PROCEEDINGS REPORT

Pulmonary rehabilitation 2007: From bench to practice and back

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Abstract

COPD is a disease that is not confined to the airways and the lungs, but also produces systemic consequences. Muscle weakness is one of these. It is produced by a multitude of factors including deconditioning, systemic inflammation, oxidative stress, nutritional imbalance, reduced anabolic status, systemic corticosteroids, hypoxemia, hypercapnia, electrolyte disturbances, cardiac failure. The most important factors appear to be inactivity and systemic inflammation. Inactivity was shown to be present in patients with COPD from early in the course of the disease on. Systemic inflammation was shown to be predominantly present during COPD exacerbations. IL-6 has the propensity to reduce muscle function in experimental animals. At present there is no evidence of local production of cytokines in the muscle in patients with COPD. Muscle weakness is also important in the clinical course of the disease as it is associated with exercise intolerance, reduced quality of life, enhanced utilization of health care resources and reduced survival.

Rehabilitation is the best treatment for muscle weakness and deconditioning in patients with COPD. Indeed, it is the intervention with the largest effect on health status and exercise capacity in these patients. Several factors that may enhance the effects of rehabilitation have been studied. These include: growth hormone/ IGF-I, anabolic steroids, clenbuterol, creatine, anti-cytokine treatment, erythropoietin, oxygen, non-invasive mechanical ventilation and electrical stimulation. Recently, the potential of protease-inhibitors in reversing deconditioning-induced

muscle dysfunction was demonstrated. Adjuncts are potentially particularly useful in patients who do not respond to a rehabilitation programme. Analysis of large databases demonstrated that about one third of the patients does not respond to rehabilitation. A follow-up study suggests that decline in exercise capacity after a rehabilitation programme is particularly present in these patients and not in the patients with a clear initial response. A better understanding of the factors controlling the response to rehabilitation, may lead to significant advances in this field.

COPD is a highly prevalent disease affecting 5-10 % in the 50+ population in most Western Countries.¹ The prevalence of undetected COPD is particularly high. COPD is characterized by airflow obstruction that is not fully reversible.² In addition COPD is further characterized by a progressive loss in pulmonary function.^{3,4} At present, smoking cessation is the only therapy known to reduce the progression of the disease.⁵ There is some evidence that pharmacotherapy with inhaled corticosteroids and long-acting β_2 -agonists⁶ and long-acting anti-cholinergics^{7,8} may reduce the progression of the disease.

In recent years it has become more and more clear that COPD is not confined to the airways but also has

FIGURE 1. Quadriceps force, expressed as a percentage of the predicted value, in normal subjects (left) and in patients with COPD (right).

Causes of muscle weakness in COPD patients

- Deconditioning
- Systemic inflammation
- Oxidative stress
- Nutritional imbalance
- Reduced anabolic status
- Systemic corticosteroids
- Hypoxemia, hypercapnia
- Electrolyte disturbances
- Cardiac failure

TABLE 1. Overview of causes of muscle weakness in patients with COPD.

systemic consequences and significant co-morbidities.^{9,10} COPD patients randomly selected from 1,522 patients who were enrolled in a health maintenance organization in 1997 had, on average, 3.7 co-morbid conditions compared with 1.8 in controls.¹¹ The most prevalent of these co-morbidities included: cardiovascular disease^{12,13}, lung cancer¹⁴, deconditioning, exercise intolerance^{15,16}, muscle wasting¹⁷, depletion of fat free mass or obesity¹⁸, diabetes^{18,19}, osteoporosis²⁰⁻²², anxiety/depression.²³ All were associated with excess morbidity and mortality⁹.

One of the first recognized consequences of COPD was muscle weakness^{24,25} both affecting the respiratory and peripheral muscles. Fig.1 shows measurements of quadriceps force in patients with COPD compared with age matched controls. Quadriceps force is reduced in patients with COPD albeit that there is substantial variance among patients with COPD. The present manuscript will focus on peripheral muscle weakness in patients with COPD. It will specifically focus on: 1) the causes and 2) consequences of muscle weakness in patients with COPD; 3) the potential for pulmonary rehabilitation to reverse muscle weakness in patients with COPD.

Muscle weakness in COPD patients

Muscle weakness in COPD is believed to result from a variety of factors. Hyperinflation, which is prominently present in patients with COPD, reduces the force of the inspiratory muscles²⁴, although sarcomere adaptation is likely to restore sarcomere length to optimal length.^{26,27} Hence, the reduction in force with hyperinflation appears to result primarily from geometrical changes in the diaphragm and parasternal intercostals muscles putting these muscles at a mechanical disadvantage at lung volumes above functional residual capacity, FRC.

The peripheral muscles take part in the generalized muscle weakness which is known to be present in patients with COPD.²⁵ This muscle weakness is known to result from a multitude of factors which all interact to produce muscle weakness. They are summarized in table 1. They include: deconditioning, systemic inflammation (circulating inflammatory markers and presence of inflammation in other organs)²⁸, oxidative stress²⁹, nutritional imbalance, reduced anabolic status, cardiac failure^{30,31}, systemic steroid treatment^{32,33}, hypoxemia, hypercapnia, and

FIGURE 2. Activity expressed in daily minutes spent walking in healthy controls in patients with COPD (GOLD I and II, GOLD III and GOLD IV). Modified according to Pitta et al.³⁵

electrolyte disturbances.³⁴ At present deconditioning and systemic inflammation seem to be the prime factors and therefore, they are discussed in greater depth in the present article.

Inactivity was suspected to be present for a long period of time in patients with COPD because they tend to avoid dyspnea, but until recently measurements of activity were not possible. Pitta et al. in our laboratory developed a technique to measure activity based on tri-axial accelerometry (Dynaport®).³⁵ This technique allows determination whether a patient is lying down, sitting, standing or walking at any point of the day. Using this technique we demonstrated that walking time in patients with COPD is reduced to about 50% of the walking time in healthy subjects (50 minutes vs. 100 minutes per day).³⁵ Remarkably, this reduction starts as of the early stages of the disease (Figure 2). During exacerbations walking time is further reduced to almost zero and, even 1 month after the onset of the exacerbation, walking time is still considerably below the walking time in stable COPD patients.³⁶ Inactivity thus seems to be present from early in the disease and aggravated substantially during exacerbations. The latter explains part of the deleterious effects of exacerbations on health related quality of life and exercise capacity.

Along the same lines, exacerbations were shown to reduce peripheral muscle force substantially in patients with COPD. Indeed, Spruit et al. demonstrated that during a COPD exacerbation quadriceps force was reduced compared with stable COPD, this muscle weakness only recuperated slowly after the exacerbation and during the exacerbation there was a further loss of about 1% per day.²⁸ This study showed convincingly that a COPD exacerbation is associated with a reduction in muscle weakness. The mechanism of this reduction could be related to the profound inactivity known to be present during a COPD exacerbation. A second potential mechanism is the circulating systemic inflammatory markers and cells that are released during an exacerbation. Along these lines in the study from Spruit et al. we found significant relationships between IL-8 and IL-6 serum levels in COPD patients both during an exacerbation and in stable patients.²⁸ These relationships, however, are by no means necessarily causal, as more severe exacerbations or more severe airway inflammation would likely be associated with both higher levels of IL-6 and IL-8 and more pronounced muscle weakness.

To further examine the propensity of these cytokines to cause muscle weakness we developed an animal model in which rats were treated for one week with IL-8 and IL-6 and their ventilatory and peripheral muscle function was examined at the end of treatment. IL-8 even in doses up to 200 µg/kg/day did not affect muscle function.³⁷ Rats were also treated with IL-6 treatment in doses of 50, 100 and 250 µg/kg/day.³⁸ The latter dose caused a 20% reduction in the cross-sectional area of all muscle fibres in the diaphragm and gastrocnemius. Further experiments revealed that this was not due to a direct effect of IL-6 on the muscle, but rather by an indirect effect. Indeed, IL-6 caused high output cardiac failure, associated with an increased cardiac output, a reduction in preload recruitable stroke work, a reduction in end-systolic pressure in the left ventricle and an increase in cardiac dimensions particularly of the right ventricle.³⁷ Because of the reduction in end-systolic pressure muscle blood

flow was reduced leading to a reduced muscle function. The latter study thus showed that systemic inflammatory markers may indeed affect muscle function in experimental animals. Whether these data may be extrapolated to patients is not yet clear.

One study³⁹ demonstrated that in frail elderly increased expression of TNF- α was present in the vastus lateralis both at the protein level and the mRNA level. After 8 weeks of resistance training this expression was substantially reduced. This study indicated that, in frail elderly subjects, local production of cytokines in the vastus lateralis could contribute to muscle weakness and that the observed training effect could in part be related to a reduction in the expression of these cytokines. In view of the potential significance of this concept it was studied by several groups in COPD patients as well. We studied the expression of IL-6, IL-8, TNF- α in vastus lateralis of patients with stable disease and during exacerbations at the protein level and mRNA-level.⁴⁰ For the latter RT-PCR was used. We found that TNF- α expression was below the detection limit. The expression of IL-6 and IL-8 was very low (about 0.1 copies per 1000 copies of house keeping gene, and 0.005 copies per 1000 copies of house keeping gene, respectively). Exacerbation did not affect these expression levels. This study indicated that local production of cytokines does not play a major role in the muscle weakness caused by COPD and its exacerbations.

Muscle weakness in patients with COPD results in a number of important consequences that clearly affect patient centered outcomes. It was shown to limit exercise capacity.^{16,41,42} It may reduce health related quality of life. It is associated with enhanced utilization of health care resources.⁴³ Finally, convincing evidence is present that muscle weakness is related to mortality in patients with COPD.^{44,45}

Effects of pulmonary rehabilitation

The appropriate treatment for muscle weakness in patients with COPD appears to be pulmonary

rehabilitation. This treatment and its beneficial consequences are now well established. The major benefits appear to be an increase in health related quality of life and an increase in functional status as measured with the 6 min walking distance.⁴⁶ It should be noted that the observed increases in health related quality of life are substantial and often exceed the effects produced by long-acting β 2-agonists, inhaled steroids, long-acting anti-cholinergics or a combination thereof. Whether rehabilitation improves survival is at present unclear as studies that are sufficiently powered to address this question are presently not available.

Response to pulmonary rehabilitation

In view of these tangible effects, pulmonary rehabilitation was reimbursed in Belgium from 2000 in four centres: Leuven, Ghent, Liège and Sainte Ode. Since then we have collected data on 1,312 patients. Analysis of the data has taught us a number of things that were hitherto unknown. First, the response to rehabilitation, in terms of the increase in 6-minute walking distance and quadriceps force, is virtually identical in all GOLD stages (Figure 3). Tangible increases are also present in patients who were candidates for lung transplantation. Hence the latter patients are good candidates for rehabilitation as well. Pre- and postoperative rehabilitation in these patients is highly recommended.

Second, not all patients seem to respond equally to a pulmonary rehabilitation programme. If response is defined as at least a 50 m increase in 6-minute walking distance, then the response to a 6-month lasting rehabilitation programme can be described as follows: 47% of the patients are responders after three and six months. Fifteen percent of the patients are non-responder after 3 months, but become responders after 6 months. Four percent of the patients had a response after three months, but no longer after six months and finally, 34% of the patients had no response after 3 or 6 months. Consequently, about one third of the patients did not respond to a pulmonary rehabilitation

FIGURE 3. Increase in 6-minute walking distance (left) and quadriceps force (right) observed during a 6-month lasting rehabilitation programme in patients in different stages (GOLD II, III, IV and patients enrolled in a pre-transplant rehabilitation programme). Line marks minimal clinical important difference.

programme. This pattern of response is clearly different from what has been observed in normals.

The reasons for this poor response in a tangible number of patients are presently unclear. The absence of ventilatory limitation and the presence of muscle weakness seem to help to identify responders, but the discrimination between responders and non-responders was poor.⁴⁶ Other factors such as hemoglobin, gene expression, expression of cytokines both systemically and locally in the muscle, still need to be examined. Analysis of the maintenance of the effects appears to suggest that patients who have a clear response during a rehabilitation programme also exhibit good maintenance of the effect, whereas patients who do not have a response lose functional exercise capacity rapidly in the two years after the programme. This suggests that future efforts to improve the effects of rehabilitation should be directed towards the non-responders rather than to the responders.

An alternative approach would be to try to enhance the effects of rehabilitation. Several approaches may be used to this end: growth hormone/IGF-I, anabolic steroids^{47;48}, clenbuterol, creatine, anti-cytokine treatment, erythropoietin, oxygen⁴⁹, non-invasive mechanical ventilation⁵⁰ and electrical stimulation.^{51;52}

Some of these adjuncts like testosterone and anabolic steroids were shown to be useful and therefore their combination with a rehabilitation programme seems logical at this point in time.

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