

## EDITORIAL

## Exercise desaturation and oxygen therapy in ILD and COPD: Similarities, differences and therapeutic relevance

**Key words:** interstitial lung disease, oxygen therapy, pulmonary fibrosis.

The interstitial lung diseases (ILD) and chronic obstructive pulmonary disease (COPD) are chronic lung diseases with markedly different aetiologies, incidences, prevalences, pathologies and prognoses. Patients with both ILD and COPD present with increasing breathlessness as a common symptom and exhibit physiological derangements which may include oxygen desaturation during exercise. In COPD, the mechanism of desaturation relates largely to ventilation-perfusion (V/Q) mismatch;<sup>1</sup> although V/Q mismatch is an important causative mechanism in ILD, diffusion limitation contributes to a significant degree, as do reductions in mixed venous oxygen content and hypoxic pulmonary vasoconstriction.<sup>2</sup>

The authors of a retrospective study from Canada in this issue of *Respirology* compared the pattern of oxygen desaturation during a walk test in patients with fibrotic ILD with that of a group of patients with COPD. The aim of the study was to identify predictive factors for exercise desaturation in both groups.<sup>3</sup> The majority of patients included had undergone a 6-min walk test (6MWT) during pulmonary rehabilitation or ILD clinical assessment, while around a quarter of the ILD group had undergone a 'walking oximetry test' instead of the 6MWT to assess exercise desaturation when under consideration for ambulatory oxygen. This study of just over 400 patients found that exertional hypoxaemia was more common and more severe in ILD than in COPD, independent of lung function and that a low carbon monoxide diffusing capacity (DL<sub>CO</sub>) was the predominant predictor of oxygen desaturation in both groups. In the ILD patients, who had mild to moderate disease as determined by lung function testing, 49% had a nadir arterial oxygen saturation measured by pulse oximetry (SpO<sub>2</sub>) ≤ 88% and 75% had a decline in SpO<sub>2</sub> ≥ 4% from baseline. In the COPD group, who had moderately severe disease as reflected in lung function tests, nadir SpO<sub>2</sub> ≤ 88% occurred in just over a quarter of patients, while around 50% had a fall in SpO<sub>2</sub> ≥ 4% from baseline. The link between reduction in DL<sub>CO</sub> and level of desaturation in COPD has been described previously<sup>4</sup> and is postulated to relate to degree of emphysema and/or pulmonary hypertension. In both COPD and ILD, exercise-induced hypoxaemia is associated with a poorer prognosis.<sup>5,6</sup> Some degree of pulmonary hypertension is common in both conditions, occurring in up to 45% of patients with advanced idiopathic pulmonary fibrosis (IPF).<sup>7</sup> Patients with ILD (especially IPF) and pulmonary hypertension have a lower DL<sub>CO</sub>,

worse exercise tolerance, more exercise-induced oxygen desaturation and a poorer prognosis.<sup>8</sup>

A description of similarities and differences in the exercise responses of patients with these two chronic lung diseases has the potential to contribute to a better understanding of the pathophysiology. Will it result in improved treatment?

Oxygen therapy is prescribed for continuous use in patients with either COPD or ILD who demonstrate persistent severe resting hypoxaemia. The results of studies which demonstrated the life-prolonging benefits of continuous oxygen therapy in patients with COPD and severe resting hypoxaemia were published in the 1980s.<sup>9,10</sup> It seems extraordinary that, although nearly 35 years has elapsed since the publication of the results of these trials, there is still no direct evidence for a similar mortality benefit in patients with severe resting hypoxaemia as a consequence of ILD, mainly due to the absence of controlled studies. This may be because of the presumed difficulty of recruiting patients to study at such a late stage of their disease, or perhaps because it is thought that there is lack of equipoise and no clear justification to deny patients potentially life-prolonging therapy (as well as potential symptomatic improvement).

There is convincing evidence that prescription of supplemental oxygen in patients with COPD and exertional desaturation in the absence of severe resting hypoxaemia does not improve real-world outcomes.<sup>11,12</sup> Whether exertional desaturation in patients with ILD without resting hypoxaemia should be treated with supplemental oxygen is unclear. A recent Cochrane meta-analysis of studies of exertional oxygen in patients with IPF found only three low-quality studies.<sup>13</sup> Two of the three studies showed no benefit of exertional oxygen on exercise capacity or exertional dyspnoea; however, it was noted that the oxygen was not titrated to prevent ongoing exertional desaturation. A recent Japanese study found no benefit of supplemental oxygen versus air in a cross-over randomized controlled trial in 20 patients with IPF; however, the oxygen flow rate of 4 L/min via a demand oxygen delivery device was once again inadequate to maintain oxygen saturations >88% in the oxygen group.<sup>14</sup>

The authors of the current study remind us that oxygen desaturation with exertion is common in ILD and, as in COPD, is associated with a reduction of DL<sub>CO</sub>. Mechanisms underlying the desaturation merit research and future studies would ideally include some assessment of pulmonary artery pressure at rest and with exertion, with and without supplemental oxygen. Whether desaturation on exertion in ILD requires treatment with oxygen therapy is uncertain. In a recent systematic review of oxygen

therapy for ILD, there were no observed effects of oxygen therapy on dyspnoea during exercise in ILD, although exercise capacity was increased.<sup>15</sup> Larger randomized controlled trials of oxygen therapy in ILD, hopefully providing adequate supplemental oxygen to abolish hypoxaemia during exertion, are already underway<sup>16</sup> or soon will be (ACTRN12617000054314): their results are eagerly awaited.

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## REFERENCES

- Wagner PD, Dantzker PR, Dueck R, Clausen JL, West JB. Ventilation-perfusion inequality in chronic obstructive pulmonary disease. *J. Clin. Invest.* 1977; **59**: 203–6.
- Troy LK, Young IH, Lau EM, Corte TJ. Exercise pathophysiology and the role of oxygen therapy in idiopathic interstitial pneumonia. *Respirology* 2016; **21**: 1005–14.
- Du Plessis J, Fernandes S, Jamal R, Camp P, Johansson K, Schaeffer M, Wilcox PG, Guenette JA, Ryerson CJ. Exertional hypoxemia is more severe in fibrotic interstitial lung disease than chronic obstructive pulmonary disease. *Respirology* 2017. <https://doi.org/10.1111/resp.13226>.
- Owens GR, Rogers RM, Pennock BE, Levin D. The diffusing capacity as a predictor of arterial oxygen desaturation during exercise in patients with chronic obstructive pulmonary disease. *N. Engl. J. Med.* 1984; **310**: 1218–21.
- Lama VN, Martinez FJ. Resting and exercise physiology in interstitial lung disease. *Clin. Chest Med.* 2004; **25**: 435–53.
- Waatevik M, Johannessen A, Gomez Real F, Aanerud M, Hardie JA, Bakke PS, Lind Eagan TM. Oxygen desaturation in 6 min-walk test is a risk factor for adverse outcomes in COPD. *Eur. Respir. J.* 2016; **48**: 82–91.
- Shorr AF, Wainwright JL, Cors CS, Lettieri CJ, Nathan SD. Pulmonary hypertension in patients with pulmonary fibrosis awaiting transplant. *Eur. Respir. J.* 2007; **4**: 715–21.
- Polomis D, Runo JR, Meyer KC. Pulmonary hypertension in interstitial lung disease. *Curr. Opin. Pulm. Med.* 2008; **14**: 462–9.
- 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**: 681–6.
- Nocturnal Oxygen Therapy Trial Group. Continuous or nocturnal oxygen therapy in hypoxemic chronic obstructive lung disease: a clinical trial. *Ann. Intern. Med.* 1980; **93**: 391–8.
- Moore RP, Berlowitz DJ, Denehy L, Pretto JJ, Brazzale DJ, Sharpe K, Jackson B, McDonald CF. A randomised trial of domiciliary, ambulatory oxygen in patients with COPD and dyspnoea but without resting hypoxaemia. *Thorax* 2011; **66**: 32–7.
- The Long-Term Oxygen Treatment Trial Research Group. A randomized trial of long-term oxygen for COPD with moderate desaturation. *N. Engl. J. Med.* 2016; **375**: 1617–27.
- Sharp C, Adamali H, Millar AB. Ambulatory and short-burst oxygen for interstitial lung disease. *Cochrane Database Syst. Rev.* 2016; **7**: CD011716.
- Nishiyama O, Miyajima H, Fukai Y, Yamazaki R, Satoh R, Yamagata T, Sano H, Iwanaga T, Higashimoto Y, Nakajima H *et al.* Effect of ambulatory oxygen on exertional dyspnea in IPF patients without resting hypoxemia. *Respir. Med.* 2013; **107**: 1241–6.
- Bell EC, Cox NS, Goh N, Glaspole I, Westall GP, Watson A, Holland AE. Oxygen therapy for interstitial lung disease: a systematic review. *Eur. Respir. Rev.* 2017; **26**: 160080.
- Ryerson CJ, Camp PG, Eves ND, Schaeffer M, Syed N, Dhillon S, Jensen D, Maltais F, O'Donnell DE, Raghavan N *et al.* High oxygen delivery to preserve exercise capacity in patients with idiopathic fibrosis treated with nintedanib. *Ann. Am. Thorac. Soc.* 2016; **13**: 1640–6.