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Journal club

Does ambulatory oxygen improve quality of life in patients with fibrotic lung disease? Results from the AmbOx trial

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Commentary on:

Visca D, *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.

Context

The fibrotic interstitial lung diseases (ILDs) encompass a heterogenous group of conditions affecting the lung parenchyma, resulting in progressive, irreversible scarring. While prognosis varies between conditions, they commonly have a significant adverse impact both on health-related quality of life (HRQoL) and on survival. For idiopathic pulmonary fibrosis (IPF), the most common and fatal ILD, antifibrotic therapies (nintedanib [1] and pirfenidone [2]) have been shown to slow rate of progression, but the disease remains incurable. Management of all fibrotic ILDs therefore requires symptomatic and supportive care as well as interventions aimed at modifying the disease course [3].

Progressive fibrotic ILD causes cumulative impairment in gas transfer, with resultant desaturation and dyspnoea on exertion, even if oxygen saturations are acceptable at rest. As the disease progresses, even simple activities of daily living can be limited by severe dyspnoea, significantly impacting HRQoL. A small number of studies have been undertaken to investigate the effect of effect of supplemental oxygen on exercise performance in ILD, with a Cochrane review concluding that there was insufficient evidence to support or refute ambulatory oxygen therapy (AOT) or short-burst oxygen therapy in patients with exercise-induced desaturation [4]. However, none of the three studies included in this review nor two subsequent publications [5, 6] looked at HRQoL as an outcome, focusing instead on physiological parameters in a laboratory environment.

HRQoL refers to subjective experiences reported by the patient. It can be formally assessed using a variety of tools that have been developed for use in respiratory conditions (*e.g.* the St George's Respiratory Questionnaire (SGRQ)) [7] or in ILD specifically (*e.g.* King's Brief Interstitial Lung Disease Health Status Questionnaire (K-BILD) [8]). These assess self-reported patient experience across a variety of domains (*e.g.* chest symptoms, psychological, breathlessness and activity). They are of increasing interest as a research outcome as it is recognised that interventions that improve objective markers of disease progression (including antifibrotic therapy in IPF) may not improve quality of life. Research is therefore needed into interventions that improve quality of life in advanced fibrotic ILD.

The AmbOx study [9] was designed to investigate the impact of AOT on HRQoL in patients with fibrotic ILD.

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The AmbOx trial provides RCT evidence for ambulatory oxygen therapy improving HRQoL in patients with fibrotic ILD http://ow.ly/uHC030nEzsz

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Methods

This was a prospective randomised control trial (RCT) performed across three centres in the UK. It involved patients aged ≥18 years with a fibrotic interstitial lung disease, who were not hypoxic at rest (resting saturations >94%) but had exercise-induced desaturation, defined as a fall in transcutaneous oxygen saturations to ≤88% on a 6-min walk test (6MWT). The study used a crossover design with patients randomly allocated to either AOT or no intervention for a period of 2 weeks, after which they swapped to the other arm. For the trial itself, there was no placebo control or blinding. However, for the baseline 6MWT performed at the start of the trial, placebo air was used for those randomised to the control group, with labels on the gas cylinders covered to ensure blinding of participants.

The primary outcome of the study was HRQoL as measured by the K-BILD questionnaire, with a minimal clinically important difference (MCID) considered to be 8 (total score range for the questionnaire 0–100). A K-BILD questionnaire was completed by all participants at baseline, the end of the first 2-week trial block and at the end of the second 2-week trial block after crossover of treatment arms. A variety of secondary outcomes were also examined. These included other self-reported outcome questionnaires: the University of California San Diego Shortness of Breath Questionnaire, the SGRQ and the Hospital Anxiety and Depression Scale (HADS). Patients were given personal activity monitors to investigate whether ambulatory oxygen was associated with increased physical activity levels. The results for the baseline 6MWT, performed on either oxygen or placebo air, were also reported.

Main results

84 patients were randomised, with 41 allocated to oxygen first and 43 to no oxygen. These groups were well matched at baseline, with no difference in age and sex distribution, lung function, cardiac function or performance on 6MWT. IPF accounted for a similar proportion of fibrotic ILD cases in both arms (56% and 60%, respectively) and there were no significant differences in K-BILD scores (the primary outcome of the study) at baseline (mean 51.2 in the oxygen first arm and 49.7 in the no oxygen first arm). As would be expected from a study in this patient population, participants had moderate to severe restrictive lung disease, with mean diffusing capacity of carbon monoxide of 39.8% and 37.3% predicted, and a forced vital capacity of 71.1% and 75.1% predicted in the oxygen first and no oxygen first arms, respectively.

The first question the study investigated was the effect of oxygen on performance in the 6MWT. This was performed as a blinded placebo-controlled trial, with air-filled cylinders used in the placebo arm. Patients on oxygen walked nearly 20 m further than those on air (373.2 m *versus* 354.7 m, p=0.001) and had significantly shorter oxygen saturation recovery time measured by pulse oximetry (117 s *versus* 217.7 s, p<0.0001). They also had significantly lower Borg dyspnoea and fatigue scores, as well as faster Borg score recovery times (112 s *versus* 171 s, p=0.0008).

Although the results of the 6MWT suggest a physiological benefit of supplemental oxygen during exertion, that does not necessarily correspond to the main focus of this study: quality of life. The primary outcome of the investigation was HRQoL assessed by the K-BILD score. This is composed of three components (breathlessness and activities, chest symptoms, and psychological symptoms) as well as an overall score. It is scored out of 100, with higher scores reflecting better HRQoL. There was a statistically significant improvement in breathlessness and activities (mean 44.4 *versus* 35.8, p<0.0001), chest symptoms (mean 65.5 *versus* 57.9, p=0.009) and total scores (mean 55.5 *versus* 51.8, p<0.0001) in the AOT arm, with no improvement in psychological symptoms (mean 55.2 *versus* 52.8, p=0.12). However, although the differences were statistically significant, the mean difference in the total score was small (3.7 out of 100).

The study also looked at two other patient outcome scores. The SGRQ, a general respiratory HRQoL tool (scored out of 100, with lower scores reflecting better HRQoL), similarly showed small but statistically significant improvement in the Activity (61.5 *versus* 68.9, p=0.003) and Total (48.7 *versus* 52.4, p=0.018) components, but no difference in the Symptoms section (53.3 *versus* 54.9, p=0.51). There were no differences between oxygen and non-oxygen treated patients in the Depression and Anxiety components of the HADS.

The study also used patient activity monitors to investigate whether ambulatory oxygen correlated with increased levels of activity. These results were available for 41 patients, and demonstrated no difference in activity levels or step counts between the ambulatory oxygen and no oxygen periods (mean 5277 steps per day on oxygen *versus* 4799 on no oxygen, p=0.19).

Commentary

There is a paucity of evidence for interventions that improve HRQoL in ILD. This study therefore represents an important step not only in providing evidence-based recommendations for interventions that address this but also in demonstrating that HRQoL can be used as a primary outcome in a RCT in this disease. However, there are some limitations, both in the design of the study and in the findings.

Firstly, apart from the initial 6MWT, this study was not placebo controlled. This study design is reasonable, as the provision of dummy air-filled canisters and accompanying paraphernalia may

place an unfair burden on participants. However, it does make it difficult to determine what effect was due to oxygen and what due to placebo. Conversely, since HRQoL was the primary outcome, and the logistical, social and psychological burden of home oxygen therapy may itself adversely impact patient well-being [10], the study design is appropriate for looking at overall patient experience with AOT.

A second limitation is the short length of the crossover periods, which means we are unable to determine whether quality of life differences persist beyond the 2-week study period. The HOT-HMV trial of home noninvasive ventilation (NIV) in chronic obstructive pulmonary disease, another trial that involved bringing medical equipment into the home environment, showed an initial improvement in HRQoL in the NIV arm, which disappeared beyond month 3 [11]. Longer-term follow up is needed to see whether the improvement seen in AmbOx is maintained.

While AmbOx did yield a positive outcome for the AOT arm, the real-world clinical significance we can extract from these results also needs to be considered. Firstly, although there was a statistically significant difference in total K-BILD score, this difference was small (only 3.7) and well below the previously reported MCID of 8 [12]. The authors address this, citing evidence that in more severe disease (as in the AmbOx study population), a difference of 4 is clinically significant [9]. Regardless of the exact numbers, the small but positive improvements in HRQoL should inform discussions with patients when choosing whether or not to have AOT.

Of the three components of the K-BILD score, the biggest difference between the AOT and control arms was in Breathlessness and Activities, where a mean difference of 8.6 was noted. It is therefore surprising, as well as somewhat disappointing, to see that the data from the activity monitors showed no increase in activity levels in the AOT arm. The reasons for this are not clear but it suggests that drivers and limitations of "activity" in advanced ILD are complex. Other interventions, such as pulmonary rehabilitation, may play a bigger role here, and there is a current study (HOPE-IPF) investigating whether oxygen supplementation may enhance exercise training in IPF [13].

A final notable result from the study is that only 67% of patients chose to continue using AOT at the end of the trial. Unsurprisingly, patients who reported higher improvements in breathlessness and walking ability with AOT were more likely to choose to continue. The fact that a third of patients did not wish to continue using AOT demonstrates the limitations of this intervention in ILD and this should again inform conversation with patients regarding the decision to start home oxygen.

Implications for practice

The AmbOx trial provides RCT evidence for AOT providing a small but significant benefit in HRQoL in patients with advanced fibrotic ILD. Given the paucity of other interventions, this should be recognised and should prompt clinicians to consider this for their patients. When discussing this, clinicians can be positive about the beneficial effects identified, but given the results of the study, discussions should be tempered by realism: improvements are likely to be small, and there is a logistical, social and psychological burden associated with home oxygen therapy [10]. Furthermore, given that this study found that AOT itself did not lead to increased activity levels, the provision of AOT should not be considered sufficient in itself; other interventions, such as pulmonary rehabilitation and addressing co-existing depression or anxiety, remain essential in the management of fibrotic ILD.

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Conflict of interest

A.W. Creamer has nothing to disclose. S.L. Barratt has nothing to disclose.

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