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Rehabilitation and acute exacerbations

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Acute exacerbations of chronic obstructive pulmonary disease (COPD) are commonly described as events in the natural course of the disease characterized by a change in the patient's baseline dyspnea, cough, and/or sputum that is beyond normal day-to-day variations, is acute in onset, and may warrant a change in regular medication[1;2]. The majority of those 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 oftentimes involve an obvious deterioration of health status leading to hospitalization[5], which are the primary driver of all COPD-related medical care costs, accounting for 50 to 75% of the direct COPD associated health care costs[6;7].

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

This review aims at describing the systemic consequences of acute exacerbations of COPD 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.

Impact of exacerbations

Symptoms

Recently, the EXACT-PRO consortium identified symptoms that characterize an exacerbation from a patient-centered perspective. They found breathlessness, chest tightness, chest congestion, cough, sputum production, chest discomfort, feeling weak or tired, sleep disturbance, and feeling scared or worried to be the most universally reported symptoms[11]. None of these items, however, could be considered a specific characteristic of exacerbations, as all symptoms were also experienced by stable patients. The authors reported that exacerbations are characterized by quantitative changes in symptom severity, rather than by the onset of unique new symptoms. In the PERCEIVE study, increased coughing was reported by

42% of patients as having a strong impact on well-being during exacerbations, followed by increase in shortness of breath (37% of patients), increased fatigue (37%) and increased sputum production (35%)[12]. Interestingly, up to 45% of patients reported to stay in bed or in the couch 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 six-minute walking distance (6MWD). Cote et al. reported that even patients who only experienced one severe exacerbation showed a striking 72m decline (20%) in 6MWD after an exacerbation which did not recover afterwards, despite an appreciable recovery of lung function and symptoms[9].

Peripheral muscle dysfunction is a systemic consequence of exacerbations that might have an underlying role in the observed prolonged exercise intolerance. Quadriceps peak torque decreases by approximately 1% per day during hospitalization for an exacerbation[8;13]. Micro-array 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 to stable patients[15].

The cause of muscle dysfunction during exacerbations is multi-factorial and is likely variable 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, steroid treatment) and aggravate breakdown (inflammation, inactivity, oxidative stress, steroid treatment).

During exacerbations, patients experience excessive symptoms of dyspnea, weakness and tiredness even during low-intense 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 hospitalization for an exacerbation, Pitta et al.[13] reported that the majority of hospitalized patients spent less than 10 minutes per day walking, even when they were close to discharge. Not surprisingly, the daily amount of weight-bearing activities was related with isometric quadriceps strength at

hospital discharge. Ten days of bed rest are associated with a 6% decrease in lower limb lean body mass and a 15% decrease in isokinetic quadriceps strength in healthy elderly[17]. In healthy young subjects, Krogh-Madsen et al[18] reduced the participants' daily levels of activity from about 10000 to 1000 steps per day for two 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 patients.

Acute exacerbations are also associated with enhanced systemic inflammation, as shown by higher blood levels of C-reactive protein, interleukin-6, interleukin-8, tumor 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. reported increased systemic levels of IL-8 that were inversely correlated (r=-0.53) with isometric quadriceps strength during exacerbations[8]. 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 remains to be discovered.

Another mechanism that is possibly involved in the onset of muscle dysfunction is the compromised energy balance during acute exacerbations[25]. This makes patients more vulnerable to tissue depletion. Resting metabolic rate is increased in patients with stable disease compared to healthy elderly[26] and is acutely elevated during the first days of hospital admission[25]. Within the same time frame, dietary intake was reported to be very low probably due to the inability to eat more, primarily because of dyspnea and fatigue symptoms[25]. Furthermore leptin, a hormone suppressing appetite and an inflammatory cytokine[27], was 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 elderly[29;30], leading to sarcopenia[31]. Whether this is aggravated during exacerbations of COPD has not been studied to the author's knowledge, but the negative nitrogen balance reported in patients with acute exacerbations would support this hypothesis[32;33]. The resulting catabolic state is possibly an additional underlying factor to explain 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 (Grade A evidence)[2]. Decramer et al. showed that the average daily dose of systemic corticosteroids in the preceding six months is associated with peripheral muscle function, explaining 51% of the variance in quadriceps strength[35]. Interestingly, the corticosteroid treatment in this trial consisted primarily of bursts that patients received for exacerbation treatment, with only one patient receiving daily corticosteroids. Hopkinson et al. did not observe any change in respiratory or quadriceps muscle strength in stable COPD outpatients following a 2 week course of 30 mg of prednisolone daily[36]. Regardless of the ongoing debate on the muscle-related side effects of short-bursts of systemic corticosteroids, it is clear that corticosteroid treatment can lead to steroid-induced myopathy, 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 to an 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 antioxidants, 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 on the detrimental influence of physical inactivity is irrefutable.

Long-term consequences of exacerbations

Although acute exacerbations are by definition temporary events, in a proportion of 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, leading to a high risk period of 8 weeks after the exacerbation to experience a new exacerbation[52]. In line with this, hospitalization for COPD in the previous year is a risk factor for exacerbation-related hospitalization, independent of disease severity[53]. Frequent exacerbations are related with 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 they require hospital admission[57;58]. Since exacerbations seem not to be random events, health care providers should be particularly alert in patients that suffered from exacerbations. Efforts to prevent exacerbations should be directed particularly to those that suffered from an exacerbation.

A striking observation in the study of Pitta et al.[13] was that physical activity levels one month after hospital discharge were still clearly below levels observed in stable patients with similar disease severity[59]. Patients spent 135 minutes of the day in weight-bearing activities one 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.

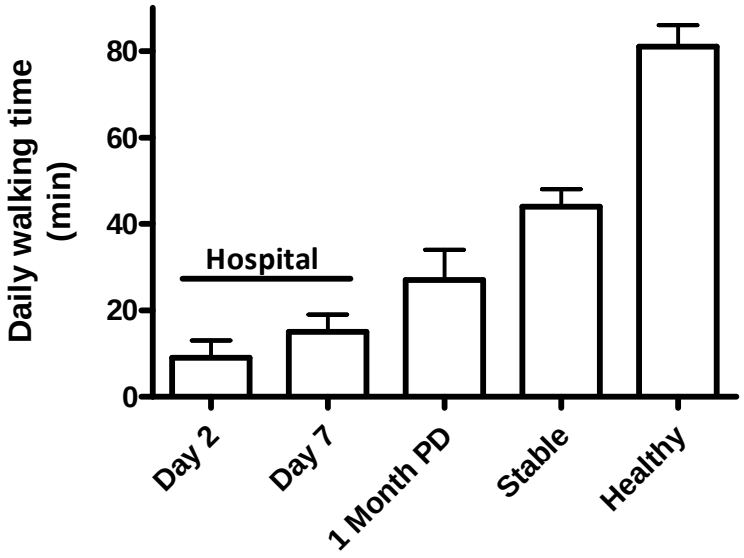

Figure 1. Daily walking time during an exacerbation-related hospitalization (day 2 and day 7) and follow-up (± day 40)[13], in stable patients and healthy elderly[59]. PD = post discharge. Data are means ± standard error of the mean.

Interestingly, those patients who already experienced an exacerbation-related hospitalization in the previous year (53% of the sample) showed less spontaneous recovery in daily physical activity levels after one month. Furthermore, patients that were readmitted in the follow-up year had a lower walking time one month after discharge. These findings are confirmed by the observations of Donaldson et al. that frequent exacerbators (identified using symptom diary cards) show 70% more decline in the time spent outdoors over an 8-year period, increasing the risk of becoming housebound[14]. The relationship between daily physical activity level on one hand and risk for hospitalization and mortality on the other hand 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].

Putting all the pieces of information together, hospitalizations for an acute exacerbation seem 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 (see below) strongly suggests causation.

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

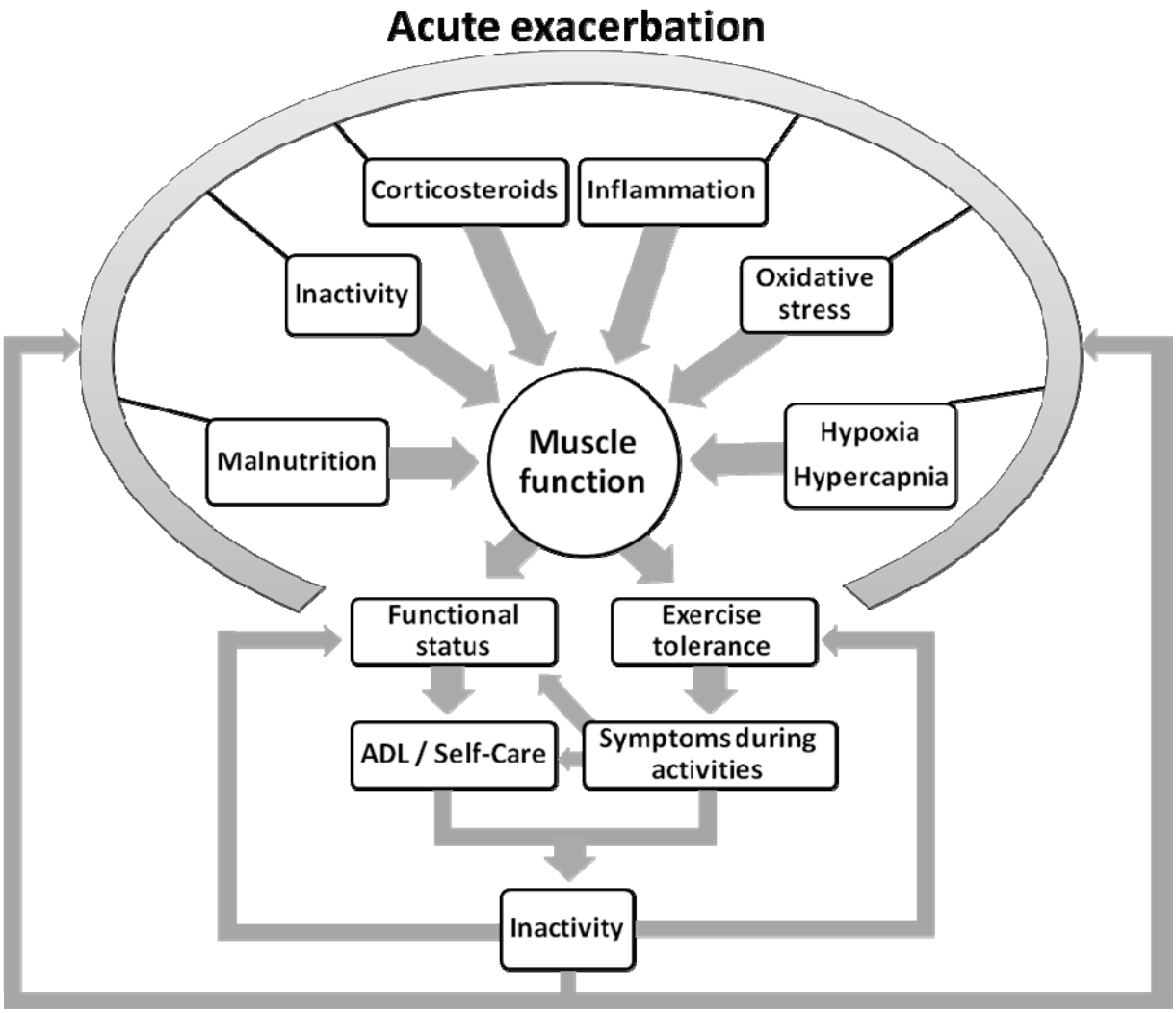

Fig 2. Schematic overview of the systemic consequences of acute exacerbations of COPD. Possible intermediate steps in the onset of muscle dysfunction (e.g. blunted anabolic hormone levels linked with steroid use and hypoxia) are not visualized.

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 in light of the markedly increased dyspnea and fatigue 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 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 increased local muscle endurance capacity by 25% and prevented exercise-induced oxidative stress[72]. The role of NAC to prevent local oxidative stress at the muscle level during acute exacerbations has not yet been 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 dyspnea 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 dyspnea with oxygen supplementation during exercise is associated with a suppression of the ventilatory drive and with reduced blood lactate levels[76].

Recently, helium-hyperoxia mixtures (heliox; 40% O_2, 60% He) were found to significantly reduce work of breathing and dyspnea 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 improvements in dyspnea and exercise endurance in stable patients with COPD[78-80]. Non-invasive positive pressure ventilation also reduces hypoxia during walking in patients with severe COPD[81] and can be combined with heliox[82].

These strategies might have 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 ICU setting training has been successfully carried out with ventilatory support[83-85].

Resistance training

Resistance training is a successful intervention in partially reversing 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 training modality in patients with severe symptoms of dyspnea. Importantly, a recently published randomized controlled trial (RCT) showed that high-intensity quadriceps resistance training did not yield higher systemic inflammation, as measured with CRP and neutrophil counts[88]. In this trial, 40 patients admitted to the hospital for a COPD exacerbation were randomized to receive usual care or to conduct an additional quadriceps resistance training program from the second day of hospitalization (typical duration of 7 days). The training consisted of three daily sets of eight repetitions against a load initially equaling 70% of the one-repetition maximum. The load was increased gradually and reached 113% of the initial load by the end of the program. The training was well tolerated by most of the patients which is reflected by mean dyspnea and fatigue symptom scores ranging between 3 and 6 on a modified borg scale throughout the program. Despite the short training period, isometric quadriceps force increased by 10% in the intervention group. Muscle biopsies confirmed the favorable 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 one month after discharge.

Potential pharmacological support: Whether testosterone supplementation may be of benefit to be combined 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 showed to improve lower limb muscle strength more than any of the two interventions alone[91]. As testosterone levels acutely decrease during acute exacerbations[46], it could be speculated that short-term testosterone supplementation could optimize the effect of resistance training in selected patients.

Neuromuscular electrical stimulation

By all means, 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 inpatient rehabilitation program should be avoided where possible because of the cost burden and the risk associated to hospital admission[92]. As early discharge 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 program as described before in all admitted patients. In light of this, the application of neuromuscular electrical stimulation (NMES) showed 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 that experience intolerable symptoms during or after active (resistance) training. The metabolic response to NMES is significantly lower compared to 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 programs showed 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 RCT's evaluating the use of NMES in respiratory compromised patient populations. They all provide results in favor of electrical stimulation except for a study that was performed in septic ICU

patients in which electrical stimulation did not prevent in any way the onset of muscle atrophy[102]. A recently published controlled pilot study reports on a six-week NMES program in an in-patient setting, initiated during admission to the intensive care for an acute COPD exacerbation[96]. One-hour sessions of bilateral electrical stimulation of both quadriceps and hamstring muscles were conducted five days per week. The training group showed enhanced effects on muscle force, 6MWD and proportion of type-1 fibers, without aggravating local oxidative stress to the muscles.

Table 1. RCT's of NMES in respiratory compromised patients

Author + Design	Patient characteristics	Training details	Effects
Zanotti 2003[99] NMES + ALM vs ALM	COPD patients with chronic hypercapnic failure and need for mechanical ventilation (> 30d bed-bound) n=24	Quadriceps and glutei 30 min, 5d/week 4 weeks Freq: 35 Hz; PD: 350 µsec	Higher peripheral muscle strength (which muscles?) and lower number of days needed to transfer from chair to bed (mean 3.5 days)
Gerovasili 2009[103] NMES vs control	ICU patients with stay > 48h and APACHE II score ≥ 13 n=49	Quadriceps and peronei longi 55 min daily, d2 to 9 after admission Freq: 45 Hz; PD: 400 µsec	Less decrease in CSA of rectus femoris (-8% vs -14%) and vastus intermedius (-13% vs -22%) in NMES group
Routsi 2010[104] NMES vs control	ICU patients with APACHE II ≥ 13 n=52	Quadriceps and peronei longi 55 min daily, d2 until ICU discharge Freq: 45 Hz; PD: 400 µsec	Higher MRC score[105] for muscle strength when sufficiently conscious (58 vs 52) Lower proportion of CIPNM in NMES group (13% vs 39%)
Gruther 2010[106] NMES vs sham	Short- and long-term ICU patients (hospital stay of < 7 days and > 14 days respectively) n=33	Quadriceps 30 to 60 min, 5d/week 4 weeks Freq: 50 Hz; PD: 350 µsec	More favorable change of quadriceps CSA (mean of rectus femoris and vastus intermedius) in NMES group (+5% vs -3%) in long-term patients; no differences in short-term patients
Abdellaoui 2011[96] NMES vs sham	COPD patient admitted to a respiratory ICU for an AE n=15	Quadriceps and hamstrings 60 min, 5d/week 6 weeks Freq: 35 Hz; PD: 400 µsec	More increase in quadriceps MVC (+10 kg vs +3kg) and 6MWD (165 vs 58m) in NMES group
Poulsen 2011[102]	ICU patients with septic	Quadriceps	Quadriceps volume

Single leg with other leg as paired control	shock n=8	60 min, 7 consecutive days Freq: 35 Hz; PD: 300 µsec	decreased similarly in stimulated and control leg (-2.9% per day vs. -2.3% per day respectively)

NMES = neuromuscular electrical stimulation, ALM = active limb mobilization, COPD = chronic obstructive pulmonary disease, d = days, freq = frequency of the current, Hz = Herz, PD = pulse duration of the current, µsec = microseconds, ICU = intensive care unit, APACHE = Acute Physiology and Chronic Health Evaluation, mA = milleamperes, CSA = cross-sectional area, CIPNM = critical illness polyneuromyopathy, AE = acute exacerbation, MVC = maximal voluntary contraction, 6MWD = six-minute walking distance.

Nutritional intervention

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

Potential pharmacological support: Several nutritional supplements or pharmacological interventions may support nutritional interventions. Supplementation of essential amino acids increases body weight and fat-free mass in weight-losing and frail patients with COPD[110;111], making these food supplements a yet unexplored area of interest during exacerbations. Another potentially interesting intervention would be to supplement patients with polyunsaturated fatty acids. When administered in stable patients enrolled in a pulmonary rehabilitation program, 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 may enhance the effects of nutritional interventions needs to be studied further. Statin therapy has recently received attention. Simvastatin showed to reduce leptin levels in patients with coronary heart disease[114] and it has been suggested that they may reduce hospital readmission rates[115]. It is tempting to speculate that the association of statins to 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

Comprehensive pulmonary rehabilitation programs have the ability to reduce the use of health-care services and the number of days spent in hospital during one year follow-up in stable patients with COPD[117]. These programs 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], dyspnea symptoms[121] and composite severity scores, such as the BODE-index[122].

Evidence is accumulating that rehabilitation programs are also feasible and particularly effective when applied immediately after the initial exacerbation recovery. A Cochrane meta-analysis by Puhan et al.[123] concludes that pulmonary rehabilitation following an exacerbation reduces hospital admissions, with the follow-up period ranging from 3 to 18 months. The number of patients needed to treat to have one admission less is 4 (95% confidence interval 3 to 8). This finding is extremely relevant in this specific patient group with high risk for readmission. Changes in health-related quality of life well exceed the minimal important difference[123]. Similarly pooled differences in six-minute walking test and shuttle walking test between intervention and control groups after termination of the program were significant and clinically relevant in favor of rehabilitation[123]. Two trials also reported benefits in terms of quadriceps strength[65;124]. Since this Cochrane meta-analysis one RCT has been published to the author's knowledge. This study reported no effects on exercise capacity and readmission rate[125].

The programs that are reported to be successful in randomized controlled trials are very heterogeneous in terms of initiation, duration, setting and program content. They include eight-week comprehensive outpatient programs initiated within 7 days after hospital discharge[65;126], a ten-day inpatient walking program starting within one week after admission[127], an 18–month supervised home-based walking program initialized in the hospital[128] and a six-week home-based whole-body exercise program[124]. Direct comparisons between different settings have not yet been reported. In most of the programs reported in literature, exercise training consisted of

a combination of aerobic and resistance training with intensities similar to programs 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 which combined exercise training during and after exacerbations. Patients were included 2.6 days after hospital admission for an acute exacerbation and received a daily 30-minute exercise training session including walking and resistance training. After discharge, they entered an 8 week whole-body exercise training program, but training intensity was not described. Compared to the usual care group, the attendees showed better improvements in anxiety feelings, SF-36 physical function score and a trend towards better BODE-index, but no differences in 6MWD, which improved by more than 100 meters in both groups.

Interestingly, two studies in literature that identified no trend towards decreased hospital admission also found no effects on exercise capacity[125;130]. One of these trials reported a low adherence, with only 40% of patients randomized in the rehabilitation group attending 75% of the sessions[130]. As other trials report that 20 to 30% of patients that finished the rehabilitation program attended fewer than 50% of the sessions[65;126], adherence appears to be an important attention point 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 where patients are not lost if they cannot cope with one specific program, 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 programs[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 behavior and preventing hospital admissions[134]. The aim of self-management programs for COPD should be to recognize exacerbations as soon as possible and act appropriately. Despite the detrimental impact of exacerbations on the

course of the disease, patients often have difficulties to recognize 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 an underreporting 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 hospitalization. Action plans for acute exacerbations emphasizing 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 summarized the results of 14 controlled trials reporting on the effectiveness of self-management programs 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 for exacerbations. The authors reported a significant reduction in the probability of experiencing at least one hospital admission among patients receiving self-management education compared to those receiving usual care (Odds Ratio 0.64; 95%CI 0.47 to 0.89). There was no difference in number of exacerbations or emergency department visits. Most pulmonary rehabilitation programs after exacerbations described in literature report to have included self-management interventions[65;126;129;143;144]. This seems the right way forward as self-management interventions may help to act early in case of new exacerbations, whereas exercise training may be a preventive strategy for new exacerbations to occur. 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 know 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 enhancing behavior that increases the risk for exacerbations, 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 in patients suffering from dyspnea or patients that 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 outcomes after acute exacerbations of COPD, it cannot prevent the occurrence of acute exacerbations during the program or during follow-up. The onset of exacerbations could in turn compromise the effects of rehabilitation[150] and are frequently mentioned as a reason for drop out or prolonged non-attendance in an exercise program[151;152]. Exacerbations are probably 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 program may offer an opportunity to enhance the self-management of dealing with the recovery of physical activity after the exacerbation. To the authors' knowledge only one trial investigated the effectiveness of 3-week bursts of rehabilitation after occurrence of an acute exacerbation, during the one year follow-up of a similar pulmonary rehabilitation program[144]. These repeat programs yielded clinically important improvements in dyspnea five weeks after the acute exacerbation in patients that did not have a second exacerbation during that follow-up period. Unfortunately, differences in functional exercise capacity were not observed. In a community setting, van Wetering et al also offered six extra training sessions after an exacerbation during the 20-month follow-up period of their INTERCOM rehabilitation program, but did not further report on the effectiveness of this part of the intervention[131].

Conclusion

We 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 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 behavior might play an important role in optimizing long-term outcomes and prevent relapse after a severe exacerbation.

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