Review Article

Oxygen therapy for COPD

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Abstract: Chronic obstructive pulmonary disease (COPD) is a leading cause of disability and death globally, characterised by progressive breathlessness, loss of function and, in its later stages, chronic hypoxaemia. Long-term continuous oxygen therapy increases life expectancy in patients with severe resting hypoxaemia. However, there are few data to support the use of oxygen in patients with only mild hypoxaemia and more research is required to determine any benefits of oxygen supplementation in COPD in such individuals.

Keywords: Oxygen; oxygen usage; chronic obstructive pulmonary disease (COPD)

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Introduction

As we mark the centenary of the First World War, it is opportune to recall that the medical use of oxygen was popularised when Haldane first used it in treating gas inhalation injuries during World War I (1). Physicians before and after Haldane used oxygen intermittently for treatment of a range of conditions, but it was not until the 1950s (2) saw the development of techniques to facilitate point of care arterial blood gas analysis that the use of oxygen and its titration to a measured sample became common place. In the mid-late 20th century two randomised trials were performed almost simultaneously which have had a profound effect on the management of chronic obstructive pulmonary disease (COPD) over the last three decades.

Benefits of long-term oxygen therapy in COPD: review of original trials

In the 1970s physicians in the United Kingdom and the United States conducted two separate but similar studies to determine whether treating hypoxaemia in COPD could improve mortality. These trials, the UK Medical Research Council (MRC) (3) study and the US Nocturnal Oxygen Therapy Trial (NOTT) (4), showed that long-term oxygen therapy when given for greater than 15 hours per day improved survival in patients with COPD and chronic hypoxaemia (PaO_2 ≤55-60 mmHg), with or without hypercapnia. The UK study included 87 hypercapnic patients with PaO_2 40-55 mmHg on two measurements over a 3-week exacerbation-free observation period. Exclusions were co-existent fibrotic lung disease, pulmonary thromboembolism, hypertension and ischaemic heart disease or other life-threatening illness. In this unblinded controlled study, patients received oxygen via concentrator for 15 hours/day or no oxygen at all. No portable oxygen was provided and patients were not excluded if they continued to smoke. Patients were followed for three years or until death (3). The US Nocturnal Oxygen Treatment Trial (NOTT) enrolled 203 patients with stable hypoxaemia (PaO_2 ≤55 or 59 mmHg in the presence of cor-pulmonale, haematocrit ≥55% or electrocardiographic evidence of P pulmonale) on two measurements over a 3-week exacerbation free period (4). The patients received continuous or nocturnal oxygen and were also followed for a period of 3 years or until death. Those on continuous oxygen received portable oxygen as well. In this study the oxygen flow rate provided was sufficient to increase PaO_2 to 60-80 mmHg, with flow rates increased by 1 L/min during sleep and exercise. In both studies the majority of subjects

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were male with a mean age of 65 years. In the MRC study mortality at three years was 45.2% in the oxygen treated group and 66.7% in controls. In the NOTT mortality rates at 24 months were 27% for the continuous group and 41% for the nocturnal group, demonstrating a significant survival advantage in the continuous oxygen group, in whom the average oxygen usage was 18 hours per day, compared with the nocturnal oxygen only group.

Because of the many similarities between these two trials, the results came to be considered together to demonstrate that oxygen for 15 hours per day was better than no oxygen (data from the MRC study) and that continuous oxygen had a greater mortality benefit than nocturnal oxygen (data from the NOTT) (3,4). These results significantly altered treatment of hypoxaemic COPD and, to this day, domiciliary oxygen is the only therapy (apart from smoking cessation) that has been shown to reduce mortality in COPD (3-5). As a consequence, most international guidelines for the management of oxygen therapy in COPD recommend that oxygen should be considered for patients with stable COPD, who have an oxygen partial pressure in arterial blood (PaO_2) consistently less than or equal to 55 mmHg (7.3 kPa) at rest when awake and breathing air and for patients with PaO_2 56-59 mmHg (7.4-7.8 kPa) with polycythaemia (haematocrit >0.55) or clinical, electrocardiographic or echocardiographic evidence of pulmonary hypertension and or right heart failure (6-9). At assessment, the patient's condition must be stable and all reversible factors (such as anaemia) should have been treated (9). In the Thoracic Society of Australia and New Zealand Position Statement, it is recommended that assessments should be made at least one month after the patient has stopped smoking, given that gas exchange may improve substantially on ceasing smoking (9,10). However, other guidelines do not necessarily recommend smoking cessation and it is to be remembered that at least one of the two studies on which the recommendations are based included current smokers (3). It is generally recommended that oxygen should be used for as many hours of the day as possible; ideally a minimum of 15+ hours.

These recommendations for oxygen therapy are based on two randomised non-placebo-controlled trials containing fewer than 300 patients, conducted over 30 years ago. The indications for prescription of oxygen therapy were the results of pragmatic decisions by the trial designers and the studies were performed in COPD populations that would not necessarily be representative of today's COPD patients, many of whom are older and have more co-morbidity. There have not been any subsequent, high quality randomised controlled studies of long-term oxygen therapy in severely hypoxaemic COPD. A retrospective analysis of South Australian COPD patients prescribed long term home oxygen from a single centre between 1977 and 1999 found the annual death rate was 20-33% per year—worse than that for the control (no oxygen) group in the UK MRC study (11). Reasons for the differences between the prospective MRC study and this retrospective review may include the older age of the patients being prescribed oxygen, the presence of co-morbidities, continued smoking, inadequate treatment of hypoxaemia, lack of adherence or the fact that this was a real world situation rather than a clinical trial. It would seem important to clarify the true impact of long term oxygen therapy on all-cause mortality in those patients who are currently receiving it, many of whom are elderly with multiple co-morbidities. The introduction of local or national databases aimed at capturing information about patients receiving home oxygen could provide an ideal means of obtaining prospective data on patients currently receiving oxygen therapy. The introduction of such a national database in Denmark was associated with an improvement in adherence to guidelines and slight reduction in mortality (12).

Other benefits of long-term oxygen therapy

There is little convincing evidence from studies to date that long-term oxygen therapy has significant benefits other than on survival. Indeed, the mechanism for the improvement in survival with oxygen therapy still remains unclear, despite the observation of small improvements in some haemodynamic parameters in the NOTT (4). Endpoints in the MRC study were physiological characteristics and mortality (3). In the NOTT, neuropsychological tests were assessed in both continuous and nocturnal oxygen groups at baseline and at six months. Only 42% of patients showed improvements at six months and there were no differences between the continuous and nocturnal groups (13). It should be reiterated that the lack of a control group (intranasal air) makes it difficult to determine whether the improvements in neuropsychiatric function were due to more than placebo effect.

With the potential restriction of movement imposed by long-term continuous oxygen therapy, it is possible that the treatment may only prolong suffering rather than improving quality of life (QOL). Non-placebo-controlled trials differ in showing either no benefit or a small benefit

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in health related QOL in subjects commenced on long term continuous oxygen therapy (14,15). Although small improvements in QOL were found in the NOTT (4), the study did not have a placebo (air) arm and thus the presence of a placebo effect is not excluded. Whether oxygen therapy is worthwhile in the context of a particular individual's management should be determined by a comprehensive clinical assessment rather than solely, or mainly, by the increase achieved in PaO_2.

Nocturnal desaturation in COPD: is oxygen therapy indicated?

The clinical consequences of nocturnal hypoxaemia in patients with COPD and daytime PaO_2 ≥60 mmHg (8.0 kPa) are unclear. Although it has been suggested that repetitive transient desaturations throughout sleep may be one mechanism underlying the development of pulmonary hypertension in COPD, the primacy of hypoxia as a driving force in the development of pulmonary hypertension in COPD is now questioned, with systemic inflammation suggested as one of several possible alternative factors. Chaouat *et al.* showed that elevated circulating levels of interleukin-6 correlated with elevations in mean pulmonary artery pressure (16).

C-reactive protein levels have also been shown to correlate with both pulmonary artery pressure and levels of endothelin-1, a potent vasoconstrictor postulated to play a role in vascular remodelling and pulmonary hypertension (17). The issue of the role of inflammation in pulmonary hypertension complicating COPD remains controversial (18). However, *in vitro* animal models of pulmonary artery remodelling related to tobacco smoke studies support such a mechanism (19).

Although a New Zealand study suggested that isolated nocturnal desaturation was very uncommon in a general COPD outpatient population, and that patients with nocturnal desaturation had no worse sleep quality, QOL or daytime somnolence than those without desaturation (20), other studies have reported sleep fragmentation (21) as well as surges in both systemic and pulmonary blood pressure (22) as a consequence of nocturnal desaturation. Fletcher *et al.* suggested that nocturnal desaturation in patients with PaO_2 >60 mmHg occurred in 27% of patients, where desaturation was defined as a desaturation below 90% for five minutes or more, with a nadir saturation of at least 85% (23). Although a small retrospective study by Fletcher *et al*. suggested that patients with nocturnal oxygen desaturation had a poorer survival than those without (24) a subsequent small prospective study by Chaouat *et al.* found that COPD patients with nocturnal desaturation did not develop pulmonary hypertension more than a group of patients without nocturnal desaturation and their prognosis was no different over 6 years of follow-up (25). Whether nocturnal hypoxaemia alone can lead to substantial pulmonary hypertension remains controversial. Fletcher *et al.* demonstrated that nocturnal supplemental oxygen at 3 L/min over three years was associated with a smaller rise in pulmonary artery pressure than in a control group receiving supplemental air (26). However, there was no effect on mortality. A larger 2-year study of patients with COPD and modest daytime hypoxaemia [PaO_2 56-59 mmHg (7.4-7.8 kPa)] who desaturated to a pulse oximeter oxygen saturation (SpO_2) <90% for >30% of the night found no survival benefit in the group receiving oxygen supplementation and no effect on pulmonary haemodynamics (27). There is no international consensus regarding provision of nocturnal oxygen in COPD for patients with daytime PO_2 >60 mmHg.

Episodes of nocturnal hypoxaemia due to hypoventilation or worsening ventilation-perfusion in patients with COPD should be distinguished from those associated with sleep apnoea caused by upper airway obstruction, obesity hypoventilation syndrome or central sleep apnoea. Apnoea syndromes are diagnosed by overnight polysomnography and generally require other forms of therapy (such as continuous positive airway pressure or nocturnal ventilation) rather than supplemental oxygen.

Ambulatory oxygen

In those fulfilling criteria for long term continuous oxygen therapy

Ambulatory oxygen therapy may be used as part of continuous oxygen therapy, in which case its use is aimed at maximising the number of hours per day a person with COPD can use their oxygen for, at the same time as maintaining adequate physical activity including engaging in pulmonary rehabilitation. Pulmonary rehabilitation has been demonstrated to improve exercise capacity and QOL in COPD (28), whilst reduced physical activity is associated with increased risk for hospitalisation and for mortality (29). Patients in the "continuous" arm of NOTT, whose survival benefit was greatest, used both stationary and ambulatory systems in order to enable an average usage of 18 hours per

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day (4). Extrapolation from the studies of long term oxygen therapy (3,4) may suggest that using ambulatory oxygen during activity would enhance the benefits of LTOT but there are few data to support this.

In those not fulfilling criteria for long term continuous oxygen therapy

Despite the observation of small, acute benefits of oxygen therapy during laboratory-based exercise tests in COPD (30), the subject of ambulatory oxygen use in patients who do not fulfil criteria for LTOT remains controversial. Ambulatory oxygen is often provided for patients who desaturate with exertion because of such short-term in-laboratory studies which have demonstrated modest improvements in exercise capacity and/or dyspnoea. Interestingly, these small benefits may be noted in patients who do not desaturate on exertion as well as in those who do and have been attributed to reductions in dynamic hyperinflation induced by a hyperoxia-driven reduction in ventilation (31,32). The underlying mechanisms for dyspnoea and exercise limitation in COPD are complex (33). In a study of ten patients with severe COPD and mild hypoxaemia by Somfay *et al.* (34), endurance time on a symptom-limited incremental exercise test was increased whilst breathing increasing concentrations of oxygen up to 50%, with small but statistically significant decreases in dyspnoea score, end-expiratory and end-inspiratory lung volume, minute ventilation and breathing frequency. These authors determined that there was a dose-dependent improvement in exercise endurance and dyspnoea which may be partly related to a reduction in hyperinflation and reduced breathing frequency. Although widely prescribed, usually on the basis of relief of exertional desaturation during a laboratory-based test, the use of domiciliary ambulatory oxygen is not strongly evidence-based. Two studies of cross-over design which examined the impact of portable oxygen therapy on QOL had conflicting findings in terms of QOL and a small multiple n-of-one study found no benefit (35-37). In an adequately powered study of patients with COPD who remained breathless on exertion despite maximal treatment, Moore *et al.* randomised patients without severe resting hypoxaemia to use ambulatory oxygen or ambulatory air at 6 L/min during exertion for 3 months at home (38). Included patients (n=143) had PaO_2 greater than 60 mmHg at rest on room air, with a third desaturating to SpO_2 <88% on exertion. Although there was a trend to improvement in both arms of treatment, there was no difference between supplemental air and supplemental oxygen used during exercise with regards to dyspnoea, QOL or function, and the presence of exertional desaturation was not predictive of outcome. These results suggest a substantial placebo effect from the administration of intranasal gas, possibly relating to the wearing of nasal cannulae (39). Nonetheless, in the study by Nonoyama *et al.*, where investigators performed multiple n-of-1 studies, occasional patients (n=2 out of 27) achieved clinically significant reductions in dyspnoea, so blinded assessments may be useful in selected individuals (37).

Oxygen for pulmonary rehabilitation in COPD

Theoretical reasons to support the use of supplemental oxygen during training include the potential for amelioration of exercise-induced elevations in pulmonary arterial pressure (40,41) and the potential for reductions in minute ventilation and dynamic hyperinflation (34). However, there is no evidence to support this practice.

"Palliative" oxygen

Supplemental oxygen has been used in an attempt to provide symptomatic relief for patients with intractable dyspnoea due to terminal illnesses, including late-stage lung disease such as COPD, even in the absence of hypoxaemia. In the first large, international multi-centre trial examining this question, Abernethy *et al.* randomly allocated 239 patients with life-limiting disease, including COPD (64%) and cancer (16%), to receive oxygen or medical air (42). Both were delivered at 2 L/min through nasal cannulae via a concentrator for seven days. Primary outcomes were impact on breathlessness and QOL. The study found that both medical gases induced small improvements in dyspnoea and QOL, with more severe baseline breathlessness predicting this benefit. They also found that most of the improvement occurred in the first three days. The conclusion was that palliative oxygen had no benefits over medical air for relieving dyspnoea or for improving QOL for the whole population and that there were small improvements with both arms of the treatment. A therapeutic trial of medical air or oxygen over 3 to 4 days was thus proposed as a way of assessing those dyspnoeic patients who might benefit. It is thought that relief of breathlessness with either oxygen or air, as described in the abovementioned study, could be due to stimulation of nasal receptors by gas flow, however, the mechanism by which this occurs is not known. The role of air flow as an intervention has been explored and cold air directed on the face has been shown to

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reduce breathlessness induced by inspiratory resistive loading and hypercapnia in normal subjects (39) and in patients with COPD (43). A placebo controlled study using a handheld fan in patients with intractable dyspnoea from different causes showed benefit (44).

Oxygen in moderate hypoxaemia

Despite the mortality benefits from long term oxygen therapy in patients with COPD and severe hypoxaemia, there is no such benefit for continuous oxygen supplementation in patients with milder degrees of hypoxaemia. A trial reported by Górecka and colleagues (45) found that LTOT (oxygen for a mean of 17 hours/day to raise PaO_2 to ≥65 mmHg) had no effect on survival over a mean observation period of 40.9 months in patients with COPD and only moderate hypoxaemia (56-65 mmHg). One hundred and thirty five patients with mean FEV_1 of 0.83 L were included. The overall mortality in this study was 11-12% per annum, which is close to that of patients on continuous oxygen therapy in the NOTT (4). Younger age, better spirometric values and higher body mass index predicted better survival.

Cognitive function, hypoxaemia and driving

Cognitive dysfunction has been described in people with COPD. The frequency of cognitive dysfunction varies depending upon the battery of neuropsychological tests used, with the domains most influenced being memory and attention. COPD diagnosis was linked with an 83% higher risk for developing non-amnestic mental decline in a recent prospective study of aging adults (46). Although hypoxaemia may be one several mechanisms by which COPD induces mild cognitive impairment in COPD there is limited evidence for benefit of long term oxygen therapy on cognition (47). Previous guidelines on fitness to drive in Australia recommended patients on long term oxygen therapy should use supplemental oxygen whilst driving a motor vehicle (48). However, there is no evidence for either improvement in cognition (49,50), or in simulated driving performance with acute oxygen therapy in this patient group (51). Thus, there is currently no recommendation for hypoxaemic patients to use portable oxygen therapy whilst driving in Australia and/or New Zealand (52).

Risks of oxygen in acute exacerbations of COPD

It has been known for decades that patients with acute exacerbations of COPD may develop worsening hypercapnia with the application of supplemental oxygen, particularly at high concentrations. The mechanisms underlying this phenomenon relate to a combination of (I) worsening ventilation perfusion mismatch secondary to attenuation of hypoxic pulmonary vasoconstriction; (II) the Haldane effect which involves displacement of carbon dioxide bound to haemoglobin by increased oxygen concentration; and (III) hypoventilation. The adverse effects of high concentrations of supplemental oxygen were recently confirmed in a study by Austin *et al.* which reported an increase in mortality for patients randomised to receive high concentration oxygen versus those who received low concentration titrated oxygen to a target saturation range of 88-92% when transported via ambulance with acute exacerbation of COPD (53).

Current research and future research needs

Oxygen is a widely used treatment for COPD and a range of other chronic lung diseases. Apart from the demonstrated evidence of mortality benefit with LTOT in patients with severely hypoxaemic COPD and minimal co-morbidities, the evidence for significant benefit with oxygen in a range of other circumstances is lacking.

Currently recruiting studies

Long term oxygen treatment trial (LOTT)

The currently recruiting LOTT is sponsored by the National Heart Lung and Blood Institute and Centers for Medicare & Medicaid Services in the United States. Its stated aims are to determine whether continuous supplemental oxygen increases time to a composite outcome of all-cause mortality or all-cause hospitalisation as well as examining deterioration in QOL. Patients will receive either continuous oxygen for 24 hours/day if they have moderate resting hypoxaemia or supplemental oxygen for sleep and activity for those with exercise desaturation. There will be no placebo (supplemental air) arm which is disappointing given there is clinical equipoise. The reason for the absence of a placebo arm is unclear, but it may relate to the (no doubt significant) costs of supporting such a study. The absence of a placebo arm is extremely disappointing as there are clearly demonstrated placebo effects of intranasal gas flow and such a study would have provided an excellent opportunity to explore the question in detail. The

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NOTT was not able to clearly determine any benefits on QOL or cognition because of the lack of a placebo arm.

Supplemental oxygen in pulmonary rehabilitation trial (SuppORT)

This currently recruiting trial sponsored by the Australian National Health and Medical Research Council (NHMRC) is a randomised controlled trial of supplemental oxygen versus medical air in people with COPD aimed at determining whether supplemental oxygen improves the exercise capacity and QOL of patients with COPD who desaturate with exertion.

Studies of oxygen therapy are difficult to undertake because of the severely disabled population of patients involved and the lack of funding sources, however, further studies are needed. Research questions include whether oxygen for exertional use can improve QOL and activity levels if the delivery device is more "user friendly". Although recent studies of exertional oxygen used over medium term durations in COPD have not demonstrated benefits over portable air; it is the case that patients do not use their portable oxygen delivery devices more that about 40 minutes per day. Future studies should try and determine whether the absence of oxygen use relates to the ineffectiveness of the treatment or to the physical properties of the portable device being clumsy or heavy or embarrassing to use and cancelling out any the small magnitude of any potential benefits gained.

A large study to determine whether nocturnal desaturation has short and long term sequelae on sleep quality, pulmonary haemodynamics and QOL is also warranted.

Conclusions

Oxygen therapy is known to improve mortality in patients with severe hypoxaemia and COPD. Patients currently receiving this treatment are often older and have more co-morbidities than the patients who were enrolled in the original long term oxygen studies. Further studies and the development of national and perhaps international registries should allow clarification of the impact of oxygen therapy on COPD patients receiving oxygen therapy currently. Benefits from oxygen in patients with milder degrees of hypoxaemia who may desaturate on exertion or nocturnally are unclear and require further study. Such future prospective studies should include a placebo arm in order to distinguish benefit due to oxygen from placebo effect.

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