Enhancing physical performance in chronic obstructive pulmonary disease

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The ambition of all athletes is to outperform competitors in their chosen discipline. To this end, ever more sophisticated training schedules are used to maximise physical performance. In recent years some sportsmen and women have resorted to illegal pharmacological methods to augment their training programmes and so gain an unfair advantage over their rivals.

Patients with chronic obstructive pulmonary disease (COPD) are disabled by their inability to carry out many activities of daily living because of exercise intolerance. This leads to increasing social isolation, depression, and dependence. Improving physical performance is therefore an important therapeutic goal in these patients. It has been thought that exercise limitation in COPD was simply due to a limit to pulmonary ventilation. However, a number of observations have indicated that this is not true for many COPD sufferers. Firstly, the relationship between exercise capacity and lung function impairment is poor^{1,2} and bronchodilator therapy often fails to have a meaningful impact on disability in patients with COPD. Furthermore, patients who have their lung function restored to normal by transplantation may not achieve their predicted exercise capacity following the procedure.^{3,4} Finally, exercise reconditioning during pulmonary rehabilitation results in impressive improvements in exercise capacity while having no impact on lung function impairment.⁵⁻⁷

Other factors are clearly involved in exercise limitation and it is now evident that peripheral skeletal muscle dysfunction is one of the primary determinants of disability in chronic lung disease.⁸ Far from being illegal, pharmacological improvement of peripheral muscle performance could be of therapeutic benefit in these patients.

Skeletal muscle dysfunction in COPD

Observational studies have demonstrated a reduction in muscle strength and bulk in COPD.⁹⁻¹¹ These measures have also been shown to predict peak exercise capacity.^{12,13} A number of techniques have been developed in recent years which have increased our understanding of peripheral muscle function in patients with COPD. Maltais and colleagues have carried out studies examining biopsy specimens taken at rest from the quadriceps muscle of COPD patients. These have shown that there is a reduction in oxidative enzyme

concentrations compared with healthy controls while glycolytic enzymes are unaffected.¹⁴ In addition, histochemical analysis has shown altered fibre type profiles compared with healthy controls, with COPD patients showing a reduction of type I ("slow twitch") fibres and a lower fibre to capillary ratio.¹⁵

The performance of the peripheral muscles during exercise can be studied using magnetic resonance spectroscopy (MRS). This technique measures the concentrations of inorganic phosphate, high energy phosphate compounds (phosphocreatine (PCr), ATP, and ADP), and intracellular pH.¹⁶ Breakdown of PCr is the principal source of energy during early muscular exercise.¹⁷ The rate of PCr breakdown and re-synthesis is an indirect measure of oxidative phosphorylation.¹⁸ MRS studies have indicated greater PCr breakdown and slower PCr re-synthesis in patients with COPD than in controls.^{19,20} MRS has the advantage of being able to obtain data on muscle energy metabolism during exercise, but it is limited in only being able to measure high energy phosphate compounds. The calculation of energy flux through other pathways is possible using MRS but there is evidence from a comparative study with muscle biopsy specimens taken from healthy subjects that this may be inaccurate because of assumptions made about the pH buffering capacity of the intracellular milieu.²¹ Furthermore, the modes of exercise that can be studied with MRS are limited.

The findings of muscle biopsy and MRS studies in COPD suggest that oxidative phosphorylation is impaired in the peripheral muscles with a resultant increase in glycolytic metabolism and lactate release. This has been supported by the findings in several studies that lactate is released at lower workloads in patients with COPD than in healthy controls.^{22,23} The degree to which this occurs correlates with the reduction in oxidative enzyme concentrations.¹⁴

The causes of peripheral muscle dysfunction are multifactorial and are likely to vary from patient to patient. In most, however, deconditioning will be a crucial component. Patients with COPD have significantly reduced levels of physical activity and often avoid exertion because of the fear of dyspnoea. The character of muscle dysfunction is similar to that seen in detrained or immobilised healthy subjects.^{24,25} Whether there is a specific myopathy associated

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with COPD is a matter of some debate, but skeletal muscle in these patients may also be adversely affected by malnutrition, hypoxia, hypercapnia, and drug therapy. Systemic corticosteroids are known to cause a myopathy and this may be an issue for some patients.²⁶ Beta agonists have an anabolic effect on skeletal muscle^{27, 28} and have been used illegally by athletes to increase muscle bulk. There is evidence from studies of performance in asthmatic subjects that inhaled β agonists do not have significant ergogenic effects.^{29, 30} Some patients, however, do use large doses of these drugs by nebuliser and the impact of this on muscle function is unknown.

Strategies for improving physical performance

TRAINING AND PHYSICAL AIDS

Given that deconditioning due to low physical activity is one of the principal causes of muscle dysfunction in COPD, exercise training is the logical first step to improving performance. Pulmonary rehabilitation is now established as effective treatment for patients with COPD.^{5, 7} It is clear that, if exercised at appropriate intensities, COPD patients show metabolic adaptations to training.^{22, 31} Patients with COPD are able to train closer to their maximum capacity than healthy subjects and studies that had previously failed to show such adaptations probably involved an insufficient training stimulus.³² Much is still to be learnt about the type of training that will most benefit patients, but the lesson from studies of sports physiology is that training is mode selective.¹⁷ In other words, endurance training leads to increases in endurance but not strength and vice versa. This is likely to apply to the training of COPD patients and means that the choice of outcome measure to evaluate a particular training activity is crucial. If pharmacological therapy is to be used to augment training, clinical trials will require similar care in their selection of outcome measures. Treatments that increase muscle bulk, for example, are unlikely to have an impact on endurance but may increase muscle strength.

The disablement caused by COPD is frequently hidden and there is evidence that patients with COPD take up less of their entitlement to social support than those disabled by other conditions.³³ The use of physical aids to mobility (such as wheeled frames) can increase exercise capacity and reduce the oxygen cost of physical activity.^{34, 35} These approaches are often forgotten.

Attempts have been made to lift the ceiling on exercise capacity by unloading the ventilatory muscles using inspiratory pressure support.³⁶⁻³⁸ There is evidence that it is possible to do this under experimental conditions but, while it may be of scientific interest, this sort of treatment is unlikely to provide practical benefits to patients in the domestic setting.

DRUGS AND NUTRITION

The importance of nutrition to performance in sport is now well recognised.³⁹ This is an appealing area for study in COPD because many

patients are undernourished and a significant proportion of the remainder show relative reductions in muscle mass.^{40, 41} Low body weight and muscle mass predict both physical performance and prognosis.^{12, 42} Reversing undernutrition, however, has proved difficult and nutritional supplementation programmes have in general failed to result in significant weight gain. A recent meta-analysis of trials of nutritional supplementation has confirmed this impression.⁴³ The reasons for this may lie with the difficulty in achieving adequate calorie intake in elderly subjects who may offset supplementation with a reduction in normal food intake.⁴⁴ To be effective, nutritional supplementation will need to be combined with an anabolic stimulus such as exercise but surprisingly few studies have done this. The study by Schols *et al* combined nutritional supplementation with rehabilitation and demonstrated significant weight gains for underweight patients (albeit in fat mass) in the supplemented group.⁴⁵ A further group received additional treatment with anabolic steroids and these patients increased lean mass rather than fat mass. None of the patients increased walking distance above those who received rehabilitation alone, but physical performance was not the primary outcome of the study. The performance measure used (the 12 minute walk test) was unlikely to have responded to treatment aimed primarily at increasing muscle mass. Most nutritional programmes have attempted to maximise calorie intake by using high fat supplements. Carbohydrate intake has often been deliberately kept low because of concerns about the ventilatory cost of carbohydrate oxidation to COPD patients. Although an increase in ventilation following a high carbohydrate meal can be demonstrated experimentally, the clinical significance of this is unclear.⁴⁶

The importance of carbohydrate intake to physical performance in healthy subjects is now well documented⁴⁷ but the impact of nutrition on physical performance in patients with COPD has received little attention. COPD patients might particularly benefit from carbohydrate supplementation because the muscles of deconditioned subjects are especially reliant on carbohydrate as a source of energy.^{48, 49} Providing balanced nutrition to patients undergoing rehabilitation might be important in maximising performance.

Hormones have been used illicitly by a number of athletes to increase muscle bulk and this has also been tried in COPD. In addition to the study of anabolic steroids by Schols *et al*,⁴⁵ attempts have been made to augment rehabilitation programmes with growth hormone.^{50, 51} Exercise capacity did not increase in these studies but again these studies were primarily aiming to increase weight in nutritionally depleted COPD patients. Furthermore, the outcome measures used contained a high endurance component which were less likely to respond to an intervention aimed at increasing muscle bulk and strength. Anabolic therapies may be useful in patients with COPD, particularly those with low muscle bulk and strength, but their benefit will be maximised in combination with suitable strength training pro-

grammes. The outcome of this type of treatment is likely to be reflected in an increase in strength and peak exercise performance rather than endurance.

OXYGEN

Many disabled patients with COPD are hypoxaemic and there is evidence to suggest that providing oxygen to these patients during exercise increases performance.⁵²⁻⁵³ In the United States the use of portable liquid oxygen systems for patients with COPD is widespread although this is not the case in Europe.⁵⁴ The role of such systems for patients who are normoxic at rest but desaturate during exercise is less clear, but it is likely that performance will also be improved in this group. The mechanism for these increases in performance is uncertain. A number of studies have suggested that oxygen reduces dyspnoea by a reduction in minute ventilation during exercise.⁵⁵⁻⁵⁶ It would be expected that increasing the oxygen content of the blood would have a beneficial effect on oxidative metabolism in peripheral muscle leading to an increase in exercise capacity, and there is support for this from MRS studies.⁵⁷⁻⁵⁸ However, there is also evidence that mitochondrial function is independent of oxygen delivery. In a detailed study of the metabolic responses of the leg muscles to exercise, Maltais and colleagues found that lactate output from the muscles showed no relationship to oxygen delivery.⁵⁹ This implies that the failure of oxidative metabolism in peripheral muscle lies with its inability to extract oxygen rather than the inability of the lungs to provide oxygen to it. This may limit the performance benefit of oxygen supplementation to COPD patients and emphasises the value of addressing muscle dysfunction in COPD.

A distinction needs to be made between the immediate effect of oxygen on exercise performance and the role of supplemented oxygen in training programmes. The latter has received far less attention but is an issue of practical importance because most rehabilitation programmes provide oxygen for hypoxic patients during exercise. This has been driven by concerns about safety but there is little evidence to support this and many of these patients carry out home exercises safely without oxygen. It could be argued that oxygen might permit training at higher intensities, thereby improving the outcome of rehabilitation. However, athletes frequently seek hypoxic conditions at altitude in which to train, suggesting that supplementing oxygen to patients undergoing rehabilitation could be counterproductive. The benefits of these conditions appear to reside in improvements in oxygen transport and utilisation, although these may be offset by a reduction in training intensity.⁶⁰ More recently the concept of "living high, training low" has become popular.⁶¹ This approach seeks to reap the benefits of the central adaptations to altitude without curtailing training intensities. The case for living and training under hypoxic conditions remains unproven, but its popularity emphasises the

importance of systemic oxygenation to the outcome of training.

Little is known about the effect of hypoxia and oxygen supplementation on training in COPD. Two recent studies have shown no benefit from supplemental oxygen during rehabilitation for desaturating patients,⁶²⁻⁶³ but these studies were small and may have lacked adequate power to detect significant benefits. Further studies in this area are needed, particularly concerning the impact of training under hypoxic conditions on muscle metabolism.

Future strategies

There are a number of interesting developments in the field of muscle physiology which may lead to new treatments targeted at peripheral muscle performance in patients with COPD. It is becoming clear that ATP production by oxidative phosphorylation is not limited simply by oxygen supply as previously thought.⁶⁴ It can be shown that significant lactate is produced in the presence of adequate oxygen supplies and that other factors are crucial to the integration of oxidative and glycolytic metabolism. Lactate accumulation is likely to be determined by the balance of pyruvate production and oxidation in the mitochondria. In this respect, the role of the pyruvate dehydrogenase complex (PDC) appears to be pivotal. This enzyme is situated on the mitochondrial membrane and regulates the irreversible entry of pyruvate to the mitochondrion and the tricarboxylic acid cycle. The enzyme exists in an active and inactive form and the degree to which it is activated determines the rate of oxidation of pyruvate and hence the degree to which lactate accumulates.⁶⁵ PDC can be activated pharmacologically by infusing dichloroacetate⁶⁶ and this has been shown to attenuate lactate accumulation and increase maximal work rates in healthy subjects.⁶⁷ Dichloroacetate is toxic when administered chronically,⁶⁸ but these findings suggest that pharmacological approaches to improving oxidative metabolism in patients with COPD are worth pursuing.

Many athletes use creatine supplementation to improve performance. This is a naturally occurring substance that can increase muscle bulk and high intensity exercise capacity in healthy subjects.⁶⁹ This is probably because of an increase in the available high energy phosphate pool within muscle cells and possibly a stimulatory effect on PCr re-synthesis.⁷⁰ No studies on the effect of creatine supplementation in COPD have been published to date, but this is an appealing stratagem because there is evidence from biopsy specimens taken from COPD patients that muscle PCr levels are lower than in healthy subjects.⁷¹ Creatine uptake is increased by exercise and it is likely to be of most benefit when combined with exercise training.⁷²

Conclusion

There is an opportunity to develop new treatments targeted at improving peripheral muscle performance in patients with COPD. In

common with athletes, such treatments will probably be of most benefit when combined with an appropriate training programme. Sports training regimens are highly sophisticated and directed to specific performance goals. Similar sophistication will be needed to ensure that performance enhancing treatment meets the everyday exercise needs of individual COPD patients.

A greater understanding of the limitations to exercise and muscle performance in patients with COPD would also be helpful. This may allow us to predict who will benefit from training or other performance enhancing treatment, and determine what mode of enhancement will be most useful to that individual. For such treatment to be realised, a change in philosophy is needed in drug development so that the broader consequences of COPD are considered in addition to the underlying pulmonary pathology. Moreover, it is likely that such treatments will be of benefit to patients disabled by other chronic lung diseases.

The use of performance enhancing drugs may be considered unfair for those who engage in competitive sport. A different view is required for patients with chronic lung disease who wish to enhance their ability to carry out basic activities of living by improving their exercise performance.

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