Oxygen therapy in COPD

Oxygen: the good, the bad, and the necessary…

T Troosters

The use of oxygen therapy in COPD needs more careful study

Long term oxygen therapy (LTOT) is one of the few treatments which has significant survival benefits in patients with severe hypoxaemia. It may modify disease progression, as indicated by a slower progression of hypoxia induced pulmonary hypertension,[1–4] and the acute reduction in pulmonary hypertension to oxygen administration has been suggested as predictive for the survival benefit in individual patients. Reduced pulmonary vascular resistance and hence the reduced load on the right heart is probably the most important working mechanism of LTOT. In less severe hypoxaemic patients the benefits of LTOT on survival are less clear.[5] Other benefits of oxygen administration are generally accepted. Reduced ventilation, especially during exercise, helps to avoid dynamic hyperinflation and hence reduces symptoms and increases exercise tolerance in the majority of patients with chronic obstructive pulmonary disease (COPD), even in patients with mild hypoxaemia.[6] There is also some evidence to support the suggestion that LTOT may improve cognitive function in hypoxaemic COPD patients[7] and may improve health related quality of life.[8]

LTOT is therefore a recognised treatment in hypoxaemic patients[9] and has been reimbursed in most healthcare systems. During exercise training oxygen supplements are administered to enhance training intensity[10] or relieve symptoms.

Despite the proven benefits of oxygen therapy, researchers should remain critical towards interventions.[11] In this issue of *Thorax* Carpagnano *et al*[12] present interesting data that potentially invite us to refine our view on the benefits of oxygen therapy in COPD. The authors investigated the effects of acute administration of hyperoxia (F_{IO_2} 28%) on markers of oxidative stress and inflammation in exhaled breath condensate. They found that exposure to increased inspiratory oxygen fractions for 1 hour exacerbated 8-isoprostane and interleukin (IL)-6 concentrations (already raised breathing ambient air) compared with control subjects. Intriguingly, the effect of oxygen breathing was comparable between healthy subjects (IL-6 +68%, 8-isoprostane +79%) and patients with COPD (IL-6 +31%, 8-isoprostane +49%). In other words, the effects of oxygen breathing were not restricted to COPD. In addition, the increases in both markers were significantly interrelated.

Although the data by Carpagnano *et al* are tantalizing for researchers in this field, the clinical relevance of the findings is not yet clear. Firstly, the use of markers in exhaled air is not an easy technique and it is difficult to reproduce findings in other laboratories.[13 14] Secondly, the magnitude of the increase in IL-6 and 8-isoprostane is difficult to put into context. The same research group has already shown that, in smokers, IL-6 levels in exhaled air were more than double (+115%) those observed in non-smokers. In heavy smokers IL-6 was +184% above control levels. The changes observed with oxygen breathing (+68% in healthy subjects and +31% in COPD patients) are therefore relatively subtle—and the clinical relevance might also be.[15] Thirdly, the authors studied only one time point (after 1 hour of oxygen breathing), which makes it difficult to extrapolate to LTOT. It would be useful to know whether the observed effects are transient or whether the increased oxidative stress and inflammatory markers remain. Lastly, oxygen administration may exert different effects in the lungs from the ''periphery''. COPD is more and more recognised as a systemic disease[16] or a disease with systemic consequences. Oxygen administration may protect against the systemic consequences of COPD. For instance, oxygen administration has been shown to protect against systemic oxidative stress during a bout of exercise[17] and, interestingly, Carpagnano *et al*[18] have confirmed elsewhere that temporary hypoxia induced, for instance, by sleep apnoea leads to an increase in the markers of oxidative stress. These are normalised when overall oxygenation is improved with continuous positive airway pressure (CPAP). In patients with severe gas exchange disturbances, hyperoxia in the alveolar spaces may be needed to guarantee relative normoxia in the periphery of these patients. It is generally recognised that tissue hypoxia contributes to weight loss through the activation of the NF-κB pathway, which activates an inflammatory cascade releasing IL-6 and tumour necrosis factor (TNF)-α[19] leading to tissue wasting. Weight loss—especially the loss of lean tissue—is in itself is a negative prognostic factor and should be avoided in COPD.[20] Since the same NF-κB pathway has been suggested to play a role in hyperoxia induced oxidative stress, it is not clear at present whether increased F_{IO_2} is good or bad.

Hyperoxia up to concentrations of 80% F_{IO_2} did not seem to lead to weight loss in rats.[21] In the MRC LTOT trial[1] patients surviving in the LTOT arm did not tend to lose weight, nor did their lung function deteriorate more rapidly than in the control arm. Hence, somewhat increased F_{IO_2} values used in LTOT or during exercise to improve tissue oxygenation are therefore probably clinically superior to normoxia in the lungs, leading to relative tissue hypoxia. Evidence of ''harm'' induced by relatively modest F_{IO_2} is absent. Oxygen therapy therefore remains recommended—if not necessary—in patients at risk of tissue hypoxia.

In summary, the study reported by Carpagnano *et al* may shed new light on the effect of clinical doses of pulsed oxygen therapy on patients with COPD, and could be interpreted as a potential sign to be cautious in using oxygen therapy in these patients as it may exacerbate rather than alleviate the bronchial inflammation by inducing hyperoxia induced oxidative stress.

This study invites further research rather than a change in clinical routine.

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NIV in acute exacerbations of COPD

Non-invasive ventilation in acute exacerbations of COPD: what happens after hospital discharge?

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The role of domiciliary NIV in patients with COPD

Now that non-invasive ventilation (NIV) is well established in clinical practice, particularly for chronic obstructive pulmonary disease (COPD),[1 2] it is likely that more patients will survive an acute exacerbation, especially in countries such as the UK where comparatively few patients with COPD are ventilated invasively. However, it is possible that some patients are now just being saved for a future life of poor quality at home, punctuated by recurrent admissions to hospital because their respiratory reserve is so marginal that even trivial exacerbations are sufficient to provoke life threatening ventilatory failure.

Before NIV was widely available, Connors *et al*[3] showed that hypercapnia during an admission with an acute exacerbation of COPD was a poor prognostic indicator. In a prospective study of a cohort of 1016 patients who were admitted with an exacerbation of COPD and a $Paco_2$ of 50 mm Hg (6.6 kPa) or more, they found that 11% of the patients died during the index hospital stay. The 60 day (20%), 180 day (33%), 1 year (43%), and 2 year (49%) mortality rates were all high; 446 patients (44%) were readmitted 754 times in the following 6 months. At 6 months only 26% of the cohort were both alive and able to report a ''good'', ''very good'', or ''excellent'' quality of life. Survival time was independently related to severity of illness, body mass index (BMI), age, prior functional status, Pao_2/Fio_2, congestive heart failure, serum albumin, and the presence of cor pulmonale. Given that current recommendations state that patients with an acute respiratory acidosis (pH <7.35) after initial treatment and a $Paco_2$ above 6 kPa should be offered NIV,[4] all patients who have received NIV acutely fall into this poor prognostic group.

LONG TERM OUTCOME FOLLOWING NIV IN HOSPITAL

A number of studies have looked at the longer term follow up after an admission requiring NIV. Overall the prognosis is poor, but patients receiving NIV acutely appear to fare better than those who require endotracheal intubation (ETI) and mechanical ventilation (MV). In their randomised controlled trial comparing NIV with immediate ETI and MV, Conti *et al*[5] showed that, in those who could be managed successfully with NIV, there was an advantage both in the short term and also in the year after hospital discharge. There were fewer admissions to hospital and ICU, and fewer patients needed de novo long term oxygen therapy (LTOT). There was also a trend towards improved survival (74% *v* 54%, $p = 0.43$). This confirms the findings of two previous studies comparing NIV patients with historical controls who had been invasively ventilated.[6 7] Imperfect matching is one possible explanation in these studies,[8] but patients who are intubated and mechanically ventilated may lose a considerable amount of muscle bulk rendering them susceptible to further episodes of ventilatory failure.[9 10] Longer term follow up from the study by Plant *et al*[11] failed to show any statistically significant benefit from NIV compared with conventional therapy. It may be significant that few patients in either group were intubated and ventilated and this is an important difference when compared with the studies mentioned above. The study showed a median survival of 13 and 16 months in the conventional and NIV groups, respectively. In a retrospective study of 120 patients who had received NIV acutely, Scala *et al*[12] found a 6 month mortality rate of 35%; this was greater in those with chronic co-morbidities (54%) than in those without (30%), and was greater in those with low activities of daily living scores.

In this issue of *Thorax* Chu *et al*[13] report their experience on post-discharge