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Rehabilitation and acute exacerbations

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ABSTRACT: **Recent evidence indicates that acute exacerbations of chronic obstructive pulmonary disease aggravate the extrapulmonary consequences of the disease. Skeletal muscle dysfunction, a sustained decrease in exercise tolerance, enhanced symptoms of depression and fatigue are reported. Avoidance of physical activities is likely to be a key underlying mechanism and increases the risk of new exacerbations. Pulmonary rehabilitation is an intervention targeting these systemic consequences. Exercise strategies need to be adapted to the increased feelings of dyspnoea and fatigue.**

This review aims to describe the systemic consequences of acute exacerbations and compiles evidence for the feasibility and effectiveness of different rehabilitation strategies to counteract these consequences during and/or immediately after the acute phase of the exacerbation. Resistance training and neuromuscular electrical stimulation have been applied safely in frail, hospitalised patients and have the potential to prevent muscle atrophy. Comprehensive pulmonary rehabilitation, including general exercise training, can be implemented immediately after the exacerbation, leading to a reduction in hospital admissions and an increase in exercise tolerance and quality of life. Self-management strategies play a crucial role in changing disease-related health behaviour and preventing hospital admissions.

KEYWORDS: **Chronic obstructive pulmonary disease, exacerbation, exercise training, physical activity, pulmonary rehabilitation, skeletal muscle**

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Acute exacerbations of chronic obstructive pulmonary disease (COPD) are commonly described as events in the natural course of the disease that are characterised by a change in the patient's baseline dyspnoea, cough and/or sputum, which is beyond normal day-to-day variations, is acute in onset and may warrant a change in regular medication [1, 2]. The majority of these are thought to be caused by complex interactions between the host, bacteria, viruses and environmental pollution [3], leading to increased upper and lower airway and systemic inflammation [1]. Due to bronchospasm, mucosal oedema and sputum inspissation, airway resistance is increased [4]. Severe exacerbations often involve an obvious deterioration in health status, leading to hospitalisation [5], which is the primary driver of all COPD-related medical care costs, accounting for 50–75% of the direct COPD-associated healthcare costs [6, 7].

Although exacerbations are diagnosed based on respiratory symptoms, evidence has arisen that they also have systemic consequences, including a detrimental influence on skeletal muscle function [8], exercise tolerance [9] and mood status [10].

This article aims to describe the systemic consequences of acute exacerbations of COPD, and compiles evidence of the feasibility and effectiveness of different rehabilitation strategies to counteract these consequences during and/or immediately after the acute phase of the exacerbation.

IMPACT OF EXACERBATIONS

Symptoms

Recently, the EXACT-PRO (Exacerbations of Chronic Pulmonary Disease Tool Patient-Reported Outcome) consortium identified symptoms that characterise an exacerbation from a patient-centred perspective. They found that the following were the most universally reported symptoms: breathlessness, chest tightness, chest congestion, cough, sputum production, chest discomfort, feeling weak or tired, sleep disturbance, and feeling scared or worried [11]. None

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of these items, however, could be considered a specific characteristic of exacerbations, as all symptoms were experienced by stable patients. The authors reported that exacerbations are characterised by quantitative changes in symptom severity, rather than by the onset of unique new symptoms. In the Perception of Exacerbations of Chronic Obstructive Pulmonary Disease (PERCEIVE) study, increased coughing was reported by 42% of patients as having a strong impact on well-being during exacerbations; this was followed by increases in shortness of breath (37%), fatigue (37%) and sputum production (35%) [12]. Interestingly, 45% patients reported having stayed in bed or on the sofa all day during the exacerbation [12], which points at the severe inactivity confirmed by others [13, 14].

Systemic impact of exacerbations

Exacerbations can lead to a sustained decrease in exercise tolerance and patients with exacerbations have a faster decline in 6-min walking distance (6MWD). COTE *et al*. [9] reported that even patients who only experienced one severe exacerbation showed a striking 72-m decline (20%) in 6MWD after an exacerbation, and did not recover afterwards, despite an appreciable recovery of lung function and symptoms.

Peripheral muscle dysfunction is a systemic consequence of exacerbations that might have an underlying role in observed prolonged exercise intolerance. Quadriceps peak torque decreases by ~1% per day during hospitalisation for an exacerbation [8, 13]. Microarray analysis confirms the onset of muscle dysfunction during exacerbations by showing increased expression of markers of the ubiquitin-dependent catabolism pathway and downregulation of the mitochondrial respiration pathway, compared with stable patients [15].

The cause of muscle dysfunction during exacerbations is multifactorial and is likely to vary from patient to patient. In order to maintain muscle mass, a delicate balance between muscle build-up (anabolism) and breakdown (catabolism) should be maintained. Exacerbations may inhibit build-up (nutritional depletion, lack of physical activity or steroid treatment) and aggravate breakdown (inflammation, inactivity, oxidative stress or steroid treatment).

During exacerbations, patients experience excessive symptoms of dyspnoea, weakness and tiredness even during low-intensity activities. Avoidance of physical activities is likely to be a key underlying mechanism of muscle dysfunction in these patients. From the patient's perspective, the impact of exacerbations on normal daily life activities is more important than experiencing symptoms [16]. Although patients do not have a strict bed rest prescription during hospitalisation for an exacerbation, PITTA *et al*. [13] reported that the majority of hospitalised patients spent <10 min per day walking, even when they were close to discharge. Not surprisingly, the daily amount of weight-bearing activities was related to isometric quadriceps strength at hospital discharge. 10 days of bed rest is associated with a 6% decrease in lower limb lean body mass and a 15% decrease in isokinetic quadriceps strength in healthy elderly subjects [17]. In healthy young subjects, KROGH-MADSEN *et al*. [18] reduced the participants' daily levels of activity from ~10,000 to 1,000 steps per day for 2 weeks. This better mimics the activity levels of patients during exacerbations. The authors observed a 3% decline in lower limb lean mass and a 7% decline in maximal oxygen consumption. Interestingly, they also reported a deterioration of insulin sensitivity in these subjects.

Acute exacerbations are also associated with enhanced systemic inflammation, as shown by higher blood levels of C-reactive protein, interleukin (IL)-6, IL-8, tumour necrosis factor-α, leptin, endothelin-1 and fibrinogen, among others [19–23]. This acute systemic inflammatory state also has a potential role in the development of muscle dysfunction [24]. SPRUIT *et al*. [8] reported increased systemic levels of IL-8 that were inversely correlated (r= -0.53) with isometric quadriceps strength during exacerbations. Despite the enhanced systemic inflammatory state, inflammatory markers in the skeletal muscle have not been reported. Hence, the precise pathways through which inflammation acts on the peripheral muscle during exacerbations remain to be discovered.

Compromised energy balance during acute exacerbations may also be involved in the onset of muscle dysfunction [25]. This makes patients more vulnerable to tissue depletion. Resting metabolic rate is increased in patients with stable disease compared with healthy elderly subjects [26], and is acutely elevated during the first days of hospital admission [25]. Within the same time frame, dietary intake has been reported to be very low, probably due to the inability to eat more, primarily because of dyspnoea and fatigue symptoms [25]. Furthermore, leptin, an appetite-suppressing hormone and inflammatory cytokine [27], has been reported to be increased during exacerbations [28]. This may further reduce appetite. On top of this, the muscle protein synthetic response to amino acid intake in food is blunted in the elderly [29, 30], leading to sarcopenia [31]. To the authors' knowledge, it remains to be studied whether this is aggravated during exacerbations of COPD, but the negative nitrogen balance reported in patients with acute exacerbations would support this hypothesis [32, 33]. The resulting catabolic state may be an additional underlying factor that explains the observed inactivity, as the negative energy balance might prompt patients to preserve their energy. This is an important concept from a therapeutic perspective, as exercise-related interventions will influence energy balance [34].

The use of systemic corticosteroids is recommended in the hospital management of exacerbations of COPD (evidence level A) [2]. In a previous study, DECRAMER *et al*. [35] showed that the average daily dose of systemic corticosteroids in the preceding 6 months is associated with peripheral muscle function, explaining 51% of the variance in quadriceps strength. Interestingly, the corticosteroid treatment in this trial consisted primarily of bursts received for exacerbation treatment, with only one patient receiving daily corticosteroids. In their study, HOPKINSON *et al*. [36] did not observe any change in respiratory or quadriceps muscle strength in stable COPD outpatients following a 2-week course of 30 mg prednisolone daily. Regardless of the ongoing debate on muscle-related side-effects of short bursts of systemic corticosteroids, it is clear that corticosteroid treatment can lead to steroid-induced myopathy, which is associated with severe peripheral and respiratory muscle weakness, at least in selected patients [37, 38]. It remains unclear which doses are required to induce this myopathy and how the individual susceptibility for it varies among patients.

In patients with respiratory failure, hypoxia adds to the muscle dysfunction. Hypoxia is associated with the activation of pro-inflammatory cytokines [39] and increased oxidative stress damage [40]. The local levels of oxidative stress could be further enhanced in the presence of systemic inflammation [41]. Free radicals, when inadequately scavenged by anti-oxidants, can cause damage to proteins and lipids, leading to altered activity of the mitochondrial respiratory chain complex [41]. During severe exacerbations, respiratory pump failure, due to airflow obstruction and/or respiratory muscle weakness or fatigue, can lead to hypercapnic respiratory failure. Acute hypercapnia-induced intracellular acidosis has a negative influence on cell metabolism and respiratory and limb muscle contractility [42–45].

The observed reduction of anabolic hormone levels during exacerbations [46] has been linked with corticosteroid use [47] and hypoxia [48], and is another possible factor facilitating skeletal muscle wasting during acute exacerbations [49].

Whereas the role of inflammatory pathways, oxidative damage and corticosteroids in the onset of muscle dysfunction is still under debate, the evidence of the detrimental influence of physical inactivity is irrefutable.

Long-term consequences of exacerbations

Although acute exacerbations are, by definition, temporary events, in some patients, symptoms and lung function do not recover to baseline values even after 3 months [50]. Recovery seems to be even more compromised in patients with an early re-exacerbation [51]. Recent evidence shows that exacerbations are not random events but cluster together in time; there is a high-risk period of 8 weeks after the exacerbation during which time a new exacerbation may be experienced [52]. In line with this, hospitalisation for COPD in the previous year is a risk factor for exacerbation-related hospitalisation, independent of disease severity [53]. Frequent exacerbations are related to accelerated lung function decline [54] and decreased health-related quality of life [55, 56]. Furthermore, mortality increases with the frequency of severe exacerbations, especially if hospital admission is required [57, 58]. As exacerbations do not seem to be random events, healthcare providers should be particularly aware of patients who have suffered from exacerbations; efforts to prevent exacerbations should be directed particularly toward those who have suffered an exacerbation.

A striking observation in the study by PITTA *et al*. [59] was that physical activity levels 1 month after hospital discharge were still clearly below levels observed in stable patients with similar disease severity. Patients spent 135 min of the day performing weight-bearing activities 1 month after discharge from hospital. This was 44% less than patients with stable COPD and 64% less than healthy controls [13, 59]. Figure 1 illustrates these findings by reporting daily walking time during and after exacerbations, in stable patients and in healthy elderly subjects.

Interestingly, patients who had already experienced an exacerbation-related hospitalisation in the previous year (53% of the sample) showed less spontaneous recovery in daily physical activity levels after 1 month. Furthermore, patients readmitted in the follow-up year had a lower walking time 1 month after discharge. These findings are confirmed by the

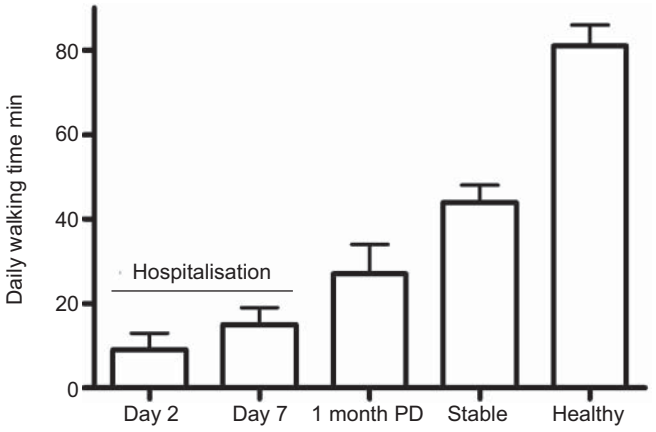

FIGURE 1. Daily walking time during an exacerbation-related hospitalisation (day 2 and day 7) and follow-up (day 40) [13], in stable patients and healthy elderly subjects [59]. PD: post-discharge. Data are presented as mean±SEM. Data from [13, 59].

observations of DONALDSON *et al*. [14], who showed that frequent exacerbators (identified using symptom diary cards) have a 70% greater decline in the time spent outdoors over an 8-yr period, increasing their risk of becoming housebound. The relationship between daily physical activity level on one hand and the risk of hospitalisation and mortality on the other, has also been documented in large prospective cohort studies [60–63]. Patients with frequent exacerbations also experience a greater decline in fat-free mass over time [64]. Similarly, subsequent exacerbations requiring emergency department attendance or hospital admission are associated with reductions in quadriceps strength [65].

Drawing all of this information together, hospitalisation for an acute exacerbation seems to be associated with marked and prolonged inactivity, and an inactive lifestyle is an independent risk factor for exacerbations. The fact that rehabilitation, which is likely to enhance physical activity [66], does reduce readmission after exacerbations (discussed further later) strongly suggests causation.

Figure 2 provides an overview of the systemic consequences of acute exacerbations.

INTERVENTIONS DURING ACUTE EXACERBATIONS

Given the multitude of mechanisms that could attenuate muscle function during exacerbations, interventions to prevent or immediately counteract these changes are indicated. Whole-body exercise training has the potential to improve skeletal muscle function [67]. Modalities and intensity of training need to be chosen with consideration for the markedly increased dyspnoea and fatigue experienced during exacerbations. In order to avoid excessive respiratory symptoms, ventilatory requirements and dynamic hyperinflation should be kept to a minimum. Furthermore, one could speculate that exercise training during or following exacerbations may aggravate local inflammatory and oxidative stress to the muscle. Whereas skeletal muscle inflammation induced by exercise remains an area of controversy [68, 69], high-intensity exercises performed until exhaustion are associated with increased muscle oxidative stress in stable patients with COPD [70, 71]. The challenge lies in the development of interventions that are tolerated by highly

symptomatic patients and that do have a net anabolic effect on the skeletal muscles or, as a minimum, prevent catabolism.

Potential pharmacological support

Administration of *N*-acetylcysteine (NAC) in patients with stable COPD has been shown to increase local muscle endurance capacity by 25% and prevent exercise-induced oxidative stress [72]. The role of NAC in preventing local oxidative stress at the muscle level during acute exacerbations is yet to be investigated.

Reduction of ventilatory requirements and work of breathing

Oxygen therapy is an important component in the management of acute respiratory failure during exacerbations [73]. Its primary objective is to raise arterial oxygen tension, optimise oxygen delivery to peripheral tissues and alleviate dyspnoea symptoms. In acidotic hypercapnic exacerbations, noninvasive mechanical ventilation (in the form of pressure support ventilation or continuous positive pressure ventilation) unloads the respiratory muscles, enhances inspiratory flow rate, corrects hypoventilation and resets the central respiratory drive [74].

The use of both oxygen supplementation and noninvasive mechanical ventilation improves exercise endurance and maximal exercise tolerance in stable patients with COPD [75]. The observed relief of exertional dyspnoea with oxygen supplementation during exercise is associated with a suppression of the ventilatory drive and reduced blood lactate levels [76]. Recently, helium hyperoxia mixtures (heliox; 40% O_2, 60% He) have been found to significantly reduce work of breathing and dyspnoea during exercise [77]. The helium component improves dynamic hyperinflation, leading to a greater increase in exercise endurance than with hyperoxia alone. Similarly, the use of noninvasive mechanical ventilation reduces the work of breathing and leads to improvement in dyspnoea and exercise endurance in stable patients with COPD [78–80]. Noninvasive positive pressure ventilation also reduces hypoxia during walking in patients with severe COPD [81] and can be combined with heliox [82].

These strategies might play a role in allowing the most severely disabled patients to perform adapted exercise training during acute exacerbations by reducing respiratory symptoms and preventing desaturation during exercise. Data to support this hypothesis are currently lacking in COPD, although in the intensive care unit (ICU) setting, training has been successfully carried out with ventilatory support [83–85].

Resistance training

Resistance training is a successful intervention that partially reverses muscle dysfunction in stable patients with COPD [86]. The inherent focus on specific muscle groups results in a relatively limited cardiorespiratory burden [87], which makes resistance training an interesting modality in patients with severe symptoms of dyspnoea. Importantly, a recently published randomised controlled trial (RCT) showed that high-intensity quadriceps resistance training did not yield higher systemic inflammation, as measured with C-reactive protein and neutrophil counts [88]. In this trial, 40 patients admitted to hospital for a COPD exacerbation were randomised to receive usual care or to conduct an additional quadriceps resistance training programme from the second day of hospitalisation (typical duration of 7 days). The training consisted of three daily sets of eight repetitions against a load initially equalling 70% of the one-repetition maximum. The load was increased gradually and reached 113% of the initial load by the end of the programme. The training was well tolerated by most of the patients, reflected in the mean dyspnoea and fatigue symptom scores ranging 3–6 on a modified Borg scale throughout the programme. Despite the short training period, isometric quadriceps force increased by 10% in the intervention group. Muscle biopsies confirmed the favourable impact of the intervention on the anabolic–catabolic balance, in particular by avoiding the upregulation of the catabolic factor myostatin. Interestingly, the beneficial effects on muscle strength were still present 1 month after discharge.

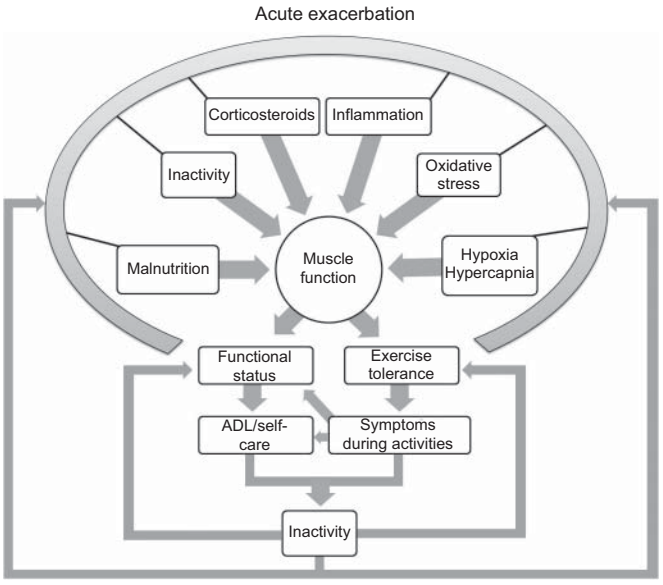

FIGURE 2. Schematic overview of the systemic consequences of acute exacerbations of chronic obstructive pulmonary disease. Possible intermediate steps in the onset of muscle dysfunction (*e.g.* blunted anabolic hormone levels linked with steroid use and hypoxia) are not presented.

Potential pharmacological support

Whether it may be of benefit to combine testosterone supplementation with resistance training remains controversial due to the reported side-effects [89, 90]. In stable hypogonadal patients, the combination of testosterone supplementation and resistance training has been shown to improve lower limb muscle strength more than either of the two interventions alone [91]. As testosterone levels acutely decrease during acute exacerbations [46], it could be speculated that short-term testosterone supplementation optimises the effect of resistance training in selected patients.

Neuromuscular electrical stimulation

Hospital admission for exacerbations should be kept as short as possible. Interventions during the acute exacerbation should therefore not lengthen the duration of hospital stay. Enrolling patients in an in-patient rehabilitation programme should be avoided where possible because of the cost burden and the risk associated with hospital admission [92]. As early discharge

TABLE 1 Randomised controlled trials of neuromuscular electrical stimulation (NMES) in respiratory compromised patients

First author [ref.]	Study design	Subjects n	Subject characteristics	Training details	Effects
Zanotti [99]	NMES plus ALM *versus* ALM	24	COPD patients with chronic hypercapnic respiratory failure and the need for mechanical ventilation (>30 days bedbound)	Quadriceps and glutei 30 min, bi-daily, 5 days·week-1, 4 weeks Freq: 35 Hz; PD: 350 μs	Higher peripheral muscle strength (specific muscle not reported) and lower number of days needed to transfer from chair to bed (mean 3.5 days)
Gerovasili [103]	NMES *versus* control	49	ICU patients with a stay of >48 h and an APACHE II score of ⩾13	Quadriceps and peronei longi 55 min daily, days 2–9 after admission Freq: 45 Hz; PD: 400 μs	Less decrease in CSA of rectus femoris (-8 *versus* -14%) and vastus intermedius (-13 *versus* -22%) in NMES group
Routsi [104]	NMES *versus* control	52	ICU patients with APACHE II score of ⩾13	Quadriceps and peronei longi 55 min daily, day 2 until ICU discharge Freq: 45 Hz; PD: 400 μs	Higher MRC sum score [105] for muscle strength when sufficiently conscious (58 *versus* 52). Lower proportion of CIPNM in NMES group (13 *versus* 39%)
Gruther [106]	NMES *versus* sham	33	Short- and long-term ICU patients (hospital stay of <7 days and >14 days, respectively)	Quadriceps 30–60 min, 5 days·week^{-1}, 4 weeks Freq: 50 Hz; PD: 350 μs	More favourable change of quadriceps CSA (mean of rectus femoris and vastus intermedius) in NMES group (+5 *versus* -3%) in long-term patients; no differences in short-term patients
Abdellaoui [96]	NMES *versus* sham	15	COPD patient admitted to a respiratory ICU for an AE	Quadriceps and hamstrings 60 min, 5 days·week^{-1}, 6 weeks Freq: 35 Hz; PD: 400 μs	Greater increase in quadriceps MVC (+10 *versus* +3 kg) and 6MWD (165 *versus* 58 m) in NMES group
Poulsen [102]	Single leg with other leg as paired control	8	ICU patients with septic shock	Quadriceps 60 min, 7 consecutive days Freq: 35 Hz; PD: 300 μs	Quadriceps volume decreased similarly in stimulated and control leg (-2.9 per day *versus* -2.3% per day, respectively)

ALM: active limb mobilisation; COPD: chronic obstructive pulmonary disease; freq: frequency of the current; PD: pulse duration of the current; ICU: intensive care unit; APACHE: Acute Physiology and Chronic Health Evaluation; CSA: cross-sectional area; MRC: Medical Research Council; CIPNM: critical illness polyneuromyopathy; AE: acute exacerbation; MVC: maximal voluntary contraction; 6MWD: 6-min walking distance.

strategies appear to be feasible and increasingly become routine clinical practice in uncomplicated COPD exacerbations [93], it might not be feasible to apply a progressive exercise programme, as previously described, in all admitted patients. With this in mind, the application of neuromuscular electrical stimulation (NMES) has been shown to be a promising alternative. Recent NMES devices are small and easy to use, which allows patients to continue the intervention at home during the period immediately following hospital admission [94]. NMES is also a potential alternative strategy in patients who experience intolerable symptoms during or after active (resistance) training. The metabolic response to NMES is significantly lower compared with that of a resistance exercise training session [95]. Furthermore, NMES does not increase muscle oxidative stress [96]. When applying a minimum of 16 sessions, NMES training programmes have been shown to improve peripheral muscle strength, exercise capacity and, to a lesser extent, health-related quality of life [97, 98]. Importantly, recent reports show that NMES is safe and effective in frail patients with severe respiratory or cardiovascular impairment [99–101]. Table 1 provides an overview of RCTs evaluating the use of NMES in respiratory compromised patient populations. They all present results that are in favour of electrical stimulation, with the exception of a study that was performed in septic ICU patients, in which electrical stimulation did not prevent the onset of muscle atrophy in any way [102]. A recently published controlled pilot study reports on a 6-week NMES programme in an in-patient setting, initiated during admission to the ICU for acute COPD exacerbation [96]. 1-h sessions of bilateral electrical stimulation of both quadriceps and hamstring muscles were conducted 5 days per week. The training group showed enhanced effects on muscle force, 6MWD and the proportion of type-1 fibres, without aggravating local oxidative stress to the muscles.

Nutritional intervention

As active training requires energy, adequate nutritional support should be considered an important parallel intervention, especially in patients with an already impaired energy balance (*i.e.* depleted and weight-losing patients). Nutritional interventions during hospitalisation for an exacerbation lead to improved protein and total energy intake, without a drop in normal dietary intake [32, 107]. A protein intake of 1.2–1.5 g·kg body weight^{-1} has been identified to prevent the onset of sarcopenia [108]. Protein requirements for COPD are not available but whole-body protein turnover is already increased in clinically stable condition [109]. Consequently, protein intake during nutritional interventions has exceeded 1.5 g·kg body weight^{-1} [32, 107].

Potential nutritional supplements and pharmacological support

Supplementary essential amino acids increase body weight and fat-free mass in weight-losing and frail patients with COPD [110, 111], making these food supplements an as yet unexplored area of interest during exacerbations. Another potentially interesting intervention would be supplementary polyunsaturated fatty acids. When administered in stable patients enrolled in a pulmonary rehabilitation programme, additional improvements in peak and endurance exercise tolerance were observed, even after adjustment for fat-free mass [112]. Polyunsaturated fatty acids are also suggested to have an anti-inflammatory effect [113]. Whether other anti-inflammatory therapies would enhance the effects of nutritional interventions needs to be studied further. Statin therapy has recently received attention. Simvastatin has been shown to reduce leptin levels in patients with coronary heart disease [114] and may reduce hospital readmission rates [115]. It is tempting to speculate that the association of statins with rehabilitation after acute exacerbations would be beneficial, although one needs to be aware of the potential deleterious effects of statins on skeletal muscle function in selected patients [116].

INTERVENTIONS IMMEDIATELY AFTER ACUTE EXACERBATIONS

Pulmonary rehabilitation

It has been shown that comprehensive pulmonary rehabilitation programmes have the ability to reduce the use of healthcare services and the number of days spent in hospital during 1 yr of follow-up in stable patients with COPD [117]. These programmes target several disease-related outcomes that are reported to be predictors of acute exacerbations, including physical activity levels [118], respiratory and peripheral muscle weakness [119], health-related quality of life [120], dyspnoea symptoms [121] and composite severity scores, such as the BODE (body mass, index, airflow obstruction, dyspnoea and exercise capacity) index [122].

Evidence is accumulating that rehabilitation programmes are also feasible and particularly effective when applied immediately after the initial exacerbation recovery. A Cochrane Collaboration meta-analysis by PUHAN *et al*. [123] concluded that pulmonary rehabilitation following an exacerbation reduces hospital admissions, with the follow-up period ranging 3–18 months. The number of patients needed to treat to prevent one exacerbation-related admission is four (95% CI 3–8). This finding is extremely relevant in this specific patient group who have a high risk for readmission. Changes in health-related quality of life well exceed the minimal important difference [123]. Similarly, pooled differences in 6-min walking test and shuttle walking test between intervention and control groups after termination of the programme were significant and clinically relevant in favour of rehabilitation [123]. Two other trials have also reported benefits in terms of quadriceps strength [65, 124]. Since the Cochrane meta-analysis, to the authors' knowledge, one RCT has been published, which reported no effects on exercise capacity and readmission rate [125].

The programmes that are reported to be successful in RCTs are very heterogeneous in terms of initiation, duration, setting and programme content. They include: 8-week comprehensive outpatient programmes initiated within 7 days of hospital discharge [65, 126]; a 10-day in-patient walking programme starting within 1 week after admission [127]; an 18-month, supervised, home-based walking programme initialised in the hospital [128]; and a 6-week home-based whole-body exercise programme [124]. Direct comparisons between different settings have not yet been reported. In most of the programmes reported in the literature, exercise training has consisted of a combination of aerobic and resistance training, with intensities similar to programmes in stable patients [65, 124, 126, 129]. This implies that applying whole-body exercise training with an appropriate training intensity is feasible within days after an acute exacerbation. This statement is confirmed by two trials that explicitly recorded adverse events and identified none [126, 128].

Only one trial provided an intervention that combined exercise training during and after exacerbations [130]. Patients were included 2.6 days after hospital admission for an acute exacerbation and received a daily 30-min exercise training session that included walking and resistance training. After discharge, they entered an 8-week whole-body exercise training programme; training intensity was not described. Compared with the usual care group, the attendees showed improvements in feelings of anxiety, 36-item Short Form Health Survey physical function scores and a trend towards a better BODE index, but no difference in 6MWD, which improved by >100 m in both groups.

Interestingly, two studies in the literature that identified no trend towards decreased hospital admission also found that there was no effect on exercise capacity [125, 130]. One of the trials reported a low adherence, with only 40% of patients randomised in the rehabilitation group attending 75% of the sessions [130]. As other trials have reported that 20–30% of patients who finished the rehabilitation programme attended <50% of the sessions [65, 126], adherence appears to be an important point requiring attention in the outpatient setting. Specific strategies may need to be put in place to facilitate compliance. Such strategies may lean more towards better integrated care, so that patients are not lost if they cannot cope with one specific programme but can be offered effective alternatives that fit with their needs and abilities. An area of interest that addresses this issue is the implementation of community-based rehabilitation programmes [126, 131, 132] and tele-rehabilitation [133].

Self-management strategies

Whereas exercise training is generally considered to be the cornerstone of pulmonary rehabilitation, interventions that specifically target the patient's self-management seem to play a crucial role in changing disease-related health behaviour and preventing hospital admissions [134]. The aim of self-management programmes for COPD should be to recognise exacerbations as soon as possible and act appropriately. Despite the detrimental impact of exacerbations on the course of the disease, patients often have difficulty recognising the symptoms of an exacerbation early after the onset, as they are an aggravation of their usual symptoms beyond normal day-to-day variation [135]. This leads to under-reporting of exacerbations [136]. Time to symptom recovery increases by 0.4 days per day delay in seeking therapy [137]. Furthermore, a failure

to report exacerbations is associated with an increased risk of emergency hospitalisation. Action plans for acute exacerbations that emphasise prompt initiation of adequate medical treatment at the onset of symptoms have been described in literature [138–140] and are associated with a shorter recovery time in terms of symptoms [141]. A Cochrane meta-analysis summarised the results of 14 controlled trials reporting on the effectiveness of self-management programmes in patients with COPD [142]. It has to be noted that these trials were generally conducted in stable patients who were not at increased risk of exacerbations. The authors reported a significant reduction in the probability of experiencing at least one hospital admission among patients receiving self-management education compared with those receiving usual care (OR 0.64, 95% CI 0.47–0.89). There was no difference in the number of exacerbations or emergency department visits. Most pulmonary rehabilitation programmes after exacerbations that are described in the literature have included self-management interventions [65, 126, 129, 143, 144]. This seems the right way forward as self-management interventions may improve reaction time when new exacerbations occur, whereas exercise training may be a preventive strategy against new exacerbations. In light of this, it is impossible to differentiate which part of the comprehensive rehabilitation intervention leads to beneficial results in terms of hospital readmission.

Other aspects

A number of known risk factors for exacerbations can be tackled by other members of a comprehensive multidisciplinary rehabilitation team. These include the treatment of nutritional deficits [107] and depressive symptoms [145], and adjusting behaviour that increases the risk of exacerbation, by providing smoking-cessation interventions in active smokers [146] and promoting physical activity in inactive patients [147, 148]. The latter may be facilitated by providing walking aids for patients suffering from dyspnoea or patients who are oxygen dependent after exacerbations [149]. Wheeled walking aids (rollators) improve functional exercise capacity by improving ventilatory capacity and/or walking efficiency [149].

INFLUENCE OF NEW EXACERBATIONS DURING REHABILITATION

Even though the compiled evidence shows that pulmonary rehabilitation has the potential to improve outcome after acute exacerbations of COPD, it cannot prevent the occurrence of acute exacerbations during the programme or during follow-up. The onset of exacerbations could, in turn, compromise the effects of rehabilitation [150] and is indicated as a reason for drop out or prolonged non-attendance in an exercise programme [151, 152]. Exacerbations may be strategically important time-points to reinforce the importance of physical activity and exercise in patients. Clearly, the symptoms experienced during exacerbations form a barrier to physical activity. The involvement in a pulmonary rehabilitation programme may offer an opportunity to enhance the self-management of physical activity after the exacerbation. To the authors' knowledge, only one trial has investigated the effectiveness of 3-week bursts of rehabilitation after the occurrence of an acute exacerbation, during the 1-yr follow-up of a similar pulmonary rehabilitation programme [144]. These repeat programmes yielded clinically important improvements in dyspnoea 5 weeks after the acute exacerbation in patients who did not experience a second exacerbation during follow-up. Unfortunately, differences in functional exercise capacity were not observed. In a community setting, VAN WETERING *et al.* [131] also offered six extra training sessions after an exacerbation during the 20-month follow-up period of their INTER disciplinary COMmunity-based COPD management programme (INTERCOM), but did not further report on the effectiveness of this part of the intervention.

CONCLUSION

We have reviewed evidence that acute exacerbations are associated with muscle dysfunction and physical inactivity, which are in turn independent risk factors for hospital readmission. Patients with frequent exacerbations show a faster decline in lung function, quality of life and time spent outdoors. Consequently, it is important to counteract these changes whenever possible. Exercise training strategies have been shown to be feasible and effective when implemented both during the acute phase of the exacerbation (*e.g.* resistance training, neuromuscular electrical stimulation) or as soon as possible after the acute exacerbation period (*e.g.* aerobic training, resistance training). Interventions tackling self-management issues and physical activity behaviour could play an important role in optimising long-term outcomes and prevent relapse after a severe exacerbation.

SUPPORT STATEMENT

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STATEMENT OF INTEREST

A statement of interest for M. Decramer can be found at www.erj.ersjournals.com/site/misc/statements.xhtml

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