Automated O₂ titration improves exercise capacity in patients with hypercapnic chronic obstructive pulmonary disease: a randomised controlled cross-over trial

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ABSTRACT

Automatically titrated O₂ flows (FreeO₂) was compared with constant O₂ flow on exercise capacity, O₂ saturation and risk of hyperoxia-related hypercapnia in patients with severe COPD with baseline hypercapnia and long-term oxygen therapy (LTOT). Twelve patients were enrolled in a randomised double-blind cross-over study to perform exercise with either FreeO₂ or constant flow. Endurance time (primary outcome) and SpO₂ were both significantly improved with FreeO₂ compared with constant flow ($p<0.04$), although pCO₂ was similar in both conditions. Automated titration of O₂ significantly and clinically improved endurance walking time in patients with severe COPD receiving LTOT, without worsening of pCO₂.

Trial registration number Results, NCT01575327

INTRODUCTION

Acute oxygen (O₂) supplementation improves oxygenation and exercise tolerance in patients with severe COPD when used in a laboratory setting.¹ However, home-based and long-term use of oxygen supplementation is generally unsuccessful in improving exercise tolerance in COPD.² This could be related to insufficient oxygen flow rates to correct exercise-induced hypoxaemia during daily tasks. For example, 24-hour home-based SaO₂ monitoring performed in patients while breathing O₂ at their prescribed flow rate (1–3 L/min) showed inadequate oxygenation during daily tasks³ and mean SaO₂ of 88% during walking.⁴ Indeed, current recommendation is to increase O₂ flow rates during exercise by adding 1 L/min to resting O₂ flow, which might be insufficient. On the other hand, high O₂ flow rates may be considered at risk to worsen hypercapnia in patients with severe COPD.⁵ Closed-loop titration of oxygen flow rates based on pulsed oxygen saturation (SpO₂) continuous measurements may help in optimising oxygen supplementation during exercise.^{6–8} We hypothesised that the FreeO₂ system, a new closed-loop O₂ device that automatically titrates O₂ flows to maintain SpO₂ within predetermined targets, would improve exercise tolerance in patients with severe COPD without worsening hypercapnia.⁷

METHODS

Intervention

In a randomised double-blind cross-over study, we compared the effects of automatically titrated versus constant O₂ flows on exercise tolerance during walking in patients with Global Initiative

for Chronic Obstructive Lung Disease (GOLD) 3–4 COPD. We also studied the impact of these two oxygen supplementation systems on oxygenation and capillary pCO₂ (PcCO₂) during and after exercise. (ClinicalTrials.gov number: NCT01575327, Results).

Outcomes

The primary outcome of the study was endurance time (and the corresponding walking distance) during the endurance shuttle walking test (ESWT) performed at 85% estimated peak VO₂.⁹ Secondary outcomes included time spent within pre-specified SpO₂ targets (<88%, 88%–91%, 92%–96% and >96%), capillary blood gases (pH, PcCO₂), heart rate (HR), dyspnoea and leg fatigue. In addition to the parameters continuously collected by the FreeO₂ system, O₂ flow rates, SpO₂, HR and earlobe capillary blood gases were obtained before, at the end and 10 min after exercise. A modified Borg scale was used to assess dyspnoea and leg-fatigue scores at 1 min intervals during exercise and at the end of exercise. Isotime exercise was assessed for HR, dyspnoea and leg fatigue. It corresponded to the longest time duration reached during the ESWT under both conditions (automatically adjusted O₂ flows and constant O₂ flows). Warm-up was included in the calculation of the endurance time. The washout period between the two walking tests averaged 4.0±4.6 days.

Patient characteristics

Twelve patients (age 65±10 years, Body Mass Index 25±7 kg/m²) with GOLD 3 (n=4) or 4 (n=8) COPD, long-term oxygen therapy (LTOT, mean baseline O₂ flow rates: 1.9±1.0 L/min for 5.5±4.5 years) and resting hypercapnia (mean PaCO₂ 48.7±3.0 mm Hg) were included in the study. The pulmonary function is described in online supplementary table E1. Briefly, FEV₁ was 0.70±0.25 L, 30%±9% predicted, FEV₁/FVC was 50%±15%, TLC was 124%±25% predicted, RV was 225%±76% predicted, inspiratory capacity was 1.42±0.50 L and diffusing capacity of lung for CO was 32%±18% predicted. Patients had a smoking history of 41±19 pack-years (three current smokers) and with 1.3±0.5 respiratory exacerbation per year. They had a 6 min walking distance of 363±72 m, a modified Medical Research Council dyspnoea score of 3.3±0.7

Figure 1 Individual data and mean±SE of endurance time (A) and walking distance (B) during the endurance shuttle walking test when using constant O₂ flows (grey bars) or automatically titrated O₂ flows (FreeO₂) (blue bars). Both endurance time and walking distance were improved in the FreeO₂ condition as compared with constant O₂ flows (p=0.02 and p=0.03, respectively).

and a self-reported spontaneous physical activity of <10 min per day. Sixty-six and 33% of patients respectively exhibited cardiovascular and metabolic comorbidities (see online supplementary table E1). Following baseline assessment, patients performed, on two separate visits, one ESWT receiving either automatically titrated O₂ flows with the FreeO₂ system aiming for a SpO₂ target of 94%⁷ or constant O₂ flows (usual O₂ flow rate +1 L/min). The FreeO₂ system can deliver O₂ flows from 0 to 20 L/min, with 0.1 L/min incremental/decremental steps, on a per-second basis.⁷ More information on the methodology can be found in online supplementary data.

Statistical analysis

Data are expressed using mean±SD. Variables were analysed using a mixed model (and a log-transformed for some variables to fulfil the model assumptions) or using a statistical approach replacing observations by their rank within subjects, called rank transformation. Posteriori comparisons were performed using Tukey's comparison. The level of significance was set at p values <0.05 (R V.3.0.2 and SAS V.9.4).

RESULTS

Here, we found for the first time that patients with severe COPD improved endurance time and walking distance when using automatically titrated O₂ flow compared with constant O₂ flows (+127±236 m, p=0.02 and +138±269 m, p=0.03, respectively, figure 1A and B). This functional improvement was associated with greater O₂ flow rates during exercise (FreeO₂: 5.4±2.7 vs constant O₂ flows: 3.1±1.2 L/min, p=0.01) leading to better O₂ saturation. Indeed, patients spent less time with hypoxaemia while also avoiding hyperoxia with FreeO₂ (figure 2). The lowest O₂ saturation was 83.6%±7.0% with constant O₂ flow versus 89.5%±3.9% with FreeO₂ (p<0.001). Patients spend more time exercising within the pre-specified SpO₂ target (88%–92%) while using FreeO₂ compared with constant O₂ flows while avoiding hyperoxia (figure 2). Despite higher O₂ flow rates with FreeO₂, P_cCO₂ was similar in both conditions across resting, walking test and recovery, suggesting that hypercapnia was not worsened

using higher O₂ flows in these patients (p=0.71, figure 3). Lastly, dyspnoea and leg fatigue scores were significantly reduced at isotime with FreeO₂ compared with constant O₂ flow (5.3±2.1 vs 7.0±2.8, p=0.048 and 1.4±2.0 vs 2.6±2.7, p=0.028, respectively). Changes in endurance time with FreeO₂ correlated with diffusing lung capacity (r=−0.78, p=0.02). No other relationship was found between baseline pulmonary function, blood gas parameters or O₂ flows during exercise.

DISCUSSION

This is the first study to demonstrate that automated oxygen titration improves exercise tolerance in patients with severe COPD. This is a novel and promising result in this population. Indeed, previous studies did not report significant improvement in this outcome compared with constant O₂ flows, despite reduction in hypoxaemia.^{6 8 10} In addition, the +127±236 s increase in endurance time (+33%) found in the present study was beyond the minimal clinically relevant difference for this parameter.¹¹ The severity of the disease may account for the discrepancy between studies since patients with advanced disease are more responsive to adequate oxygenation during exercise.¹² Moreover, the shuttle walking test used in the present study is more responsive to interventions than the 6 min walking test used in previous studies.^{6 8} Lastly, the ability to deliver high oxygen flows is superior with the FreeO₂ device (delivering up to 20 L/min) than other devices.^{6 8} In our study, FreeO₂ enabled 7 out of 12 patients (58%) to use O₂ flow rates above 5 L/min during exercise. Hence, patients with advanced COPD and chronic respiratory failure seem to be good candidates for automatically titrated O₂ supplementation during exercise.¹²

Several mechanisms may explain the improvement in exercise performance with oxygen supplementation in severe COPD. By reducing hypoxaemia, O₂ supplementation may have reduced VE and decreased dynamic hyperinflation.¹ The significant reduction in dyspnoea score found at isotime exercise in the present study with automatically titrated O₂ would support this hypothesis. In addition, the lower leg fatigue score suggests a reduced respiratory metaboreflex allowing better perfusion and

Figure 2 (A) Percentage of time spent in different ranges of SpO₂ during the endurance shuttle walking test when using constant O₂ flows (grey bar) or automatically titrated O₂ flows (FreeO₂) (blue bar). Time spent in the range SpO₂ <88% was reduced when using FreeO₂ compared with constant O₂ flow ($p=0.01$), although time spent in the range SpO₂ (92%–96%) was increased ($p=0.02$). Hyperoxia (time spent in the range of SpO₂ >96%) was not increased by FreeO₂ compared with constant O₂ flow but rather tended to be reduced ($p=0.51$). (B and C) Example of individual traces of SpO₂ (%) (B) and corresponding O₂ flows (C) for a given patient (#2) during the endurance shuttle test while using constant O₂ flows (grey line) or automatically titrated O₂ flows (FreeO₂) (blue line).

oxygenation of contracting muscles, in turn reducing fatigue occurrence.¹³ It is to note, however, that not all the patients were good responders to automated O₂ titration (figure 1). Our results suggest that patients with lower diffusing lung capacity had higher gain in endurance time with FreeO₂ compared with constant O₂ flow. In these patients, it is likely that higher O₂ flows increased O₂ diffusion, which in turn increased muscle oxygenation and consequently aerobic capacity.

Physicians might be reluctant to use high O₂ flows in patients with severe COPD, particularly those with resting hypercapnia, fearing to induce further CO₂ retention.⁵ In the present study, the absence of worsening in hypercapnia was likely linked to the reduced time with hyperoxia due to the working principle of the

FreeO₂ device. Indeed, the FreeO₂ device is set to automatically reduce O₂ flow rates when the measured SpO₂ is above the set SpO₂ target.

Methodological considerations

One limitation of our study is the relatively small sample size. However, a predefined sample size calculation was performed based on preliminary data in this very specific population (see online supplementary data). Another potential limitation was the slightly high SpO₂ target (94%) compared with general recommendation in patients with COPD (88%–92%).¹⁴ However, this threshold was based on previous observations showing that

Figure 3 Earlobe blood capillary pCO₂ measured at baseline (rest), end of exercise (exercise) and 10 min after exercise (recovery) when using constant O₂ flows (grey line and markers) or automatically titrated O₂ flows (FreeO₂) (blue line and markers). There was no significant difference between groups in pCO₂ at any time before, during exercise or during recovery ($p=0.71$).

the use of this 94% SpO₂ target did not induce hypercapnia compared with constant O₂ flows.¹⁰ Lastly, we used arterialised capillary instead of arterial blood samplings. However, capillary samplings were cautiously collected after adequate vasodilation of the earlobe and, in this condition, they are considered as appropriate replacements for arterial samplings.¹⁵

Clinical impact

Ambulatory oxygen therapy had failed to demonstrate long-term benefits in COPD,² perhaps due to insufficient correction of hypoxaemia during daily activities. By allowing adequate oxygenation during activities of daily life such as walking, continuous and precise O₂ titration with automated devices may improve exercise tolerance, a strong determinant of quality of life and survival in patients with COPD.¹⁶ Hence, automated titration such as FreeO₂ may increase the clinical benefits of oxygen therapy in this population.

In summary, we found that automatic titration of O₂ during walking had significant and clinically relevant impact on endurance time in patients with severe COPD receiving LTOT, without worsening pCO₂. Such technological improvements should improve titration of O₂ therapy tailored to individual needs who are constantly changing during daily activities. Nevertheless, caution should be used before generalising the present results to a broader population of patients. Further studies will be necessary to determine which SpO₂ upper limit represents the best trade-off value between optimised oxygenation and minimised CO₂ retention risk. In addition, the fact that larger and heavier O₂ source may be mandated to allow higher O₂ flows during exercise needs to be further considered in subsequent studies.

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