Attacking the disease spiral in chronic obstructive pulmonary disease

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ABSTRACT – Chronic obstructive pulmonary disease (COPD) is the commonest respiratory cause of mortality and morbidity in adults in the UK. Although the condition is initially a pulmonary one, data exist to support the concept that factors associated with COPD, including immobility, gives rise to secondary effects, including a quadriceps myopathy, which in turn cause anaerobic metabolism at low work rates. This, through bicarbonate buffering, leads to CO_2 retention which, because of constraints imposed by pulmonary mechanics, cause acidosis and dyspnoea. Various therapeutic strategies to reverse this spiral may be employed including pulmonary rehabilitation, quadriceps strength training and surgical or bronchoscopic lung volume reduction.

KEYWORDS: chronic obstructive pulmonary disease, lung volume reduction, pulmonary rehabilitation, quadriceps

Chronic obstructive pulmonary disease (COPD) is a common and serious problem. It is currently the fourth leading cause of chronic morbidity and mortality in the USA and is predicted to rank fifth in the worldwide burden of disease by 2020.[1] COPD is one of the few major chronic diseases that continues to increase in both prevalence and mortality rate. With the exception of smoking cessation,[2] no intervention has been shown to reduce progression of the condition. Despite maximal medical therapy with inhaled steroids and bronchodilators, people with COPD are frequently symptomatic and may be admitted with acute exacerbation. As a consequence, every physician practising general internal medicine will regularly encounter patients with advanced COPD.

Although COPD is initially a pulmonary disease, two arguments exist to support the notion that a wholly pulmonary disease is not a useful construct when considering patients with advanced COPD. First, the cardinal index of airflow obstruction, the volume expired in the first second of a forced expiration (FEV_1), is a very poor guide to symptoms[3] and a

relatively weak guide to mortality.[4] Second, correction of the pulmonary abnormality by double lung transplantation fails to restore exercise performance to normal.[5]

From this basis, we have developed the concept of a disease spiral that seems to better suit the clinical path of patients with COPD. It is important to emphasise that, as with many medical ideas, the concept is merely a resynthesis of previously described ideas, but it has nevertheless been helpful in generating hypotheses for ongoing studies. The overall schema is shown in Fig 1.

Does evidence exist to support the disease spiral?

Breathless on exertion

Most physicians accept that patients with COPD experience dyspnoea on exertion. However, in a landmark paper, Killian and co-workers identified that a surprisingly high number of patients with COPD also experience symptoms of leg fatigue (see later).[6] We revisited this problem and took the opportunity to study both cycle and treadmill-walking exercise.[7] We found that during a walking task, the majority (about 75%) of patients stopped walking because of dyspnoea alone, although a minority placed leg fatigue as an equal or more important cause of exercise limitation. For cycle exercise, the proportion of patients citing breathlessness alone as the cause of exercise limitation was diminished.

Quadriceps myopathy

It is reasonably well accepted that patients with COPD have quadriceps wasting and weakness.[8] At a microscopic level, the changes associated with COPD are characterised by a loss of fatigue-resistant type I fibres and of oxidative enzymes[9,10] without differences in capillarity or mitochondria.[11] Interestingly, type II fibres seem to have reduced mechanical efficiency and consequently reduced power output for a given level of oxygen uptake. The importance of quadriceps involvement in COPD is demonstrated by its association with increased use of healthcare resources[12] and

**Fig 1. Disease spiral in chronic obstructive pulmonary disease (COPD).**
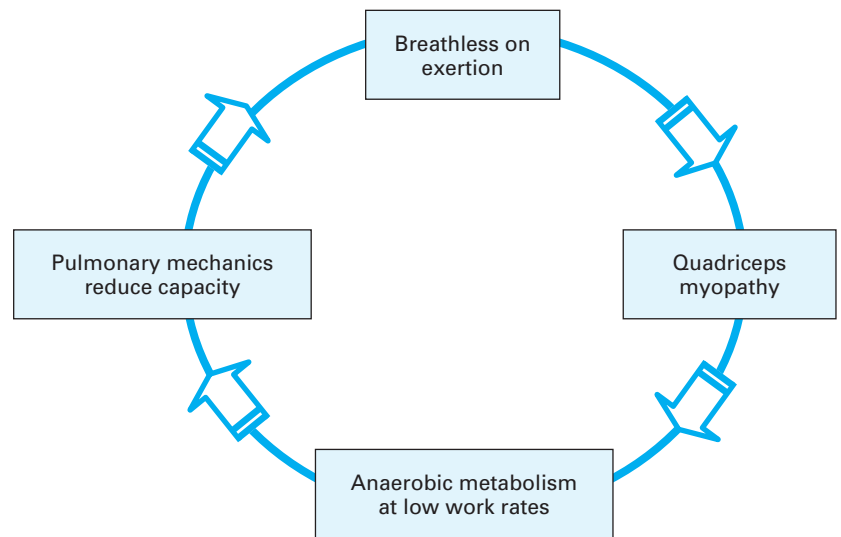
by the fact that, independently of FEV_1, reduced quadriceps cross-sectional area is associated with a poorer prognosis (Fig 2).[13]

The origin of quadriceps weakness in COPD remains a matter of considerable controversy; for a more detailed review, see Couillard and Prefaut.[14] The simplest hypothesis, and that used in the disease spiral, is simply that weakness arises as a result of immobility induced by the breathlessness. However, the picture is complicated by the clinical observation that quadriceps weakness may also complicate steroid administration, although this seems a less important problem in stable patients at the doses used in a conventional steroid trial.[15] The picture is also clouded by the link between COPD and cachexia. Cachexia is certainly associated with a poor prognosis in COPD,[16,17] but quadriceps weakness may occur in patients without nutritional depletion

and this, therefore, cannot account entirely for quadriceps weakness. That disuse is a necessary condition for weakness is supported strongly by the finding that in patients with quadriceps muscle weakness, the strength of the diaphragm, adductor pollicus[18] and abdominal muscles[19] is normal; the relevance of these muscles is that they are continuously active, even in patients with the most severe disease. The presence of cofactors with immobility is not excluded by these data. In normal life,[20] and especially during acute exacerbation, people with COPD have substantially reduced physical activity. It is well known that muscle strength is lost rapidly during disuse,[21] and it is inevitable that quadriceps strength was shown recently to exhibit a significant reduction during admission for acute exacerbation of COPD.[22] Spruit *et al* hypothesised a role for the cytokine interleukin 8 (IL-8) for muscle weakness in this

Fig 2. Risk of death in chronic obstructive pulmonary disease (COPD) stratified according to the volume expired in the first second of a forced expiration (FEV_1) and quadriceps bulk assessed as mid-thigh cross-sectional area (MTCSA) assessed using computed tomography (CT). If FEV_1 is less than 50% predicted, then muscle wasting wields a more marked effect. Reproduced from Marquis *et al* (2002), reprinted with permission from the American Thoracic Society © American Thoracic Society.[13]
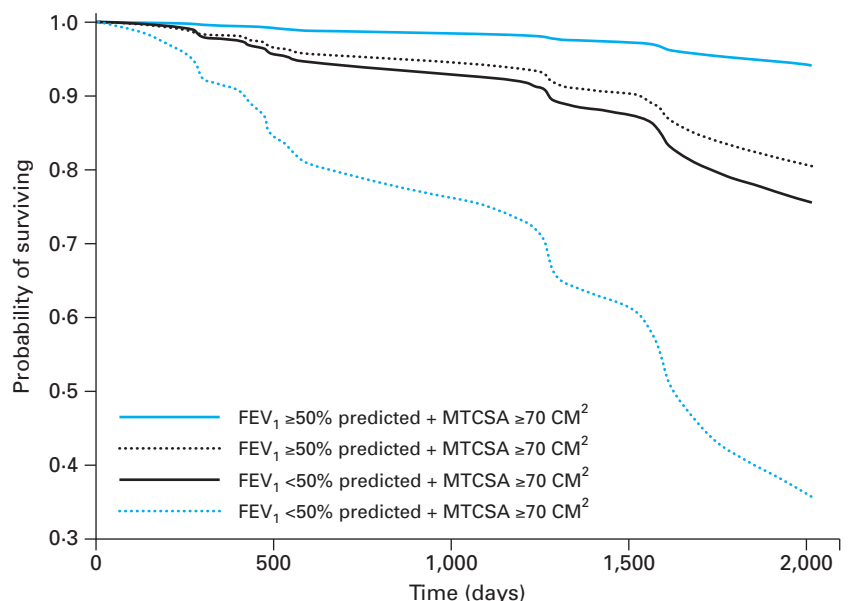
context, and other groups have separately suggested a role for tumour necrosis factor alpha (TNF-α)[23] and interleukin 6 (IL-6).[24] Other factors may also be relevant, in particular gene polymorphisms: we have established recently that, independent of lung function, patients with the II polymorphism of the gene that codes for angiotensin-converting enzyme is associated with reduced quadriceps strength in patients with COPD but not in age-matched controls.[25]

Recently, data have emerged to confirm that quadriceps fatigue is symptom-generating in COPD. Thirty-two patients underwent a constant-rate exercise test; magnetic stimulation of the femoral nerve was undertaken before and after the test.[26] This measurement was developed by our group[27] and is a sensitive test for the identification of quadriceps fatigue.[7] Of the 32 patients, 22 developed quadriceps fatigue; these patients had more glycolytic enzymes and fewer capillaries than non-fatiguers. Importantly, patients who developed fatigue had higher leg-symptom scores, suggesting that fatigue is associated directly with symptom generation.

Anaerobic metabolism at low work rates

The reduction in oxidative enzymes results in patients with COPD producing lactic acid as a by-product of anaerobic metabolism at much lower rates of exercise compared with age-matched controls.[10] Lactic acid is buffered by bicarbonate to produce carbon dioxide (CO_2) and water. The lungs can normally excrete CO_2, but this is not the case in patients with COPD, who have flow limitation. One would therefore predict that such patients would retain CO_2 during whole-body exercise. When we tested this hypothesis in patients with a mean FEV_1 of 24% predicted, we found this to be the case, with a mean rise of $Pa\,CO_2$ during constant-rate treadmill exercise from 5.38 kPa to 6.32 kPa and a fall in pH from 7.41 to 7.36.[28]

Pulmonary mechanics reduce capacity

Breathlessness may arise for several reasons. The proposition that pulmonary mechanics limit exercise in COPD is not synonymous with the start of our spiral, patients becoming breathless on exertion. The observation that flow limitation was present in COPD is longstanding,[29,30] but it has become apparent that increasing lung volumes during exercise – dynamic hyperinflation – contribute to symptom generation in COPD[31] and a reduction in dynamic hyperinflation can reduce dyspnoea in the absence of changes in FEV_1.[32,33] Dynamic hyperinflation can be measured easily using the inspiratory capacity measurement technique (Fig 3) and should form part of future intervention studies.

Are there treatment opportunities in the spiral?

Preventing development of myopathy

Pulmonary rehabilitation is an established treatment option[34] endorsed by the National Institute of Health and Clinical Excellence (NICE), which believes that 'Pulmonary rehabilitation should be made available to all appropriate patients with COPD' (www.nice.org.uk/pdf/CG012_niceguideline.pdf). It is clear that in patients with mild disease, high-intensity pulmonary rehabilitation can elicit a true training benefit[35] and pulmonary rehabilitation can increase the oxidative enzyme content of skeletal muscle.[36]

If skeletal muscle were to develop weakness in a stepwise manner around exacerbations, as proposed by Spruit et al,[22] then logically it would be appropriate to target pulmonary rehabilitation around the time of exacerbation. This was done in a study by Man and coworkers, in which patients admitted with acute exacerbation were randomised at discharge to receive usual care or, in addition, to receive pulmonary rehabilitation.[37] The intervention group had a significant reduction in visits to accident and emergency departments at 3 months (10% v 43%, p=0.01) and greater improvement in shuttle walking distance (+90 m v –25 m, p=0.002). Although this approach seems promising, it is unknown whether over a longer period early pulmonary rehabilitation confers a greater advantage than standard pulmonary rehabilitation and, if so, whether this benefit is conferred by improvements in muscle strength.

Fig 3. Example of dynamic hyperinflation induced by exercise in a patient with chronic obstructive pulmonary disease (COPD) in our laboratory. EELV = end expiratory lung volume; EILV = end inspiratory lung volume; TLC = total lung capacity.
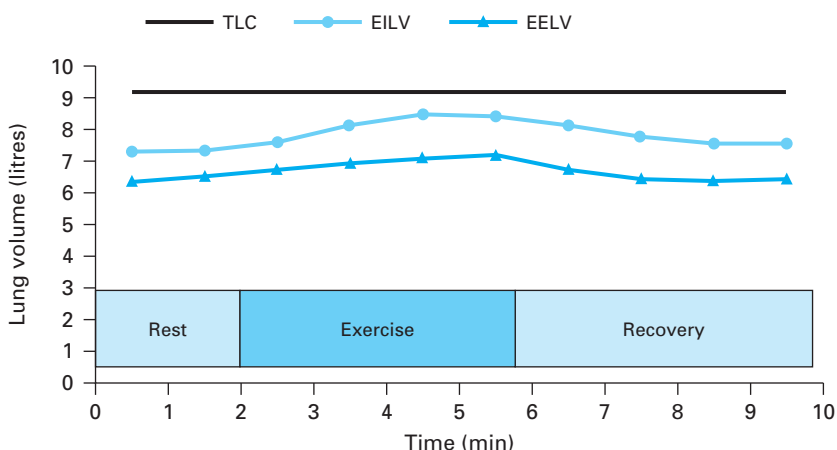
Train the quadriceps muscle

As noted above, in patients with mild to moderate disease, it is possible to train the quadriceps muscle using pulmonary rehabilitation. However, the same approach does not work in patients with more severe COPD, as they are unable to reach a sufficiently high work intensity.[38] An alternative approach is to train the quadriceps muscle in isolation using percutaneous electrical stimulation. Two studies have trialled this approach,[39,40] but although significant benefits have been claimed from these studies the method has not yet moved into general use. One problem is that it is hard to design an appropriate placebo, since the recipient is aware of the electrical stimuli. Therefore, in our own approach to this problem, we have opted to train only one leg and to use the other leg as a control and to assess response in terms of muscle-biopsy appearances and the twitch tension elicited by magnetic stimulation of the femoral nerve,[27] since these measures are independent of patient effort. Studies are ongoing and we plan to report in early 2007.

Reduce the impact of anaerobic metabolism

High-intensity exercise in COPD gives rise to acidosis and hypercapnia. Intuitively, approaches to rehabilitation that allow the patient to exercise with reduced minute ventilation could allow the patient to cope better with hypercapnia. Little detailed work has been done in this regard, although it has been established that very-high-intensity supplemental oxygen reduces dynamic hyperinflation,[41] and this approach is in use by some groups.

An obvious option is to use non-invasive ventilation (NIV) to assist exercise in pulmonary rehabilitation. NIV is an established therapy in the care of patients admitted with acute exacerbations of COPD.[42,43] When used acutely during exercise in COPD, NIV reduces respiratory muscle work[44,45] and attenuates exercise-induced lactataemia. Based on these findings, we hypothesised that NIV given during a PR programme could allow patients to reach a higher level of exercise and therefore achieve a true physiological training benefit. We tested this hypothesis in a prospective randomised controlled study in 19 patients with severe COPD.[46] The patients receiving NIV during exercise were able to achieve a higher level of exercise and, when studied during a constant-rate exercise test without NIV after the programme, such patients had a 30% reduction in blood lactate compared with patients who had exercised without NIV (Fig 4). This difference showed a trend towards statistical significance (p=0.09), and a larger multicentre study to assess the place of NIV in pulmonary rehabilitation is required. Two other studies have addressed this question: one showed benefit[47] and one did not.[48] The only clear factor that explains the difference is that our study and that of Costes *et al*[47] enrolled patients with more severe disease compared with Bianchi *et al*,[48] and it seems reasonable that this adjunctive therapy would be most helpful in patients with more severe disease.

Improving pulmonary mechanics

It has become clear that a variety of drugs may improve pulmonary mechanics in the absence of a clear improvement in FEV_1, including beta$_2$ agonists,[49] tiotropium[50] and low-density gas mixtures.[51]

Lung transplantation, either single or double, may provide a considerable improvement in lung function,[52] but this is not a therapeutic option for most patients because of the shortage of donor organs and because the mortality of the procedure (15%

Fig 4. Mean work rates achieved each week in people with chronic obstructive pulmonary disease (COPD) undergoing pulmonary rehabilitation (PR) with (closed symbols) and without (open symbols) the benefit of non-invasive ventilation (NIV). Data from Hawkins *et al* (2002), reproduced with permission from the BMJ Publishing Group© BMJ Publishing Group.[46]
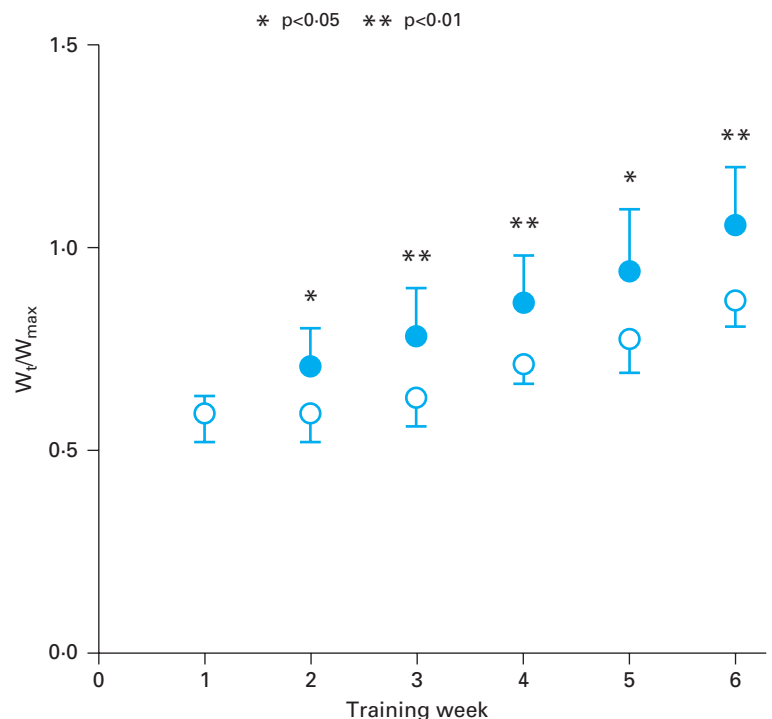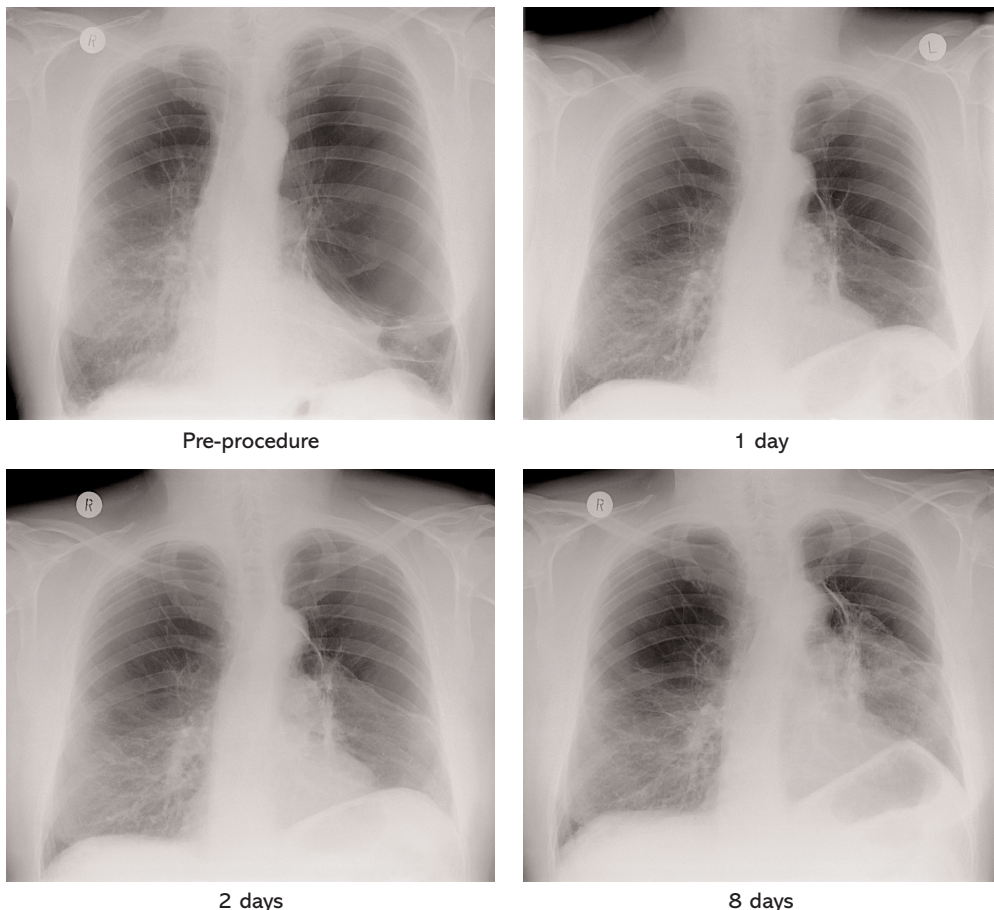
Fig 5. Examples of consecutive X-rays from a responder to bronchoscopic lung volume reduction.

Pre-procedure

1 day

2 days

8 days

at 1 year, 50% at 5 years) is unattractive to patients with all but the most severe disease.

Lung-volume reduction surgery (LVRS) was revived in the mid 1990s,[53] and randomised controlled studies have established that the procedure can improve exercise performance and mortality in patients with heterogeneous upper-zone bullous emphysema.[54,55] Unfortunately, there are several drawbacks to LVRS. First, the surgery is beneficial only in patients with upper-lobe bullous disease, who constitute at most 25% of patients with emphysema. Second, the mortality rate of approximately 5% is unattractive to many patients. Third, in order to minimise mortality, most groups, including our own, set minimum fitness criteria for patients being considered for LVRS of a shuttle walk distance of more than 150 m and a carbon monoxide gas transfer (TL_{CO}) greater than 30% predicted. In practice, this means that many patients prepared to consider the operation fail on safety criteria. Finally, even in the best hands, improvement does not occur in about 25% of patients, and no good method of identifying non-responders preoperatively has been found.

It has become a matter of interest to find a less invasive method of achieving lung-volume reduction. Two main approaches have been advocated. One is to create an extra-pulmonary pathway to allow additional drainage of air from the lung. Ex vivo this approach is satisfactory,[56] but no in vivo data are yet in the public domain. An alternative concept is to place a one-way valve in the airway, which prevents air entering the subtended lobe but allows air to exit. The theory is that the subtended lobe will then collapse, causing volume reduction. This certainly can work (Fig 5); importantly, in series reported from our[57,58] and other[59–61] institutions, it seems to be free of major side effects. As with LVRS, a beneficial response is not universal, but the valves can at least be removed if desired. Physiological analysis indicates that improvement in walking distance can be explained almost entirely by a reduction in dynamic hyperinflation and improved ventilation/perfusion matching.[58] Current thinking is that the best choice of treatment (extra-pulmonary bypass versus endobronchial blocker) may be influenced by the presence or absence of collateral ventilation (desirable with the former approach, not with the latter), and this can be conveniently assessed at bronchoscopy.[62]

Conclusion

COPD is not simply a pulmonary disease, and consideration of the disease spiral may allow for additional treatment and research opportunities that may be of considerable benefit to patients.

Conflict of interest

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