condition. However, this speculation would not explain the apparent decrease in some countries. In this regard, it is likely that improved medical treatment, especially the use of inhaled steroids, has contributed.[16] It has been argued that many patients do not benefit from new treatment because their disease is not diagnosed and/or treated adequately.[22 23] In this sense, the increased prevalence of diagnosed asthma reported by Chinn *et al*, in the absence of an increased symptom prevalence, could also be a reflection that medical care of asthma patients has changed for the better. Whatever the explanation, the findings of Chinn *et al* are in line with those of other recent studies and may, in fact, be good news.

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Oxygen in COPD

Short burst oxygen therapy for relief of breathlessness in COPD

C M Roberts

More evidence against the effect of short burst oxygen therapy, but doubts remain

In this issue of *Thorax* Stevenson and Calverley[1] provide more evidence for a lack of effect of short burst oxygen therapy in the relief of dyspnoea following exercise in patients with chronic obstructive pulmonary disease (COPD). This study follows other recent publications that appear to draw the same conclusion. Despite this mounting evidence, oxygen cylinders for ''as needed'' use are still frequently prescribed at great cost.[2 3] Oxygen used in this way is often perceived as life saving by patients, but can this continuing practice of short burst oxygen use for COPD patients be justified in the light of the emerging evidence?

Oxygen therapy for the management of chronic COPD comes in various forms. Long term oxygen therapy (LTOT) prescribing has an accepted evidence base and any patient considered for short burst treatment should first have undergone an assessment for LTOT. Ambulatory oxygen has been shown to have some beneficial effect in some patients researched in a number of studies that demonstrate some concordance. It is a continuing challenge to the respiratory establishment, however, that the form of oxygen most commonly prescribed in the UK lacks such an agreed evidence base. Short burst oxygen use for the palliation of dyspnoea is fairly widespread among patients with severe COPD.[2] Anecdotally, it is beloved by them and often given at their request by respiratory specialists and general practitioners when other options have been exhausted. When it is given there is some evidence that it is used inconsistently[4]—either before or after exercise—and that the delivery mode is non-standardised with both face masks and nasal cannulae being used with flow rates set usually at 2 or 4 l/min, but often left to the discretion of the non-specialist or patient to determine.

This sounds like a mess that needs sorting out and it is notable that the initial British Thoracic Society,[5] American Thoracic Society,[6] and European Respiratory Society[7] management guidelines for COPD had little to say on this subject. More disappointingly, the contemporary GOLD[8] document virtually ignores short burst oxygen and recommendations from the 2004 NICE guideline[9] consist of rather vague statements based on levels C and D evidence. Although this

perceived paucity of an historical evidence base has previously precluded authoritative guidance, a number of contemporary studies examining the effectiveness of short burst oxygen therapy are now available for us to analyse. The problem for the jobbing clinician is that the available evidence has yet to be synthesised into a whole and, practically, this is a challenging exercise for a number of reasons evident on review of the literature.

REVIEW OF THE EVIDENCE

Perhaps the best evidence for a positive effect of short burst oxygen therapy in exercise for subjects with COPD comes from a single paper published some years ago. Woodcock *et al*[10] showed that pre-dosing with oxygen for as little as 5 minutes at a rate of 4 l/min using nasal cannulae before both a submaximal treadmill test and a 6 minute walk test increased walking distance compared with administered air in COPD subjects. Dyspnoea, however, was reduced only for the shorter treadmill test and not for the 6 minute test. The subjects were not severely hypoxic at rest and real time oxygen saturation was not measured.

Two further papers provide borderline positive findings. Evans *et al*[11] studied 19 hypoxic subjects with severe COPD of mean age 65 years. Subjects undertook three simulated step tests breathing via a face mask, 67% oxygen, 10 l/min compressed air, or room air with no mask. Breathing oxygen after exercise was associated with a shortened dyspnoea recovery time from 3.6 minutes to 3.0 minutes. This study is remarkable because it is one of only two cited in the literature that has specifically tested the reproducibility of patient discrimination between oxygen and air. Little consistency was found after a time interval and the authors concluded that, despite the reduction in recovery time observed in the first part of the trial, the poor reproducibility of this finding cast doubt on the justification for short burst therapy following exercise.

Most recently, Killen and Corris[12] reported in this journal the use of short burst oxygen given either before or after stair climbing in 18 subjects with COPD. Air or oxygen was delivered for 5 minutes at a rate of 2 l/min via a face mask before and after ascending stairs in subjects who desaturated on exercise. Three combinations were provided of air and air, air then oxygen, or oxygen then air. Although there was no statistical difference in dyspnoea scores between these three groups, a statistically significant difference in dyspnoea was seen (visual analogue score of 7 mm) when the oxygen subgroups were combined compared with those breathing air. Recovery times were not measured. The authors suggest that this level of dyspnoea reduction represented a significant benefit of short burst oxygen therapy.

One further paper which deserves comment is that of Swinburn *et al*.[13] This study also found a reduction in the dyspnoea score in 12 subjects with severe COPD at rest breathing 28% oxygen via a face mask compared with compressed air at the same flow rate. Visual analogue scores reduced from 46 mm on air to 30 mm on oxygen. The subjects were asked repeatedly when blinded if they felt better breathing air or oxygen by mask compared with room air; compressed air helped in 15 of 24 occasions tested and oxygen in 22 of 24. Although often quoted as a study supporting short burst oxygen therapy, it must be noted that the subjects were tested at rest and the effects of exertion were not studied.

While these studies at best provide evidence of partial benefit, there is inconsistency in the subject groups, exercise performed, and outcome measures. Moreover, there are other studies with distinctly negative results. McKeon *et al*[14] examined the effect of predosing with air or oxygen at a rate of 2.5 l/min via nasal cannulae prior to a treadmill exercise test in 20 subjects with COPD (mean FEV_1 31% predicted). No effect was observed on the dyspnoea score during exercise. Rhind *et al*[15] presented similar findings in 12 subjects with COPD.

More recently, Nandi *et al*[16] reported the effect of both predosing for 10 minutes with either 28% oxygen by face mask or compressed air at a rate of 4 l/min and also post exercise dosing with similarly blinded gas mixtures. Six minute walk tests were undertaken and oxygen was found to have no benefit compared with compressed air in terms of relief of dyspnoea in either arm of the study in the 34 subjects included (mean FEV_1 34% predicted). All of these subjects had significant oxygen desaturation. In a not dissimilar study Lewis *et al*[17] also used the 6 minute walk test to study 22 patients with COPD (mean FEV_1 34% predicted) without resting hypoxia but most of whom desaturated on exercise. In this study the gas mixture was administered for 5 minutes at a flow rate of 2 l/min via nasal cannulae. No effect was observed on the dyspnoea score with either pre or post dosing with oxygen compared with compressed air.

In contrast to these at best equivocal and conflicting results, there is a clearer—although by no means perfect—consensus on the use of ambulatory oxygen therapy as an adjunct to reducing dyspnoea and improving exercise tolerance. A number of studies have reported benefits,[18–20] although not in all subjects.[21] The mechanism for this apparent reduction in dyspnoea is postulated as the reduced work of breathing when hypoxaemia is prevented or reduced in severity.[22] So why is oxygen helpful in the ambulatory setting but of less value following exercise? One key element of the increased work of breathing in patients with limited expiratory flow is the development of dynamic hyperinflation.

STUDY BY STEVENSON AND CALVERLEY

It is argued by Stevenson and Calverley[1] in this issue of *Thorax* that a reduction in dynamic hyperinflation may hold the key to the successful identification of those subjects who will benefit from oxygen and, specifically in this study, those using it as a short burst dosing intervention following exercise.

Stevenson and Calverley administered oxygen at an inspired oxygen fraction of 0.4 or air at a similar flow rate (10 l/min) to 18 moderately severe COPD patients (FEV_1 40% predicted) after standardised exercise. In this study subjects exercised both ''instrumented'' in a full cardiorespiratory exercise test breathing via a mouthpiece and ''non-instrumented'' breathing from a face mask. The hypothesis tested was that oxygen administration should reduce the work of breathing and aid resolution of dynamic hyperinflation by reducing tidal volume breathing and allowing an increased expiratory time. Administration of oxygen after exercise was associated with a reduced ventilatory effort and more rapid resolution of dynamic hyperinflation but no significant reduction in dyspnoea. The findings were essentially negative in that, although observed changes occurred, these did not produce a significant reduction in breathlessness as measured by a Borg scale when oxygen administration was compared with that of air. A significant difference in recovery time of dyspnoea was noted, however, between the instrumented mouthpiece tests (11.38 (1.49) minutes) and those when face masks alone were used (7.94 (1.12) minutes).

The study by Stevenson and Calverley adds to the evidence that there is no single easily measured mechanism by which oxygen reduces dyspnoea after exercise, and that the mechanisms which may operate to prevent dyspnoea when oxygen is administered during exercise may not be the same as those which may operate in influencing dyspnoea after exercise. The authors point out that the reduced recovery time observed in the subjects when receiving

oxygen by face mask may reflect stimulation of facial receptors that could reduce dyspnoea perception.[23] Even this suggestion is contentious in the context of clinical use of short burst oxygen after exercise. The best evidence for a positive effect of oxygen was derived from a study using nasal cannulae rather than masks,[10] and a recent study examining the effect of mask versus room air breathing concluded that any apparent benefit is an order effect of exercise rather than a result of either oxygen or delivery apparatus.[24]

CLINICAL IMPLICATIONS

The difficulty for those trying to develop guidelines in this arena is the disparate nature of these studies. In some the study end points were dyspnoea and in others exercise tolerance; the nature and duration of exercise was different; the inspired oxygen tensions, flow rates and delivery systems were not standardised; and perhaps most challenging of all were the settings for the studies. Finally, as clinicians we must ask practical questions—are the study subjects included the ones we would consider recommending for short burst oxygen therapy and are the study circumstances those in which patients commonly use this form of oxygen?

What we may deduce so far is that short burst oxygen therapy either before or after exercise probably does not benefit the majority of patients with moderately severe COPD who exercise for more than a very short period of time. Before comprehensive recommendations can be made we still require specific studies to re-evaluate the work of Swinburn[13] and Killen[12] in subjects at rest and after very short episodes of exertion set in the circumstances of everyday living.

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Regulatory T cells and asthma and allergy

Regulation: the art of control? Regulatory T cells and asthma and allergy

D S Robinson

A better understanding of the immunology of regulation may allow preventive or disease modifying treatment for asthma and other respiratory diseases

Much is currently made of the control of asthma in therapeutic guidelines. Both the British guidelines and the Global Initiative for Asthma (GINA) define measures of control of the disease, and recent studies have defined strategies for control using available anti-inflammatory and bronchodilator therapy such as inhaled steroids and long acting β_2 agonists.[1 2] However, currently available treatments suppress inflammation but do not modify the underlying immunological predisposition to the disease.

Asthma is widely recognised as an inflammatory airway disease driven by activation of Th2-type T lymphocytes in both atopic allergic and intrinsic or non-allergic forms.[3–5] Recent advances in our understanding of the control of the immunological process have identified regulatory suppressive T cells which can prevent activation of self-reactive or pathological T cells in autoimmune or infectious disease models.[6–8] Does this understanding of immune regulation hold the prospect of disease control or even prevention for asthma?

MECHANISM OF ACTION

The interest of immunologists in actively suppressive T cells was re-awoken by the finding by Sakaguchi and co-workers that depletion of CD4+CD25+ T lymphocytes from mice led to development of autoimmune