio 9.1, 95% CI 4.08–20.6). Hypoxemia was also associated with adverse outcomes (odds ratio 2.16, 95% CI 1.11–4.20). Hyperoxia was defined as an $S_{pO_2} > 96\%$, and hypoxemia as an S_{pO_2} of $< 88\%$.

OXYGEN ALERT CARD

Patient's Name _____

I am at risk of respiratory failure with a high CO_2.
Please use a 28% Venturi mask to maintain my S_{pO_2} between 89% and 92% if I am ill.
If I need nebulizer treatments, use room air to operate the nebulizer and deliver oxygen via nasal cannula at 2 L/min.

Fig. 2. Proposed example of an oxygen alert card that can be provided to patients with chronic respiratory disease at risk for hypercarbia. This includes patients with COPD as well as those with neuromuscular disease and obesity hypoventilation syndrome. From Reference 53.

These findings make a strong case for the use of titrated oxygen delivery in the patient with COPD.

Austin et al[55] compared high flow 100% oxygen versus titrated oxygen treatment in a group of subjects admitted with COPD exacerbation. Mortality was 9% (11 of 117) in the high-flow oxygen group and 2% (2 of 97) in the titrated oxygen group. Subjects receiving high-flow oxygen were far more likely to have acidosis or hypercapnia. Other authors have made similar findings.[56]

The British Thoracic Society has been a leading source for change in an effort to reduce excess oxygen exposure in COPD.[57] The key to success is translation of this information into emergency medical services practice. This will require specialized equipment to provide high-flow, low F_{IO_2} to patients at risk.[58,59] The British Thoracic Society recommendations are that each ambulance include a nonrebreathing mask for high-flow oxygen delivery, a nasal cannula or simple mask for low-flow oxygen delivery, tracheostomy masks for patients with tracheostomy or laryngectomy, and a 28% air entrainment mask. Another recommendation is that pre-hospital providers operate up-draft nebulizers for bronchodilator delivery with room air if pressurized metered-dose inhalers are unavailable. During aerosol therapy, oxygen can be provided via nasal cannula. The British Thoracic Society has also introduced cards identifying patients as having COPD and requesting use of a low F_{IO_2} air entrainment mask during ambulance transport. An example of such a card is shown in Figure 2.

Changing care paradigms for COPD patients in pre-hospital and emergency room settings will require a full-scale educational initiative. To date, these ideas have not had widespread support. The fear of hypoxemia, rightfully so, has overshadowed the known consequences of hyperoxia in COPD. Training ambulance crews in the physiology behind carbon dioxide retention and the use of oxygen delivery devices is paramount.

Oxygen for Palliative Care in COPD

COPD is a progressive, irreversible disease that is primarily managed by symptom control. At the end stages of life, COPD subjects suffer from debilitating dyspnea and fear of suffocation.[60]

Dyspnea is profound in the last days of life, and oxygen for relief of symptoms is commonly prescribed, often at the request of families.[61,62] Palliative oxygen is delivered to relieve persistent breathlessness in advanced disease or life-limiting illness.[63]

The common-sense approach that oxygen can relieve dyspnea is not based in fact.[23,64-67] In the absence of hypoxemia, the use of oxygen to alleviate breathlessness is not supported by the literature. A randomized controlled trial of oxygen versus air in subjects at the end of life failed to show any advantage of oxygen.[19] Campbell et al[65] found no reduction in respiratory distress in subjects near death from respiratory failure. A meta-analysis demonstrated a positive effect of oxygen on dyspnea in COPD subjects who failed to meet the requirements for LTOT. Interestingly, dyspnea was improved by continuous-flow oxygen, but not with pulse-dose oxygen delivery.[25] It is possible that oxygen delivery acts on carotid body output or another physiologic mechanism that is not fully understood.[66] Davidson and Johnson[67] recommend that if palliative oxygen is instituted, the success should be evaluated within 3 d. These findings suggest that perhaps the impact of nasal oxygen flow at the end of life is secondary to washing out the upper-airway dead space versus increasing oxygenation. If this is true, high-flow nasal oxygen or air may be useful in alleviating dyspnea in palliative care.[68]

A recent study by Nagata et al[69] compared high-flow nasal cannula (HFNC) with traditional LTOT in 32 subjects with stable hypercapnic COPD. At the end of a 12-week study period, subjects receiving HFNC had improved health-related quality of life scores and a reduction in hypercapnia compared with traditional oxygen therapy. In these subjects, arterial carbon dioxide was reduced by an average of 4 mm Hg. However, there were no changes in arterial oxygenation, dyspnea, spirometry, lung volumes or 6-min walk distance.[69] These results need to be replicated, and the additional cost of HFNC at home seems a challenge in the current reimbursement environment. HFNC disrupts our normal classification of oxygen therapy appliances. Traditionally there are low flow (1–6 L/min) and high flow devices (> 6 to 25 L/min). The addition of heat and humidity and a wider bore heated cirucit allows the cannula to transition to a high flow device. In this context, it is delivered oxygen (FDO2) and hyperoxia that is dangerous in COPD. High flow at low inspired oxygen concentrations, preventing hyperoxia is safe with the added benefit of washing out the deadspace and providing a low level of end expiratory pressure.

Table 3. Medicare Requirements for an Oxygen Prescription

Medicare requires the written order (prescription) prior to delivery, must include:
Items to be dispensed
Dosage or concentration, if applicable
Route of administration, if applicable
Frequency of use
Duration of infusion, if applicable
Quantity to be dispensed
Number of refills, if applicable
Additionally the physician's office must provide:
Estimated length of need for oxygen
The diagnosis code that represents the primary reason for ordering the item and additional codes that further describe the patient's medical need
Patient's clinical information

From Reference 71.

Home Oxygen Delivery Systems

Patients who qualify for LTOT have a number of options for home oxygen delivery. An extensive review of these devices was published by McCoy in 2013.[70] The following will address issues in home oxygen therapy for LTOT.

The Oxygen Prescription

Medicare provides a 35-page document that details the requirements for reimbursable home oxygen therapy.[71] This includes the written order prior to delivery. On one hand these rules are explicit and complex (Table 3). From a clinical standpoint, however, the orders fail to address issues related to maintenance of adequate oxygen saturation at all levels of activity.

Concerns regarding oxygen prescription appear to be universal, as publications from the United States, the United Kingdom, Spain, and Australia have all addressed this issue in the last 20 years.[72-76] One area of concern relates to the ability of a given oxygen therapy device provided by the supplier to meet the demands of the patient and the goals of the prescription. Complicating this problem is that home oxygen therapy reimbursement focuses on the equipment, not the care provided by a respiratory therapist familiar with the nuances of device performance. The recent Medicare change to a competitive bidding process for home oxygen therapy appears to put further cost pressures on suppliers and limits options for patients.

A successful home oxygen therapy program begins with a clear and cogent prescription for oxygen therapy that is goal-oriented. The current system tends to default to the supplier which device to choose, despite unknown efficacy. A pre-

Table 4. Advantages and Disadvantages of Oxygen Therapy Systems for Use at Home

Oxygen Delivery System: Stationary and Portable/Backup	Advantages	Disadvantages
Stationary concentrator with cylinders	Provides continuous flow for home use and ambulation	Depending on flow, cylinders have limited duration
	Cylinders can be used for backup oxygen	Overnight trips are difficult; stationary concentrator is heavy, and traveling with excess cylinders is hazardous
	Usual maximum flow 5 L; 10 L with larger devices	Noise, power consumption
	Cost	Required regular maintenance
	Ease of use	Cannot be used on aircraft
	Simple operation	
Stationary concentrator with cylinders and pulse dose regulator	Provides continuous flow for home use and pulse dose from cylinder for ambulation	Overnight trips are difficult; stationary concentrator is heavy, and traveling with excess cylinders is hazardous
	Cylinders can be used for backup oxygen	Weight of cylinders
	Usual maximum flow 5 L; 10 L with larger devices	Cannot be used on aircraft
Portable oxygen concentrator	Can be used for home stationary unit and for ambulation	Limited battery duration
	Typically includes a power cord allowing use in automobile, allowing extended trips	May not offer continuous flow
	Usual maximum flow pulse dose reported as equivalent to 6 L; 0.5–3 L of continuous flow offered	May not meet patient demands
	Cost	Noise, power consumption
	Ease of use	Required regular maintenance
	Simple operation	
	Can be used on aircraft	
Concentrator and compressor to fill cylinders (with pulse dose regulator)	Provides continuous flow for home use and pulse dose for ambulation	Overnight trips difficult; stationary concentrator is heavy, and traveling with excess cylinders is hazardous
	Cylinders can be used for backup	Cannot be used on aircraft
	Patient can fill their own cylinders; no deliveries required	
Liquid vessel and liquid portable	Does not require electricity	Overnight trips difficult; liquid vessel very heavy and hazardous to transport, liquid portable will not last overnight
	Provides continuous flow for home use and pulse dose for ambulation	Cost
	Patient can fill their own portable; no deliveries required	Cannot be used on aircraft
	Can deliver high flow	

scription that is explicit with respect to desired S_{pO_2}, with and without activity, should be the standard. Whether this is possible under the changing reimbursement system remains to be seen.

Oxygen Source

Based on reimbursement, logistics, and performance, there are a number of options for home oxygen delivery. In many cases, this includes a device for in home use, a portable device for mobility, and a backup system.[70] These will be considered briefly below. Table 4 lists the advantages and disadvantages of home oxygen delivery devices.

Cylinders

Oxygen cylinders represent the original source of oxygen supply. Cylinders can provide continuous flow or be fitted with demand regulators to prolong duration of operation and efficacy. However, the short duration of operation, weight, handling, and logistics of replacing cylinders render this the least favorable option for home therapy. Small cylinders continue to be used for ambulation or as back-up systems in some situations.[70]

Liquid

Liquid oxygen systems provide a number of advantages compared with other devices. Liquid oxygen is more easily stored, transported, and transfilled than gaseous oxygen.[70] One L of liquid oxygen expands to 860 L of gaseous oxygen, allowing liquid systems a period of prolonged operation. Stationary liquid systems can be used to fill portable devices to enhance patient mobility. Liquid systems are also capable of high flows and are the best option for subjects with greater oxygen requirements. At present, the logistics and costs of

liquid systems have limited its adoption in home care. Portable liquid systems extend the time patients can be away from home but cannot be used for air travel.

Concentrators

Oxygen concentrators are the most common device used for home oxygen therapy. Devices can provide a wide range of oxygen flows (1–10 L/min) at an oxygen purity of 90 ± 5%. When discussing oxygen concentrators, purity is essentially the F_{IO_2} of the gas delivered to the patient. Concentrators are also capable of pulse-dose delivery to maximize efficacy and minimize power use. Current stationary concentrators weigh between 30 and 35 pounds and run more efficiently than previous devices. This includes lower power consumption, quieter operation, and reduced costs of ownership.[70] Stationary concentrators typically allow a connecting tube up to 100 feet in length to allow the patient to be mobile within the home.

Certain portable concentrators allow filling of small cylinders to allow the patient to travel away from home. These devices have greater costs, and there are a number of logistics issues that must be overcome. Patient acceptance of this responsibility is important for successful use.

Portable Oxygen Concentrators and the Meaning of Settings

Portable oxygen concentrators (POCs) provide patients prolonged mobility outside the home through the use of batteries and operation from automobile power and other sources. Most POCs are also safe for air travel. POCs can provide continuous flow or pulse dose (also known as short-burst or intermittent flow). Depending primarily on size, POCs can provide a continuous flow of 0.5–3.0 L/min.[70] This is an important distinction, as patients often prefer the smallest device, when oxygen production is the primary determinant of efficacy.

A common clinical conundrum with POC is the use of the pulse-dose mode. Most devices are labeled with dimensionless settings of 1–3 or 1–6. Presumably, these values are equivalent to continuous-flow settings at these same values in L/min. This labeling is confusing for caregivers and patients alike. Again, the complicating factor is the patient's choice of a small, attractive, unobtrusive device that in all likelihood will not relieve hypoxemia during activity. The dose of oxygen during a 24-h period is important to achieve the therapeutic objective. The POC may fail in this goal if not chosen properly.[70]

A number of investigations have highlighted this problem.[77-86] For a given maximum oxygen generation (in L/min), a POC can provide a pulse volume that is based on the patient's breathing frequency. For example, a device with a maximum oxygen-generating capacity of 0.5 L/min can deliver a volume of 25 mL/breath at a frequency of 20 breaths/min at the desired oxygen purity. A device capable of generating 3 L/min can provide a maximum pulse volume of 150 mL/breath at a frequency of 20 breaths/min. In these 2 examples, the maximum setting (1–6) for each device provides drastically different oxygen delivery to the patient.

This issue is further complicated when respiratory frequency exceeds the oxygen-generating capacity of the POC. In this case, the operation of the POC must adopt one of 3 methods: (1) deliver a constant pulse volume at a reduced oxygen purity; (2) deliver a reduced pulse volume at a constant oxygen purity; (3) Deliver a constant pulse volume, responding only to every 2–3 breaths.

These are clinically relevant differences that may result in drastically different oxygen saturations in active subjects. Choice of a POC should be a joint decision that includes patient desires for simplicity, cost, and weight along with testing to assure adequate patient oxygenation during use.

Jacobs et al[87] have recently described patient perceptions related to home oxygen therapy. They analyzed almost 2,000 responses. The majority of respondents used oxygen 24 h/d for 1–5 y, with 31% using high-flow oxygen with exertion. Only 29% of subjects adjusted oxygen flow based on oximeter readings. The majority (65%) of subjects reported not having their S_{pO_2} checked when equipment was delivered and set-up. Instruction at the time of delivery was provided by the delivery person (64%) or clinician (8%), or no instruction was given (10%). A third of subjects reported feeling very or somewhat unprepared to operate their equipment. Half of respondents reported oxygen problems, most frequently reporting equipment malfunction, lack of physically manageable portable systems, and lack of portable systems with high flows. Limitations in activities outside the home due to inadequate portable oxygen systems was a common reported issue, occurring in 44% of subjects.

Importantly, subjects living in Competitive Bidding Program areas reported oxygen problems more often than those who did not. Those subjects reporting problems with their oxygen systems also experienced increased healthcare resource utilization.[87]

I agree with previous discussions suggesting that POC should be labeled with the pulse volume at each setting to make the capabilities more transparent to patients and caregivers.[70]

Closed-Loop Control of Oxygen at Home

Several investigators have explored the use of closed-loop oxygen flow to overcome problems associated with varying

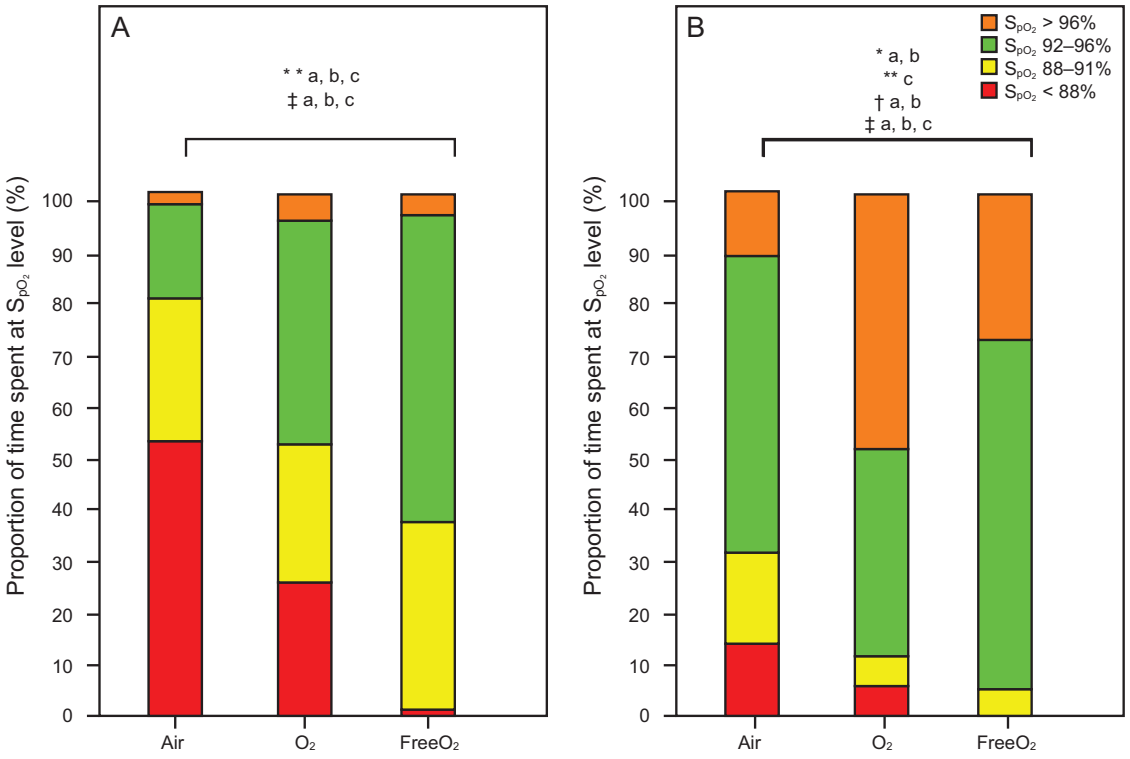

Fig. 3. Percentage of time spent within the predefined S_{pO_2} ranges during the 3 tested conditions (compressed air, constant low-flow oxygen [O_2], and $FreeO_2$), during the endurance shuttle walk test (A) and during the 10-min recovery period (B). The percentage of time within the oxygenation target (S_{pO_2} = 92–96%) was significantly higher with $FreeO_2$. The percentage of time with S_{pO_2} < 88% was significantly lower with $FreeO_2$. The percentage of time with hyperoxia (S_{pO_2} > 96%) was higher with constant oxygen flow. * $P < .05$ between groups for S_{pO_2} > 96%; ** $P < .05$ between groups for S_{pO_2} 92–96%; † $P < .05$ between groups for S_{pO_2} 88–91%; ‡ $P < .05$ between groups for S_{pO_2} < 88%; a $P < .05$ between air and O_2; b $P < .05$ between air and $FreeO_2$; c $P < .05$ between O_2 and $FreeO_2$. From Reference 91.

patient demand during activity and changes in patient condition.[88-92] These systems use pulse oximetry to control oxygen flow or pulse volume to maintain a desired S_{pO_2}. A least one system is FDA-cleared.[88]

Lellouche and colleagues[91-94] have generated much of this work, using a system known as $FreeO_2$. They demonstrated efficacy and greater duration of time in desired saturation ranges compared with traditional oxygen therapy during exercise, during COPD exacerbations, and in emergency care. Figure 3 demonstrates duration of time at S_{pO_2} target between $FreeO_2$ and conventional oxygen therapy during exercise (walking).[91]

These closed-loop systems are deceptively simple, and safety concerns related to excess oxygen delivery, monitoring respiratory frequency, and alerts to caregivers are important components. In fact, the use of an alert, letting caregivers know when oxygen requirements have increased, could be an underappreciated advantage of closed-loop oxygen flow.[95] Unfortunately, the current cost pressures on home oxygen therapy and the new competitive bidding process may prevent this potentially valuable technology from reaching patients in the home.

Oxygen Therapy and Noninvasive Ventilation

The use of noninvasive ventilation (NIV) in chronic respiratory disease combined with oxygen therapy at home has recently been reported.[96] Murphy et al[96] report a randomized clinical trial of 116 subjects with hypercapnia in the United Kingdom allocated to receive either LTOT alone or LTOT plus NIV. Median oxygen flow was 1.0 L/min in both groups, and median NIV settings were an inspiratory pressure of 24 cm H_2O, PEEP of 4 cm H_2O, and a set frequency of 14 breaths/min.

After 12 months, 64 subjects completed the 12-month trial. The median time to readmission or death was 4.3 months (interquartile range 1.3–13.8 months) in the LTOT plus NIV group versus 1.4 months (interquartile range 0.5–3.9 months) in the LTOT alone group. The adjusted hazard ratio was 0.49 (95% CI 0.31–0.77, $P = .002$). The 12-month risk of readmission or death was 63.4% in the LTOT plus NIV group versus 80.4% in the LTOT alone group. This demonstrated an absolute risk reduction of 17.0% (95% CI 0.1–34.0%). At 12 months, 16 patients had died in the LTOT plus NIV group versus 19 in the LTOT alone group. They concluded that

Table 5. Recommendations Regarding Issues in Home Oxygen Therapy From the 2013 RESPIRATORY CARE Journal Conference

Prescriptions and therapy for LTOT should focus on patient outcomes with oxygen saturations > 90% at all activity levels.
Prescriptions should allow for a titration to a specific saturation at all activity levels.
Labeling of the metering devices used with LTOT should include oxygen flow with a clinically acceptable F_{IO_2} range.
Dose volume for intermittent-flow devices should be labeled based on calculated volume, in mL, with the volume delivered in a breathing frequency range identified for 15–40 breaths/min.
Oxygen purity monitoring should be available for all oxygen concentrator devices.
Alarms should initiate at concentrations < 85% purity for > 5 min.
Portable concentrator alarms should initiate at breathing frequencies that produce oxygen purity < 85%.
A new titration standard for oxygen prescriptions at all activity levels should be developed to ensure adequate patient oxygenation with the devices provided.
Appropriate and targeted reimbursement for RT professional service in the home is required to ensure that effective LTOT is provided.
Reimbursement for home oxygen equipment should reflect the cost of both products and services related to the effective delivery of the drug oxygen.

From Reference 70.
LTOT = long-term oxygen therapy
RT = respiratory therapy

adding home NIV to home LTOT prolonged the time to readmission or death within 12 months.[96]

Summary

Oxygen therapy is a mainstay of treatment in COPD patients with resting hypoxemia. Other uses of LTOT for moderate hypoxemia, exercise-induced hypoxemia, nocturnal oxygen desaturation, and palliative care do not have strong evidence-based support. Despite these findings, oxygen is often delivered in these scenarios. Oxygen therapy during an exacerbation of COPD is potentially life-saving, but excessive oxygen is often delivered, to the detriment of survival. Current use of oxygen in pre-hospital and emergency care needs to match the knowledge regarding excess oxygen delivery from half a century ago. Closed-loop oxygen delivery might play a role in this arena. Devices for home oxygen delivery continue to face cost pressures, and reimbursement for professional respiratory care services is limited. A better appreciation of POC performance by caregivers and patients may lead to improved efficacy. A number of these issues have remained unchanged since the last RESPIRATORY CARE Journal Conference on oxygen therapy (Table 5).

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Discussion

Williams: I was really intrigued by an earlier comment you made about the coronary vasoconstrictor effect, and I'd be interested in your opinion. Of course, I think we know that O_2 is a vasodilator in pulmonary hypoxic conditions. So one of the situations in which you didn't talk about the use of O_2 and my experience and interest is this rationale for the patient with an asthma attack who has increased work of breathing but still has adequate O_2 saturation but is going to get aggressive β-agonist therapy and may have this paradoxical hypoxemia. Is that a situation where it's reasonable to supplement O_2?

Branson: The data on O_2 therapy and asthma are virtually nonexistent. If you have asthma and you need O_2, that is a real poor predictor of how well you're doing. Conventional wisdom suggests that if you're going to give an updraft nebulizer for their asthma, that you should power it with O_2. There is a study[1] looking at the impact of oxygenation in subjects with asthma showing the same rise in P_{CO_2} and fall in pH, almost what you see in COPD. It's not as severe, but again that's changing ventilation perfusion, because you're filling the alveoli that have low ventilation with O_2 and allowing them to collapse.

***Hess:** Neil [MacIntyre], I'm going to turn the tables and ask you a question that you would probably ask me if our roles were reversed. You and Bob [Wise] were coauthors on the LOTT study.[2] When do you prescribe O_2 for patients with COPD with mild hypoxemia or who desaturate during exercise or at night?

MacIntyre: I think Bob would love to answer that one.

Wise: This has caused a huge uproar in the community.

***Hess:** Which is why I asked the question.

Wise: Yes, thank you. Sam [Giordano], maybe you can respond – Sam has been at the center of this vortex. Perhaps you can at least explain what the uproar has been.

Giordano: I'll be glad to. I'm speaking in my role as chair of the United States COPD Coalition, which is a patient advocacy group consisting of state coalitions. There indeed is a lot of concern in the patient community. They're afraid that CMS [Centers for Medicare and Medicaid Services] will use the results of this study to raise the threshold requirement for reimbursement of supplemental oxygen. The Coalition invited Bob to provide a briefing at one of our member webinars on the study a few months ago. He did a wonderful job of putting the results in perspective and offering reassurance to patients and providers. I think that the salient takeaway from the study – and it seems like patients seem to get it – is what you told me on the telephone several months ago, Bob. The results do not mean they will not get O_2 if they get some symptom relief. But, and again as Bob pointed out, there are certain patients who may be on O_2 who fall into the moderately hypoxemic category who don't want to be on supplemental oxygen, and derive no symptom relief. This study indicates that there isn't a medical reason for them to continue.

MacIntyre: I'll chime in and generally agree with everyone here. There are data, and Rich reviewed them, on the hypoxemic subject with exercise who gets on O_2. Not in all studies, but in general, increase their 6-min walk test distance, and they get functional benefit from it. I think that's real. There are other studies that show that it will reduce pulmonary artery pressure, and that seems to be real. What the current studies show is that those physiologic changes don't necessarily spill over into mortality or exacerbation benefits. Nevertheless, these intermediate values of increased exercise tolerance, reduced symptoms, and the like are legit, and from every indication I get, CMS is not interested in going after those indications. I think the chances of the rules changing, at least in the foreseeable future, are pretty low.

Giordano: Exactly on point. We spoke with CMS regarding this concern. They were involved in discussions we had with the Coalition and the community. They were emphatic that they're not going to change reimbursement policy based on one study. I would like to transition to CMS reimbursement policy for O_2, which is something Rich threw out to the group during his presentation. For the first time in over 30 years, I think CMS is aware of the mistake we made by trying to commoditize O_2. There are far too many technical nuances associated with supplemental oxygen systems to make this approach work for patients. Because

it's treated like a commodity, you can buy a case of Depends with bidding but you can't really bid on O_2 and still offer a full range of delivery systems without the potential for underserving patient needs. Rich showed us several pictures of O_2 concentrators, and the long and the short of it is if a concentrator is not continuous-flow-capable, its output cannot be equated to L flow. On the other hand if the device is capable of continuous flow, weight and battery life are factors. Even when set in pulse-dose mode it's going to have an equivalency in L/min. Devices incapable of continuous flow output do not have their outputs calibrated in L/min. This variance in performance is confusing to patients and physicians alike. The Internet offers so many benefits, but in this case, perhaps not. It seems patients get online and contact manufacturers directly. They are told by some sales people that their device will meet their needs but then discover the opposite in some cases. I am beginning to think that CMS does understand, now, that it may be time to change the way we prescribe O_2. I started as an inhalation therapist a couple of years before Medicare was passed and implemented. I was just on the tail of O_2 tents and iron lungs. So, I remember the oxygen prescription was to maintain a target O_2 concentration inside of a tent. When we finally made the complete switch to catheters, cannulas, and masks, then it was prescribed as a device output in L/min. At the time, we never anticipated having all of these different delivery devices with a wide variety of technical capabilities. The biggest common denominator, with regard to the O_2 prescription should be targeting a pulse oximeter saturation range. This change would allow physicians to prescribe a target saturation range as a substitute for L/min, while recognizing the technological advances in terms of delivery systems. Better yet, have a respiratory therapist or a nurse who has delved into this technology, as several have, or a physical therapist or others to provide advice regarding the right piece of equipment for each patient. However, the certificate of medical necessity form (CMN484) makes no provision for a prescription unless it's in L/min. Something came out of CMS about 3 or 4 months ago that indicated that their documentation for the order – Rich had mentioned some from the United Kingdom – but with CMS slightly over 48% of the certificates for medical necessity for home O_2 were incomplete. We're not even getting the proper order. They know about changing the form; we hope they will do that.

†Newhouse: I'm amazed that we're still debating controlled O_2. Campbell demonstrated very clearly in the late 50s that it was essential not to go above 40%, and he developed the air-entrainment mask. And here we are 60 years later still debating what was demonstrated very clearly then.[3]

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