Oxygen in interstitial lung diseases

Ricardo Cordeiro[1], André Nunes [1], Oliver Smith[2] and Elisabetta A. Renzoni[3,4]

[1]Centro de Responsabilidade Integrada de Pneumologia, Hospital de Torres Vedras, Centro Hospitalar do Oeste, Torres Vedras, Portugal. [2]Rehabilitation and Therapies Directorate, Royal Brompton Hospital, London, UK. [3]Interstitial Lung Disease Unit, Royal Brompton Hospital, London, UK. [4]Margaret Turner Warwick Centre for Fibrosing Lung Diseases, NHLI, Imperial College London, London, UK.

Corresponding author: André Nunes (andre.nunes@choeste.min-saude.pt)

Shareable abstract (@ERSpublications)
Oxygen therapy is of key importance in hypoxaemic ILD patients. Key unmet research areas include thresholds of hypoxaemia triggering intervention, the impact of nocturnal hypoxaemia treatment and development of user-friendly oxygen delivery systems. https://bit.ly/3YtmFXi

Cite this article as: Cordeiro R, Nunes A, Smith O, *et al*. Oxygen in interstitial lung diseases. *Breathe* 2023; 19: 220271 [DOI: 10.1183/20734735.0271-2022].

Received: 2 Dec 2022
Accepted: 2 Feb 2023

Abstract

Domiciliary oxygen is essential in the care of hypoxaemic interstitial lung disease (ILD) patients. Guidelines concur in advising prescription of long-term oxygen therapy (LTOT) for ILD patients with severe hypoxaemia at rest, in view of its beneficial impact on breathlessness/disability and extrapolating potential survival benefits seen in COPD patients. A less severe hypoxaemia threshold for initiation of LTOT is recommended for patients with pulmonary hypertension (PH)/right heart failure, requiring careful evaluation in all ILD patients. In light of evidence suggesting a link between nocturnal hypoxaemia, development of PH and poor survival, studies assessing the impact of nocturnal oxygen are urgently needed.

Severe exertional hypoxaemia is frequent in ILD patients, with impact on exercise tolerance, quality of life and mortality. Ambulatory oxygen therapy (AOT) has been associated with improvement in breathlessness and quality of life in ILD patients with exertional hypoxaemia. However, given the paucity of evidence, not all current AOT guidelines are in agreement. Ongoing clinical trials will provide further useful data. Despite its beneficial effects, supplemental oxygen imposes burdens and challenges to patients. A key unmet area of need is the development of less cumbersome and more efficient oxygen delivery systems to reduce the negative impact of AOT on patients' lives.

Introduction

The first study of long-term oxygen therapy (LTOT) was performed in Denver, in 1968, in a cohort of COPD patients [1]. Since then, supplemental oxygen has been a vital part of treatment in many acute/chronic medical conditions [2]. Globally, COPD and interstitial lung disease (ILD) are the two most common indications for domiciliary oxygen therapy. This article will highlight key questions and the available evidence for oxygen therapy in ILD.

When and why should patients with ILD be started on LTOT?

Chronic resting hypoxaemia usually develops in advanced ILD, and is associated with disabling breathlessness, and a median survival of less than a year [3]. The use of LTOT is largely based on two large randomised controlled trials (RCTs) in COPD, which showed improved survival in patients with severe resting hypoxaemia treated with supplemental oxygen for at least 15 h a day [4, 5]. There are no published RCTs of LTOT in ILD, with only one small (N=62) unpublished study with high risk of bias, reporting no difference in the survival of patients with ILD treated with LTOT compared with room air [6]. However, despite a limited evidence base, all major ILD international guidelines strongly recommend LTOT (for at least 15 h a day) in ILD patients with stable severe daytime hypoxaemia (arterial oxygen tension (P_{aO_2}) <56 mmHg (<7.4 kPa)) or less severe resting hypoxaemia (P_{aO_2} 56–59 mmHg (7.4–8 kPa)) with evidence of hypoxic organ damage, including pulmonary hypertension (PH)/right heart failure [7–9]. The guidelines have extrapolated the evidence from COPD trials, in consideration of the markedly reduced

survival of hypoxaemic ILD patients [3], the beneficial palliative effects of supplemental oxygen in relieving breathlessness [10], and the potential prevention of hypoxic-induced organ damage. However, it is uncertain whether LTOT prevents adverse clinical outcomes in patients with ILD, such as hospitalisation or acute exacerbation, or affects overall survival [11].

As the disease progresses, patients with ILD often suffer from debilitating symptoms, particularly dyspnoea. Palliative care support can be a valuable intervention but is not always available and is often offered late [12, 13]. In recommending supplemental oxygen in hypoxaemic patients at rest, it is recognised that oxygen has a role in symptom palliation in the hypoxaemic ILD patient, particularly for the relief of dyspnoea in advanced ILD [12, 14]. In the severely hypoxaemic patient, high-flow nasal oxygen has been shown to be associated with a similar survival to noninvasive ventilation in ILD patients with do-not-intubate orders, but to be better tolerated, allowing oral intake and for patients to be able to converse right up to death [15].

It is not clear whether earlier initiation of LTOT would benefit ILD patients with less severe resting hypoxaemia. In COPD patients with moderate resting hypoxaemia, LTOT was not associated with improved survival or quality of life [16–18]. However, a recent study found that patients with ILD and moderate resting hypoxaemia (P_{aO_2} 56–59 mmHg (7.4–8 kPa) without hypoxic organ damage) untreated with LTOT, had a comparably poor prognosis to those with severe resting hypoxaemia treated with LTOT, and significantly worse than that of patients with COPD with hypoxaemia (whether moderate or severe) [19]. The authors hypothesised that LTOT may be indicated earlier in ILD than in COPD. In response to these findings, the population-based retrospective DISCOVERY study [20] collected data from the Swedish registry on 2408 ILD patients with moderate (56–65 mmHg (7.4–8.7 kPa)) or severe (<55 mmHg (<7.4 kPa); 56–60 mmHg (7.4–8 kPa) with hypoxic damage) hypoxaemia treated with LTOT. After controlling for confounders, no difference was observed in transplant-free survival in ILD patients with moderate compared with severe hypoxaemia despite LTOT. However, as acknowledged by the authors, patients with moderate resting hypoxaemia treated with LTOT may have been more likely than untreated patients to have other comorbidities including PH or heart failure. Although suggestive of a lack of benefit of LTOT initiation in patients with less severe hypoxaemia, the findings of this study would need to be confirmed prospectively.

Is ambulatory oxygen therapy helpful in ILD patients and when should it be considered?

Severe exertional hypoxaemia is frequent in ILD patients, often occurring in the absence of resting hypoxaemia, and contributing to exercise intolerance, poor quality of life and reduced survival [21, 22]. In patients with exertional hypoxaemia, ambulatory oxygen therapy (AOT) can be used during exercise and/or activities of daily life [7, 23, 24]. AOT can be delivered *via* liquid oxygen, oxygen gas cylinders or portable oxygen concentrators (POCs). As POCs concentrate oxygen from the air, most only provide oxygen with pulsed rather than continuous delivery, reaching lower maximum flows than oxygen cylinders or liquid oxygen. Pulsed delivery with lower oxygen flows may be insufficient to correct hypoxaemia in patients with advanced ILD experiencing severe exertional desaturation.

The more severe exertional hypoxaemia seen in patients with ILD, compared with COPD, highlights the need for ILD-specific studies [25]. The 2-week crossover Ambulatory Oxygen in Fibrotic Lung Disease (AmbOx) trial showed that AOT was associated with improvement in breathlessness and quality of life in patients with ILD and isolated exertional hypoxaemia (peripheral capillary oxygen saturation (S_{pO_2}) ⩽88% on 6-min walk test (6MWT)) [26].

Current practice guidelines provide contradictory indications for initiating AOT in ILD patients. The British Thoracic Society guidelines state that AOT should not routinely be offered to patients who are not eligible for LTOT, although recognising that some breathless patients may benefit from AOT [7]. By contrast, the more recent American Thoracic Society guidelines, published after the AmbOx trial, reached a conditional recommendation for AOT prescription for patients with ILD with severe exertional desaturation (S_{pO_2} ⩽88% on 6MWT), despite low certainty due to the paucity of evidence [8]. The Australian guidelines also recommend AOT for these patients [9]. An international Delphi survey supports AOT in ILD patients with exertional desaturation, although a consensus on desaturation thresholds for initiation of AOT was not reached [11].

The currently recruiting PFOX trial is a double-blind placebo-controlled trial comparing quality of life and physical activity between ambulatory oxygen and placebo air delivered *via* POC for 6 months in ILD patients with exertional desaturation [27, 28]. The benefits of AOT are likely to depend on whether optimal correction of exertional hypoxia is achieved, particularly with more strenuous exertion. Many currently

available modes of oxygen delivery may not provide enough oxygen to fully relieve hypoxaemia in ILD patients. The ongoing High Oxygen Delivery to Preserve Exercise Capacity in Patients with IPF treated with Nintedanib (HOPE-IPF) trial will evaluate the impact of exercise training using high oxygen delivery (60% oxygen) on cycle endurance time and symptoms, compared with exercise training where oxygen supplementation is targeted at S_{pO_2} ⩾88% [29]. It is hypothesised that the higher oxygen flows will allow greater exercise intensity and thereby improved exercise tolerance and quality of life [29, 30]. Interestingly, a pilot crossover study of domiciliary high-flow nasal cannula oxygen (HFNC) in 10 ILD patients already on either AOT or LTOT, where patients were asked to use the HFNC for 8 h a day, was associated with improvements in 6MWT distance and breathlessness, suggesting this modality should be further studied in ILD patients [30, 31].

How can exertional desaturation be assessed?

Ensuring adequate ambulatory oxygen prescription in ILD relies upon regular testing for exertional desaturation [22, 32]. The 6MWT is a widely used field exercise test [33], enabling monitoring of disease progression and supplemental oxygen need [34, 35]. Desaturation to ⩽88% on 6MWT is the most used threshold for AOT prescription [8], although ILD patients with less severe desaturation may benefit from AOT [36, 37]. The 6MWT shows responsiveness to change with acute oxygen administration [14] and is used to titrate the flow of oxygen needed to correct hypoxaemia. However, the 6MWT is time- and space-consuming, due to the need for a 30-min break between the two tests and a 30-m corridor [34]. Of late, the 1-min sit-to-stand test (1STS) has gained popularity. Significant correlations were seen between distance walked during 6MWT and number of repetitions on 1STS, as well similarities in maximal oxygen uptake, nadir S_{pO_2} and frequency of desaturation [38–40], suggesting that the 1STS may offer a simpler alternative to the 6MWT, with potential for primary care use. However, responsiveness to acute oxygen administration has not been demonstrated.

The "DeOx" score is a simple score (from 0 to 2) to predict exertional desaturation to ⩽88% in ILD patients. A score of 2, reached when resting saturation is ⩽95% and the diffusing factor for carbon monoxide (D_{LCO}) is ⩽40%, successfully predicted exertional desaturation in 78.5% of patients in a cohort of 300 [41]. In busy outpatient clinics, this simple score could be used to screen patients requiring exertional desaturation tests.

What about nocturnal oxygen?

Nocturnal hypoxaemia is common in patients with ILD and is not tightly related to daytime hypoxaemia or ILD severity [42]. It can occur with or without obstructive sleep apnoea syndrome. Troy *et al.* [43] observed that nocturnal hypoxaemia, defined as >10% total sleep time spent with S_{pO_2} <90%, was associated with development of PH, as measured by echocardiography, and with worse survival. Future

TABLE 1 Summary of the indications/evidence for oxygen therapy in interstitial lung disease (ILD)

Long-term oxygen therapy	Recommended by all major ILD guidelines in severe resting hypoxaemia (<56 mmHg; <7.4 kPa) or moderate resting hypoxaemia (56–59 mmHg; 7.4–8 kPa) with hypoxic organ damage. The benefit of LTOT in moderate resting hypoxaemia is uncertain in ILD.
Testing for exertional desaturation	The 6MWT is the most commonly used test to assess for exertional desaturation, although the 1STS is gaining popularity. Tools like the "DeOx" score could be used to screen for the need for formal assessment in time-pressured settings.
Ambulatory oxygen therapy	Ambulatory oxygen may improve quality of life and breathlessness in ILD patients with significant exertional desaturation (S_{pO_2} ⩽88%). Whether less marked exertional desaturation is associated with benefit from ambulatory oxygen is unclear. In ILD patients with marked exertional hypoxaemia, certain modes of oxygen delivery may not fully relieve hypoxaemia.
Nocturnal oxygen therapy	Nocturnal hypoxaemia can occur in the absence of daytime hypoxaemia at rest, and appears to be associated with worse outcomes. Further studies are needed to understand the impact of different thresholds of nocturnal hypoxaemia on prognosis, and whether correction of nocturnal hypoxaemia is associated with benefit.

LTOT: long-term oxygen therapy; 6MWT: 6-min walk test; 1STS: 1-min sit-to-stand test; "DeOx" score: deoxygenation score; S_{pO_2}: peripheral capillary oxygen saturation.

studies are needed to assess the impact of different thresholds of nocturnal hypoxaemia on ILD progression, development of PH and survival, and to investigate the impact of treating nocturnal hypoxaemia in ILD patients.

Future recommendations

Given the limited evidence base specific to ILD, clinical trials and quasi-experimental trial designs are necessary to better define the use of supplemental oxygen in ILD (table 1). Studies are needed to assess whether treatment of nocturnal hypoxaemia could prevent/reduce the development of PH and improve survival. Importantly, research into more effective and user-friendly ambulatory oxygen delivery systems is urgently needed for ILD patients whose life is significantly restrained by the practicalities of AOT, to allow independent and active lives, with fewer burdens despite the respiratory limitations [44].

Conflict of interest: None declared.

References

1 Petty TL, Finigan MM. Clinical evaluation of prolonged ambulatory oxygen therapy in chronic airway obstruction. *Am J Med* 1968; 45: 242–252.
2 Jacobs SS, Lindell KO, Collins EG, *et al.* Patient perceptions of the adequacy of supplemental oxygen therapy. Results of the American Thoracic Society nursing assembly oxygen working group survey. *Ann Am Thorac Soc* 2018; 15: 24–32.
3 Khor YH, Gutman L, Abu Hussein N, *et al.* Incidence and prognostic significance of hypoxemia in fibrotic interstitial lung disease: an international cohort study. *Chest* 2021; 160: 994–1005.
4 Continuous or nocturnal oxygen therapy in hypoxemic chronic obstructive lung disease: a clinical trial. Nocturnal Oxygen Therapy Trial Group. *Ann Intern Med* 1980; 93: 391–398.
5 Long term domiciliary oxygen therapy in chronic hypoxic cor pulmonale complicating chronic bronchitis and emphysema. Report of the Medical Research Council Working Party. *Lancet* 1981; 1: 681–686.
6 Crockett AJ, Cranston JM, Antic N. Domiciliary oxygen for interstitial lung disease. *Cochrane Database Syst Rev* 2001; 3: CD002883.
7 Hardinge M, Annandale J, Bourne S, *et al.* British Thoracic Society guidelines for home oxygen use in adults. *Thorax* 2015; 70: Suppl. 1, i1–i43.
8 Jacobs SS, Krishnan JA, Lederer DJ, *et al.* Home oxygen therapy for adults with chronic lung disease. An official American Thoracic Society clinical practice guideline. *Am J Respir Crit Care Med* 2020; 202: e121–e141.
9 McDonald CF. Home oxygen therapy. *Aust Prescr* 2022; 45: 21–24.
10 Swinburn CR, Mould H, Stone TN, *et al.* Symptomatic benefit of supplemental oxygen in hypoxemic patients with chronic lung disease. *Am Rev Respir Dis* 1991; 143: 913–915.
11 Lim RK, Humphreys C, Morisset J, *et al.* Oxygen in patients with fibrotic interstitial lung disease: an international Delphi survey. *Eur Respir J* 2019; 54: 1900421.
12 Kreuter M, Bendstrup E, Russell AM, *et al.* Palliative care in interstitial lung disease: living well. *Lancet Respir Med* 2017; 5: 968–980.
13 Higginson IJ, Bausewein C, Reilly CC, *et al.* An integrated palliative and respiratory care service for patients with advanced disease and refractory breathlessness: a randomised controlled trial. *Lancet Respir Med* 2014; 2: 979–987.
14 Bell EC, Cox NS, Goh N, *et al.* Oxygen therapy for interstitial lung disease: a systematic review. *Eur Respir Rev* 2017; 26: 160080.
15 Koyauchi T, Hasegawa H, Kanata K, *et al.* Efficacy and tolerability of high-flow nasal cannula oxygen therapy for hypoxemic respiratory failure in patients with interstitial lung disease with do-not-intubate orders: a retrospective single-center study. *Respiration* 2018; 96: 323–329.
16 Albert RK, Au DH, Blackford AL, *et al.* A randomized trial of long-term oxygen for COPD with moderate desaturation. *N Engl J Med* 2016; 375: 1617–1627.
17 Górecka D, Gorzelak K, Sliwiński P, *et al.* Effect of long-term oxygen therapy on survival in patients with chronic obstructive pulmonary disease with moderate hypoxaemia. *Thorax* 1997; 52: 674–679.
18 Lacasse Y, Casaburi R, Sliwinski P, *et al.* Home oxygen for moderate hypoxaemia in chronic obstructive pulmonary disease: a systematic review and meta-analysis. *Lancet Respir Med* 2022; 10: 1029–1037.
19 Khor YH, Harrison A, Robinson J, *et al.* Moderate resting hypoxaemia in fibrotic interstitial lung disease. *Eur Respir J* 2021; 57: 2001563.
20 Palm A, Ekström M. Hypoxemia severity and survival in ILD and COPD on long-term oxygen therapy – the population-based DISCOVERY study. *Respir Med* 2021; 189: 106659.
21 Nishiyama O, Taniguchi H, Kondoh Y, *et al.* Health-related quality of life in patients with idiopathic pulmonary fibrosis. What is the main contributing factor? *Respir Med* 2005; 99: 408–414.
22 Flaherty KR, Andrei AC, Murray S, *et al.* Idiopathic pulmonary fibrosis: prognostic value of changes in physiology and six-minute-walk test. *Am J Respir Crit Care Med* 2006; 174: 803–809.

23 Arizono S, Furukawa T, Taniguchi H, *et al.* Supplemental oxygen improves exercise capacity in IPF patients with exertional desaturation. *Respirology* 2020; 25: 1152–1159.
24 Kozu R, Shingai K, Hanada M, *et al.* Respiratory impairment, limited activity, and pulmonary rehabilitation in patients with interstitial lung disease. *Phys Ther Res* 2021; 24: 9–16.
25 Du Plessis JP, Fernandes S, Jamal R, *et al.* Exertional hypoxemia is more severe in fibrotic interstitial lung disease than in COPD. *Respirology* 2018; 23: 392–398.
26 Visca D, Mori L, Tsipouri V, *et al.* Effect of ambulatory oxygen on quality of life for patients with fibrotic lung disease (AmbOx): a prospective, open-label, mixed-method, crossover randomised controlled trial. *Lancet Respir Med* 2018; 6: 759–770.
27 Holland AE, Corte T, Chambers DC, *et al.* Ambulatory oxygen for treatment of exertional hypoxaemia in pulmonary fibrosis (PFOX trial): a randomised controlled trial. *BMJ Open* 2020; 10: e040798.
28 Khor YH, Holland AE, Goh NSL, *et al.* Ambulatory oxygen in fibrotic interstitial lung disease: a pilot, randomized, triple-blinded, sham-controlled trial. *Chest* 2020; 158: 234–244.
29 Ryerson CJ, Camp PG, Eves ND, *et al.* High oxygen delivery to preserve exercise capacity in patients with idiopathic pulmonary fibrosis treated with nintedanib. Methodology of the HOPE-IPF study. *Ann Am Thorac Soc* 2016; 13: 1640–1647.
30 Harada J, Nagata K, Morimoto T, *et al.* Effect of high-flow nasal cannula oxygen therapy on exercise tolerance in patients with idiopathic pulmonary fibrosis: a randomized crossover trial. *Respirology* 2022; 27: 144–151.
31 Weinreich UM, Burchardt C, Huremovic J. The effect of domiciliary high flow nasal cannula treatment on dyspnea and walking distance in patients with interstitial lung disease – a pilot study. *Chron Respir Dis* 2022; 19: 14799731221137085.
32 Vainshelboim B, Kramer MR, Izhakian S, *et al.* Physical activity and exertional desaturation are associated with mortality in idiopathic pulmonary fibrosis. *J Clin Med* 2016; 5: 73.
33 du Bois RM, Weycker D, Albera C, *et al.* Six-minute-walk test in idiopathic pulmonary fibrosis: test validation and minimal clinically important difference. *Am J Respir Crit Care Med* 2011; 183: 1231–1237.
34 Holland AE, Spruit MA, Troosters T, *et al.* An official European Respiratory Society/American Thoracic Society technical standard: field walking tests in chronic respiratory disease. *Eur Respir J* 2014; 44: 1428–1446.
35 Lama VN, Flaherty KR, Toews GB, *et al.* Prognostic value of desaturation during a 6-minute walk test in idiopathic interstitial pneumonia. *Am J Respir Crit Care Med* 2003; 168: 1084–1090.
36 Singh SJ, Puhan MA, Andrianopoulos V, *et al.* An official systematic review of the European Respiratory Society/American Thoracic Society: measurement properties of field walking tests in chronic respiratory disease. *Eur Respir J* 2014; 44: 1447–1478.
37 Gao J, Kalafatis D, Carlson L, *et al.* Baseline characteristics and survival of patients of idiopathic pulmonary fibrosis: a longitudinal analysis of the Swedish IPF Registry. *Respir Res* 2021; 22: 40.
38 Tremblay Labrecque PF, Harvey J, Nadreau É, *et al.* Validation and cardiorespiratory response of the 1-min sit-to-stand test in interstitial lung disease. *Med Sci Sports Exerc* 2020; 52: 2508–2514.
39 Oishi K, Matsunaga K, Asami-Noyama M, *et al.* The 1-minute sit-to-stand test to detect desaturation during 6-minute walk test in interstitial lung disease. *NPJ Prim Care Respir Med* 2022; 32: 5.
40 Briand J, Behal H, Chenivesse C, *et al.* The 1-minute sit-to-stand test to detect exercise-induced oxygen desaturation in patients with interstitial lung disease. *Ther Adv Respir Dis* 2018; 12: 1753466618793028.
41 Alfieri V, Crisafulli E, Visca D, *et al.* Physiological predictors of exertional oxygen desaturation in patients with fibrotic interstitial lung disease. *Eur Respir J* 2020; 55: 1901681.
42 Kolilekas L, Manali E, Vlami KA, *et al.* Sleep oxygen desaturation predicts survival in idiopathic pulmonary fibrosis. *J Clin Sleep Med* 2013; 9: 593–601.
43 Troy LK, Young IH, Lau EMT, *et al.* Nocturnal hypoxaemia is associated with adverse outcomes in interstitial lung disease. *Respirology* 2019; 24: 996–1004.
44 Dakkak J, Tang W, Smith JT, *et al.* Burden and unmet needs with portable oxygen in patients on long-term oxygen therapy. *Ann Am Thorac Soc* 2021; 18: 1498–1505.