Long-Term Oxygen Therapy in COPD*
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Over the last decade, there has been substantial expansion in the use of chronically-administered oxygen among patients with chronic obstructive pulmonary disease (COPD). Such expansion reflects the following two facts: (1) the major mortality and disability impact of COPD; and (2) the frequency of demonstrable hypoxemia among such patients. Banking as the sixth cause of death in the United States, COPD is also second only to coronary artery disease as a cause of permanent disability among American adults. The frequency of arterial hypoxemia among COPD patients is widely-appreciated and well-documented. However, the use of long-term oxygen therapy implies a linkage between these two facts, one that has been difficult to establish. Put simply, that linkage requires a positive answer to the following question: Does relief of arterial hypoxemia alter either the mortality or the extent of disability among COPD patients?

Evidence accumulated has indicated that the answer to this question is “yes, under certain circumstances.” Since those circumstances define how and when oxygen should be prescribed, the existing data-base on long-term oxygen therapy in COPD has been reviewed. Specifically, the data regarding the following have been examined: (1) the proven and potential benefits of extended oxygen therapy; (2) which COPD patients are most likely to achieve these benefits; (3) how candidates for long-term oxygen use should be selected; (3) the optimal methods for oxygen delivery; and (4) the hazards and costs involved.

As will be seen, final answers to all of these questions are not available. However, this brief review indicates the current state of knowledge and those areas in which further information is needed to improve decision-making capabilities.

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The Benefits of Oxygen Therapy
Proven

Available data indicate that the use of long-term oxygen therapy in selected populations of COPD patients with arterial hypoxemia at rest improves the duration of survival.

A large, well-controlled study in hypoxemic, hypercapnic COPD patients showed a statistically significant improvement of survival rates in patients treated with oxygen 15 hours per day as compared to a group treated with no oxygen therapy. It was shown that, during a five-year period, 45 percent of oxygen-treated patients died, while 67 percent of control (no oxygen) patients died. The mortality was higher in women than men. In men, mortality among both treated and control groups was similar for the first 500 days. In another large, well-controlled study of patients with arterial hypoxemia at rest, nocturnal oxygen administration was compared with continuous administration. It was found that during a mean follow-up period of 19 months, 40 percent of COPD patients treated with nocturnal oxygen only died, whereas only 23 percent of COPD patients treated with continuous oxygen died. These studies indicated that in terms of survival among selected hypoxemic COPD patients, some oxygen is more effective than none, and that continuous oxygen is more effective than nocturnal oxygen.

There is also substantial evidence that long-term oxygen administration is associated with an improvement in intellectual functioning. Measures of memory, motor coordination, depression, and hypochondriasis improved with long-term oxygen therapy in COPD patients with arterial hypoxemia at rest. While these observations were not controlled for placebo effect, they indicate that long-term oxygen therapy can contribute to improvement in the function of such patients with regard to the activities of daily living.

Increased red blood cell mass is a known potential...
consequence of arterial hypoxemia. There is ample evidence that the red blood cell mass and hematocrit level decrease with long-term oxygen therapy.5,6,8

Chronic pulmonary hypertension is another common finding among such patients. Its origins are multifactorial with pulmonary arterial vasoconstriction, increased blood viscosity, and anatomic vascular loss among the major contributors. The bulk of evidence indicates that pulmonary vascular resistance falls with long-term use of oxygen, though the changes are modest and variable.5,6,8,9 There are also data supporting the conclusion that long-term oxygen therapy ameliorates the severity of clinical right heart failure in COPD patients.5,9

Potential Benefits

Long-term oxygen therapy is associated with several types of subjective improvement in hypoxemic COPD patients. Most such patients have felt less dyspneic while using extended oxygen therapy.5,9 A few have resumed gainful employment,5,11 and some were freed from a bed-and-chair existence to participate more actively in their own care.5,9 It is possible that such subjective improvement may reflect a placebo effect; in one small study, nine hypoxemic COPD patients treated for five weeks with air and oxygen showed similar general subjective improvement.15

Most reports indicate that hypoxemic COPD patients increase their exercise ability while using oxygen. Earlier studies suggested that oxygen therapy might improve exercise ability as much as 50 percent;6,13 and a more recent study showed significantly-improved acute exercise tolerance in a small number of COPD patients who received supplemental oxygen.14 Other studies, however, question whether COPD patients, with or without hypoxemia, do improve exercise tolerance while receiving oxygen therapy.6,15

There is ample evidence that participation in comprehensive medical rehabilitation programs decreases the days of hospitalization among patients with COPD.1,16 Long-term oxygen administration is often a component of such programs, but its variable application makes identification of its specific contribution difficult. One study of ten patients showed a 14-day decrease in hospital days for respiratory illness during one year after oxygen therapy, as compared to the year prior to oxygen therapy. This study suggested that the savings in hospital expenses could pay the cost of continuous oxygen therapy. A larger, more recent study found that although patients receiving continuous oxygen tended to be hospitalized less often and for shorter durations than those receiving nocturnal oxygen therapy, the differences were not statistically significant.6 Similarly, a study comparing 15 hours per day oxygen to no oxygen found that durations of hospitalization due to exacerbations of respiratory failure were not affected by oxygen therapy.5

Recent investigations have shown that COPD patients may suffer profound hypoxemia with associated pulmonary hypertension during sleep.17-19 Arterial blood gas analyses in these COPD patients while awake did not predict which patients would suffer severe nocturnal hypoxemia.19 Among a small group of COPD patients monitored during sleep, the hypoxemia was moderated and the degree of pulmonary hypertension was greatly reduced with low flow oxygen administered during sleep.17,18 These findings suggest that nocturnal oxygen may prevent or delay the development of cor pulmonale in some COPD patients with relatively normal awake, resting values of arterial oxygen tension. A recent study suggests that awake, resting hypercarbia may positively correlate with severe arterial hypoxemia during sleep in COPD patients.20

Similarly, some COPD patients with relatively normal arterial oxygen values at rest demonstrate substantial declines in such values during exercise.21 However, whether prevention of exercise-induced hypoxemia enhances the safety of exercise or the exercise capabilities of such patients remains to be demonstrated.

Patient Selection

Virtually all of the data regarding the proven and potential benefits of long-term oxygen therapy have been derived from COPD patients with arterial hypoxemia at rest. Therefore, documentation of arterial hypoxemia at rest is the major criterion for selection of patients. While any definition of hypoxemia is subject to exception, there is general consensus that an arterial oxygen tension below 55 to 60 mm Hg (or a comparable oxygen saturation) while breathing room air constitutes hypoxemia warranting long-term oxygen therapy. It is important to note that this degree of hypoxemia should be documented when the patient is stable and not during an acute exacerbation. One study has shown that 21 percent of COPD patients who initially qualified for extended oxygen therapy on the basis of documented hypoxemia demonstrated enough improvement during one month of outpatient observation to allow cessation of oxygen administration.6 Therefore, while it is acceptable to initiate long-term oxygen therapy for hypoxemia demonstrated at hospital discharge, or when the patient is first seen as an outpatient, the need for its continuance should be documented when the patient has achieved a stable status under optimal medical therapy.

As noted previously, there are valid reasons for considering use of long-term oxygen therapy among patients who develop significant hypoxemia only with exercise or during sleep. The potential acute and chronic hazards of such hypoxemia are clear. The magnitude of such hazards and the extent to which
they are modified by oxygen administration remain to be fully defined. Identification of such patients requires that they be studied during exercise and during sleep because, as noted, resting arterial blood gas values may not be predictive. Having documented hypoxemia during sleep or exercise, prudence would appear to dictate prescribing oxygen to prevent this hypoxemia. Future investigations are needed to define whether prudence translates into an impact on mortality or functional status.

Special exceptions also may exist. The presence of severe right heart failure or coronary artery disease may legitimately be invoked to raise the level of hypoxemia at which oxygen is prescribed. Again, the benefits derived from these and other exceptions remain to be demonstrated.

**Prescribing Oxygen Therapy**

Having concluded that a COPD patient warrants extended oxygen administration, the physician must provide a specific oxygen prescription: the flow rate to be used, the specific conditions of use (eg, continuous, during sleep, during exercise), and the device to be used for delivery. Prescriptions for "pm" use are not acceptable.

In order to provide an adequate prescription, the effect of a given flow rate of supplemental oxygen should be assessed directly. Ideally, that flow rate which will maintain a satisfactory level of oxygenation (\(\text{PaO}_2, 60 \text{ to } 80 \text{ mm Hg} \)) at rest, during exercise, and during sleep should be determined. However, practices in this regard currently vary. Furthermore, existing data have not established the need for studies during sleep and exercise. Some investigators arbitrarily have prescribed 2 L per minute of oxygen continuously to those with resting hypoxemia; some empirically have added 1 L per minute oxygen flow during exercise and sleep; still others advocate measurements during exercise and sleep to define the oxygen flow required.

Present data would suggest that the COPD patient with resting arterial hypoxemia should receive oxygen continuously at a flow rate which elevates the arterial \(\text{Pao}_2\) to 60 to 80 mm Hg, with either empiric or measured adjustments upward during exercise and sleep. Those with exercise-only or sleep-only hypoxemia may, at the discretion of their physician, receive oxygen only under those conditions, at a flow rate documented to avoid a \(\text{PaO}_2\) below 60 mm Hg (or a comparable oxygen saturation). However, at this time, there is no evidence supporting (or refuting) the treatment of exercise-only or sleep-only hypoxemia.

Nasal prong delivery has been used exclusively in all recent investigations of long-term oxygen therapy, and there is consensus that these prongs are the most convenient and comfortable mode of oxygen access for patients. Delivery systems using compressed oxygen, liquid oxygen, and oxygen concentrators all have been used. At present, there appears to be no particular advantage to one system. Therefore, availability, cost, convenience, and patient comfort should determine which oxygen delivery system is prescribed.

Finally, the patient must remain under close medical supervision and undergo re-evaluation of his oxygen prescription if his clinical status changes. Also, the patient and his family must be willing to become familiar with the proper operation and standard safety measures of oxygen therapy devices. Unfortunately, such patient education has been shown to be deficient. In a recent survey of 100 patients receiving extended oxygen therapy, less than one-half recalled receiving more than ten minutes of instruction on their oxygen therapy. Only one in six patients recalled receiving any instructions on their oxygen therapy from a physician.

**The Potential Hazards and Costs**

**Potential Hazards**

Since oxygen supports combustion, concern regarding fire hazard is commonly raised with regard to long-term oxygen therapy. Experience has shown this risk to be very small and mainly limited to minor fires involving oxygen tubing. A nationwide survey conducted by the Committee on Rehabilitation of the American College of Chest Physicians in 1976 disclosed no instance of a catastrophic accident associated with the use of long-term oxygen. Cessation of smoking is highly desirable among patients who are to receive oxygen therapy for many reasons, including concern about fire hazard. However, long-term oxygen therapy has been used safely and effectively in a population of COPD patients who were unable to stop smoking.

Long-term oxygen therapy can cause structural abnormalities in the lungs of some COPD patients. A substantial percentage (40 percent to 50 percent) of oxygen-treated COPD patients showed proliferative and fibrotic changes suggestive of oxygen toxicity at autopsy. Similar changes were not found in patients with like degrees of COPD who had not received extended oxygen therapy. However, there is no evidence that these pathologic changes adversely affect a patient's clinical course or survival.

In some patients with severe COPD, administration of oxygen in high concentration may accentuate hypoventilation, hypercapnea, and may induce carbon dioxide narcosis. In most studies, patients receiving long-term oxygen therapy have demonstrated at most a small increase in mean arterial carbon dioxide tension. However, this degree of hypercarbia is well tolerated.

In a recent study of 42 hypercapnic COPD patients, none developed carbon dioxide reten-
tion requiring cessation of oxygen therapy. Another recent study disclosed that only one of 203 COPD patients treated with long-term low flow oxygen therapy experienced severe respiratory acidosis (pH<7.30). Thus, chronic carbon dioxide retention is not considered a contraindication to a monitored trial of low flow oxygen therapy.

Costs

The costs of patient evaluation, including rest and exercise arterial blood gas studies, can range from $200 to $500 in our area. Sleep measurements add an additional potential cost, as do follow-up blood analyses to document continued need. However, obtaining complete data prior to prescribing oxygen is warranted because long-term oxygen therapy itself is very expensive. In our community, regardless of the delivery system used, the monthly cost for continuous delivery of 2 L per minute of oxygen by nasal prongs exceeds $300. This cost rises rapidly with higher oxygen flow rates. Consideration of such costs warrants continued efforts to define further the benefits of extended oxygen therapy, to develop more specific criteria for patient selection, and hopefully, to examine methods for reducing the cost of oxygen delivery.

REFERENCES