Supplemental Oxygen in Interstitial Lung Disease: An Art in Need of Science

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Abstract

Interstitial lung disease (ILD) comprises a large and heterogeneous group of disorders that often lead to progressive fibrosis and premature death. Oxygen supplementation is typically used in patients with advanced lung disease with resting hypoxemia; however, there is a paucity of evidence guiding the use of supplemental oxygen in ILD, and significant heterogeneity in clinical practice. It remains unclear whether supplemental oxygen improves clinically meaningful outcomes, and the role of ambulatory oxygen supplementation in isolated exertional hypoxemia is particularly controversial. In some regions, the lack of robust data creates barriers to funding support and access to supplemental oxygen for patients with ILD. Further research into the role of oxygen supplementation is needed to optimize the comprehensive care of this patient population.

Keywords: pulmonary fibrosis; exercise; policy; oxygen

(Received in original form February 14, 2017; accepted in final form June 23, 2017)

Author Contributions: K.A.J., K.M., and C.J.R. conceived of the idea for this work; all authors contributed to the preparation of the manuscript and approved the final version.

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Ann Am Thorac Soc Vol 14, No 9, pp 1373–1377, Sep 2017

DOI: 10.1513/AnnalsATS.201702-137OI
Internet address: www.atsjournals.org

Interstitial lung disease (ILD) comprises a heterogeneous group of diseases characterized by inflammation and/or fibrosis of the lung parenchyma. Some forms of ILD are irreversible, characterized by progressive hypoxemia and frequent early mortality, and with few pharmacotherapies of proven benefit.

Supplemental oxygen is often prescribed for patients with advanced ILD; however, there are limited data guiding its use in this population. This lack of evidence has made it challenging for providers to know when to prescribe oxygen and for patients to understand when it should be used. This has also led to variable criteria for funding of supplemental oxygen across healthcare regions, with particular uncertainty regarding which patients should be provided ambulatory oxygen (i.e., oxygen supplementation only with ambulation and not at rest). Herein, we present the evidence base examining the use of oxygen in patients with ILD and discuss how the limited data have created significant barriers to accessing this therapy in many regions. We highlight some of the practical limitations to oxygen use and identify priorities that we believe warrant additional research on the role of supplemental oxygen in patients with ILD with resting or exertional hypoxemia.

Rationale and Evidence for Oxygen in ILD

Patients with advanced ILD frequently develop hypoxemia due to multiple physiologic derangements, including diffusion limitation, ventilation–perfusion mismatching, and abnormalities of the pulmonary vasculature (1–3). Exertional desaturation can be profound in some patients with ILD (2, 4), contributing to exertional dyspnea that is distressing and associated with depression, functional impairment, and reduced quality of life (5, 6). Hypoxemia during exercise impairs maximal work load and endurance time, attenuating the benefits gained from pulmonary rehabilitation (7, 8). Hypoxemia may also contribute to the development of pulmonary hypertension (9, 10), a prognostically important comorbidity with no proven therapy in ILD (11–13). Supplemental oxygen can improve many of these adverse changes; however, there is

no clear consensus on the threshold below which oxygen supplementation is warranted, given the sparse and inconsistent data (14). Despite the paucity of evidence, clinical supplemental oxygen is used by 11–28% of patients with mild-to-moderate idiopathic pulmonary fibrosis (IPF) at the time of clinical trial enrolment (15–18).

The use of continuous supplemental oxygen for resting hypoxemia in ILD is primarily extrapolated from studies in patients with chronic obstructive pulmonary disease (COPD) that were published over 35 years ago. The NOTT (Nocturnal Oxygen Therapy Trial) and MRC (Medical Research Council) studies were randomized, controlled trials that demonstrated a mortality benefit from supplemental oxygen in patients with COPD with severe resting hypoxemia (19, 20). Additional smaller studies have since demonstrated that supplemental oxygen improves oxygen delivery, cardiac output, arterial oxygen content, minute ventilation, exertional dyspnea, and exercise endurance in patients with hypoxemia and COPD (21–24). Extrapolating from these data, IPF clinical practice guidelines make a strong recommendation for the use of oxygen in patients with resting oxygen saturations below 88% (25), despite no direct evidence of benefit in this clinical context.

There are no high-quality studies evaluating the use of supplemental oxygen in patients with ILD who desaturate only with exertion. A recent study of patients with stable COPD with mild resting hypoxemia or moderate exercise-induced hypoxemia found no impact of supplemental oxygen on functional capacity, quality of life, need for hospitalization, or mortality (26). Patients with advanced ILD frequently have more rapid and more severe exertional hypoxemia compared with those with COPD, suggesting that it is likely inappropriate to extrapolate these data to ILD (27). An observational study of 133 patients with IPF with mild exertional hypoxemia reported no mortality benefit of supplemental oxygen; however, this study was underpowered to detect a meaningful benefit (28). A double-blind, placebo-controlled crossover study of 20 patients with IPF with exertional desaturation found that breathing 4 L/min of supplemental oxygen via nasal prongs did not improve 6-minute-walk distance compared with breathing room air (29).

In contrast, several small studies in patients with ILD demonstrate that breathing supplemental oxygen or hyperoxia during exercise improves endurance time, walk distance, dyspnea, maximal oxygen uptake, and maximal workload (30–34). These studies have several important limitations, including small sample sizes, mostly retrospective study designs, lack of blinding with sham oxygen, and inconsistent consideration of potential confounders, such as disease severity or pulmonary hypertension. It is also unclear whether these findings apply to patients with resting or exertional hypoxemia, and what degree of hypoxemia reversal must be achieved to obtain clinical benefit. Furthermore, there are no studies that have adequately evaluated the role of longer-term ambulatory oxygen supplementation in this patient population, and no studies have assessed quality of life. An ongoing randomized, controlled trial will address some of these limitations by examining potential functional and symptomatic benefits of supplemental oxygen during an 8-week exercise program in patients with IPF who do not qualify for resting oxygen supplementation (clinical trial registered with www.clinicaltrials.gov [NCT02551068]) (35). An additional randomized, controlled crossover trial of ambulatory oxygen will evaluate the longer-term role of supplemental oxygen for the treatment of isolated exertional hypoxemia in patients with ILD (clinical trial registered with www.clinicaltrials.gov [NCT02286063]) (36).

It is unknown whether oxygen supplementation could conversely be associated with an increased risk of acute exacerbation of ILD or other adverse effects. Although acute exacerbations of IPF are more common in patients with advanced disease (37), including many on oxygen supplementation, there are no data specifically suggesting toxicity of supplemental oxygen for patients with stable ILD with resting or exertional hypoxemia. Acute exacerbations in patients with IPF receiving high amounts of oxygen have primarily occurred in mechanically ventilated patients during surgical procedures (38), and are not directly applicable to an outpatient population. One small crossover study of patients with IPF found no difference in biomarkers of oxidative stress after exercise while breathing supplemental oxygen compared with medical air, suggesting that oxygen is likely a safe intervention, at least in the short term (39); however, there remains a need for future studies to evaluate the potential toxicity of oxygen in patients with ILD.

Recommendations for Oxygen Supplementation in ILD

The 2011 IPF guideline, endorsed by several respiratory societies, recommended that patients with IPF with resting oxygen saturation less than 88% should be treated with supplemental oxygen (25); however, specific criteria for patients with isolated exertional hypoxemia were not provided. A 2008 multisociety guideline recommended that ambulatory oxygen be considered for patients with IPF who are breathless, mobile, and who desaturate with exercise (oxygen saturation $<$90%), provided there is also improvement in exercise capacity and/or breathlessness with supplemental oxygen (40). A 2015 guideline from the British Thoracic Society comments that long-term oxygen therapy may improve tissue oxygenation and survival in patients with ILD with chronic resting hypoxemia, while preventing complications, such as pulmonary hypertension, and suggests that patients with ILD with severe breathlessness could be considered for palliative oxygen therapy (41). However, this guideline further states that ambulatory oxygen should not be routinely offered to patients without chronic hypoxemia at rest (grade B recommendation).

The recommendations made in these guidelines are based primarily on expert opinion, given the paucity of strong and direct evidence. The limited data and absence of any cost analysis has similarly led to opinion-based local funding criteria in many health regions; however, these criteria are often more restrictive than current guideline recommendations. The variable funding criteria across health regions and their frequent discrepancies with guideline recommendations have contributed to the confusion among patients and health care providers, indicating the need for updated guideline recommendations supported by major international societies.

Criteria for Oxygen Supplementation

Regional criteria for funding of supplemental oxygen are heterogeneous, with each regulatory agency establishing policy for their local population, and some agencies not funding oxygen for exertional hypoxemia at all. Criteria for resting oxygen supplementation are typically consistent with the NOTT and MRC trials, including severe resting hypoxemia ($Pa_{O_2} < 55$ mm Hg) or moderately severe resting hypoxemia ($Pa_{O_2} < 60$ mm Hg) with complications of chronic hypoxemia (e.g., cor pulmonale, polycythemia).

Funding for ambulatory oxygen often requires a combination of exertional hypoxemia that is reversed with oxygen supplementation, with additional requirement in some regions of a substantial improvement in either walk distance or dyspnea. The severity of what qualifies as significant exertional hypoxemia varies, with some regulatory agencies funding oxygen only with desaturation to less than 80% (42), whereas others provide funding for an ambulatory saturation less than 88% (43). Some agencies also require that specific criteria be met on tests performed over multiple days, whereas others have complex pretesting algorithms that must be met before patients are even eligible for testing (42). An improvement in walk distance is required in some regions (e.g., improvement in walk distance of 30 m and 20–25% compared with the walk distance achieved on room air). However, patients with chronic lung disease can suffer from significant deconditioning that may prohibit immediate benefit of oxygen supplementation, indicating that a single test may not provide an adequate assessment of potential benefit from longer-term oxygen supplementation. The United States' Centers for Medicare and Medicaid do not have a "distance" criterion for oxygen funding (44); however, these criteria are similarly not evidence based, but rather appear to rely on expert opinion.

Additional criteria exist within specific regions and patient populations. Some regulatory agencies require that candidates for ambulatory oxygen supplementation first meet criteria for "severe lung disease" (42); however, the provided definition of "severe lung disease" is extrapolated from mortality prediction models in IPF that have not been validated to predict benefit from supplemental oxygen in ILD or any other chronic lung disease (45, 46). Clearly, eligibility criteria for oxygen funding must be established, but the extensive variability in specific criteria highlights that the optimal metrics of assessment and qualification for ambulatory oxygen remain unclear.

Barriers to Oxygen Use

Oxygen is a costly therapy that is not funded for some patients who appear to derive significant benefit. Some populations and regions have no funding for supplemental oxygen in cases of isolated exertional hypoxemia (47, 48), whereas some patients have substantial out-of-pocket costs before insurance coverage applies. This limited access to funding requires many patients to choose between large personal expenses or rationing their oxygen use.

There are many additional challenges to the use of supplemental oxygen. Some patients find oxygen burdensome and perceive that it makes them look old and infirm (49, 50), leading to use of oxygen only in the setting of significant functional limitation and/or breathlessness. Providers may advise patients to use oxygen only during exercise; however, this may cause confusion as to what degree of exertion warrants its use and what flow rates to use. It can also be difficult to justify use of oxygen to patients who are relatively asymptomatic despite significant desaturation, including patients who have developed symptomatic tolerance to chronic hypoxemia. Conversely, oxygen may provide relatively little symptomatic relief in some patients who thus abandon oxygen as an ineffective therapy despite other potential physiological benefits (50). There are additional practical issues related to oxygen tubing, tanks, and other equipment that can impact compliance in patients who are frequently frail. Importantly, patients with advanced ILD may require high oxygen flow rates that exceed the capacity of portable or compact systems, resulting in limited mobility and hindering their ability to leave the home. These common barriers to oxygen use highlight the complexity of individual needs and expectations that must be considered when developing an approach to oxygen therapy (51).

Conclusions

Supplemental oxygen is frequently prescribed to patients with advanced ILD; however, there is a lack of rigorous data supporting its use, and there are significant barriers to accessing this therapy in many regions. Patients with ILD with resting hypoxemia are typically provided supplemental oxygen; however, there is a pressing need for a consistent approach to oxygen therapy for patients with ILD, particularly those with isolated exertional hypoxemia. The current lack of evidence may result in overprescription of oxygen in some jurisdictions, whereas, in our experience, it has created complex barriers to accessing this therapy. Prospective, randomized, controlled trials of ambulatory oxygen therapy in patients with ILD with exertional hypoxemia are needed to assess clinically meaningful outcomes. Until such data become available, our patients will likely continue to have poor access to an intervention that may significantly impact symptoms, patient independence, and quality of life. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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