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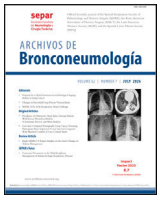

Editorial

Isolated Exertional Hypoxaemia in Pulmonary Fibrosis: A Complex Story Without a Satisfying Ending

At the time of diagnosis, it is very likely that a person with pulmonary fibrosis (PF) will report exertional breathlessness, will probably experience fatigue, and will almost certainly be less physically active than their healthy peers [1,2]. Up to 40% of these patients already have isolated exertional hypoxaemia [3], which can be present even when lung function is well preserved. In patients who do not yet have exertional hypoxaemia, an additional 40% will develop it within 5 years [3]. The presence of exertional hypoxaemia is, quite rightly, troubling for both patients and health professionals. Its association with increased mortality has been understood for more than 20 years [4], with potential contribution to development of pulmonary hypertension and/or resting hypoxaemia. For patients, it may prompt the first conversations about use of oxygen therapy, perceived by many as a highly significant 'touchpoint' in their illness [5].

Current clinical practice guidelines make weak or conditional recommendations in favour of ambulatory oxygen therapy for exertional hypoxaemia in PF [6,7]. With the lack of data related to disease progression or death, these recommendations are underpinned by laboratory-based exercise studies suggesting acute improvements in exercise capacity with supplemental oxygen, together with the 2-week AmbOx crossover trial suggesting a positive effect on quality of life [8]. Whilst ambulatory oxygen is often assumed to enable higher levels of daily life activities with less breathlessness, evidence supporting this premise has been lacking. Unsurprisingly, this gap has contributed to variation in access to ambulatory oxygen therapy across jurisdictions, causing patient distress and exacerbating inequities in care.

The recent PFOX trial of ambulatory oxygen therapy [9] highlights the importance of clinical trials to address key evidence gaps, even for treatments that have become embedded in routine practice. This multinational randomised sham-controlled trial recruited people with PF and isolated exertional hypoxaemia, and compared ambulatory oxygen vs. ambulatory air delivered by portable concentrator over 6 months. There was no between-group difference for the primary outcome of daily-life physical activity at 3 months. The minimal clinically important difference for this outcome lay well outside the 95% confidence interval, making a clinically important effect unlikely. There were no effects favouring ambulatory oxygen for secondary outcomes, including breathlessness, fatigue and quality of life. Adherence was low, with 25% of participants discontinuing the portable concentrator at 6 months, and the remainder using it for <40 min/day. These results indicate that the exertional hypoxaemia story may be more complicated than previously appreciated, and its treatment with a portable concentrator may not be routinely indicated.

Whilst the PFOX trial did not provide a satisfying ending to the story of isolated exertional hypoxaemia in PF, it offers important lessons for both research and clinical practice.

The PFOX trial has demonstrated that rigorous sham-controlled trials of ambulatory oxygen therapy are feasible in PF, using outcomes that reflect how patients feel and function, with a clinically meaningful follow-up period [9]. Non-drug treatments for PF and other lung conditions should be held to the same standards of evaluation as pharmacotherapies, with measures taken to reduce the risk of bias that are common to such trials. The PFOX trial successful blinded participants, clinicians and researchers and maintained follow-up regardless of treatment adherence. Like other major trials of home oxygen therapy in the last decade [10–12], recruitment proved challenging, highlighting the importance of international collaborative networks for future trials.

Whilst future clinical trials will be critical to write the next chapter of the exertional hypoxaemia story, the PFOX trial suggests a pause is necessary to address two major limitations. Firstly, we need a clearer rationale for treating exertional hypoxaemia in PF. Are we aiming to address symptoms and wellbeing, or to modify long-term risks such as pulmonary hypertension and mortality? Clarity on proposed mechanisms of action for ambulatory oxygen therapy, and biomarkers of response, would be a game changer. Secondly, we need smaller, lighter devices capable of delivering higher oxygen flow rates. Patients consistently tell us that current oxygen devices are burdensome and do not meet their needs [13]. Both portable concentrators and oxygen cylinders fail to completely correct exertional hypoxaemia in PF [14]; and the PFOX trial further demonstrated that correction of exertional hypoxaemia in daily life was not fully achieved [9]. Innovation in ambulatory oxygen technology that meets oxygen demand during daily life activities is urgently needed [15]. Until then, future trials cannot determine whether ambulatory oxygen is an effective treatment.

In clinical practice, ambulatory oxygen therapy for PF will not disappear. It continues to have a role for patients using long-term oxygen therapy for resting hypoxaemia, supporting community ambulation. It is important to acknowledge some individuals with PF and isolated exertional hypoxaemia derive substantial benefit from this treatment [13]. The challenge for health professionals is identifying those individuals in whom the benefit outweighs the considerable burden. Efforts to identify 'responders' to ambulatory oxygen in chronic obstructive pulmonary disease have met with

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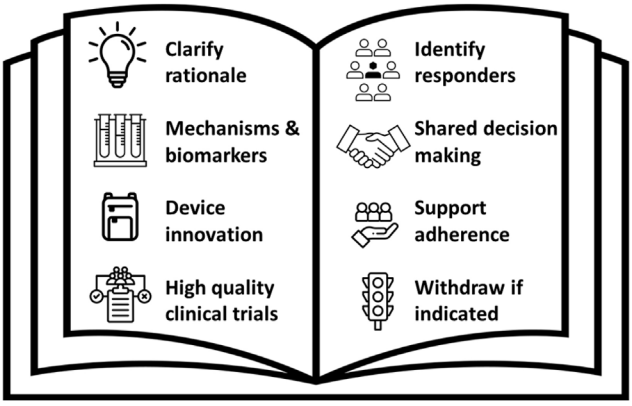

Fig. 1. Future approaches to ambulatory oxygen therapy in pulmonary fibrosis.

little success – in patients with airways disease, improvements in breathlessness were not related to the acute response to oxygen, degree of exertional hypoxaemia, severity of lung disease or sex [16]. Limited evidence from PF suggests that physiology may be only part of the story. In the AmbOx trial, the strongest determinants of ongoing ambulatory oxygen use after the trial were perceived improvements in breathlessness or walking ability [8]. This highlights the importance of behavioural factors in uptake of this complex intervention, and the role of shared decision making in both initiating and continuing therapy.

The story of exertional hypoxaemia in PF is far from over, but we do have a better understanding of the important plot elements to shape its next chapter (Fig. 1). These include a clear rationale for treatment, biomarkers reflecting mechanism, innovative devices delivering optimal oxygen flow, high quality clinical trials, identification of those most likely to benefit, shared decision making, support for uptake and adherence, and consideration of withdrawal where burden exceed benefit. Patients have been telling us for years that our approach to ambulatory oxygen is not good enough [13]. Now we are listening, and ready to change the story.

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Conflict of interests

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