



REVIEW

Exercise training and pulmonary rehabilitation: new insights and remaining challenges

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ABSTRACT: Pulmonary rehabilitation is now regarded as an evidence-based treatment for symptomatic patients with chronic obstructive pulmonary disease. It has been shown to enhance exercise tolerance, improve symptoms and health-related quality of life, and reduce exacerbations in patients with recurrent exacerbations. In this article we review the mechanisms through which exercise training results in beneficial effects. We also review three challenges that currently remain: 1) the fine tuning of exercise training and multidisciplinary programmes; 2) the timing of rehabilitation; and 3) efforts to enhance the accessibility and adherence to pulmonary rehabilitation programmes. Further research is needed in order to apply the now well-established principles of pulmonary rehabilitation to unusual patient populations, or patient populations that are unlikely to participate in conventional outpatient programmes.

KEYWORDS: Chronic obstructive pulmonary disease, muscle, physical activity, rehabilitation

Pulmonary rehabilitation is a dynamic therapeutic field which has rapidly evolved over the last decades. Exercise training remains the cornerstone of rehabilitation programmes and offers benefits to exercise tolerance that are complementary to the effects obtained from pharmacotherapy in patients with chronic obstructive pulmonary disease (COPD). Both pharmacotherapy and rehabilitation enhance health-related quality of life and exercise tolerance, and reduce exacerbation rate; however, the mechanisms leading to these benefits are different. Pharmacotherapy essentially improves lung function, pulmonary inflammation and dynamic hyperinflation during exercise, while pulmonary rehabilitation impacts on the systemic (extrapulmonary) consequences of the disease (physiological, psychological and perceived symptoms) [1]. Contemporary “combination therapy” should, therefore, include optimal pharmacotherapy and pulmonary rehabilitation programmes. This is more increasingly recognised by those to have to pay for health care. A recent example is the reimbursement of pulmonary rehabilitation by the Medicare system in the USA as of January 1, 2010.

Clearly, pulmonary rehabilitation has the most solid foundation in patients with COPD. In recent

years, however, comparable effects have been shown in other respiratory diseases, including restrictive lung diseases [2], pulmonary fibrosis [3], stable pulmonary hypertension [4] and following lung transplantation [5, 6].

Although the effects of pulmonary rehabilitation are recognised, several challenges remain and avenues for further improvement of the field remain open. These challenges are directly related to the intervention offered, to the timing of the intervention and to the organisational aspects, the access and flexibility of programmes. These aspects will be reviewed in more detail later.

THE INTERVENTION OFFERED

Pulmonary rehabilitation programmes are multidisciplinary programmes that are built around an exercise training intervention. The aim of the exercise training is to reverse the systemic consequences of COPD, in particular the skeletal muscle dysfunction. Furthermore, exercise training enhances the mechanical efficiency of physical activities (particularly walking) and may also reduce the sensitivity to dyspnoea. In order to reverse the skeletal muscle abnormalities, exercise training needs to be of high intensity in order to result in an anabolic stimulus. When exercise training is offered at a high intensity it improves

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the oxidative capacity of the skeletal muscle. This leads to enhanced exercise capacity and, through its reduction of ventilation at submaximal work loads, also reduces the symptom burden in patients. Effective exercise training enhances anabolic processes in the muscle [7]. The interventions and the principles through which they lead to enhanced exercise capacity are demonstrated in figure 1.

To be effective, a training stimulus needs to be applied three times per week for a minimum of 8 weeks. The training intensity in healthy subjects is set at 55–85% of the heart rate reserve [8]. In patients with COPD, however, the exercise limitation is often the ventilatory system, which makes it complex with whole body endurance training to impose sufficient training load to the skeletal muscle. In the last few years, strategies have been developed to enhance the local load on the skeletal muscle in severely ventilatory limited patients. One strategy is that peak ventilatory capacity can be maximised using optimal bronchodilator therapy. Thus, optimal bronchodilator therapy allows enhanced training intensity and yields superior results than training performed without optimal bronchodilator therapy [9]. Another way to enhance the maximum breathing capacity of patients is the administration of gas mixtures with a density below ambient air; helium is such a gas. Breathing a gas mixture where N_2 is replaced by helium acutely enhances exercise tolerance. It unloads the respiratory system allowing a higher peripheral oxygen delivery. Heliox reduces the metabolic cost of exercise and renders the peripheral muscle less fatiguable [10]. Recently, a study showed superior effects of helium breathing during exercise training. In this study [11], a mixture of helium and an increased oxygen fraction was used, which makes it difficult to dissect the effects of helium and the effect of the oxygen supplements. Besides being impractical, the cost of these mixtures is currently substantial and may render their application expensive. Unloading the respiratory muscles, thus yielding a larger oxygen delivery to peripheral muscles, can also be achieved using noninvasive mechanical ventilation (NIMV). Although

this has been performed successfully in severe COPD patients to aid the exercise regimen during pulmonary rehabilitation [12, 13], the application of NIMV during rehabilitation remains difficult and time consuming. Nevertheless, in very severe patients (e.g. those on a waiting list for lung transplantation) NIMV application may render a difficult-to-train patient trainable. In patients with respiratory failure, the combination of night-time noninvasive ventilation and daytime pulmonary rehabilitation may be more efficient [14].

The former interventions aim at supporting the impeded ventilatory system in patients with COPD. Another strategy may be to limit the ventilatory requirements during exercise. This may also give more comfort during exercise training to the ventilatory limited patient or, alternatively, allow for a higher training intensity. The first approach is to offer oxygen supplements to patients. This reduces the ventilatory drive and, thus, pulmonary ventilation for a given work load at the expense of hypercapnia. Due to the enhanced oxygen delivery it also delays lactic acidosis, which further contributes to reduced ventilator needs. EMTNER *et al.* [15] showed that it was possible to train patients at a higher training intensity when oxygen supplements were given. As a result they showed larger improvements in whole body endurance in the patients who trained with oxygen supplements [15]. A second approach may be to reduce the muscle bulk used during the training; this obviously reduces the metabolic demand of exercise. If training load is focused on a smaller group of muscles these can be loaded more without utilising the full ventilator capacity. DOLMAGE *et al.* [16] used this paradigm in a study comparing single leg cycling exercise training to conventional cycling training and showed superior effects when each leg was trained separately. A final approach to reduce the ventilator needs during exercise is to use interval training rather than endurance training. During interval training small bursts of training are offered to patients. Due to the short exercise duration and the slow kinetics of pulmonary ventilation, the ventilation does not rise to high levels, even when the imposed work load is high. Interval training has comparable effects to endurance training [17] and leads to skeletal muscle hypertrophy [18]. Importantly patients reported fewer symptoms during this training regimen and less unexpected stops were observed.

The final strategy of interventions is specifically aimed at enhancing skeletal muscle force. Specific resistance training can be applied to enhance peripheral muscle function and, although some cross-over effect towards enhanced whole body exercise tolerance may be expected, the effect is particularly seen in the enhanced peripheral muscle strength and endurance. These are clearly important features to daily life activities. Specific resistance training has been applied in several studies and summarised in several excellent review papers [19, 20]. Resistance training (or weight lifting) significantly enhances skeletal muscle strength when applied alone or in combination with whole body exercise training [21]. Therefore, it is a powerful rehabilitation tool to enhance the skeletal muscle “machinery”. More recently, several authors have used “nonphysiological” neuromuscular electrical stimulation to enhance peripheral muscle function [22]. Electrical stimulation has also been shown to be effective in enhancing skeletal muscle function. However, as the stimulations are not

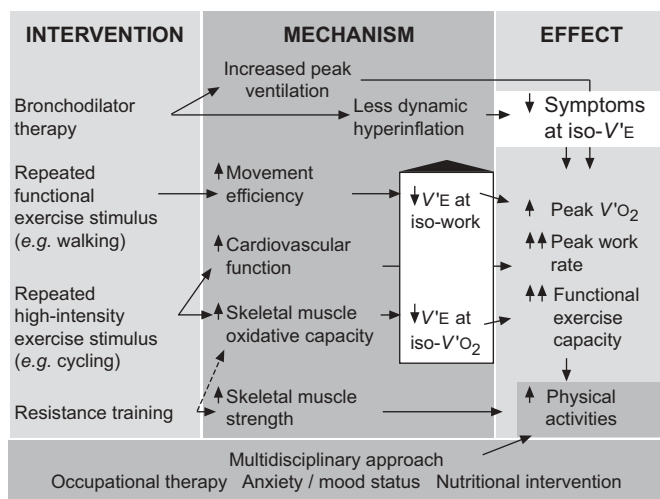


FIGURE 1. Mechanism through which pulmonary rehabilitation and pharmacotherapy may enhance physical activity. $V'E$: minute ventilation; $V'O_2$: maximal oxygen uptake.

physiologically evoked and are not embedded in neuromuscular coupling pathways, we would advise restricting the use of neuromuscular electrical stimulation to situations where prevention of the loss of skeletal muscle function is required, or in programmes where neuromuscular electrical stimulation is combined with conventional pulmonary rehabilitation. The effects of neuromuscular electrical stimulation and resistance training may be amplified by the addition of pharmacotherapy directed to improve skeletal muscle function. Testosterone supplements in addition to resistance training have been proven in hypogonadal males to restore skeletal muscle strength more rapidly compared with resistance training alone [23]. Other targets for skeletal muscle directed pharmacotherapy are being identified but, to date, its clinical application has not been validated [24]. Such therapy can target scavenging processes of oxidative stress in susceptible patients [25], anabolic signalling and substrates or key proteins of the muscle machinery. Patient selection for supplemental interventions will be crucial to show their effectiveness.

All the above interventions focus on fine-tuning the exercise training intervention. Pulmonary rehabilitation, however, consists of more than just exercise training. Surprisingly, little research has been presented in recent years on the specific effects of introducing other disciplines involved in pulmonary rehabilitation. In particular, there is little knowledge on how to transfer the gains in exercise capacity into enhanced participation in daily life activities. Several studies have assessed the effects of rehabilitation programmes on physical activity. The improvement of physical activity levels is not guaranteed after pulmonary rehabilitation, as is indicated in table 1 and figure 2. Importantly, it is unknown how much improvement in physical activity is a clinically relevant improvement. Any increase in

the proportion of patients meeting the required amount of physical activity for healthy ageing would be a significant benefit for both patients and society. Whether pulmonary rehabilitation enhances the proportion of patients meeting these goals (30 min of physical activity at moderate intensity on at least 5 days·week⁻¹) [35] has not yet been investigated. Indeed, surprisingly little research has focused on ways to facilitate the transfer of benefits to physical activity. A study from the Netherlands suggested that the use of simple pedometer devices may provide patients with real-time feedback on their physical activity levels [34]. When appropriate guidance is given this may enhance physical activity levels, much like in healthy subjects [36]. Whether other behavioural interventions may help to achieve a long-term change towards a more physically active lifestyle remains to be investigated in COPD.

TIMING OF THE REHABILITATION INTERVENTION

Most guidelines report extensively on the benefits of pulmonary rehabilitation in patients with stable lung disease. Much less is known about the effects of pulmonary rehabilitation immediately after or even during acute exacerbations. A recent meta-analysis summarised the currently available evidence and concluded that pulmonary rehabilitation established after exacerbations enhances health-related quality of life, improves exercise capacity and reduces the risk for re-admissions [37]. Following severe exacerbations leading to hospital admission, patients are at risk for re-admission and survival is severely reduced. Acutely reduced skeletal muscle force [38] and depressive symptoms (identified as an independent risk factor for mortality after exacerbations) [39] are surely amenable to rehabilitation therapy. Furthermore, patients are extremely inactive after acute exacerbations and it is very infrequent to observe recovery to normal physical activity levels in the

TABLE 1 Changes in physical activity after pulmonary rehabilitation

First author [Ref.]	Patients	Sessions of supervised rehabilitation	Duration of rehabilitation weeks	Instrument to measure physical activity	Outcome
STEELE [26]	38	16	8	TA: Tritrac R3D accelerometer	VMU per min
STEELE [27]	111	16	8	TA: RT3 accelerometer	VMU
CORONADO [28]	15	36	3	UA: self-contained activity monitor	Time at low + medium act %
MERCKEN [29]	11	40	8	UA: physical activity monitor accelerometer	Physical activity monitor score
SEWELL [30]					
Standard	59	14	7	UA: ambulatory activity monitor	Counts
Individualised	64	14	7	UA: Z80-32k V1 Int	Counts
PITTA [31]					
3 months	29	36	12	TA: dynaport	Walking time
6 months	29	60	24	TA	Walking time
WALKER [32]	23	16	8	UA: actiwatch	Time spent mobile %
DALLAS [33]	45	2-3	6-12	PE: New Lifestyles, NL-2000	Counts per h
DE BLOK [34]					
Classic	8	NR	9	PM: Yamax digi walker	Steps
Classic+pedom	8	NR	9	PM: Yamax digi walker	Steps

Data are presented as n. pedom: pedometer feedback; TA: triaxial accelerometer; UA: uniaxial accelerometer; PE: pedometer (electronic); PM: pedometer (mechanical); NR: not reported; VMU: vector magnitude units. Please also refer to figure 2.

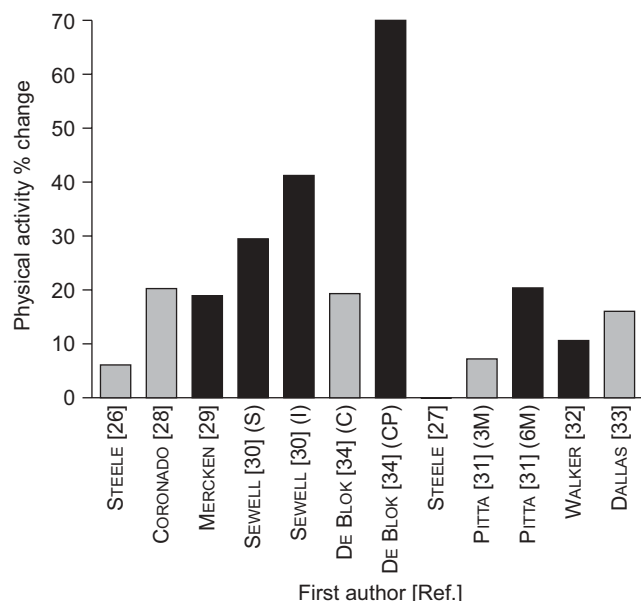


FIGURE 2. Improvement of physical activity. ■: studies that were statistically significant; ■: studies that were statistically nonsignificant. S: standard; I: individualised; C: classic; CP: classic+pedometer feedback; 3M: 3 months; 6M: 6 months.

month following a hospital admission [40]. Obviously rehabilitation faces many challenges in the period immediately after an exacerbation. Adherence to the intervention and recruitment of patients is extremely difficult [41]. In addition, exercises need to be adapted to the ventilatory impairment of the patient. Patients need to be encouraged to become physically active after exacerbations, which may warrant input from occupational therapists and/or psychological counselling to deal with anxiety or depression. Furthermore, interventions enhancing self-management are useful in these frail patients [42].

On the other side of the disease spectrum, in patients with milder disease, the efficacy of pulmonary rehabilitation is not yet supported by substantial evidence. A recent trial investigating the impact of pulmonary rehabilitation in the community in patients with a forced expiratory volume in 1 s of ~60% of the predicted value showed only modest effects [43]. Others studies have shown clear effects in these patients [44]. Further studies are required to investigate the potential of rehabilitation early in the disease process to prevent the systemic consequences of COPD. Such studies need long-term follow-up and large study populations, as the main effect of such programmes is the prevention of the incidence of systemic consequences, rather than their cure. In addition, such studies can investigate the role of enhanced physical activity on lung function decline [45].

ACCESS AND FLEXIBILITY

One of the most important challenges of pulmonary rehabilitation is retention in the programme and referral to programmes. A recent Danish study showed that only 60% of patients visiting an outpatient university hospital clinic were offered pulmonary rehabilitation [46]. In Scotland (UK) only 23% of primary-care practitioners were able to refer their patients to a

pulmonary rehabilitation programme [47]. In Canada only 9% of patients with COPD were referred for pulmonary rehabilitation [48]. A survey conducted in the UK in 2001 suggests that only 1% of COPD patients receive rehabilitation [49]. Attempts should be made to make pulmonary rehabilitation available to more patients and also to keep patients in programmes once they are enrolled. Dropout from programmes and non-adherence impede on the effects of rehabilitation. A prospective study in the Netherlands identified that 23% of patients recruited in a rehabilitation programmes quit the programme prematurely. Discontinuation was often due to medical reasons (exacerbations and infarction). Patients with poor attendance were more likely to have less social support, tended to be smokers and had a lower fat-free mass. A study from the UK reported a 31% dropout rate and identified low muscle force, smoking history, poor health-related quality of life and depressive mood status as predictors for dropout [50]. It appears as if patients not completing the rehabilitation programme are in fact theoretically good candidates for rehabilitation. Several modifications could be made to programmes to better fit with the patients' abilities to cope with the programmes. In the future, telemedicine could perhaps help to further individualise exercise training programmes for patients. However, care should be taken not to create easily accessible programmes in the community or at home at the expense of the effectiveness of the programmes. Recently a number of large studies [43, 51, 52] suggested that it is challenging to reproduce the effects of pulmonary rehabilitation observed in single-centre studies, and in multi-centre trials, where perhaps less expertise is available to individualise programmes. However, one study suggests otherwise [53]; close supervision of patients by an expert team appears to be a factor associated with the overall success, and particularly the physiological benefits, of programmes [54].

CONCLUSIONS

Pulmonary rehabilitation is now recognised an effective treatment that should be integrated in the management of symptomatic patients with COPD. Three important challenges lie ahead: 1) the implementation of these programmes into the lines of healthcare so that they are accessible to most patients who would benefit; 2) ensuring the quality of these programmes so that the effects obtained in single-centre studies and carried out in centres of excellence can be applied in less specialised centres; and 3) facilitating the transfer of the obtained rehabilitation benefits into long lasting improvements in the behaviour of patients (including smoking cessation and physical activity).

Pulmonary rehabilitation programmes are built around high-intensity exercise training to enhance exercise tolerance, skeletal muscle function and functional exercise capacity. In individual patients, other healthcare professionals, including physiotherapists, psychologists, nutritional specialists, occupational therapist, nurse specialists and doctors, contribute to the full effects of rehabilitation on health-related quality of life, psychological morbidity, reduced exacerbation rate and enhanced participation in daily life (physical activity). The latter remains a challenge and further research should focus on improving the effectiveness of rehabilitation programmes on enhancing physical activity, which is the cornerstone to long lasting benefits.

This may be of particular importance following exacerbations when physical activity levels drop dramatically and continued inactivity is a predictor of successive events.

It is important to recognise the potential of pulmonary rehabilitation in clinical practice. We have now entered the era of fine tuning the intervention and making it available, in an effective format, to larger groups of patients. We realise that this may require efforts from scientists, healthcare providers, policy makers and patients. Given the proven effectiveness of these interventions, however, no effort should be spared.

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STATEMENT OF INTEREST

None declared.

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