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Rehabilitation in chronic respiratory diseases: In-hospital and post exacerbation pulmonary rehabilitation

Wadah Ibrahim.[1*], Theresa C. Harvey-Dunstan [2*], Neil J. Greening [1,3]

[1]Department of Respiratory Science, University of Leicester, Leicester, United Kingdom

[2]Division of Physiotherapy and Rehabilitation Sciences, School of Health Sciences, University of Nottingham, UK

[3]Centre for Exercise and Rehabilitation Science, Institute for Lung Health, Leicester, UK

*Contributed jointly to manuscript

Corresponding Author

Dr Neil Greening

NIHR Leicester Biomedical Research Centre- Respiratory

Glenfield Hospital, Groby Road

Leicester, LE3 9AP

United Kingdom

neil.greening@leicester.ac.uk

Abstract

Exacerbations of chronic obstructive pulmonary disease (COPD) that require hospitalisation are important events for patients. Functional impairment and skeletal muscle dysfunction can increase the risk of hospitalisation and readmission, independent of lung function. In addition, once a patient is admitted multiple factors can lead to worsening outcome including immobility, systemic inflammation and nutritional depletion. These non-pulmonary factors are potentially amenable to exercise therapy, as part of pulmonary rehabilitation. Peri-exacerbation pulmonary rehabilitation has an important role in the management of exacerbations of COPD.

In this review we explore how functional limitation and skeletal muscle dysfunction affects patients having a severe exacerbation of COPD, the systemic impact of hospitalisation on patients including potential aetiologies and the role of pulmonary rehabilitation around the time of an exacerbation. This includes rehabilitation during the inpatient phase, post-exacerbation rehabilitation and rehabilitation bridging hospital discharge. We also describe potential future developments in peri-exacerbation pulmonary rehabilitation.

Introduction

Worldwide, COPD constitutes one of the largest health burdens with 3.17 million deaths in 2015[1]. In the UK, an estimated 1.2 million people (2% of the population) have diagnosed COPD making it the second commonest lung disease, after asthma[2].

The natural history of COPD is punctuated by acute episodes of worsening symptoms and increased airways inflammation known as exacerbations and are a major priority in the treatment of COPD. For an individual with COPD it results in marked worsening of symptoms and disease burden, far beyond the burden when in the stable state. It is also now clear that certain individuals are prone to recurrent exacerbations- known as the frequent exacerbator phenotype[3]. The strongest predictor of future exacerbations is a history of previous exacerbation. Patients with severe exacerbations requiring admission to hospital demonstrate this high risk, with 43% of patients in the UK readmitted within three months[4]. For healthcare organisations exacerbations account for more than half of all COPD costs. As well as considerable expense, the challenge on healthcare systems provide a logistic challenge, with exacerbations accounting for over a million bed days each year across the UK, presenting in an unpredictable fashion[2].

The primary pathophysiology of COPD is within the lungs and the diagnosis of COPD is confirmed by detecting airflow limitation using spirometry. However, over the past decades it has been increasingly recognised that COPD has a number of extra-pulmonary manifestations that have considerable impact on patients and the disease burden. Exercise limitation is a key symptom of COPD. It is clear that this is in part driven through leg fatigue and skeletal muscle dysfunction, with quadriceps function being an independent marker of mortality[5].

Muscle dysfunction is more common in patients with advanced COPD, as are exacerbations of COPD. The combination of these two aspects of COPD may have important consequences, as well as specific therapeutic interventions. In this review we describe the functional limitation and skeletal

muscle dysfunction in patients hospitalised for an exacerbation of COPD, the acute systemic effects on hospitalisation and the role of peri-exacerbation pulmonary rehabilitation.

The Impact of Skeletal Muscle Dysfunction and Functional Impairment on Exacerbations of COPD

Independent of disease severity, systemic markers of disease may increase the risk for patients to be admitted to hospital with an exacerbation. Physical inactivity and increased sedentary time are well recognised and described in COPD. Patients with reduced physical activity are at an increased risk of hospital admission, readmission to hospital following an index admission and death[6, 7]. These studies have corrected for factors, such as disease severity and symptom burden.

Functional measures, such as the six minute walk test, have been shown to be predictive of hospitalisation and prognosis. Indeed the most commonly used prognostic tool, the BODE score, is part comprised of walking distance[8]. The Four meter Gait Speed (4MGS) is a well validated measure, and a key part of the frailty assessment[9, 10]. In patients hospitalised with an exacerbation of COPD, 4MGS taken at the time of discharge is a marker of readmission, independent of disease severity[11]. Low skeletal muscle mass is also known to be an independent risk factor for hospital admission and mortality. Body mass index (BMI) is a crude measure of body composition, and like 6MWT, is one of the components of the BODE score, which predicts hospitalisation and mortality[12]. Direct measures of the skeletal muscle, such as the fat free mass and quadriceps function, have been shown to be a better prognostic indicator than BMI[13, 14]. In those admitted to hospital, patients with the smallest muscles measured at the bedside using ultrasound are more likely to be readmitted or die, independent of other markers of disease severity or risk of readmission[15].

Systemic Consequences of Exacerbations of COPD

Exacerbations of COPD present as increasing dyspnoea as a result of increased airways inflammation and require additional therapy to treat the lung. However, it is clear that exacerbations impact

various body systems with a number of acute non-pulmonary effects. Similar to stable disease, the skeletal muscle system and function to walk are important factors affected during the exacerbating state. In particular severe exacerbations, which require admission to hospital, have a profound effect with multiple insults all contributing to adverse impact on the whole body. This leads to a number of important consequences, such as reduced ability to protect against future insults, i.e. reduced resilience, and increased risk of hospital readmission and death (figure 1).

figure 1 here

Factors that impact on Systemic Factors of COPD in Exacerbations

Immobility

Enforced bed rest has been used as a treatment since the 19th century for a range of medical conditions since Victorian times including hysteria[16] and tuberculosis[17]. Bed rest has continued as a mainstay of therapy until the late 20th century[18]. As such public perception of bed rest as therapy for acute illness continues to today.

Bed rest studies in healthy populations have shown significant reductions in both young[19] and older[20] healthy volunteers, with larger decreases in the muscles of ambulation compared to other muscle groups [19]. These findings are echoed in the critical care population with acute skeletal muscle loss[21] and persistent long-term functional deficit[22, 23].

Whilst the effects of acute immobility are well recognised in those previously fit and well, the effects may be more marked in those with long-term conditions. In patients with COPD in the stable state there is preferential loss of oxidative type 1 muscle fibres and loss of mitochondria, which may impede the ability to protect against the detrimental effects of bedrest[24, 25]. In the acute care setting patients with COPD have increased symptoms of fatigue[26] and breathlessness, resulting in them having the perception of being too ill or frail or disabled to take part in physical activity[26].

Systemic inflammation

The mechanisms for the systemic effects of COPD are varied and multi-factorial. It has been shown that a sub-set of patients with COPD have an excess of systemic inflammation and those with persistent systemic inflammation have a poorer prognosis and are more prone to exacerbation[27]. Systemic inflammation has also been linked with increased risk of co-morbidities, such as cardiovascular disease[28].

At the time of exacerbations, systemic inflammation is particularly marked even in those without persistent inflammation. In the most severe exacerbations, such as those undergoing hospitalisation, inflammatory markers measures such as C - reactive protein are increased to a mean of 81 mg/l (SD 99)[29].

An increased systemic inflammatory response is associated with worse skeletal muscle function, with higher circulating Interleukin-8 associated with lower quadriceps strength[30]. Whether this inflammatory effect directly impacts on skeletal muscle or is an associated inflammatory response based on severity of exacerbation is unknown. Indeed, no increase in inflammatory cells are seen in quadriceps muscle at the time of exacerbation, questioning the direct impact of inflammation on acute muscle dysfunction[31].

Nutritional depletion

Involuntary weight loss, prevalent in patients with advanced COPD, is a well-recognised poor prognostic factor[32-34] and is associated with higher mortality[35].

Weight loss in COPD is multifactorial, with reduced oral intake, increased work of breathing and associated systemic inflammation. Acutely, exacerbations increase basal metabolic expenditure, when unmatched with adequate caloric intake can lead to nutritional depletion, muscle wasting and dysfunction[36]. Although nutritional supplementation in stable cachectic COPD patients is recommended, studies on nutritional repletion in the acute state have not shown efficacy.

Vermeeren et al demonstrated no additional improvements in lung function or muscle strength with caloric supplements during exacerbations[37]. Rutten et al described loss of intestinal integrity in COPD patients, so profound it was suggested that this is added as a new component in the multisystem disorder, and that simply increasing calorie intake may be inadequate[38].

Hospital-Associated Disability

The detrimental effects described above lead to a loss of physical function (figure 2). In addition to this, patients in hospital have altered sleep patterns, acute cognitive impairment and loss of autonomy. The resulting syndrome has been described as a number of phenomena, including hospital-associated disability, hospital acquired disability and post hospitalisation syndrome. Hospital-associated disability (HAD) is described in the geriatric population as a loss of activity of daily living (ADL) due to admission to hospital[39]. HAD may take months to recover or lead to irreversible changes. Despite the clinical recognition of the problem the process and natural history of HAD is poorly understood. Whilst HAD has been most widely described in the geriatric population it is likely to be a key component in chronic diseases, including COPD.

Figure 2 here

Rationale for exercise training

Currently the treatment for exacerbations of COPD is mainly focused on the primary insult to the lungs. Exercise therapy potentially lends itself to the treatment of HAD and patients with advanced COPD and pre-existing functional limitation.

Pulmonary rehabilitation in the stable setting is one of the highest value therapies in COPD and is recommended worldwide in symptomatic patients[40, 41]. Pulmonary rehabilitation consists of individualised exercises, educational and behavioural elements targeted at minimising symptom burden, maximising exercise performance, promoting autonomy and enhancing quality of life [40].

Therefore applying pulmonary rehabilitation around the time of an exacerbation, also known as peri-exacerbation pulmonary rehabilitation, has been trialled and is now internationally recommended. The remainder of this review will examine the evidence for pulmonary rehabilitation initiated following hospitalisation for an exacerbation of COPD-post exacerbation pulmonary rehabilitation (PEPR), pulmonary rehabilitation initiated during hospitalisation, and possible future developments.

Post Exacerbation Pulmonary Rehabilitation

PEPR has had a major impact on the treatment of severe exacerbations of COPD and is recommended in both National and International guidelines[40, 41]. Trials of PEPR have typically performed PR programmes similar in structure and duration to PR programmes in the stable state, but within the recovery period from severe exacerbations (defined as requiring hospitalisation).

The first randomised controlled trial to investigate PEPR was Man et al in 2004[42]. 42 patients were recruited within 10 days of discharge from hospital and underwent an eight week PR programme. In this landmark study, patients in the usual care group had not recovered at eight weeks, with a median incremental shuttle walk (ISWT) of only 90 meters. In comparison patients who underwent PEPR ISWT improved by 90m, double the minimal clinically important difference. Large clinically and statistically significant differences were also noted in health related quality of life.

The results of Man et al have been replicated in a number of other similar sized trials (Murphy 2005, Ghanem 2010, Deepak 2014), which use a similar model of 2-3 supervised exercise sessions per week starting following discharge[43-45]. A number of the trials have used supervised home-based exercise, rather than in a formal setting, potentially increasing uptake of patients who do not need to travel[43, 45, 46]. Only one trial (Ko et al 2011[47]) did not show benefit of PEPR in terms of exercise capacity or health related quality of life.

One of the secondary outcome measures in the trial by Man et al was readmission to hospital. The PEPR group had a significant reduction in rate of hospital admission at 3 months. The rationale, as

described above, was likely to be training the non-pulmonary deficits occurring following exacerbation and increasing resilience. Seymour et al[48], part of the same research group as Man et al performed a larger RCT, powered to detect a significant reduction in readmission to hospital. They recruited 60 patients in a similar model across four hospitals in London. Exercise capacity, quadriceps strength, health related quality of life improved similarly to the previous trial. An 85% reduction in hospital readmission in the PEPR group was seen during the intervention period.

The largest trial of PEPR was reported by Ko et al in 2017[46]. PEPR was a component of a larger comprehensive care programme, which also included specialist medical review, telephone support line, and regular specialist follow-up. 180 patients were included in the study. 33% (n=30) of the intervention group received supervised outpatient physiotherapy and 67% (n=60) unsupervised home exercise. Similar to the Seymour study a significant reduction in the rate of hospital readmissions was seen in the intervention group (incident rate ratio 0.668), with the greatest difference seen in the first three months. Improvements were also seen in health related quality of life questionnaires, but not in exercise capacity.

The strength of these trials has unequivocally shown strong efficacy of PEPR for severe exacerbations of COPD. However, real-life clinical implementation has proven more challenging. Recruitment and patient uptake of PEPR has been low in the UK. Jones et al demonstrated that only 9.6% of participants received and completed PEPR despite an active Pulmonary Rehabilitation service[49]. This low uptake had been indicated in Seymour et al who took three years to recruit 60 patients across four London hospitals[48]. Therefore, strategies to improve uptake to PEPR or alternative models of delivering treatment are needed.

Pulmonary Rehabilitation and Exercise Training During the Hospitalisation

As described above trials of PEPR have yielded considerable benefits for the patients who attend a programme. Whilst it helps the recovery from the impact of hospital associated disability and the impact of the exacerbation, it does not prevent or minimise the primary loss of physical function. In

order to target this, intervention may be required to start during the period of hospitalisation, ideally as early as possible. Due to nature of a severe exacerbation and acute illness of inpatients conventional models of pulmonary rehabilitation programmes are difficult to implement and interventions have been highly varied. For the purposes of this review we have considered exercise interventions performed during the hospitalisation only (i.e. ended at time of discharge), including non-volitional techniques such as neuromuscular electrical stimulation (NMES) and training that includes both during the inpatient and post-discharge periods.

Training during the inpatient phase only

Two trials of inpatient rehabilitation reported outcomes 20 years ago[50, 51]. Nava et al recruited 80 patients in a respiratory intensive care unit with COPD. Length of hospital stay in these patients was more than one month. Those who received exercise intervention (comprising progressive aerobic training and respiratory muscle training) improved their walking capacity, whereas those in the usual care group (not including aerobic training) had no improvement in walking. Baseline measures were conducted as soon as patients were able, as 76% had required mechanical ventilation initially[50]. Kirsten et al also demonstrated improvements in walking capacity following aerobic training over usual care in 29 patients admitted with an exacerbation of COPD. Both trials delivered their intervention later in the admission, following initial recovery; Kirsten et al starting at days 6-8 of admission and Nava et al once able to perform cycling[51].

More recently Troosters et al[52] used resistance training to target the skeletal muscle to prevent loss of quadriceps strength. Patients were recruited in their first day on a respiratory ward and underwent a mean of 6 days of training, initially at 70% of 1 repetition max (1RM). Efficacy was shown with a 10% increase in strength in the intervention group. This was sustained at one month following discharge. Improvement in 6MWT was also seen in the intervention group, though this was not statistically different to the control group. No difference in hospitalisation rate was seen at six months.

He et al[53] also recruited patients on their second day of admission in 101 patients admitted with COPD. Patients underwent twice daily aerobic and resistance training. Those who received inpatient training improved their 6MWT, whereas those who had usual care showed no difference, though between groups were not reported. 6MWT on at time of admission was relatively well preserved (approximately 250m) and duration of intervention was not reported. In a similar study Liao et al[54] performed twice daily aerobic and resistance training for four days in 61 patients admitted with an exacerbation. Large increases (120m) in 6MWT were seen in the intervention group but not the control group. Similar improvements were also seen in dyspnoea.

Overall short-term the trials have shown that supervised training in patients who are inpatients benefit in terms of function, though the longer term effects are unknown.

Non-Volitional training

With the increased symptom burden at the time of an exacerbation training techniques that reduce the ventilatory burden of training are attractive. Neuromuscular electrical stimulation (NMES) directly stimulates skeletal muscle using electrical current resulting in muscle contraction with minimal ventilatory demand[55]. NMES has been used in the stable state in COPD and showed short term improvements in muscle function. While the effects are short-lived, it may be well placed to bridge the acute hospital admission before PEPR. Three trials have explored the use of NMES in the peri-exacerbation period; one in the intensive care unit [56], one during hospitalisation on a medical ward[57] and one in a rehabilitation unit following hospitalisation[58]. All three trials showed short-term benefit of NMES clinical efficacy in terms of statistically significant differences in muscle quadriceps strength and walking distance. However, use of NMES in the clinical setting at this time are unlikely as conclusions using this modality are limited with small numbers of patients in all trials.

Training crossing both inpatient and outpatient phase

Several trials have attempted to cover the wider peri-exacerbation period, including both during hospitalisation and the post-hospitalisation recovery period[59-61]. In the earliest trial by Behnke et al, 30 participants underwent 10 days of inpatient training, followed by six months of unsupervised home-based training[59]. They were recruited during the recovery phase of the admission (days 4-7). In a per-protocol analysis (65% of recruited patients) significant improvements in walking performance and symptoms were seen in the intervention group, when compared with the control group. The differences in exercise capacity were seen in the first 10 days of intervention, with an improvement in the intervention group of 225m on the 6MWT, but no change in the control group. Two other, more recent trials, have trialled the wider peri-exacerbation period. Both are two of the larger RCTs in the field of peri-exacerbation pulmonary rehabilitation and also attempted to recruit earlier into the hospitalisation than the Behnke trial. Eaton et al[60] recruited 97 patients which included inpatient rehabilitation followed by a standard PEPR programme. No difference was seen between groups, for hospital readmission, exercise capacity or quality of life. However, in the per-protocol sub-analysis of the 19 participants who attended the PEPR aspect a reduction in hospital readmission was seen, providing encouraging results.

In the largest trial in the peri-exacerbation pulmonary rehabilitation literature Greening et al[61] incorporated several inpatient aspects of therapy including NMES, resistance training and aerobic training. Following hospital discharge, in an attempt to increase participation and stop the high drop-out associated with PEPR a home-based programme with telephone support, but unsupervised training was provided. 389 participants were recruited. However, length of hospital stay was lower than in other trials (median 5 days), meaning the inpatient (supervised) intervention was limited. The home-based programme was poorly adhered to. Similar to Eaton et al, no between group differences in exercise capacity, health status or hospital readmission were seen. Surprisingly, separation in mortality was seen starting more than 6 months after the intervention finished, in favour of the usual care group. This is unlikely to be due to the intervention, as was separated temporally from the intervention. No signal was seen in the per-protocol analysis and is more likely

explained by case-mix of the groups, as those in the intervention group had higher baseline MRC score. Patients in the intervention group were also less likely to uptake standard supervised pulmonary rehabilitation after three months which may have impacted longer term outcomes. Another key difference in both the Eaton and Greening trials was that large increases in exercise capacity and quality of life in usual care group were observed. This is different from other reported trials, where the control groups have remained unimproved months later. In the trial by Greening et al the usual care groups received daily ward-based physiotherapy, as per usual UK practice, which may also explain the recovery seen in the usual care groups and lack of benefit with additional rehabilitation strategies.

Trials of peri-exacerbation pulmonary rehabilitation that include both inpatient and outpatient training have so have proven less successful than trials focussing on either the inpatient or outpatient components. Difficulties in adapting training across changing environments, without resulting in large drop-out need to be addressed before this is likely to be as successful as other areas of peri-exacerbation pulmonary rehabilitation.

Table 1 here

Peri-Exacerbation Pulmonary Rehabilitation in Non-COPD Patients

Until the last few years research in pulmonary rehabilitation in the stable state has almost exclusively focussed on COPD. Echoing this, peri-exacerbation pulmonary rehabilitation has not been trialled in non-COPD respiratory conditions. However, the rationale for it is no less strong in other respiratory conditions as it targets the non-pulmonary elements of the disease, other respiratory conditions experience exacerbations, and is effective in other conditions in the stable state. 15% of patients in Greening et al[61] had other chronic respiratory diseases (bronchiectasis, interstitial lung disease and chronic asthma) with no difference in outcome between those with COPD and those who didn't. Trials in other respiratory conditions such as bronchiectasis are underway and awaited[62].

Similarly, rehabilitation around the time of hospitalisation has been successfully implemented in other diseases and elderly populations[63, 64].

The Future Direction of Peri-Exacerbation Pulmonary Rehabilitation

More so than pulmonary rehabilitation in the stable state, peri-exacerbation pulmonary rehabilitation has a number of unanswered questions and is likely to evolve over the next few years. PEPR has the best efficacy, but with poor uptake has limited application to the wider population. Strategies to increase uptake to post-exacerbation pulmonary rehabilitation are therefore important. One pragmatic approach to increasing uptake post-exacerbation rehabilitation would be to delay the start of rehabilitation until recovery from the hospitalisation is complete, when patients may be more willing to attend classes. This would ensure increased participation in pulmonary rehabilitation in a high-risk, symptomatic population who would gain benefit from a more standard programme of pulmonary rehabilitation. Trials comparing early and late post exacerbation pulmonary rehabilitation have proven challenging[65, 66]. One trial showed no long-term difference between patients recruited to either immediate post exacerbation pulmonary rehabilitation or six months later, but recruited only 15% of its total planned population[66]. Results of other ongoing trials of early versus late pulmonary rehabilitation are awaited[67].

Reasons for lack of uptake to PEPR are numerous, linked to both patient perceptions of their current illness and high risk of early hospital readmission[26]. Health coaching following hospitalisation has recently been shown as a possible intervention to address these aspects. In a study by Benzo et al[68] patients received a motivational interviewing based health coaching intervention. During the intervention period there was a reduction in hospital readmission rate, as well improvements in health related quality of life. No difference in physical function was found. Techniques such as health coaching, may therefore work as a bridge to pulmonary rehabilitation, which may then offer additional benefits, such as increased exercise capacity and longer term benefits.

Growing internet use and web literacy, including among the older population make web-based interventions a potential avenue. Successful trials in the stable state have been published and may allow patients who struggle to attend rehabilitation programmes during the recovery phase a more structured and supervised home-based programme[69]. However, increased transient cognitive impairment is common in the recently hospitalised population[70] and may impact on the ability to deliver more self-management directed interventions. Web literacy may also be lower than reported in this population[71].

Improving the inpatient aspect of rehabilitation also requires further research. The acuity of the illness may prevent training similar to an outpatient PR programme, with some trials struggling to recruit[72], but other strategies may continue to develop. Anabolic agents have been trialled in the stable state[73, 74], including those with advanced disease[75]. Whilst effective at increasing muscle mass, a lack of functional improvement above exercise therapy has limited their use in the stable state. However, in the early acute care setting they may be able to protect against HAD when ability to exercise may be limited.

Summary

Acute exacerbations of COPD are a major event for patients with COPD. They have considerable adverse effects on the whole body, which is historically not treated with medical therapy. Post-exacerbation pulmonary rehabilitation offers excellent efficacy and improvements in exercise capacity, health related quality of life and reduced readmission to hospital[76]. Strategies to improve uptake to PEPR are needed however, as this has been limited. Interventions during the hospitalisation seem to offer short term functional benefit, but trials attempting to cross both inpatient and outpatient settings have been limited, probably due to lack of supervised training. In summary it is important that all potentially eligible patients are given every opportunity and support to enrol in pulmonary rehabilitation programme following an exacerbation of COPD.

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The Authors:

Dr Wadah Ibrahim is a clinical research fellow at the University of Leicester. He is currently taking time out of his specialist training in respiratory medicine to study for a PhD. His work mainly focuses on patients with acute exacerbations of airways disease and identifying volatile organic compounds in breath. Dr Theresa Harvey-Dunstan is an Assistant Professor and Physiotherapist at the University of Nottingham. She has spent the last ten years in research within pulmonary rehabilitation, including peri-exacerbation pulmonary rehabilitation. More recently she has completed her PhD, which compared the sensitivity and response of different exercise tests to pulmonary rehabilitation in COPD. Dr Neil Greening is an Associate Professor and Consultant Respiratory Physician at the University of Leicester. His main research interests are understanding systemic changes to patients with exacerbations of COPD. In 2017 he was awarded a national fellowship by the National Institute of Health Research (NIHR) to continue his work in this field.

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List of Figures

Figure 1: Multi-factorial insults and consequences on individuals following admission to hospital with an exacerbation of COPD. Blue markings demonstrate a selection of non-pulmonary organs affected (heart, skeletal muscles, bone/spine, pancreas, brain)

Figure 2: Schematic of time-course of hospital associated disability, including symptoms, insults and function

Table 1: Randomised controlled trials of peri-exacerbation pulmonary rehabilitation

Study	n=	Follow up	Primary Outcome	Outcome of Results		
				Healthcare Utilisation	Exercise capacity/ Strength	Symptoms
In-patient AECOPD						
Nava[50]	80	Hospital discharge	Exercise capacity	Length of hospital stay: No difference	6MWT: Improved in intervention but not control group. Groups not compared.	Dyspnoea: Improved in both groups. Groups not compared
Kirsten[51]	29	10 days	Exercise capacity	Not reported	6MWT & minute ventilation: Greater improvement in the intervention group	Dysnpnoea: Greater improvement in the intervention group
Troosters[52]	36	1 month	Quadriceps force	Hospital readmission: No difference at 6 months	Quadriceps strength: Greater improvement in intervention group. 6MWT: No difference between groups	Not reported
Abdellaoui[56]	15	6 weeks	Quadriceps strength	Not reported	Quadriceps force & 6MWT: Greater improvement in the intervention group	Not reported
Giavedoni[57]	11	14 days	Quadriceps strength	Length of hospital stay: No difference	Quadriceps force: Greater improvement in the intervention group	Not reported
Borges[77]	29	30 days	Quadriceps strength	Not reported	6MWT & strength: Greater improvement in the intervention group	SGRQ: No difference between groups
He[53]	97	Hospital discharge	Exercise capacity	Not reported	6MWT: Improved in intervention but not control group. Groups not compared.	CRQ & ADL: Improved in intervention but not control group. Groups not compared.
Liao[54]	61	4 days	Dyspnoea	Not reported	6MWT: Greater improvement in the intervention group	Dysnpnoea: Greater improvement in the intervention group
In-patient progressing to Out-Patient AECOPD						
Behnke[59]	46	6 months	Exercise capacity	Not reported	6MWT: Greater improvement in the intervention group	CRQ: Greater improvement in the intervention group
Eaton[60]	97	3 months	Re-admission	Hospital readmission: No difference	6MWT: No difference between groups	CRQ: No difference between groups
Greening[61]	389	12 months	Re-admission	Hospital readmission: No difference	ISWT & Quadriceps strength: No difference between groups	SGRQ: No difference between groups

Cox[78]	58	90 days	Exercise capacity	Hospital readmission: No difference	6MWT: No difference between groups	CAT: No difference between groups
Out-patient AECOPD						
Man[42]	42	8 weeks	Exercise capacity	Hospital readmission: No difference between groups	ISWT: Greater improvement in the intervention group	CRQ & SGRQ: Greater improvement in the intervention group
Murphy[43]	26	6 weeks	Exercise capacity	Exacerbation: No difference at 3 or 6 months between groups	ISWT: Improved in intervention but not control group. Groups not compared.	SGRQ: Improved in both groups. Groups not compared
Vivodtzev[58]	17	4 weeks	Quadriceps strength	Not reported	Quadriceps force & 6MWT: Greater improvement in the intervention group	Dysnpnoea: Greater improvement in the intervention group
Seymour[48]	60	3 months	Re-admission	Hospital readmission: Fewer readmissions in intervention group	ISWT & quadriceps force: Greater improvement in the intervention group	SGRQ: Greater improvement in the intervention group
Ghanem[45]	39	2 months	Exercise capacity	Not reported	6MWT: Greater improvement in the intervention group	CRQ: Greater improvement in the intervention group
Puhan[66]	36	18 months	Exacerbations	Exacerbation: No difference	Not reported	CRQ: No difference between groups
Ko (2011)[47]	60	12 months	Re-admission	Hospital Readmission: No difference between groups	6MWT & VO_{2max}: No difference between groups	SGRQ: Greater improvement in the intervention group
Deepak[44]	60	3 months	Exercise capacity	Not reported	6MWT: Greater improvement in the intervention group	SGRQ: Greater improvement in the intervention group
Ko (2017)[46]	180	12 months	Re-admission	Hospital readmission: Fewer readmissions in intervention group	6MWT: No difference between groups	SGRQ: Greater improvement in the intervention group

6MWT=six-minute walk test; VO_2max=oxygen consumption; ISWT=incremental shuttle walk test; CRQ=chronic respiratory questionnaire; SGRQ= St. Georges respiratory Questionnaire; ADL scale=Activity of Daily Living

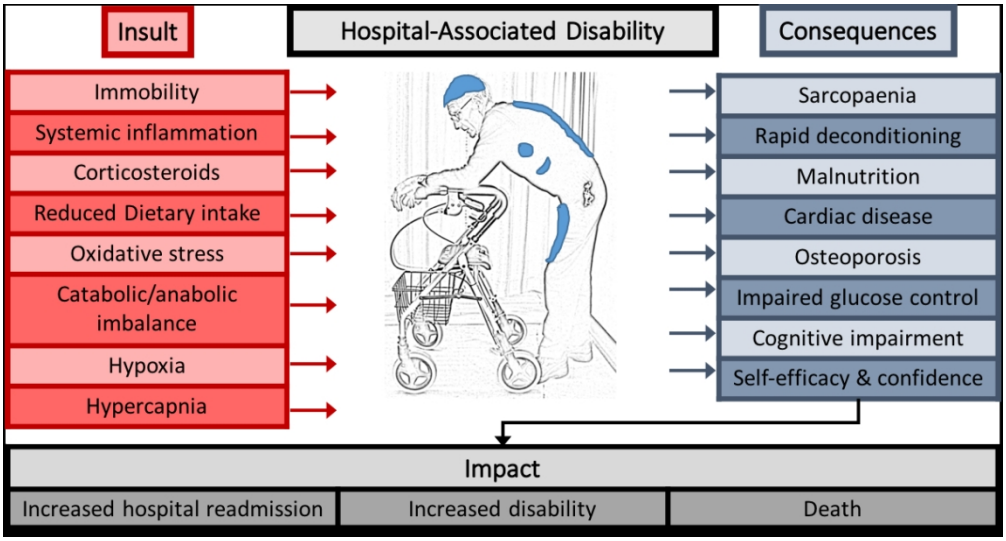

Figure 1: Multi-factorial insults and consequences on individuals following admission to hospital with an exacerbation of COPD. Blue markings demonstrate a selection of non-pulmonary organs affected (heart, skeletal muscles, bone/spine, pancreas, brain)

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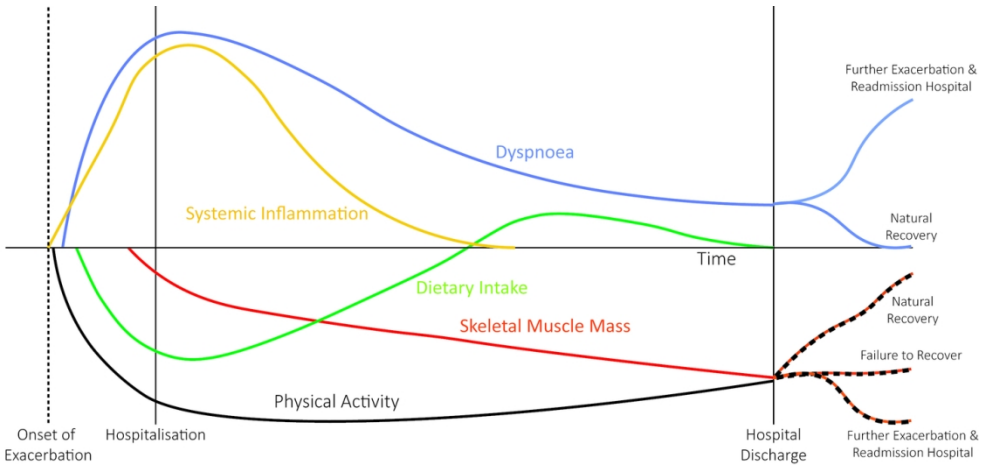

Schematic of time-course of hospital associated disability, including symptoms, insults and function

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