# EARLY PULMONARY REHABILITATION FOR EXACERBATIONS OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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By

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**Abstract** **Early pulmonary rehabilitation for exacerbations of chronic obstructive pulmonary disease**

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Exacerbations are key events in the natural history of chronic obstructive pulmonary disease (COPD), with limited recovery of physical performance, and the highest cause of readmission in the UK. This thesis explores the impact of exacerbations in COPD and chronic respiratory disease.

In the first study I have investigated the effects of an early rehabilitation intervention on healthcare utilisation, strength and exercise capacity by conducting a large randomised control trial. Using a sub-group of this cohort I have then explored factors that predict hospital readmission. Finally I have conducted a study of single leg neuromuscular electrical stimulation (NMES) in stable COPD, alongside a resistance training group.

No difference was seen following early rehabilitation in hospitalisation, healthcare utilisation or physical performance. A number of unexpected findings were noted, including an increase in 12 month mortality in the intervention group and large functional recovery in the usual care group. Using multivariate analysis three risk factors for hospital readmission were identified, including quadriceps cross sectional area, using ultrasound. In the stable state NMES was seen to significantly increase muscle mass from baseline, comparable to changes seen using resistance training.

In summary early rehabilitation in chronic respiratory disease does not impact on future hospitalisation. Identification of those with rehabilitation potential is required as the hospitalised population represent a frail group, with advanced disease.

**Acknowledgements**

The work presented in this thesis has very much been the result of a team, without which the data presented would not exist.

The continual and strong support of my supervisor Mick Steiner throughout has been fantastic and I cannot thank him enough for inspiring me to working in this field. I also wish to thank my co-supervisor Peter Bradding for all the support on the lab based work and advice.

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I would also like to thank Lorna Latimer for all the work she did on the NMES trial and her general enthusiasm for all things related to exercise physiology and also irrelevant to work.

Finally my continuing love and thanks goes to my wife, Lynn, and three children, Esme, Oliver and Alastair, who appeared at various time points throughout my PhD time. I very much look forward to spending some time with them. Also to my parents for their continued support and inspiration.

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**Abbreviations**

| | |
|---|---|
| 1RM | One repetition maximum |
| ADO | Age, dyspnoea and airflow obstruction score |
| AECRD | Acute exacerbation of chronic respiratory disease |
| ANOVA | Analysis of variance |
| BMI | Body mass index |
| BODE | Body mass index, airflow obstruction, dyspnoea and exercise capacity index |
| CAT | COPD assessment tool |
| CI | Confidence interval |
| COPD | Chronic obstructive pulmonary disease |
| CPET | Cardio-pulmonary exercise test |
| CRD | Chronic respiratory disease |
| CRQ | Chronic Respiratory Questionnaire |
| DECAF | Dyspnoea, eosinopaenia, consolidation, acidosis, fibrillation score |
| DEXA | Dual-energy X-ray Absorptiometry |
| DOSE | Dyspnoea, obstruction, smoking, exacerbation score |
| ECG | Electrocardiograph |
| ER | Early rehabilitation |
| ESWT | Endurance shuttle walk test |
| $FEV_1$ | Forced expiratory volume in one second |
| FFM | Fat free mass |
| FFMI | Fat free mass index |

| | |
|---|---|
| FVC | Forced vital capacity |
| GOLD | Global Initiative for Chronic Obstructive Lung Disease |
| HR | Hazards ratio |
| ICS | Inhaled corticosteroids |
| IL | Interleukin |
| IQR | Interquartile range |
| IRR | Incident rate ratio |
| ISWT | Incremental shuttle walk test |
| ITT | Intention to treat |
| LABA | Long acting $\beta_2$ agonist |
| LAMA | Long acting muscarinic antagonist |
| LOHS | Length of hospital stay |
| LTOT | Long term oxygen therapy |
| LVRS | Lung volume reduction therapy |
| MDT | Multi-disciplinary team |
| mMRC | modified MRC dyspnoea score |
| MRC | Medical Research Council |
| MRI | Magnetic resonance imaging |
| NICE | National Institute for Clinical Excellence |
| NIV | Non-invasive ventilation |
| NMES | Neuromuscular electrical stimulation |
| NRES | National research ethics service |
| OR | Odds ratio |
| $PaO_2$ | Partial pressure of arterial oxygen |
| PR | Pulmonary rehabilitation |

| | |
|---|---|
| $Q_{csa}$ | Rectus femoris cross sectional area |
| QMVC | Quadriceps maximal voluntary contraction |
| $Q_{thick}$ | Quadriceps thickness |
| RCT | Randomised controlled trial |
| REC | Research and ethics committee |
| ROC | Receiver operator characteristic |
| RPE | Rating of perceived exertion |
| SABA | Short acting $\beta_2$ agonists |
| SAMA | Short acting muscarinic antagonists |
| SD | Standard deviation |
| SEM | Standard error of the mean |
| SGRQ | St George's Respiratory Questionnaire |
| TNF | Tumour necrosis factor |
| UC | Usual care |
| $VO_2$ | Maximum oxygen uptake |
| WHO | World Health Organisation |

**Publications and Abstracts arising from this work**

An early rehabilitation intervention to enhance recovery during hospitalisation for an exacerbation of chronic respiratory disease. A randomised controlled trial. Greening NJ, Williams JEA, Hussain SF, Harvey-Dunstan T, Bankart MJ, Chaplin EJ, Vincent EE, Chimera R, Morgan MD, Singh SJ, Steiner MC, BMJ. 2014 Jul 8;349:g4315. doi: 10.1136/bmj.g4315

Severe hospitalised exacerbations of COPD with an eosinophilic phenotype have favourable outcomes with prednisolone therapy: sub-analysis from a prospective multi-centre randomised control trial. M Bafadhel, NJ Greening, T Harvey-Dunston, J Williams, MD Morgan, F Hussain, ID Pavord, SJ Singh, MC Steiner. British Thoracic Society 2013

Effects on health care utilisation of early pulmonary rehabilitation on hospitalisation for an acute exacerbation of chronic respiratory disease; N. Greening, J. Williams, T. Harvey-Dunstan, F. Hussain, J. Bankart, E. Chaplin, E. Vincent, R. Chimera, M. Morgan, S. Singh, M. Steiner. European Respiratory Society. 2013

Early pulmonary rehabilitation for exacerbations of chronic respiratory disease (CRD): Functional results; T. Harvey-Dunstan, N. Greening, J. Williams, J. Bankart, S. Hussain, E. Chaplin, E. Vincent, R. Chimera, M. Morgan, S. Singh, M. Steiner. European Respiratory Society. 2013

Unilateral neuromuscular electrical stimulation (NMES) of the quadriceps muscles in stable COPD; L. Latimer, N. Greening, M. Morgan, S. Singh, P. Bradding, M. Steiner. European Respiratory Society 2013

Does tolerance of neuromuscular electrical stimulation (NMES) relate to gender in patients with an acute exacerbation (AE) of chronic obstructive pulmonary disease (COPD)? Chaplin E, Houchen L, Greening NJ, Harvey-Dunstan, Steiner MC, Singh SJ. European Respiratory Society 2012

**Statement of work personally performed**

Early rehabilitation trial

I helped co-design the final stages of the early rehabilitation study. I obtained ethics approval, and R&D/CLRN approval. I was responsible for overall trial conduction and management at both sites. At the Glenfield site I was responsible for screening, consent. I performed baseline and follow up visits at the Glenfield site, along with two research physiotherapists. I was the point of contact for the Clinical Trials Unit and designed the database for data collection. The cleaned database was sent to me, which I prepared and undertook the statistical analysis. I am the principal author for the research article that has arisen from this work.

Neuromuscular electrical stimulation study

I helped conceive and design the neuromuscular electrical stimulation study. I obtained ethics approval, and R&D/CLRN approval and performed screening, consent and randomisation. I performed all baseline and follow up measures. I supervised approximately 25% of the exercise sessions. I was responsible for all statistical analysis.

# *Chapter One*

# Introduction

*1.1 Definition and epidemiology*

Chronic obstructive pulmonary disease (COPD) is a heterogeneous disease of persistent airflow limitation, which is progressive in nature and manifests as symptoms of breathlessness, exercise limitation, wheeze and sputum production. COPD is defined by the presence of both typical clinical features and persistent airflow limitation despite bronchodilatation. Underlying these features is a combination of the pathological processes of obstructive bronchiolitis and emphysema. Historically these pathological features have been separated into the phenotypes of chronic bronchitis[1] and emphysema[2]. However, many patients exhibit features of both and do not easily fit into either of these categories. As such they have been encompassed into a unifying diagnosis of COPD[3]. Airflow limitation is caused by an increase in the airways resistance. In COPD this occurs principally at the levels of the small airways and parenchyma.

Internationally accepted guidelines on the diagnosis of COPD require the presence of post-bronchodilator obstruction on spirometry ($FEV_1$/FVC ratio <0.7) in patients with dyspnoea, chronic cough or sputum production and/or a history of exposure to risk factors of the disease[4]. Severity of airflow obstruction is graded on the percentage predicted value of $FEV_1$ (table 1.1).

***Table 1.1*** *GOLD and NICE criteria for severity scoring of airflow limitation*

| $FEV_1/FVC$ | $FEV_1$ Percent Predicted | GOLD | NICE (Updated 2010) |
|---|---|---|---|
| <0.7 | ≥80% | GOLD 1: Mild | Stage 1: Mild* |
| <0.7 | 50-79% | GOLD 2: Moderate | Stage 2: Moderate |
| <0.7 | 30-49% | GOLD 3: Severe | Stage 3: Severe |
| <0.7 | <30% | GOLD 4: Very Severe | Stage 4: Very Severe** |
| * Symptoms should be present with mild airflow obstruction<br>** Or $FEV_1$ < 50% with respiratory failure | | | |

The worldwide burden of COPD is considerable, responsible for 5.8% of all deaths (3.278 million), making it the fourth most common cause of death[5]. However, the principal problem for patients and healthcare systems is the chronic, debilitating nature of the disease. In the UK, it is estimated that up to 3 million people have COPD[6].

### *1.2 Pathological processes of COPD*

The structural changes of emphysema, first described by Laennec[7], are defined as “abnormal, permanent enlargement of the airspaces distal to the terminal bronchiole, accompanied by destruction of their walls, and without obvious fibrosis”[8]. Classification of emphysema can be grouped into three main types, though all may occur within an individual; (1) panlobular emphysema, with large air spaces evenly distributed across the acinar unit; (2) centrilobular emphysema, with abnormal air spaces in association with the bronchioles; and (3) paraseptal emphysema, with the emphysematous space

occurring at the periphery of the acinar unit, abutting a fixed structure (e.g. pleura).

The structural changes of emphysema are thought to be preceded by narrowing and loss of the terminal bronchioles[9]. This obstructive bronchiolitis is the major site of increased airways resistance, which can be raised between four and forty fold in COPD [9, 10]. Causes of small airways obstruction are as a result of thickening of the airway wall, and increased lumen content by accumulation of mucous exudates as a result of inflammation which is associated with airflow obstruction severity [10].

Cough and mucus hypersecretion associated with chronic bronchitis originate within the proximal airways. This inflammatory response is driven by repeated exposure to irritants (usually cigarette smoke), resulting in hyperplasia of epithelial goblet cells and submucosal gland enlargement. This is associated with impaired mucociliary clearance leading to bacterial colonisation and further inflammatory insult and a cycle of chronic inflammation. As a result, once chronic bronchitis has developed then cessation of smoking only partially reverses mucociliary impairment.[11] This is also associated with frequent exacerbations requiring antibiotics or hospitalisation.[12]

*1.3 Clinical features of COPD*

The cardinal symptom of COPD is exertional dyspnoea, most commonly quantified using the MRC dyspnoea scale (table 1.2) [13] . Whilst there is correlation between dyspnoea and $FEV_1$, there is large variation between individuals[14]. In addition dyspnoea is better associated with health status than lung function and is a prognostic measure [15, 16]. Dyspnoea may be

affected by a number of external stimuli such as cold air, dust, cigarette smoke and exacerbations.

***Table 1.2*** *MRC dyspnoea Grade*

| MRC dyspnoea grade | Description |
|---|---|
| 1 | Not troubled by breathlessness except on strenuous exercise |
| 2 | Short of breath when hurrying on the level or walking up a slight hill |
| 3 | Walks slower than contemporaries on level ground because of breathlessness or has to stop for breath when walking at own pace |
| 4 | Stops for breath after walking about 100m or after a few minutes on level ground |
| 5 | Too breathless to leave the house, or breathless when dressing or undressing |

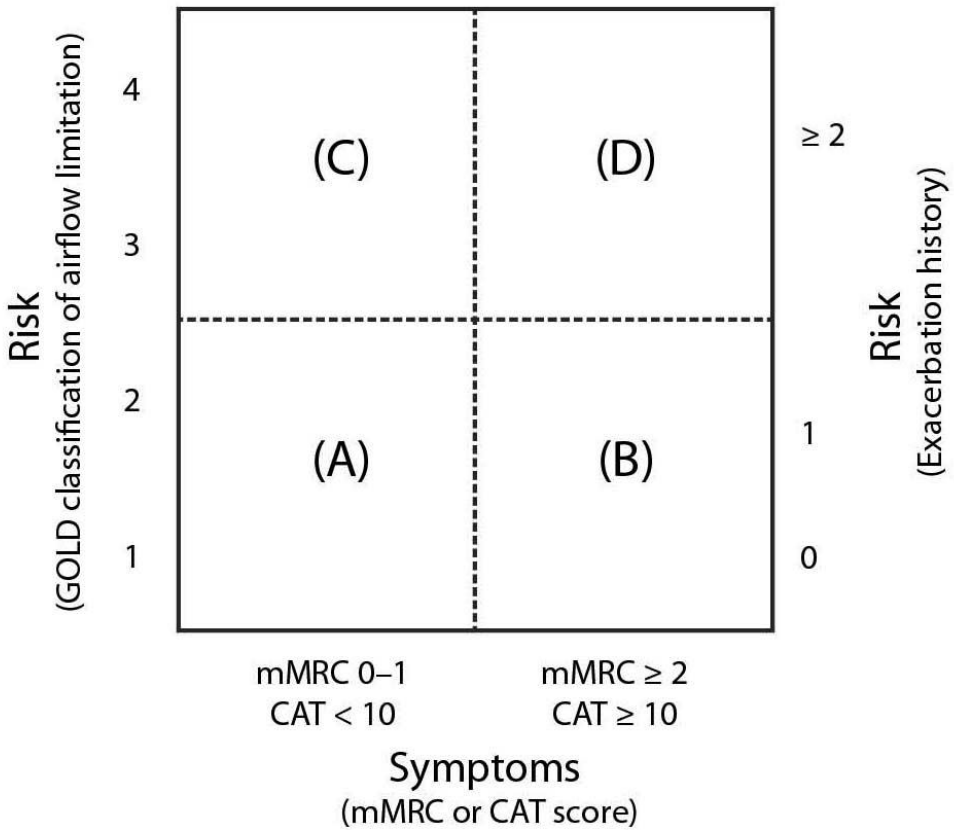
Chronic cough and sputum is often the earliest symptom of COPD, though may be ignored by individuals and attributed to a “smoker’s cough” until other symptoms appear. Cough tends to be more pronounced in the morning and over the winter months. Typically sputum is mucoid in nature and changes in sputum may indicate infection or exacerbation. High volumes of sputum production may suggest concomitant bronchiectasis, which occurs in up to 58% of people with moderate to severe COPD.[17]

*1.4 Systemic features of COPD*

While the principal initial pathology is in the lungs, there has been increasing evidence that COPD is a disease that has a number of systemic *sequelae*. These features are important as they provide information on morbidity and mortality, often more accurately than $FEV_1$[18, 19]. These include skeletal

muscle dysfunction, cachexia, ischaemic heart disease, cor pulmonale, depression, osteoporosis, diabetes mellitus and anaemia. Incorporation of some systemic features into multi-dimensional tools have been reported, including the Body-Mass Index, Airflow Obstruction, Dyspnoea and Exercise Capacity (BODE) index[16] and more recently the updated GOLD guidelines, which incorporates exacerbation frequency and dyspnoea scores with spirometry[4] (figure 1.1).

***Figure 1.1*** *The updated GOLD classification which starts to address the multidimensional aspects of COPD*



### *1.4.1 Skeletal Muscle Dysfunction*

While exertional dyspnoea is the most common cause of exercise limitation it has long been recognised that a large proportion of patients with COPD also experience leg fatigue, suggesting factors other than pulmonary pathophysiology may be important[20]. Since then there has been increasing recognition of skeletal muscle dysfunction in COPD[21], apparent even in the early stages of COPD[22].

Skeletal muscle dysfunction is more pronounced in the muscles of ambulation, in particular the quadriceps, in COPD[23-25]. Compared with normal age-matched subjects quadriceps strength is reduced by 20-30%. This is of importance as quadriceps weakness and quadriceps muscle atrophy has been linked to mortality[18, 26], exercise performance[27, 28] and health care utilisation[19], often more accurately than lung function.

The causes of skeletal muscle dysfunction in COPD have been the subject of much debate and are likely to be multifactorial in nature. These include physical inactivity (disuse atrophy), systemic inflammation, anabolic/catabolic imbalance, hypoxia, nutritional depletion, genetic predisposition, oxidative stress and drugs (figure 1.2).

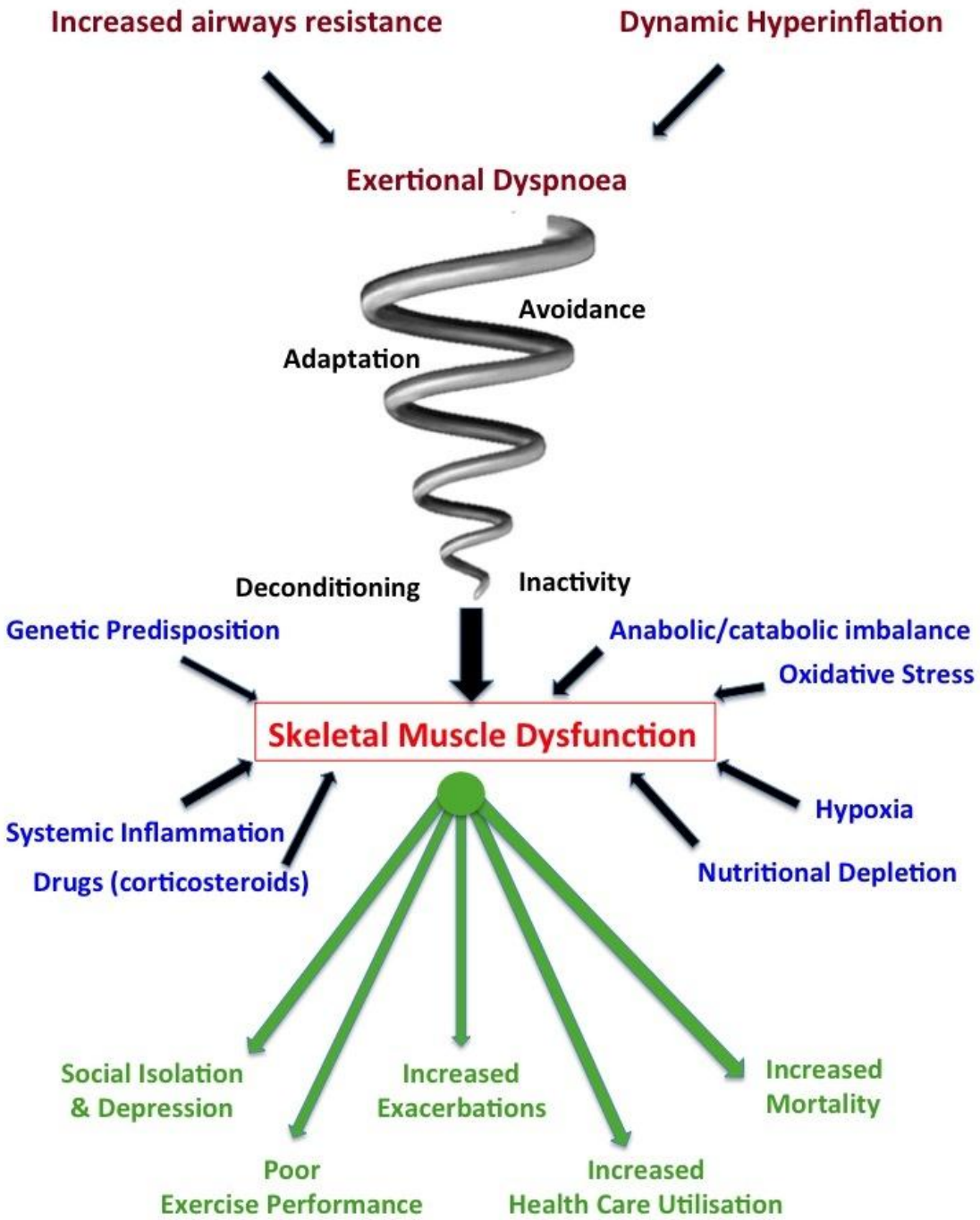



***Figure 1.2*** *Schematic diagram illustrating the causes of skeletal muscle dysfunction and its consequences. A spiral of disability due to dyspnoea leads to deconditioning and disuse atrophy, and is likely the main factor for skeletal muscle dysfunction in COPD*

Disuse atrophy is likely to be the main driving factor behind skeletal muscle dysfunction. The “downward spiral” of disability is well recognised and fits with the observation of selective involvement of the lower limb muscles. Supportive evidence of disuse atrophy is seen in the healthy population with proportionally increased quadriceps wasting, compared to other muscle groups, following enforced bed rest[29]. This is echoed in patients with COPD where reduced physical activity is common[30-32], and increased activity associated with better outcome[33, 34]. However, inactivity is unlikely to be the sole aetiology of skeletal muscle dysfunction, as there is preferential loss of type I muscle fibres in COPD[35], which is in contrast to the “normal” ageing process- where type II fibre loss is reported[36]. In addition muscle atrophy is also noted in the muscles of respiration in COPD, which are not subject to decreased activity[37]. It is possible that the skeletal muscle dysfunction in COPD represents an “extreme or accelerated” ageing process. A similar type 1 fibre type loss has previously been demonstrated in healthy subjects aged greater than 85 years[38].

The role of systemic inflammation in the pathophysiology of skeletal muscle dysfunction in COPD has been controversial. A number of other, non-respiratory, diseases, such as diabetes, are characterised by low-grade systemic inflammation in which skeletal muscle dysfunction is noted[39]. Since COPD is an inflammatory driven disease within the lungs, then “spill-over” from the lungs and resultant systemic inflammation has been postulated as a mechanism. Recent evidence has suggested that 16% of the COPD population have persistent systemic inflammation and that this population

have a worse outcome despite similar airflow obstruction[40]. Several circulating cytokines have been associated with skeletal muscle dysfunction, including IL-6[41] and IL-8[42]. Whether systemic inflammation is a causative factor or an epiphenomenon, however, is unknown. As described previously the muscles of ambulation are selectively affected, which is less likely if circulating factors are the principal aetiology. There is also a lack of data supporting local muscle inflammation in the stable COPD state[43-45], though increased neutrophilic inflammation has been demonstrated, with a significant increase following exercise[46].

The balance between anabolic and catabolic state has been suggested as a mechanism causing skeletal muscle dysfunction. Increased muscle protein breakdown has been observed in cross sectional studies[47-49], with other studies showing a reduction in anabolic hormones[41, 43]. However, direct measures of protein synthesis in the muscle have not been done and there is poor concordance between molecular markers and functional change[50], questioning a direct causal relationship.

Corticosteroids may be given as either topical inhaled therapy or as oral systemic therapy. Oral corticosteroids may be given in high doses as short-courses, as treatment for exacerbations or in lower doses as a maintenance regimen. Steroid induced myopathy is a well-recognised phenomenon, and has been reported in COPD[51, 52]. However, the role of high dose steroids may be difficult to ascertain at the time they are usually administered- exacerbations- as other factors are increased at this time, such as immobility, increased systemic inflammation, oxidative stress, and hypoxia. High dose steroids given during the stable state does not affect quadriceps strength[53].

Hypoxaemia, either at rest or during exercise is common in advanced COPD and increases oxidative stress on the quadriceps muscle following exercise[54]. Improvements in muscle contractility have also been improved with oxygen supplementation in hypoxaemic patients[55]. Other hypoxaemic states, such as high altitude living, have also been shown to induce a muscle fibre shift towards glycolytic metabolism[56]. However, skeletal muscle dysfunction occurs in the absence of hypoxaemia and is detectable in early disease. While hypoxaemia has been considered as a mechanism, local tissue hypoxia is less well described. A combination of factors such as reduced capillarisation, heart disease (and therefore stroke volume) and mild hypoxaemia may all contribute.

### 1.4.2 Cachexia

Cachexia is closely linked with skeletal muscle dysfunction in COPD and is defined as “a multifactorial syndrome characterised by severe body weight, fat and muscle loss and increased protein catabolism due to underlying disease(s)”[57]. A clinical definition exists which requires active weight loss in the presence of underlying disease plus at least three other factors including muscle weakness, fatigue, anorexia, low fat free mass index (FFMI), or abnormal biochemistry[58]. Those that fulfil the criteria are at increased risk of increased death and morbidity[59, 60]. In COPD cachexia exists and is associated with poor prognosis but attention should be paid to the requirement of active weight loss. This is because a significant proportion of patients, particularly those of an emphysematous phenotype, have a low

FFMI which predates their disease and have a different natural history to those with cachexia.

### *1.4.3 Ischaemic Heart Disease*

While there are common risk factors for coronary artery disease (CAD) and COPD (principally smoking, increased age and decreased physical activity), there is association independent of these risk factors[61, 62]. When compared to age and gender matched controls patients with COPD have been shown to have an increased risk of acute myocardial infarction (OR 1.61) and angina (OR 1.61), even when corrected for cardiovascular risk factors[63]. It has been suggested that the aetiology of ischaemic heart disease in COPD may be as a result of low grade systemic inflammation. The role of inflammation in atherosclerosis is well documented[64]. In COPD low grade systemic inflammation is associated in increased risk of ECG-diagnosed cardiac injury, irrespective of smoking or age[65]. Whether this relationship is causal or the manifestation of a genetic predisposition to end organ damage due to systemic inflammation is unknown.

As discussed earlier, treatments improving mortality in COPD are few in number. Treatment of ischaemic heart disease, which accounts for the largest single cause of mortality in mild and moderate COPD, is therefore important. Previously the use of β-blockers has been limited in COPD, but recent large retrospective data have shown the potential benefit in COPD[66].

### *1.4.4 Cor Pulmonale*

Pulmonary hypertension secondary to hypoxaemia (W.H.O. Group III[67]) is a well recognised complication of COPD. It is associated with the more advanced stages of COPD and carries a poor prognosis[68]. The mechanisms for cor pulmonale are multiple including pulmonary vasculature remodelling secondary to pulmonary vasoconstriction, increased pulmonary vascular resistance and renal vasoconstriction with sodium and water retention[69]. Therapy for cor pulmonale is based around oxygen therapy in the form of long-term oxygen therapy (LTOT). LTOT has been shown to increase survival in patients with hypoxaemia and cor pulmonale[70, 71]. Other therapies to improve oxygenation have been shown in proof of concept studies but are not yet established[72]. Other pharmacological therapies, normally used for primary pulmonary hypertension, lack evidence and may be potentially hazardous[8, 73].

### *1.4.5 Depression*

Patients with COPD, as with many other chronic diseases, have a high prevalence of psychological co-morbidities. Symptoms of depression are estimated to occur in between 6 and 42% of the population, depending on the measurement scale used[74, 75]. This is important as symptoms of depression are associated with poorer prognosis[76]. Specific interventions to improve depression and anxiety have been disappointing[77], though other therapies such as pulmonary rehabilitation are efficacious[78, 79].

*1.5 Therapies for COPD*

Removal of the aetiological insult in COPD- smoking- slows decline in $FEV_1$ and reduces mortality[80, 81], with greater effects on mortality in those with airflow obstruction or coronary artery disease[62, 82]. Smoking cessation therapies can improve unassisted quit rates with several interventions including brief clinical interventions, counselling, nicotine replacement therapy and non-nicotine medications (e.g. bupropion or varenicline),

Drug therapy for COPD is most commonly delivered via an inhaled route. The mainstays of therapy are bronchodilators and corticosteroids. Inhaled bronchodilators ($\beta_2$ agonists and muscarinic antagonists) improve symptoms, exercise capacity, $FEV_1$, dynamic hyperinflation and exacerbation frequency[83-86]. Bronchodilator maintenance treatment is now usually delivered using a long-acting formulation, meaning that only once or twice daily inhalation is required. Inhaled corticosteroids (ICS) are often given as anti-inflammatory medication in conjunction with long acting $\beta_2$ agonists. ICS therapy, when given in combination, further improves exacerbation frequency, $FEV_1$ decline and possibly mortality[83, 84, 87].

More recently low dose macrolide therapy has been demonstrated to decrease exacerbation frequency[88, 89], probably via an anti-inflammatory pathway, though this is yet to be routinely recommended in international guidelines.

Supplemental oxygen therapy is beneficial for patients with COPD when used for two separate indications. Long-term oxygen therapy (LTOT) increases survival[70, 71] and quality of life[90-92] in patients with resting hypoxaemia when used for a minimum of 16 hours per day and has a dose response for

further increased use. This is indicated in patients with resting hypoxaemia of 7.3kPa or 8.0kPa if there is evidence of cor pulmonale. Ambulatory oxygen therapy- oxygen given during exertion- may also be prescribed. This has been demonstrated to improve physical performance in patients who desaturate during exercise[93]. Ambulatory oxygen may also be given to those on LTOT, to increase their time on oxygen.

Pulmonary rehabilitation is of proven efficacy in COPD and other chronic respiratory diseases and is covered in detail in section 1.7.3.

A small sub-set of patients with COPD benefit from surgical intervention. Lung volume reduction therapy (LVRS) has been demonstrated to improve mortality, as well as dyspnoea and health status in patients with heterogeneous, upper-lobe predominant emphysema[94]. Patient selection is key for successful LVRS and rigorous selection process and MDT is required. LVRS achieves success through a number potential mechanisms; (1) by reduction in functional residual capacity of non-functioning lung, improving ventilation-perfusion mismatch[95, 96] and (2) reduced dynamic hyperinflation[97]. More recently endobronchial LVRS using a number of different techniques has been developed[98, 99], with results of definitive trials awaited.

## *1.6 Exacerbations of COPD*

### 1.6.1 Definition

Increasingly over the past years the importance of exacerbations of COPD has been noted, in terms of adverse events, natural history and patient perception. These episodes of acute lung inflammation and symptom deterioration are common in COPD, but exact definition has varied and a consensus has proven difficult. Exacerbations, depending on the circumstance, may be defined by either a symptom-based or event-based approach. Symptom-based definitions come from the patient, and as such are more subjective in nature. They are more difficult to capture and are usually done so by diary cards, and may be milder in nature. However, they are likely to be more sensitive as up to 50% will not be reported to a research team[100-102].

Anthonisen et al defined acute exacerbations during a trial of antibiotics in the treatment of AECOPD in 1987[103]. This included the presence of at least one major symptom (new onset dyspnoea, sputum production or sputum, purulence) and one minor symptom (upper respiratory exacerbation in previous five days, wheezing, cough, fever or 20% increase in respiratory rate or heart rate).

In 2000 Rodriguez-Roisin, as part of a workshop, defined an exacerbation as *"a sustained worsening of the patient's condition, from the stable state and beyond normal day-to-day variations, necessitating a change in regular medication in a patient with underlying COPD."[104]* This definition tried to account for the day-to-day variability in COPD symptoms, as well as bias

towards exacerbations with an infective aetiology. Rodriguez-Roisin also produced staging criteria for exacerbations severity (table 1.3)

The World Health Organisation/ US National Heart Lung and Blood Institute/ Global initiative for Chronic Obstructive Lung Disease (GOLD) guideline defined an exacerbation of COPD in their second report (2006, revised 2011). This is based on the Rodriguez-Roisin definition and is described as *"an acute event characterised by a worsening of the patient's respiratory symptoms that is beyond normal day-to-day variations and leads to a change in medication".[4]*

***Table 1.3*** *Staging severity of COPD exacerbations as defined by Rodriguez-Roisin*

| Severity | Level of Health-Care Utilisation |
|---|---|
| Mild | Patient has an increased need for medication, which he/she can manage in own normal environment |
| Moderate | Patient has an increased need for medication and feels the need to seek additional medical assistance |
| Severe | Patient/caregiver recognizes obvious and/or rapid deterioration in condition, requiring hospitalisation |

### 1.6.2 Aetiology of Exacerbations

Up to 80% of exacerbations are triggered by respiratory viral or bacterial infections[105, 106], with the remainder accounted for by air pollution and other environmental conditions. This results in a large inflammatory response

in the airways, which is predominantly neutrophilic in nature[107], but also is characterised by infiltration of macrophages, and CD8+ T lymphocytes. This is also associated with an increase in pro-inflammatory cytokines (TNF, Il-6, IL-8)[108]. In addition to these inflammatory pathways there is increased mucus hypersecretion and bronchoconstriction.

### 1.6.3 Impact of exacerbations and hospitalisation

Exacerbations are important events for patients as they can lead to hospitalisation and are associated with increased mortality[109]. Once patients have had a hospitalisation then they are more likely to be readmitted[33, 110], leading to cycle of recurrent admissions and declining quality of life. Hospital readmission within 28 days due to COPD is the single highest cause of any disease in the UK both in terms of absolute numbers (19,168 in 2009) and percentage (22.7% in 2009)[111]. It is unclear whether the cause of readmission is an acute increase of risk from the proceeding hospitalisation or part of the natural history and progression of the disease. Clustering of exacerbations has been observed in several cohorts suggesting an associated common link, independent of whether the individual is at risk of frequent exacerbations[112, 113]. However, increasing frequency of exacerbations is also seen with time and advancing disease[112, 114]. Death following hospitalisation for an exacerbation of COPD is common, with a 10.4% inpatient mortality rate in the UK[115]. This increase in risk of death is raised for greater than one month following hospitalisation, peaking at 44 deaths per 10,000 per day[112]. This equated to a 13.9% mortality at 90 days in the UK in the 2008 national audit[116]. Increased risk of death is seen in

certain sub-groups, including those with multiple previous admissions, age, number of co-morbidities- particularly heart disease- and hypercapnoea[109, 112, 117].

A number of scores have been used to try and predict exacerbation frequency and resultant mortality. These include the DOSE score[118], DECAF score[115], and have been shown in other multidimensional scores, such as the BODE[16] and ADO index[119]. The scores have yet to be translated into the clinical management of exacerbations for risk stratification and targeted intervention.

There is a profound and prolonged effect on exercise capacity, physical activity and quadriceps function following an exacerbation of COPD, particularly hospitalisation. Onset of muscle wasting and weakness is rapid[42], and also seen in non respiratory patients[29, 120]. Prospective studies, documenting pre-exacerbation measures, change with exacerbation and recovery are lacking, likely due to the large numbers of patients required. One study by Donaldson et al demonstrated that patients stayed indoors for greater time following exacerbation[121], but only 6.2% of the exacerbations resulted in hospitalisation, so are likely to have underestimated the effects of severe insult.

Natural recovery may be slow, following hospitalisation, with a residual functional deficit commonly present for more than one month after hospitalisation. Quadriceps strength has been shown to decline between days three and eight following hospitalisation, with recovery taking up to three months[42]. These observations are echoed when physical activity and exercise capacity are measured[30, 122].

When considering functional performance as a risk factor for hospitalisation, rather than an effect it has been shown that low physical activity and quadriceps strength are predictors of future admission[19, 33, 121]. Exacerbations have a major effect on health status in patients with COPD, with several studies reporting large improvements in the recovery phase[123, 124], though persistent deficit may remain[122]. Health status and frequency of exacerbation are also linked, with those that have frequent exacerbations having worse health related quality of life scores[100]. Alterations in health status are not just limited to severe exacerbations and hospitalisation. In unreported exacerbations, multiple events lead to a decrease in St George's Respiratory Questionnaire at one year. Single unreported events themselves have similar effects on reported, principally non-hospitalised, exacerbations[100].

Lung function is adversely affected by exacerbations. Transient reductions in $FEV_1$ are observed following an exacerbation, with a prolonged recovery phase[101, 125]. Longitudinal studies have shown a more rapid decline in lung function in patients that have frequent exacerbations[84, 126], though the difference of 8 mls per year in one study[114], may take years to be of significant clinical relevance. Patients in which there is an increased level of airways neutrophils, more common during exacerbations and in frequent "exacerbators", also have an associated faster decline in $FEV_1$[127]

### *1.6.4 Treatment of Exacerbations*

Short-acting bronchodilators, either inhaled or nebulised, are the mainstay of treatment for exacerbations. Both short acting $\beta_2$ agonists (SABA) and short

acting muscarinic antagonists (SAMA) result in improvements in bronchodilatation and symptoms of dyspnoea, with maximal effect at around 30 minutes[128-130]. While combination of SABA and SAMA therapy is recommended there is little evidence in their simultaneous use. Hospitalised patients are usually given nebulisers rather than inhalers. If good inhaler technique can be achieved then there is no advantage with nebulised therapy[131], but this group of patients are often more unwell and struggle with metered dose inhaler techniques.

The lung Inflammation and infection associated with exacerbation has been historically treated with antibiotics[132, 133] and oral corticosteroids. Despite this forming standard clinical practice, these therapies have been controversial.

Efficacy of systemic corticosteroids were first described more than 30 years ago, significantly improving $FEV_1$ with treatment[134]. Subsequently improvements in $PaO_2$[135, 136], fewer treatment failures and length of hospital stay[137-139] have been shown with steroid use. They are however, not without side effects and recent evidence has suggested the benefit may by in the sub-group that have eosinophilic driven inflammation[140].

Despite the majority of exacerbations being driven by viral and non-infective causes, antibiotics are given in a large proportion of exacerbations. The first study demonstrating benefit was by Anthonisen et al, which showed greater treatment success with antibiotics when at least two of three major symptoms were present (dyspnoea, sputum production and sputum purulence). This benefit was greatest in patients with all three symptoms[103]. The Cochrane review for antibiotics also concluded a benefit in mortality[132].

Additional supportive therapy such as controlled oxygen therapy and non-invasive ventilation (NIV) may be required, in patients who have required hospitalisation. During the acute exacerbation controlled oxygen therapy is recommended to maintain oxygen saturations between 88% and 92% (until risk of hypercapnoea is excluded)[141]. Acute NIV is of proven benefit in patients admitted with decompensated hypercapnic respiratory failure, reducing mortality and intubation rates[142-144]. This is achieved by increasing alveolar ventilation, by increasing tidal volume and thus minute ventilation via increased positive airways pressure. Typically NIV, if required, will be weaned over a period of three to four days.

Post-exacerbation pulmonary rehabilitation is of proven efficacy and is recommended nationally[122, 145, 146]. Detailed discussion of post exacerbation pulmonary rehabilitation is covered in section 1.7.5.2.

Despite the therapies as described above a fifth of patients are readmitted within one month of hospital discharge. Individual interventions have failed to have significant impact on this. However, integrated care packages have been shown to result in a reduction in hospital readmission rate[147, 148]. In the UK a reduction in trend of hospital readmissions was shown in a “real life” longitudinal analysis by implementation of a care bundle[149]. This care bundle, now adopted by the British Thoracic Society, incorporated five simple implementation elements; respiratory medication and inhaler technique assessed, an action plan and rescue therapy, smoking cessation referral, assessed and offered post exacerbation pulmonary rehabilitation, community follow up within two weeks of discharge.

## *1.7 Exercise Training*

### *1.7.1 Rationale*

COPD is a disease detrimentally affecting multiple systems outwith the lungs. Therefore, targeting therapies at these potentially reversible targets is attractive. Skeletal muscle dysfunction, combined with the principal symptom of COPD, namely breathlessness on exertion, makes exercise training an ideal candidate therapy strategy for COPD.

Exercise interventions are also comparable with drug interventions in efficacy when considering mortality for diseases such as coronary heart disease, cerebral vascular disease, heart failure and prevention of diabetes[150].

### *1.7.2 Principles of Exercise Training*

Much of the evidence for optimisation of exercise training exists in the elite athlete literature, but many principles can be extended to exercise training for health, both for the “healthy normal” population and those with morbidities. In order for exercise to be effective it must achieve a minimal threshold. This theory of overload means that the training must be over the subjects’ habitual physical activity.

For each modality of training its frequency, duration and intensity need to be considered. For example the American College of Sports Medicine recommend a training intensity of 60%- 90% of maximal heart rate or 50%-85% of $VO_2$ max[151]. However, this may be variable between individuals and depends on baseline fitness and co-morbidities. For example, those with low fitness levels will benefit more from lower intensities of training than those with

a higher level of fitness. This principle also means that exercise programmes should be progressive. In addition a frequency of a minimum of three times per week with an optimal duration of 20-30 minutes in recommended. Different modalities of training will confer different benefits and it is important that outcome measures are appropriate. For example aerobic training will result in improvements in exercise capacity and $VO_2$ peak, but resistance training will lead to improvements in strength.

### *1.7.3 Pulmonary Rehabilitation*

The benefits of exercise training in COPD were first described in 1952[152] and standardised in 1969[153]. However it was not till the 1990s that exercise training, particularly in the form of pulmonary rehabilitation, became an accepted therapy for COPD.

Pulmonary rehabilitation is a multi-disciplinary intervention, comprising individually prescribed exercise training, patient assessment, education, nutritional intervention and psychosocial support[154]. There is large variation in pulmonary rehabilitation programmes internationally, but typically in the UK it comprises a short course (4-7 weeks) of supervised and unsupervised exercise training and education[146]. This has been demonstrated to provide benefits in functional exercise capacity, dyspnoea, health status and psychological status[155, 156]. Physical improvements are typically sustained for one year [155, 157] with similar improvements seen with repeat pulmonary rehabilitation interventions [158-160].

### *1.7.4 Components of exercise training in pulmonary rehabilitation*

Historically, exercise prescription within pulmonary rehabilitation has been based on aerobic training, also described as endurance training, which is typically either walking or cycling based therapy. More recently the addition of resistance, or strength, training has been recommended to pulmonary rehabilitation programmes[146, 154].

Endurance training has a greater benefit when conducted at higher intensities, with >60% maximal work rate, sustained continuously for 20-60 minutes per session. This can be calculated from initial $VO_2$ peak or using symptom scales, such the BORG dyspnoea scale and Rating of Perceived exertion (RPE).

Whilst endurance training improves exercise performance and health status, it does not improve muscle mass or strength. This is important, as the effects of skeletal muscle dysfunction, described previously, are not fully addressed. Resistance training offers a training modality that is of proven efficacy at improving mass and strength.

### *1.7.5 Timing of Pulmonary Rehabilitation*

Prior to this point pulmonary rehabilitation has only been considered in the stable state. However, as highlighted in section 1.5.3 pulmonary rehabilitation is a treatment that may benefit a number of the effects of hospitalisation and exacerbations. Below post and peri-exacerbation rehabilitation are considered.

#### *1.7.5.1 Post exacerbation pulmonary rehabilitation*

Post exacerbation pulmonary rehabilitation has been one of the most significant changes in the management of COPD in the past five years, and comprised one of the major changes to the 2010 update of the COPD NICE guidelines. The systemic effects, with sustained reductions in exercise capacity, quadriceps strength and physical activity, from an exacerbation have been reviewed in section 1.5.3. The seminal study in this field by Man et al in 2004 demonstrated that pulmonary rehabilitation undertaken within one month of hospitalisation for an exacerbation of COPD improved exercise performance and health status[122]. These functional improvements have been repeated subsequently in other studies[145, 161].

A reduction in subsequent hospital admission was found in a recent Cochrane review (OR 0.22, 95% CI 0.08-0.58)[162]. However, this analysis has a number of flaws. Only 71 events were captured in a total of 250 patients. In the three positive papers, two only followed up for three months, in which the majority of time was spent within the programme (starting within one month and 8 week programme)[122, 145]. The other positive paper followed for a longer period (6 months) but hospitalisation was not reported in the original manuscript and contained only 12 hospitalisations[163]. In comparison the only post exacerbation pulmonary rehabilitation trials to have followed up for longer (12 months) showed no difference in hospitalisation[164].

Previous studies of post exacerbation pulmonary have all been outpatient based, and have been potentially biased by selection bias (probably self-selection by patients). The largest single study to date of 60 patients took three years to recruit at four separate sites in London, with no evidence of

number of patients screened[145]. Recent evidence by the same group has recently addressed this question demonstrating less than ten percent of hospitalised patients with COPD complete the programme[165].

#### *1.7.5.2 Rehabilitation during hospitalisation*

While post exacerbation pulmonary rehabilitation is of proven benefit the disability caused by an acute exacerbation occurs early on and its effects may be prolonged[30, 42]. The logical progression would be to intervene during hospitalisation and prevent this decline. Two interventional proof of concept studies have suggested this strategy may be of benefit, using two different training modalities- resistance training and neuromuscular electrical stimulation[166, 167]. In the resistance training study, comprising 36 patients, a significant difference of 10% was seen in quadriceps force between training and control groups at one month. This was due to an increase in the training group, with no recovery in the control group. This study involved eight days inpatient training starting within 24 hours of admission. There was, however, no effect on 6 month readmission rate.

#### *1.7.5.3 Peri-hospitalisation strategies in non-respiratory disease*

Hospital acquired disability is not unique to respiratory disease and has been observed in the healthy and elderly populations[29, 168]. In the surgical population strategies such as “enhanced recovery” have been developed to minimise hospital time and accelerate post-operative recovery. While enhanced recovery programmes vary depending on the surgical speciality the concept remains similar. These programmes, incorporating pre-operative

care, reducing the physical stress of the operation, increasing post-operative comfort and improved post operative care[169], have been shown to reduce hospital stay[170].

The adaptation of enhanced recovery to acute medical admissions has yet to be investigated, and changes would be required (as pre-admission care would not be possible). However, many aspects are similar to those of pulmonary rehabilitation and the advent of discharge care bundles.

### *1.7.6 Adjuncts to Pulmonary Rehabilitation*

The efficacy of pulmonary rehabilitation is unequivocal, but strategies to supplement this benefit have been of considerable interest, in particular within sub-groups of patients e.g. those with established respiratory failure. As such, a number of adjuncts have been trialled within pulmonary rehabilitation; including methods to improve ventilation (oxygen, heliox, non-invasive ventilation), nutrition (nutritional supplementation and hormone therapy) and alternative training methods (neuromuscular electrical stimulation, interval training, non-linear training, and inspiratory muscle training). Below, one of these adjuncts, neuromuscular electrical stimulation, is considered in detail.

#### *1.7.6.1 Neuromuscular Electrical Stimulation*

Despite the unequivocal benefits of whole body exercise training in stable disease, this intervention may be difficult to deliver in patients with severe ventilatory limitation, during acute exacerbations or those with severe muscle wasting. Non-volitional techniques, such as neuromuscular electrical stimulation (NMES), which are independent of these factors, may have a role in these settings. While it may not provide a number of benefits of whole-body exercise therapies, it may allow targeted therapy to muscles groups, until a patient is able to progress to other treatments.

Within the healthy population NMES has been trialled in multiple muscle groups, but most commonly in the quadriceps. There is evidence that NMES improves isometric strength, though variation in improvement reported is large (for review in healthy population and athletes see[171])

Functional benefit in the forms of peak torque, exercise capacity and muscle endurance were first demonstrated in the COPD population in 2002[172, 173]. Subsequent to this, functional benefit in the COPD population has been reproduced in a number of studies in both the stable and unstable population. These benefits have been the subject of two systematic reviews[174, 175]. They conclude that NMES results in significant changes in quadriceps strength, and exercise capacity. More recently Sillen et al have compared two separate frequencies for NMES and compared alongside a resistance training group[176]. Similar increases in the high frequency NMES and resistance training groups were seen, though not as large as may be expected from other standard resistance training studies in COPD.

Rather than a stand-alone therapy, one study has considered NMES in addition to standard pulmonary rehabilitation programme[177]. This unblended RCT compared 17 patients with COPD. A large additional benefit of NMES was seen in terms of QMVC and breathlessness. However, these results need to treated with much caution as the patient group were a highly selected cohort, as inclusion criteria including the presence of wasting (low BMI and weak). In addition they had all had recent hospitalisation or intensive care stay.

Despite the evidence for a functional improvement using NMES there has been little looking at the underlying mechanisms of NMES in COPD. The few studies that have considered mechanisms in COPD describe considerable variation in findings. The underlying mechanisms are important because the motor unit recruitment is different in NMES and induces smaller total MVC during training sessions. Normal motor unit recruitment follows Henneman's size principle; that is motor units are recruited in order from smallest to largest. This means type 1 oxidative fibres are recruited before type 2 glycolytic fibres. However, as NMES stimulate fibres directly then the muscle training may be different. This raises the question as to what kind of training NMES is: resistance, endurance or a unique combination. Also NMES training may result in different changes in COPD to other conditions given the preferential loss of type I muscle fibres.

In the stable population no change in muscle fibre type proportion has been seen[178, 179]. A fast to slow shift in fibre type has been described using NMES following an intensive care unit admission for COPD patients[180], though this has to be treated with caution, as genuine muscle fibre shift is

likely to require longer periods than the follow up period. Muscle fibre hypertrophy has similarly shown considerable variation between studies (selective type II hypertrophy[179], no hypertrophy[178], and selective type I hypertrophy[180]).

NMES has not yet found its clinical role within pulmonary rehabilitation, given the efficacy of establishes therapies like pulmonary rehabilitation. However, periods of enforced immobility where traditional training modalities are limited logically lends itself to NMES e.g. during and immediately post hospitalisation and/or exacerbation. Indeed, NMES may be advantageous as it can easily be applied early in the hospitalisation period, preventing the acute decline associated with hospitalisation[42], rather than treating it afterwards (such as post exacerbation pulmonary rehabilitation).

2 studies have considered the use of NMES during an exacerbation of COPD or during an ITU admission. Giovedoni et al stimulated a single leg for 14 days following hospitalisation for an exacerbation of COPD[167]. This pilot study of 11 patients showed significantly increased quadriceps strength at the end of the stimulation period and exhibited a dose response. Zanotti et al performed NMES compared with active limb mobilisation on mechanically ventilated patients with COPD[181]. Again increases in strength were seen, but also a reduction in the time taken to transfer from bed to chair. These studies offer encouraging pilot evidence of the benefits of NMES during the acute illness in COPD.

## 1.8 Aims and outline of thesis

The overarching aim of this thesis is to investigate whether an early rehabilitation can ameliorate the systemic *sequelae* of hospitalisation following exacerbation of chronic respiratory disease, particularly COPD. I aim to characterise this cohort, identifying risk factors for future events, and test the effects of a rehabilitation intervention on long term outcomes, including future hospitalisation, physical performance and health status. I also aim to further investigate a single adjunct used, neuromuscular electrical stimulation, which may be of particular benefit in the acute setting.

The hypotheses of my thesis to address the aims are

1. That an early rehabilitation programme delivered at the time, and immediately following, hospitalisation for an exacerbation of chronic respiratory disease will reduce subsequent hospital admissions and health care utilisation

2. That an early rehabilitation programme delivered at the time, and immediately following, hospitalisation for an exacerbation of chronic respiratory disease will prevent the decline seen in physical performance and health status associated with hospitalisation

3. That measures of the skeletal muscle at the time of a severe exacerbation will predict future hospitalisations of chronic respiratory disease

4. That the effects of neuro-muscular electrical stimulation on the quadriceps in stable COPD will result in changes in muscle mass in a similar manner to resistance training

In order to address the aims and hypotheses of this thesis two interventional randomised controlled trials (RCTs) have been performed. The first trial is a clinical two-centred RCT of an early rehabilitation intervention compared with usual care, with follow up for one year, powered to detect readmission rate. Chapter 3 presents the results of the health care utilisation outcomes and chapter 4 the functional measures (exercise performance, quadriceps strength and health status).

The second trial is a mechanistic study investigating the effects of unilateral neuromuscular electrical stimulation compared with resistance training, but also involving an untrained, control leg. Chapter 5 presents only the functional results of the study- there is on-going work from muscle biopsies taken at three time points.

# *Chapter Two*

# Materials and Methods

## *2.1 Ethics*

All studies presented in this thesis were approved by the National Research Ethics Service (NRES). Local Research & Development approval was provided for each site involved. Trials were prospectively registered with the ISRCTN (ISRCTN05557928 and ISRCTN87439020).

## *2.2 Funding*

Funding for the research undertaken in this thesis was provided by The National Institute for Health Research Collaboration for Leadership in Applied Health Research and Care - Leicestershire, Northamptonshire and Rutland (NIHR CLAHRC for LNR) Rehabilitation Theme.

## *2.3 Subjects*

Subjects were recruited for the early rehabilitation study during the first 48 hours of admission to hospital (Glenfield Hospital, Leicester and Kettering General Hospital, Kettering). Potentially suitable subjects were identified daily on the respective acute medical admissions units.

Recruitment for the neuromuscular electrical stimulation study was from outpatient clinics, pulmonary rehabilitation waiting list and a database of previous research participants at Glenfield Hospital, Leicester.

Informed consent was obtained from all patients. Inclusion and exclusion criteria are described in the individual chapters.

### *2.4 Anthropometric Data*

Height was measured using a freestanding height bar to the nearest centimetre. Subjects removed their shoes prior to measurement. Height was measured only at baseline and assumed to remain stable during the follow up period. Weight was measured with subjects dressed with no shoes to the nearest kilogram. Body mass index (BMI) was calculated by dividing weight by height squared.

### *2.5 Lung Function*

Spirometry was performed to British Thoracic Society (BTS) standard using a desktop spirometer (MicroLab, Carefusion). The best of three consecutive blows was used to obtain the $FEV_1$, FVC and $FEV_1$/FVC ratio. Predicted values were used to produce percent predicted values.

### *2.6 Exercise Capacity*

#### *2.6.1 Incremental Shuttle Walk Test (ISWT)*

The ISWT is a field-walking test of maximal exercise capacity. It is a progressive, externally paced test and has been demonstrated to be linearly related to peak $VO_2$ during laboratory incremental treadmill walking in COPD ($VO_{2max}$=4.19 + 0.025* ISWT distance)[182, 183].

The ISWT is performed between two cones, spaced 9 metres apart. Instructions are given via a compact disc (Glenfield Hospital, Leicester, UK). An audio signal “bleep” sounds to start the test. Subjects then walk along the course and around the cone in time for the next bleep. A triple bleep sounds every minute to signal an increase in walking speed. No additional external encouragement is given. The test is considered complete when subjects are unable to continue at the necessary pace. Heart rate, oxygen saturations, modified Borg score, exertional effort and reason for termination are also recorded pre and post ISWT.

### *2.6.2 Endurance Shuttle Walk Test (ESWT)*

The ESWT is a constant rate sub-maximal endurance field-walking test[184]. Following a 2-minute warm up, patients walk at a speed set to the equivalent of 85% of the predicted $VO_{2peak}$, calculated from the ISWT. Total time walked (excluding warm-up time) is recorded. The walking course is identical to the ISWT and is also externally paced- with 16 different speeds. If a patient achieves 20 minutes on the ESWT the test is terminated. While the baseline ESWT is a poor descriptor of exercise function, it is a more sensitive measure of change than the ISWT.

### *2.6.3 Cardio-Pulmonary Exercise Test (CPET)*

Peak exercise work capacity was measured using incremental cycle ergometry. Tests were performed on an electrically braked cycle ergometer (Ergoline) while monitored with electrocardiogram, blood pressure, oxygen saturations, and breath-by-breath pneumotach transducer (Medisoft ergocard

gas analyser and Expair software). Peak workload, $VO_2$ peak, Borg breathlessness and perceived exertion were recorded. Subjects performed one minute unloaded cycling as warm-up and then an increase by 10 watts every one minute, using a ramp protocol. Subjects performed constant rate cycling at 60 revolutions per minute until exhaustion.

## *2.7 Dyspnoea and Health Status*

### *2.7.1 MRC Dyspnoea Grade*

The MRC dyspnoea scale is a 5 point self reported tool, which differentiates exertional dyspnoea (see table 1.2). It is the most widely used assessment tool used worldwide, though may be adapted to the modified MRC scale.

### *2.7.2 Chronic Respiratory Questionnaire (CRQ)*

The CRQ is a widely used questionnaire, designed to assess health status in patients with chronic lung diseases. It consists of four domains (dyspnoea, fatigue, emotional function, mastery) that are usually reported separately[185]. A self-reported CRQ (CRQ-SR) has been developed and was used for the studies in this thesis[186]. It consists of a twenty-item questionnaire (5 dyspnoea, 4 fatigue, 7 emotional function, 4 mastery). The dyspnoea domain is individualised by asking subjects to list 5 activities that cause dyspnoea. These 5 items are selected at baseline and kept the same for later questionnaires. Each item is rated on a 7 point Likert-type scale, with higher scores indicating better health status. The questionnaire has been demonstrated to be responsive to interventions, including pulmonary

rehabilitation, with an increase of 0.5 units considered the minimum clinically important difference[187].

### *2.7.3 St Georges Respiratory Questionnaire (SGRQ)*

The SGRQ is probably the most widely used validated respiratory patient reported outcome measure of health status[188]. It comprises a two part questionnaire and assesses three domains' recollection of symptoms, current activity and disease impact. These domains can be combined to form a total SGRQ score. Scores are expressed as a percentage with a best possible score of 0% and worse possible score of 100%. A change in a score of 4 has been defined as the minimal important difference[189].

## *2.8 Quadriceps Measures*

### *2.8.1 Quadriceps Maximal Voluntary Contraction (QMVC)*

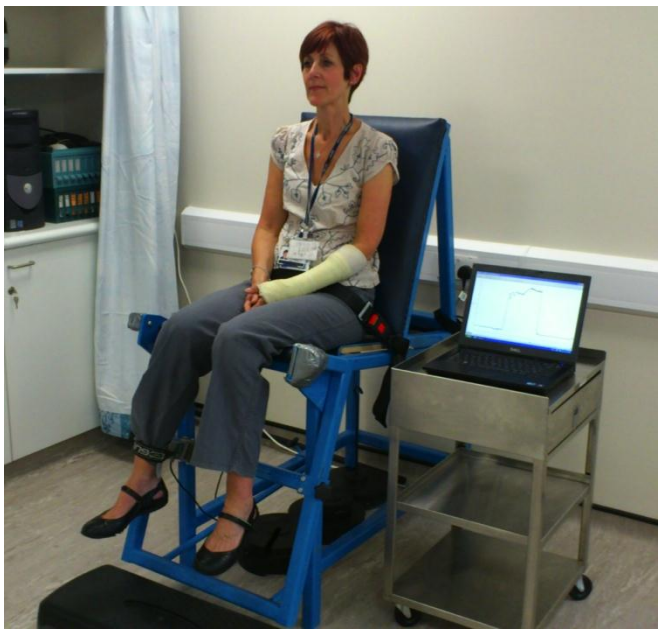
Maximal isometric quadriceps strength was measured in both studies. Strength was assessed with the knee flexed at 90° with the ankle fixed to a load cell and strap around the waist. The early rehabilitation study used a mobile chair (figure 2.1a). Five maximal contractions 30 seconds apart were taken with verbal encouragement. The best effort was taken as QMVC. Data were captured using PowerLab software (ADInstruments, New Zealand)) and analysed. QMVC was analysed as the mean over one second maximal contraction. The NMES study used a customised rigid rig and load cell (Loughbrough, UK- figure 2.1b). Data were captured and analysed using Spike 2 software (CED, UK). Six maximal contractions were conducted with

the maximal effort taken as QMVC. Peak strength was taken as maximal strength achieved.

***Figure 2.1*** *Quadriceps maximal voluntary contraction (QMVC) was measured using (a) mobile device for early rehabilitation trial (b) rigid rig for NMES study.*

(a)

(b)

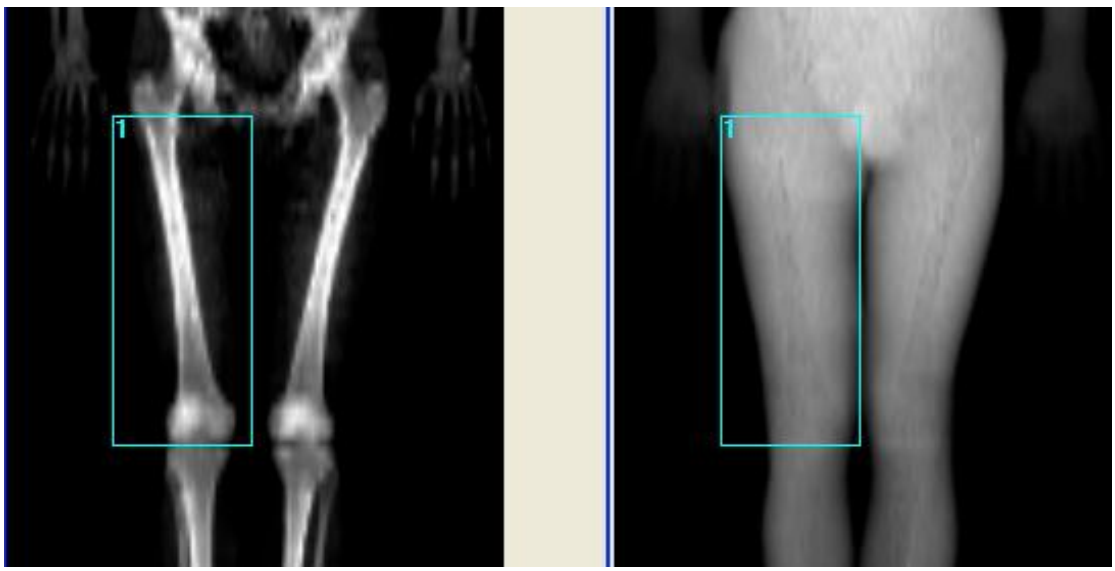


### *2.8.2 Quadriceps mass*

Total and regional (thigh) lean mass and fat free mass (FFM) were measured using Dual-energy X-ray Absorptiometry (DEXA) (Lunar Prodigy. GE Healthcare, Chalfont St. Giles, UK). FFM was calculated as lean mass plus bone mineral mass. The FFM index (FFMI) was calculated as FFM/ height$^2$. Thigh lean mass of each leg was calculated by determining a region of interest (1) vertically: from the lowest point of the ischial

tuberosity and knee joint and (2) horizontally: pubic symphysis and most lateral aspect of thigh (figure 2.2)

***Figure 2.2*** *Graphical box around region of interest for measurement of thigh lean mass.*

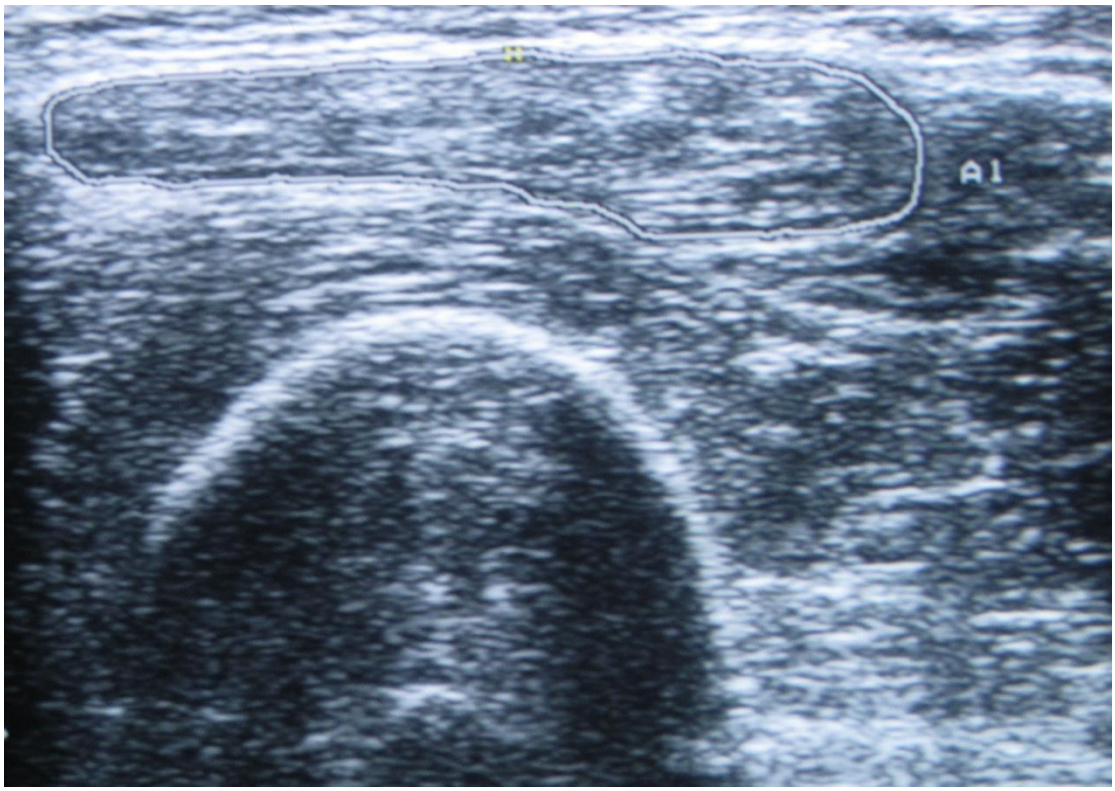



*2.8.3 Rectus femoris cross sectional area ($Q_{csa}$)*

Cross sectional area of the rectus femoris ($Q_{csa}$) was measured using B mode ultrasonography (Hitachi, Wellingborough, UK). Images were captured using a 7.5 MHz 7cm linear probe. Rectus femoris was used as a single muscle of the quadriceps as to allow whole muscle on a single image. Images were taken using the mid-distance between the greater trochanter and knee joint. This distance was measured on the anterior aspect of the thigh from the superior patellar border. The transducer was placed perpendicular to the leg, with minimal pressure to provide an adequate view in order to minimise muscle compression. Oblique images were minimised by placing the transducer at 90

degrees and ensuring minimal cross sectional area on the image. Images were frozen and the outline of the rectus femoris traced (figure 2.3) to obtain cross sectional area measurement (Hitachi, UK). $Q_{csa}$ was taken as the mean of three consecutive measurements within 10% from separate frozen images.

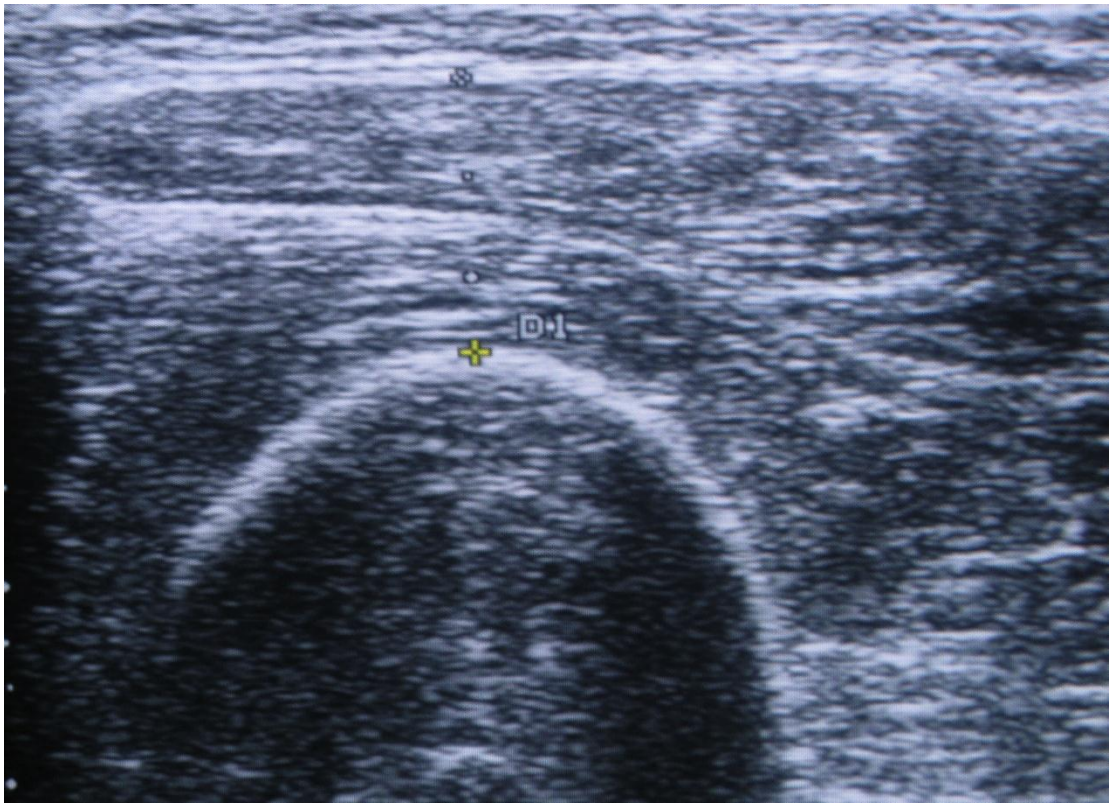
***Figure 2.3*** *Sample ultrasonographic image of left rectus femoris with outline drawn (A1) in a patient with COPD.*




### *2.8.4 Quadriceps thickness ($Q_{thick}$)*

Quadriceps thickness ($Q_{thick}$) was taken using the same methodology and at the same anatomical point described above for $Q_{csa}$. $Q_{thick}$ was defined as the point from superior aspect of rectus femoris to the base of vastus intermedius in a vertical direction (figure 2.4). Three measurements were taken and the mean calculated.

**Figure 2.4** Quadriceps thickness measurement using. Distance was from superior aspect of rectus fermoris to the superior aspect of femur. Distance in mm (D1) was repeated 3 times and mean taken.




## *2.9 Health Care Utilisation measures*

### *2.9.1 Secondary Care data*

Hospital admissions were collected from local hospital databases and GP records. Data of admission, type of admission (respiratory/non-respiratory), and length of hospital stay were recorded. Death was identified from hospital databases and GP records. Cause of death was obtained from death certificates obtained from hospital bereavement services or medical records if subject died in hospital or from GP records or departments of birth, deaths and marriages if subject died at home.

### *2.9.2 Primary Care data*

GP records were screened for number of antibiotic and steroid prescriptions during the follow up phase. Consultations (clinic consultation, telephone consultation or home visit) were recorded for the primary care teams. Pulmonary rehabilitation referral and uptake was obtained from local programmes.

## *2.10 Intervention Protocols*

### *2.10.1 Early Rehabilitation to enhance recovery following hospitalisation*

Participants allocated to the intervention group started early rehabilitation within 48 hours of hospital admission. In addition to usual care, they also received daily, supervised volitional (strength and aerobic training) and non-volitional (neuromuscular electrical stimulation) techniques. The pulmonary rehabilitation team, consisting of physiotherapists and nurses, delivered the early rehabilitation programme. The exercise programme was individually prescribed and progressed. Early rehabilitation was performed on the acute medical ward and by the participants' bedside. After discharge, participants underwent an unsupervised home based programme, supported by telephone consultations. Those who were readmitted after the six week intervention period did not receive a further early rehabilitation intervention.

#### *2.10.1.1 Non-volitional training*

NMES was initially supervised by the intervention team until the subject was deemed to be independent in its use. NMES was applied for 30 minutes daily.

The stimulation protocol consisted of a symmetrical biphasic pulse at 50 Hz, pulse duration of 300 milliseconds (ms), on time 15 and 5 seconds off. This was the preset standardised programme recommended for atrophic muscles by the manufacturer (Empi 300PV, Minnesota, USA). The surface electrodes were placed over the quadriceps femoris muscles of both legs. The intensity was increased by the therapist or patient according to tolerance. Each session lasted 30 minutes with both legs being stimulated synchronously. These were daily supervised sessions whilst the patient was in hospital. The patient was advised to continue with daily sessions of NMES when at home but these sessions were unsupervised.

*2.10.1.2 Strength Training*Patients completed daily strength training, comprising three sets of eight repetitions resistance training exercises with weights. This was performed for biceps curls, triceps curls, knee extension, sit to stand, and step-ups, which was based on the one repetition maximum. Once the rate of perceived exertion was <13 the weight was increased.

*2.10.1.3 Aerobic Training*

Daily walking was performed at a set walking speed predetermined by the endurance shuttle walk test at 85% oxygen consumption ($VO_2$) max (calculated from the incremental shuttle walk test). If participants were not able to walk 10 m in 20 seconds (1.78 km/h) then they performed daily timed walks at a manageable speed. Walking time was progressed at the prescribed walking speed, maintaining a Borg breathlessness score of between 3 and 5 (from 0 for no breathlessness to 10 for the most severe breathlessness) and a

Borg exertion score for rating perceived exertion <13 (from 6 for no exertion at all to 20 for maximal exertion).

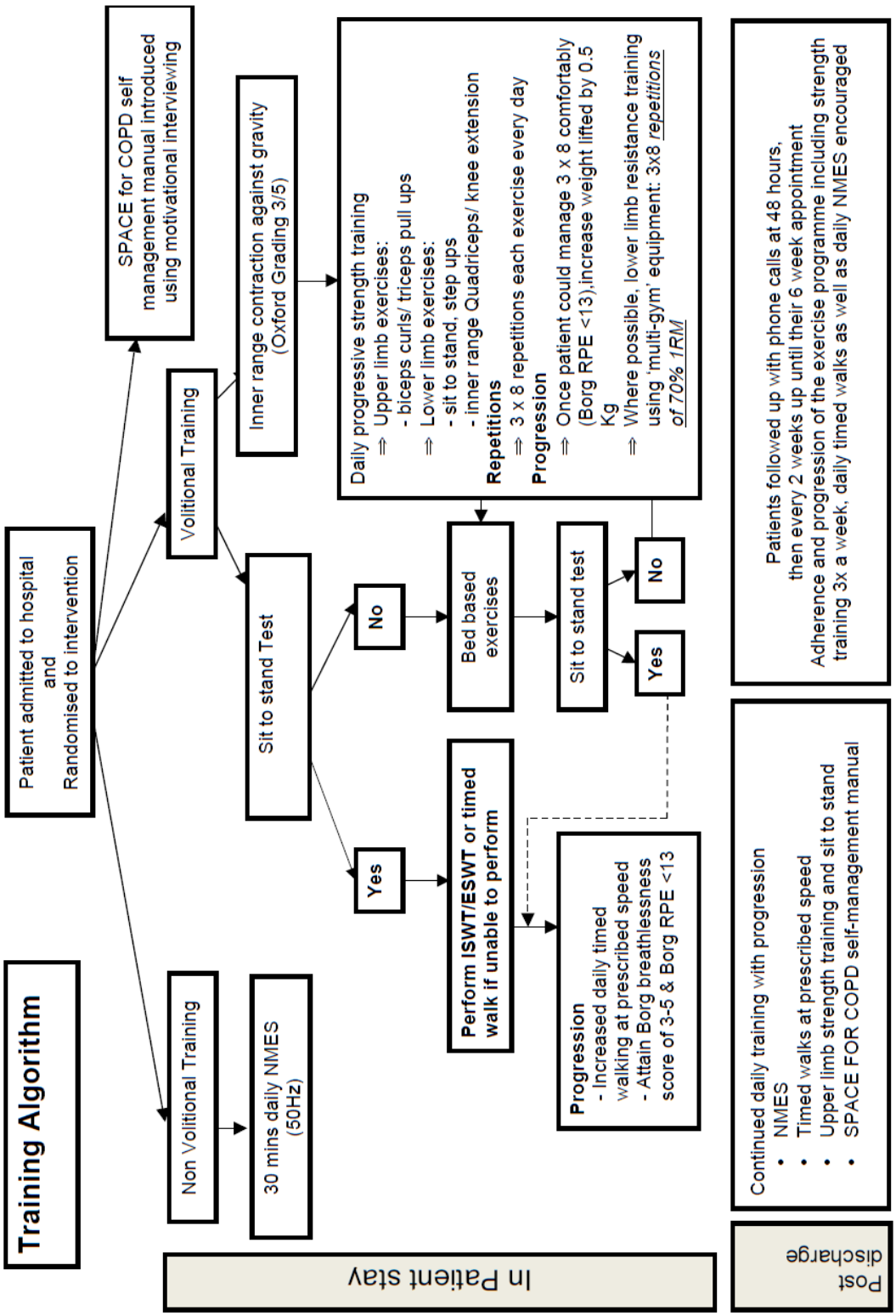
#### *2.10.1.4 Supported self-management programme*

The intervention team delivered education using the SPACE (Self-management programme of Activity, Coping and Education) manual for chronic obstructive pulmonary disease, a structured programme of exercise, education, and psychosocial support, and awarded the 'Crystal Mark for clarity' by the Plain English Campaign. Motivational interviewing techniques were used to introduce patients to the manual and to familiarise them with the content. The manual was used throughout the participants' inpatient stay and in the subsequent discussions during telephone calls.

#### *2.10.1.5 Post discharge training*

After discharge we advised the participants to follow a progressive walking based home exercise programme and to continue daily neuromuscular electrical stimulation, and we encouraged them to follow the self management programme. The post discharge training was supported by telephone consultations from the pulmonary rehabilitation intervention team, using motivational interviewing techniques, at 48 hours, two weeks, and four weeks. Participants were encouraged with adherence and progression of their exercise programme. Participants were also able to discuss any concerns that they may have and were given advice on ongoing management of their condition.

***Figure 2.5*** *Training algorithm for early intervention incorporating prescribed and progressive aerobic, resistance and non-volitional training*



### *2.10.2 Neuromuscular electrical stimulation training protocol*

#### *2.10.2.1 NMES*

NMES (Empi 300pv, USA) was performed 5 times per week (3 supervised in hospital and 2 unsupervised at home) on the quadriceps at a frequency of 50Hz for 30 minutes using intermittent stimulation (15s:5s on:off, 300μs band width, ramp period 2s). The mixed supervised and home protocol was chosen as 5 times per week as previously been shown to be effective, but to match the resistance training group in terms of investigator contact. Amplitude was maximally titrated to subject tolerability at every session and progressed throughout the study. Subjects were positioned with the knee extended and relaxed, supported on a plinth.

#### *2.10.2.2 Resistance training*

Resistance training was based on a regime previously shown to be effective within the investigating laboratory[50]. Isokinetic training was performed 3 times per week, comprising of 5 sets of 30 maximal knee extensions at 180°/second, using an isokinetic dynamometer (Cybex II Norm: CSMi, Stoughton, USA). Each set was separated by one minute's rest, and included 30 repetitions of passive warm up and warm down manoeuvres. Manoeuvres were performed with the knee at 90° at rest, extending to 180°, with encouragement by a member of the investigating team.

### *2.11 Statistical Analysis*

Data were analysed using STATA version 13 SE (Texas, USA). Survival data were graphically produced using STATA. All remaining graphs were made using Graphpad Prism version 6 (California, USA). Full statistical descriptions are provided in individual result chapters, but summarised below.

#### *2.11.1 Cross-sectional data*

Independent (unpaired) groups were compared using the Student T-test and Mann-Whitney test for parametric and non-parametric data respectively. For paired data, either a paired T-test (parametric) or Wilcoxin (non-parametric) matched paired signed rank test were used. Categorical data was compared using chi squared.

#### *2.11.2 Hospital readmissions*

In the early rehabilitation trial the primary outcome was hospital readmission. Subjects in this study were at risk of more than one mutually exclusive event i.e. death, which would then prevent hospital readmission. To account for this survival analysis was conducted using competing risks analysis, with hospital admission as outcome and death as the competing risk.

In addition to survival analysis count analysis was performed for total number of admissions and number of hospital days. These data are known to follow a Poisson distribution with overdispersion. Negative binomial regression was used to account for this, as previously described in the COPD exacerbation literature[190, 191].

### *2.11.3 Longitudinal data*

Repeated measures analysis of variance (ANOVA) was conducted for the physiological measures taken at baseline, discharge, 6 weeks, 3 months and 12 months in the early rehabilitation trial. 2 way repeated measures ANOVA using change with time and between legs as the within-group factors. Bonferroni correction was used for post-hoc analysis.

### *2.11.4 Multiple imputation*

The functional results presented in chapter 4 contain missing data, as there was attrition in the follow up in the year following admission for an exacerbation of chronic respiratory disease. Common methods for handling missing data can include removal listwise deletion or “last number carried forward”. However, these methods are prone to bias and may produce incorrect results. Multiple imputation is a method to account for this and was performed on the functional data in chapter 4. Missing values for any variable are predicted using existing values from other variables so a complete “imputed” dataset is produced. This is performed multiple times with each imputation dataset being analysed. The separate datasets are then pooled to produce an overall analysis. Multiple imputation was performed by chained equations and 40 imputed datasets produced.

# *Chapter Three*

# An early rehabilitation intervention to enhance recovery during hospitalisation for an exacerbation of chronic respiratory disease

## *3.1 Abstract*

Patients hospitalised with exacerbations of chronic respiratory disease (AECRD) are at high risk of readmission and demonstrate increased morbidity and mortality. I hypothesized that an early rehabilitation (ER) intervention initiated during the acute admission would reduce the risk of readmission over 12 months.

This prospective, randomized controlled trial compared an ER intervention with usual care during hospitalisation for AECRD. Subjects in the intervention group received a six week intervention, started within 48 hours of admission and continued after discharge. The primary outcome was re-admission rate at 12 months. Secondary outcomes included number of hospital days, mortality and primary care health care utilisation. Primary analysis was intention to treat, with pre-specified per protocol analysis as a secondary outcome. The study is registered on the ISRCTN (N05557928).

389 subjects were randomised (196 to intervention, 193 to usual care). 233 (59.9%) subjects were readmitted at least once in the following year (122/196

[62.2%] in the intervention group and 111/193 [57.5%] in the control group). No significant difference between groups was found (hazard ratio 1.1, 95% CI 0.86-1.43, p=0.440). An increase in mortality was seen in the intervention group at one year (OR 1.74, 95% CI 1.05-2.88, p=0.031), but not during the intervention period or at six months.

Early rehabilitation during hospitalisation for AECRD did not reduce the risk of subsequent readmission. The results suggest that progressive exercise rehabilitation should be deferred until after the patient has left hospital allowing in-hospital care to focus on management of the acute event and review of other aspects of chronic disease management.

### *3.2 Introduction*

Patients admitted to hospital with Acute Exacerbations of Chronic Obstructive Pulmonary Disease (COPD) and other Chronic Respiratory Diseases (AECRD) are at increased risk of mortality, morbidity and further episodes of unscheduled hospitalisation. Acute exacerbation of COPD is the second most common cause for unscheduled hospital admission in the UK, accounting for the largest component of health costs associated with the disease[192]. Physical activity and performance may be reduced for a prolonged period following hospitalisation, increasing the risk of re-admission[30, 33, 42].

Pulmonary rehabilitation (PR) is of established efficacy in stable chronic respiratory disease (CRD) and small scale trials of PR delivered after discharge from hospital have suggested a reduction in the short term risk of re-hospitalisation. An early exercise/mobility intervention is a component of wider enhanced recovery programmes, which have been successfully

implemented for patients undergoing elective surgery but have not been widely applied to unscheduled medical admissions such as AECRD[193-195].

A randomised clinical trial of a progressive, exercise based rehabilitation intervention delivered immediately following unscheduled admission to hospital for an AECRD was conducted. I hypothesized that this intervention would reduce the risk of re-admission in the following year.

The principles underpinning the intervention were; (1) That it should be delivered early in the admission with the aim of preventing the decline in physical performance; (2) That it should be provided intensively making best use of the time spent in hospital and (3) That it should be continued after discharge to maximize the restoration of physical performance and activity and obviate the need to extend the hospital spell to provide treatment. In this chapter I present data on the impact of the intervention on healthcare utilisation. Data on exercise performance, muscle strength and health status are presented in chapter 4.

## *3.3 Methods*

### *3.3.1 Study design*

This was a prospective, parallel group, single-blind randomised controlled trial conducted in two centres in the United Kingdom, an acute cardio-respiratory unit in a teaching hospital (Glenfield Hospital, University Hospitals of Leicester) and an acute medical unit in an affiliated teaching district general hospital (Kettering General Hospital).

Patients were randomly allocated to one of two treatment groups: an "early rehabilitation group" (ER) and a "usual care" group (UC). Subjects randomised to the intervention group received a six-week intervention.

The nature of the intervention meant subject blinding was not possible, but all investigators performing the outcome measures were blinded to subject allocation.

Ethical approval for the study was given by the National Research Ethics Service (NRES), Nottingham REC 1 committee (09/H0403/76) and the study was registered on the ISRCTN (N05557928).

### *3.3.2 Study population*

Subjects were recruited to the study and randomised within 48 hours of admission to hospital with an exacerbation of chronic respiratory disease. Inclusion criteria were: diagnosis of chronic respiratory disease (COPD, chronic asthma, bronchiectasis or interstitial lung disease), self-reported breathlessness on exertion when stable (MRC dyspnoea grade 3 or worse) and age 40 years or greater. Exclusion criteria were: inability to provide

informed consent, concomitant acute cardiac event, presence of musculo-skeletal, neurological or psychiatric co-morbidities that would prevent the delivery of the rehabilitation intervention, and more than four any-cause emergency hospitalisations in the previous 12 months.

### *3.3.3 Usual Care group (UC)*

Patients assigned to the usual care group received standard care from the ward multidisciplinary team as directed by the responsible clinical team. This included physiotherapist delivered airway clearance techniques, assessment and supervision of mobility and smoking cessation advice. Nutritional status was assessed in all patients, who were referred for dietetic advice and nutritional support if appropriate. A progressive exercise programme was not provided during the admission or immediately post-discharge but out-patient PR was offered to all patients 3 months after discharge as part of standard care.

### *3.3.4 Early Rehabilitation group (ER)*

Subjects allocated to the intervention group started ER within 48 hours of hospitalisation. In addition to “usual care” treatment, they also received the following intervention: daily, supervised volitional (strength and aerobic training) and non-volitional (neuromuscular electrical stimulation (NMES)) techniques. The exercise programme was individually prescribed and progressed. Details are provided in chapter 2. Patients were introduced to a supported self-management programme (SPACEFORCOPD) [196] during hospitalisation. Following discharge subjects were advised to follow a

progressive walking based home exercise programme, continued daily NMES and were encouraged to follow the self-management programme. This was supported with telephone consultations, using motivational interviewing techniques, at 48 hours, two weeks and four weeks. No further contact after six weeks was made (other than the follow up visits for both groups). Subjects who were readmitted after the six week intervention period, did not receive a further ER intervention.

### *3.3.5 Primary and secondary outcomes*

The primary endpoint was all-cause unplanned hospital re-admissions at 12 months, adjusted for site. Hospital admissions in the follow up period were captured using hospital databases and General Practice records. Secondary analyses of health care utilisation included per-protocol analysis (defined as retention within the trial during the six week intervention period, time to first re-admission, total days spent in hospital, cause of admission (respiratory or non-respiratory), and mortality (including cause of death and time from primary admission). Spirometry was measured to BTS standards[197].

### *3.3.6 Statistical analysis*

Randomisation was coordinated by the clinical trials unit (CTU), University of Leicester. Subjects were randomly allocated, using simple randomisation (1:1 ratio), using an automated internet-based randomisation service (www.sealedenvelope.com).

An intention to treat (ITT) analysis was used to assess the primary outcome. The study was powered to detect a difference in readmission rate of 15% (UC

40%, ER 25%), requiring 152 in each group (power 80%, 2-sided alpha=0.05). With the expected mortality (20%) the numbers planned to be recruited was 190 per group (380 in total). Analyses were performed using STATA version 13. Baseline measures were compared using t test, Mann-Whitney U test and chi-squared tests for parametric, non-parametric and categorical data respectively. Hospitalisation rate was calculated using a Fine-Gray competing risks analysis with death as the competing risk (adjusted for site), presented as hazard ratio (HR)[198]. Secondary outcomes of differences in number of hospitalisations and hospital days were calculated using negative binomial regression (offset by natural log of time to death), presented as incident rate ratio (IRR). Mortality odds ratios were calculated using binary logistic regression. Hazard and odds ratios are presented in comparison to the UC group. Secondary health care utilisation measures are presented both unadjusted (other than for site) and adjusted for co-variables known to affect hospitalisation risk (site, age, diagnosis, MRC grade, previous hospitalisations, quadriceps strength at baseline, number of co-morbidities). A pre-defined per protocol analysis, defined as those who remained in the study during the intervention period, was conducted for the health care utilisation,

## *3.4 Results*

### *3.4.1 Recruitment and baseline characteristics*

389 subjects were recruited between January 2010 and September 2011, with final follow up September 2012. Screening, randomisation and follow-up are presented in the consort diagram (figure 3.1). There was no statistically significant difference between the intervention and control groups in demographics and characteristics measured at baseline (table 3.1). $FEV_1$recorded in the stable state prior to the index admission (available in 267 (68%) subjects) was significantly lower in the intervention group, although there was no significant difference between groups in spirometry recorded at discharge (n=332, p=0.119). There was a trend towards a difference for a more severe MRC grade in the intervention group (p=0.076) (table 3.1).

***Figure 3.1:*** *Consort Diagram*

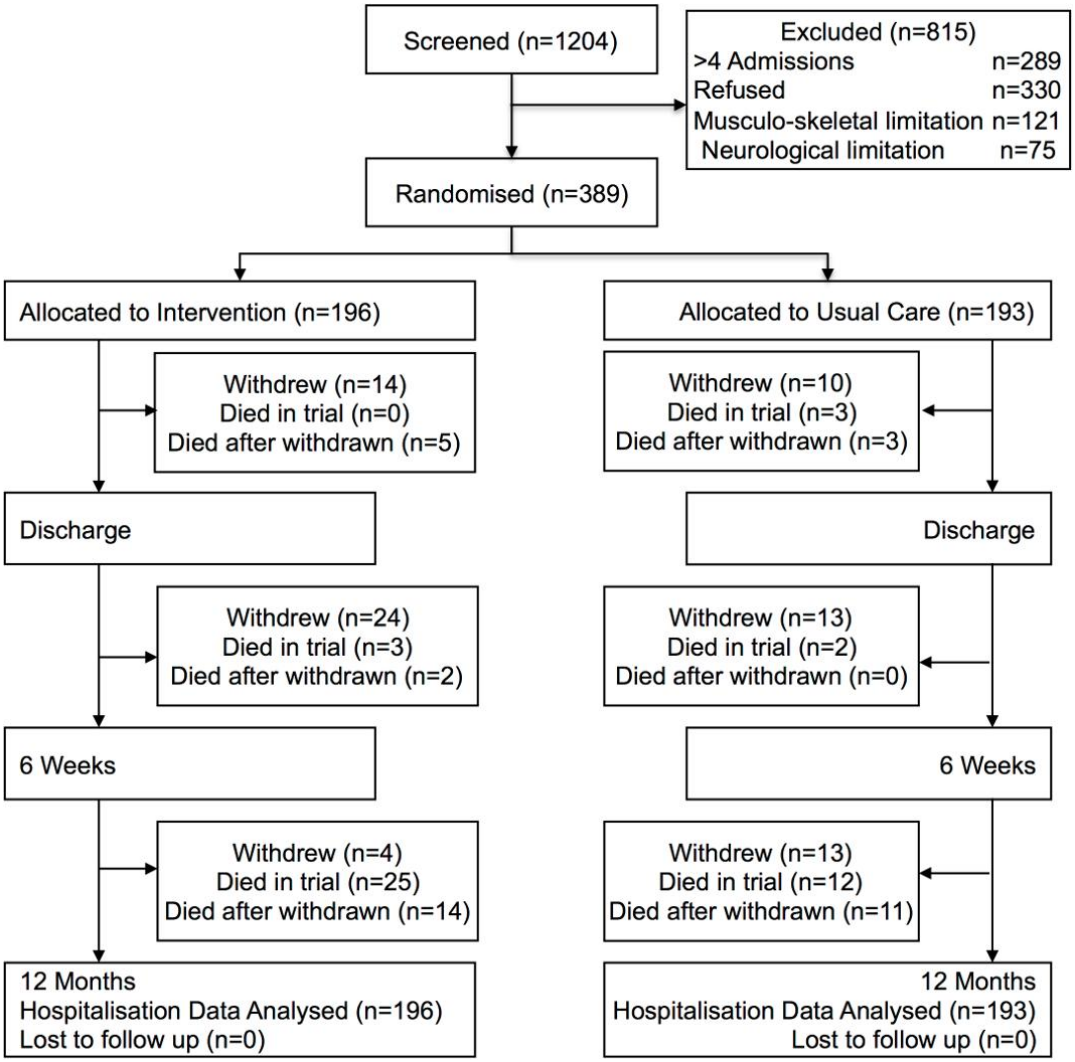


***Table 3.1:*** *Baseline demographics and characteristics*

| | Usual Care | | Intervention | | p |
|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | |
| Age (years) | 71.2 | 10.0 | 71.1 | 9.4 | 0.907 |
| Gender (% Male) | 44.0% | | 44.9% | | 0.865 |
| BMI (kg/m$^2$) | 26.3 | 7.1 | 26.6 | 6.9 | 0.669 |
| Baseline MRC (median) | 4 | IQR 3-4 | 4 | IQR 3-4 | 0.076 |
| No of Co-morbidities (median) | 2 | IQR 1-3 | 2 | IQR 2-3 | 0.523 |
| Previous $FEV_1$ (L) (n=267) | 1.28 | 0.64 | 1.12 | 0.61 | 0.043 |
| Previous $FEV_1$/FVC (%) | 52.9 | 18.3 | 49.5 | 16.4 | 0.109 |
| Previous $FEV_1$ (% Predicted) | 57.4 | 23.6 | 51.9 | 25.1 | 0.079 |
| Pack Years | 41 | 30 | 46 | 30 | 0.176 |
| Smoking | | | | | 0.950 |
| Current | 20.7% | | 22.1% | | - |
| Ex | 71.0% | | 69.7% | | - |
| Never | 8.3% | | 8.2% | | - |
| Previous pulmonary rehabilitation | 32.1% | | 37.2% | | 0.306 |
| Home Oxygen | 25.9% | | 28.1% | | 0.632 |
| Hospitalisation in previous year | | | | | 0.770 |
| No admissions | 51.8% | | 53.6% | | - |
| 1 admission | 27.5% | | 24.5% | | - |
| 2 to 4 admissions | 20.7% | | 21.9% | | - |
| Primary Diagnosis | | | | | 0.234 |
| COPD | 78.2% | | 86.2% | | - |
| Chronic Asthma | 8.8% | | 5.6% | | - |
| Interstitial Lung Disease | 6.7% | | 4.1% | | - |
| Bronchiectasis | 6.2% | | 4.1% | | - |
| Usual Respiratory Medications | | | | | 0.184 |
| LAMA+LABA+ICS | 39.4% | | 45.9% | | - |
| LABA+ICS only | 23.3% | | 25.5% | | - |
| LAMA+ICS only | 6.2% | | 9.2% | | - |
| Long-term Antibiotic | 6.2% | | 3.1% | | - |
| ICS only | 6.7% | | 2.6% | | - |
| LAMA only | 5.2% | | 3.6% | | - |
| LAMA+LABA | 1.0% | | 0.5% | | - |
| LABA only | 0.0% | | 0.5% | | - |
| Heart Rate on admission (bpm) | 90.4 | 15.0 | 92.7 | 14.7 | 0.122 |
| Required NIV on admission | 4.7% | | 3.6% | | 0.588 |

### *3.4.2 Index Admission*

The median length of hospital stay during the index admission was five days (IQR 5) for both groups (p=0.914). 86.9% and 81.5% subjects received systemic corticosteroids and antibiotics respectively on admission, with no significant differences between groups (p=0.489 and 0.582). 69.7% subjects received supplemental oxygen on admission (no difference between groups, p=0.434). There were 11 deaths during the index admission (six in the UC group and five in the ER group, p=0.259), of whom eight had withdrawn from the trial prior to death.

***Table 3.2**: Characteristics on admission and spirometry on discharge (n=332 for spirometry)*

| | Usual Care | | Intervention | | p |
|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | |
| Quadriceps strength (Kg) | 13.4 | 7.6 | 12.8 | 6.8 | 0.467 |
| Heart Rate (bpm) | 90.4 | 15.0 | 92.7 | 14.7 | 0.122 |
| O2 saturations (%) | 92.7 | 3.13 | 92.4 | 3.14 | 0.407 |
| Required acute NIV | 4.7% | | 3.6% | | 0.588 |
| $FEV_1$ (L) | 1.01 | 0.45 | 0.94 | 0.42 | 0.119 |
| $FEV_1$/FVC (%) | 51.9 | 15.9 | 49.6 | 15.7 | 0.176 |
| $FEV_1$ % predicted | 45.6 | 19.2 | 42.5 | 18.3 | 0.134 |

### *3.4.3 Hospital Readmissions*

233 (59.9%) subjects were readmitted during the follow up period, with a total of 599 admissions. A respiratory aetiology accounted for 74.6%of these readmissions. There was no significant difference in the number of subjects with at least one readmission; control 111/193 (57.5%), intervention 122/196

(62.2%) (hazard ratio 1.1, 95% CI 0.86-1.43, p=0.440). Risk of readmission over time is shown in figure 3.2.There were a mean of 1.54 (95% CI 1.33-1.75) hospital admissions per patient in the year following their index admission, with no difference between groups (p=0.917). Respiratory and non-respiratory admission data are shown in table 3.3. Median time to the first hospitalisation was not significantly different (89 days and 93.5 days for UC and ER respectively, p=0.369).

***Figure 3.2:*** *Graph of cumulative incidence of hospital readmission, using competing risks regression analysis, in the usual care (UC) and early rehabilitation (ER) groups. No difference was seen between groups (p=0.440)*

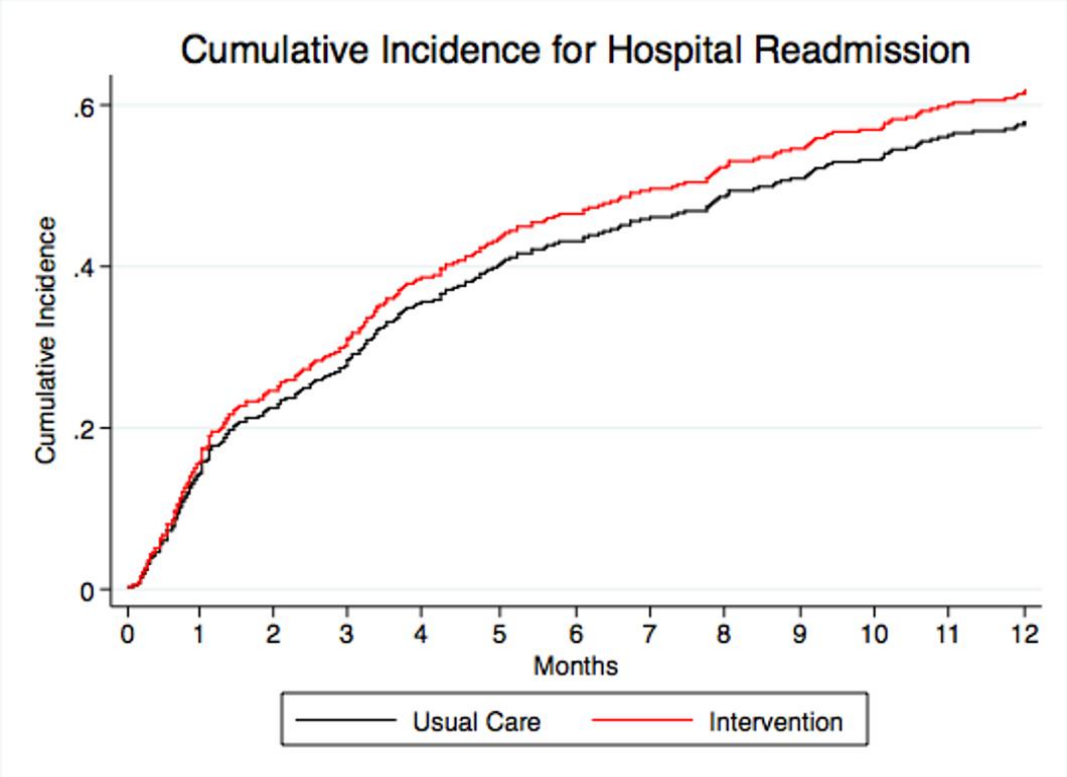


**Table 3.3** Healthcare utilisation. Comparison of number of hospital admissions per patient and hospital days per patient in 12 months after admission. Values are means (standard deviations) unless stated otherwise

| | | | Adjusted for site only* | | Adjusted for covariates† | |
|---|---|---|---|---|---|---|
| **Variables** | **Usual care** | **Early rehabilitation** | **Incidence rate ratio (95% CI)** | **P value** | **Incidence rate ratio (95% CI)** | **P value** |
| **No of hospital admissions** | | | | | | |
| Intention to treat: | | | | | | |
| Total | 1.60 (2.29) | 1.48 (1.89) | 1.02 (0.76 to 1.35) | 0.9 | 0.98 (0.74 to 1.30) | 0.9 |
| Respiratory | 1.20 (1.94) | 1.10 (1.64) | 1.02 (0.73 to 1.41) | 0.9 | 0.99 (0.72 to 1.37) | 1.0 |
| Non-respiratory | 0.39 (0.90) | 0.39 (0.81) | 1.04 (0.66 to 1.64) | 0.9 | 1.09 (0.71 to 1.70) | 0.7 |
| Per protocol: | | | | | | |
| Total | 1.67 (2.39) | 1.49 (1.87) | 0.92 (0.68 to 1.26) | 0.6 | 0.91 (0.67 to 1.22) | 0.5 |
| Respiratory | 1.28 (2.02) | 1.14 (1.65) | 0.95 (0.67 to 1.34) | 0.8 | 0.94 (0.67 to 1.33) | 0.7 |
| Non-respiratory | 0.39 (0.92) | 0.35 (0.75) | 0.87 (0.52 to 1.45) | 0.6 | 0.95 (0.58 to 1.56) | 0.9 |
| **No of hospital days** | | | | | | |
| Intention to treat: | | | | | | |
| Total | 14.8 (27.7) | 12.0 (18.0) | 0.95 (0.63 to 1.44) | 0.8 | 0.88 (0.58 to 1.34) | 0.6 |
| Respiratory | 11.2 (23.1) | 9.1 (18.5) | 0.97 (0.60 to 1.59) | 0.9 | 0.93 (0.56 to 1.53) | 0.8 |
| Non-respiratory | 3.6 (12.0) | 3.5 (9.3) | 1.24 (0.57 to 2.68) | 0.6 | 1.17 (0.55 to 2.46) | 0.7 |
| Per protocol: | | | | | | |
| Total | 15.4 (28.7) | 11.1 (16.2) | 0.81 (0.52 to 1.28) | 0.4 | 0.75 (0.48 to 1.19) | 0.2 |
| Respiratory | 11.9 (24.0) | 8.2 (13.7) | 0.83 (0.49 to 1.41) | 0.5 | 0.80 (0.47 to 1.38) | 0.4 |
| Non-respiratory | 3.5 (12.0) | 2.9 (8.0) | 0.95 (0.39 to 2.28) | 0.9 | 1.16 (0.50 to 2.73) | 0.7 |

Table shows both intention to treat and per protocol analyses, defined as participants who remained within the study during the six week intervention period. Analyses are shown both unadjusted and adjusted for covariates. Incident rate ratio is relative to the usual care group and offset for time exposed (time to death).

*Adjusted for site only.

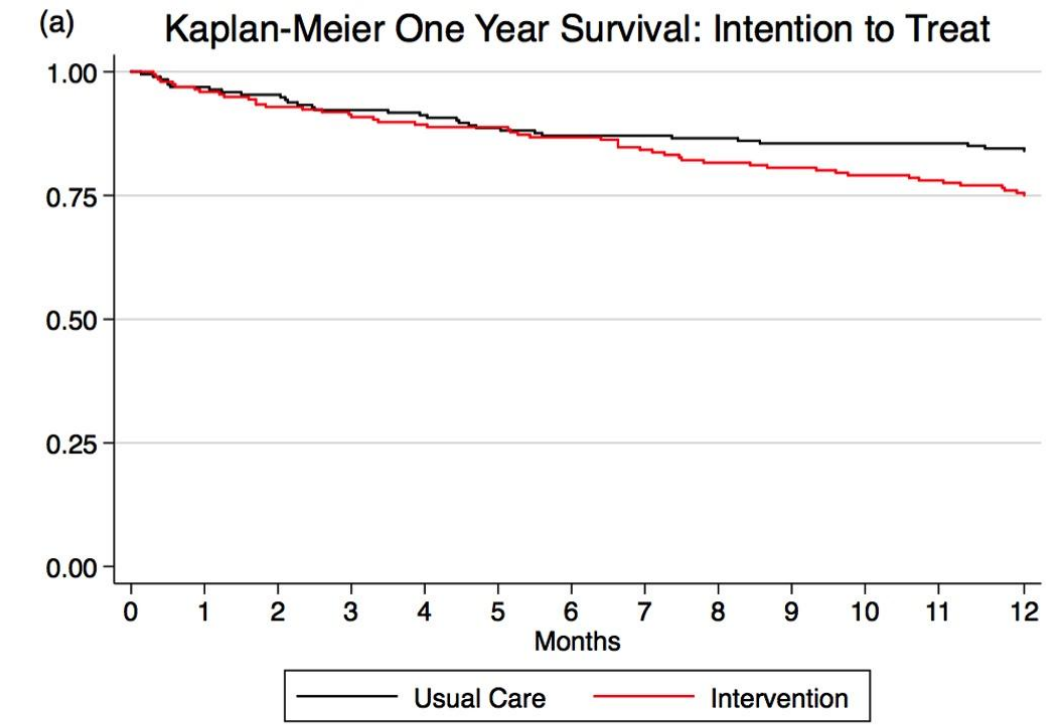
†Adjusted for site, age, diagnosis, previous hospital admissions, quadriceps strength at baseline, Medical Research Council dyspnoea grade, and number of comorbidities.

### *3.4.4 Number of Hospital Days*

There were a total of 5,211 patient hospital days during the follow-up period (2,861 and 2,350 days in the UC and ER groups respectively). Total days spent in hospital was17.9% lower in the ER group but this difference was not statistically significant. The mean number of hospital days per subject and risk ratio is shown in Table 3.3.

### *3.4.5 Mortality*

A total of 80 deaths (20.6%) occurred in the study population during the follow-up period, with 23 deaths occurring without readmission (UC 11/23, ER 12/23). Unadjusted and adjusted mortality rates were higher in the intervention group at 12 months (31/80 usual care, 49/80 intervention, OR 1.74, 95% CI 1.05-2.88, p=0.031) but not during the delivery of the intervention or at 3 or 6 months (Figure 3.3a). Cause of death is provided in table 3.4.



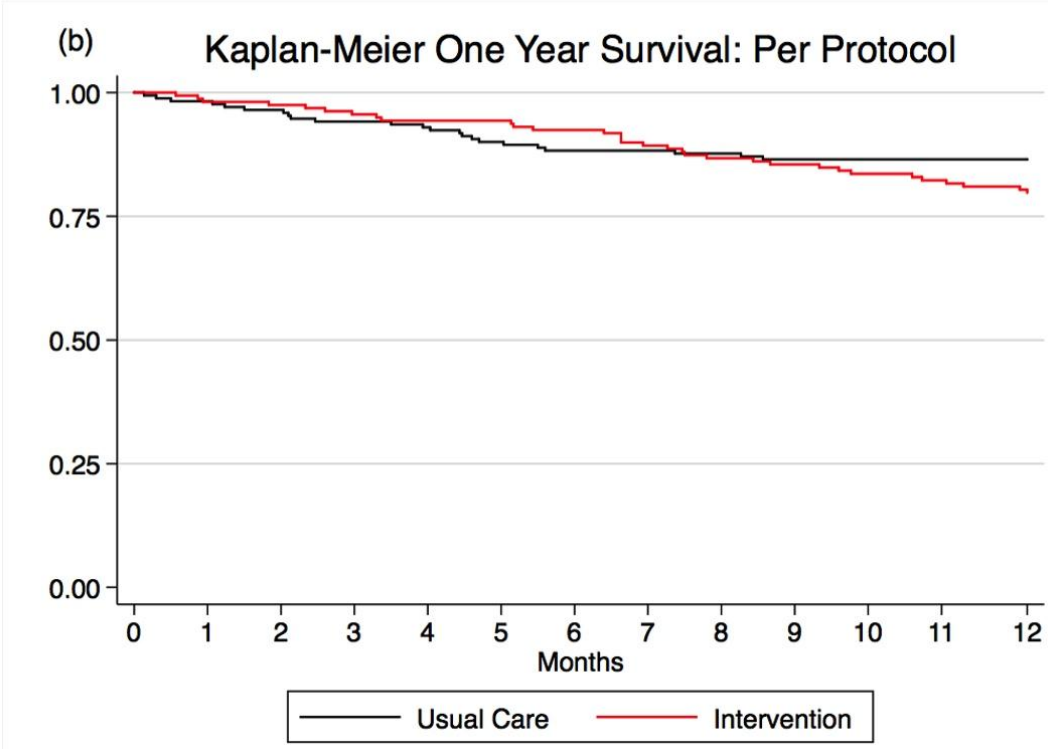




***Figure 3.3***: *Survival plots for each group (a) intention to treat (ITT) analysis and (b) Per protocol analysis. A significant difference was seen at 12 months in the ITT analysis with an excess mortality in the ER group (p=0.031)*

***Table 3.4:*** *Cause of death in both groups during the follow up period. Cause of death was identified from death certificates, or medical notes when able*

| Cause of Death | Usual care (n=31) | Intervention (n=49) |
|---|---|---|
| Pneumonia/Chest Sepsis | 10 (32.3%) | 14 (28.6%) |
| COPD | 5 (16.1%) | 10 (20.4%) |
| MI/Acute Heart Failure | 4 (12.9%) | 6 (12.2%) |
| Unknown | 3 (9.7%) | 6 (12.2%) |
| ILD | 3 (9.7%) | 2 (4.1%) |
| Lung Cancer | 3 (9.7%) | 2 (4.1%) |
| Bowel Cancer | 1 (3.2%) | 2 (4.1%) |
| Arrhythmia | 0 (0.0%) | 2 (4.1%) |
| Bowel obstruction | 0 (0.0%) | 2 (4.1%) |
| Bowel Ischaemia | 0 (0.0%) | 1 (2.0%) |
| Urinary Sepsis | 1 (3.2%) | 0 (0.0%) |
| AAA | 1 (3.2%) | 0 (0.0%) |
| Thyroid cancer | 0 (0.0%) | 1 (2.0%) |
| Laryngeal Cancer | 0 (0.0%) | 1 (2.0%) |

### *3.4.6 Adherence to early rehabilitation training*

A total of 165 (86%) participants performed inpatient aerobic training, 176 (90%) inpatient resistance training, and 176 (90%) inpatient neuromuscular electrical stimulation training. The mean number of sessions during the inpatient training was 2.7 (SD 2.6) for aerobic training, 2.5 (SD 1.9) for resistance training, and 3.6 (SD 3.2) for neuromuscular electrical stimulation training. This was associated with increases in exercise training walk times (76 s, 95% confidence interval 56 to 96 s, P<0.001), intensity of neuromuscular electrical stimulation training (4 mA, 95% confidence interval 3 to 5 mA, P<0.001), and weight used in resistance training (100 g, 95% confidence interval 60 to 140 g, P<0.001).

After discharge further improvements were reported in walking time (304 s, 95% confidence interval 152 to 457 s, P<0.001) but the change in progression of resistance training was not significant. At the end of the intervention period, continued daily adherence to the home programme was reported by 54% of participants for aerobic training and 61% for resistance training.

### *3.4.7 Per protocol analysis*

In total 61 subjects withdrew during the intervention period (UC 12% ER 19%, p=0.043). Subjects that withdrew were older, had reduced muscle strength and higher MRC score on admission compared with those that completed the intervention (p<0.001, p=0.012, p=0.021 respectively). Reason for withdraw is given in table 3.5.

There was no between group difference in hospitalisation risk in the per protocol analysis (HR 1.1, 95% CI 0.83-1.45, p=0.497) (table 2). Total days spent in hospital was 33% lower in the ER group (2,616 days and 1,752 days in the UC and ER groups respectively) but this difference was not statistically significant (adjusted or unadjusted, table 3.3).

Subjects that withdrew within the intervention period were more likely to die than those that completed, with death in 25 of the 61 subjects (41%) (OR 3.44, 95% CI 1.91-6.19, p<0.001).No difference in mortality between the ER and UC groups at any time point in the per protocol analysis (figure 2b).

***Table 3.5**: Reason for withdraw from trial during intervention period (reason given by 42/61 of subjects)*

| Reason | Usual Care | Intervention |
|---|---|---|
| Unable to cope with assessment | 3 | 0 |
| Not enough time to participate | 1 | 0 |
| Diagnosed with cancer | 2 | 3 |
| “Too much” | 3 | 5 |
| No longer wanted to do | 8 | 7 |
| Arthritis limiting intervention | 0 | 1 |
| Developed other acute co-morbidities preventing participation in trial | 2 | 7 |
| Total | 19 | 23 |

### *3.4.8 COPD subgroup*

320 subjects in the trial had a primary diagnosis of COPD (table 3.1). 192 subjects were readmitted in the COPD group with 18 subjects dying before readmission or the end of the study. Risk of readmission was similar in both groups (HR 1.19 0.90-1.60, p=0.244). There was no difference in the primary and secondary outcomes in the COPD sub-group compared with the whole population.

### *3.4.9 Uptake of Pulmonary Rehabilitation after 3 months*

Subjects were offered pulmonary rehabilitation from 3 months following recruitment. There was a significantly increased uptake in the UC group (22.2% vs 13.8%, p=0.040).

### *3.4.10 Primary Care Health Care Utilisation*

#### *3.4.10.1 Non-Hospitalised Exacerbations*

Full GP notes were available for 308 subjects. Total number of courses of steroids and antibiotics for chest infections or exacerbations were recorded from each subject. A mean of 2.45 (SD 3.77) and 2.30 (SD 3.00) courses of steroids were prescribed per subject in one year for the UC and ER groups respectively (IRR 0.90 95% CI 0.67-1.23, p=0.515). For antibiotics a mean of 3.67 (SD 4.16) and 3.69 (SD 4.18) were prescribed per subject for the UC and EE groups (IRR 1.01 95% CI 0.79-1.29, p=0.965).

#### *3.4.10.2 Contact with Primary Care*

There was no significant difference between groups in contact with subjects' GP, outpatient respiratory clinic visits, or community respiratory visit. The mean number of contacts and relative risk for each type of primary care contact are given in table 3.6.

***Table 3.6:*** *Primary healthcare utilisation. Comparison of hospital clinic visits per patient, and GP contact in the 12 months following admission. Analyses are shown both unadjusted and adjusted for co-variates. Incident rate ratio is relative to the usual care group and offset for time exposed (time to death).*

| | Usual Care | | Intervention | | Adjusted for site | | | Adjusted for co-morbidities | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | IRR | 95% CI | p | IRR | 95% CI | p |
| Hospital clinic visits | 2.9 | 3.0 | 3.4 | 3.8 | 1.22 | 1.00-1.49 | 0.050 | 1.16 | 0.95-1.42 | 0.156 |
| GP consultations | 6.3 | 5.8 | 6.7 | 6.4 | 1.02 | 0.84-1.26 | 0.819 | 1.04 | 0.85-1.28 | 0.689 |
| GP telephone calls | 2.9 | 5.3 | 2.8 | 4.1 | 0.97 | 0.69-1.35 | 0.844 | 0.97 | 0.70-1.34 | 0.857 |
| GP home visits | 1.6 | 3.4 | 1.8 | 3.5 | 1.14 | 0.71-1.83 | 0.596 | 1.06 | 0.65-1.70 | 0.841 |
| Community respiratory team | 3.2 | 5.3 | 3.8 | 6.7 | 1.16 | 0.69-1.96 | 0.583 | 1.06 | 0.63-1.77 | 0.838 |

* adjusted for site only
$adjusted for site, age, diagnosis, previous hospital admissions, quadriceps strength at baseline, MRC grade, number of co-morbidities
IRR: Incident Rate Ratio

## 3.5 Discussion

This chapter describes a randomised clinical trial of a tailored early rehabilitation intervention aimed at enhancing recovery following un-scheduled hospitalisation for acute exacerbation of Chronic Respiratory Disease. The trial was adequately powered to determine the effect of the intervention on subsequent hospitalisation but the results did not support my hypothesis that the intervention would reduce the number of readmissions in the subsequent 12 months. Mortality was increased in the intervention group at 12 months but not during the treatment period or 3 month and 6 month time points.

The lack of reduction in re-admissions in the current study is in keeping with a smaller scale study from Hong Kong[164] but contrasts with trials of peri-exacerbation Pulmonary Rehabilitation where the rate was reduced over the shorter term[145, 199, 200]. There are important differences in the population enrolled and the rehabilitation approach taken in the current trial rendering comparison with these previous studies difficult. We delivered the intervention during the acute phase of the illness as well as recovery with the objective of preserving physical function and enhancing recovery from the episode. We did not provide pulmonary rehabilitation as defined in recent guidelines[146, 154] but an exercise based intervention modified to suit the setting of the acute illness. This was by necessity lower in intensity, although it was provided daily during the hospital stay using both volitional and non-volitional training techniques. Supervision in the home recovery phase was also lighter but supported by a validated self-management programme[196] and follow-up telephone support. Participants in the current trial had a greater burden of

disease and comorbidities and had lower muscle strength and exercise capacity than most reported pulmonary rehabilitation studies. This higher general level of ill health and frailty in the study population is in keeping with national and international trends for hospitalised patients with COPD[201] but may have affected the capacity for the intervention to impact on the subsequent risk of re-admission. Frailty and advanced disease were particularly evident in our study, with nearly a quarter of the population having a stable state MRC dyspnoea grade of 5. I suggest that the limited intervention in our study was due to the specific nature of the hospitalised population. as many of the participants were unable at to exercise intensively enough to induce a physiological response at the time of the intervention. It is likely, however, that there is a sub-group of patients who may respond to an early rehabilitation intervention. It is unknown if this is the same population who self-select for post exacerbation pulmonary rehabilitation.

The finding of increased mortality in the intervention group was unexpected and observed only at the 12 month timepoint. I cannot explain this observation directly from the results but the mortality rate was not increased during the delivery of the intervention or the first six months of the follow-up period suggesting that the provision of exercise during recovery from the acute episode was not implicated. Although the increased mortality rate persisted after adjustment for baseline co-variates, the range of measurements that could be recorded before randomisation was restricted because of the limitations imposed by the acute illness (for example lung function measures). Moreover, in the per protocol analysis of patients who remained in the study at six weeks who were exposed to the maximum duration of intervention, we

did not observe an excess mortality. It remains possible therefore that the difference in mortality in the intention to treat analysis was due to a more severe case mix in the intervention group. However, I cannot exclude the possibility that the intervention resulted in alterations in health behaviour that might have modified the response to subsequent acute illness later during the follow-up period such as delays in seeking medical advice. The time course of health behaviour change in response to an intervention is uncertain but for conventional pulmonary rehabilitation, the reverse is true with benefits diminishing over the following 12 months[155]. An increased mortality was seen in the intervention group in a recent trial of a self-management intervention[202] although as with the current study, the observation could not be explained from data obtained within the trial.

I observed a lower total number of bed days in the intervention group compared with usual care (albeit not statistically significant) in keeping with trials of pulmonary rehabilitation in stable COPD[155]. This suggests that an exercise intervention may not influence the number of subsequent exacerbations but might ameliorate their impact on the patient, facilitating recovery and earlier discharge. Conversely, the magnified effect on subsequent hospital bed days in those patients who completed the intervention may be indicative of the efficacy of the intervention or identified a group of patients in better health who were more able to comply with the programme and therefore spent fewer days in hospital in the subsequent year.

A feature of the intervention in the current trial was the shift from supervised inpatient therapy to unsupervised home exercise facilitated by the provision of

a self management manual along with telephone support. Length of hospital stay was 5 days, which would be considered standard in the UK but relatively short in other healthcare systems. In many respects the intervention resembles elements of post-surgical enhanced recovery programmes or supported self management programmes rather than conventional pulmonary rehabilitation. The results suggest caution is needed in applying such programmes to recovery from acute illness, particularly exacerbation of respiratory chronic disease. A key element of enhanced recovery from surgery is pre-operative preparation, which cannot be included in an acute illness intervention.

I acknowledge some limitations to the interpretation of the current trial. Patients were enrolled with exacerbations of a variety of chronic respiratory diseases because it is increasingly accepted that patients with disabling respiratory disease benefit from pulmonary rehabilitation regardless of the nature of the pulmonary pathophysiology[146, 154]. The majority suffered with COPD and recruitment from two acute hospitals serving both urban and rural populations suggests participants were representative of UK clinical practice. A number of different chronic respiratory diseases were included in the study, including a non-airways disease group with interstitial lung disease. This population often have a diffusion problem, rather than ventilator as the aetiology of their exercise intolerance, with exertional hypoxaemia as a major sign. However, these patients with these diseases are subject to similar effects of inactivity and deconditioning that may arise from an admission which was the target for the intervention. It should also be noted that pulmonary rehabilitation is recommended for patients with ILD in recently

published guidelines for pulmonary rehabilitation and NICE recommendations for the treatment of interstitial pulmonary fibrosis. The approach in this study was based in the principle that the benefits of rehabilitation are conferred independently from the underlying chronic lung disease. This is supported by the outcome of the trial in patients with COPD which was indistinguishable from the complete cohort. Outcomes in the COPD subgroup in the current trial were indistinguishable from that seen in the whole cohort. I recognise our conclusions are restricted to patients with fewer than 5 admissions in the preceding 12 months. We chose to exclude this population because admissions of this frequency are often influenced by physical and psychological co-morbidity, social circumstances or indicative of the proximity of end of life[112] and as a result would be less modifiable by an exercise intervention.

The recognition of the negative effects of hospitalisation and the positive outcome of recent trials of post discharge PR[145, 199] has led to recommendations that PR should be offered to all patients following discharge[146]. The current trial was undertaken before post discharge PR was considered “usual care” and therefore conventional post-discharge PR was not offered to participants, although they could be enrolled in conventional outpatient PR after three months if indicated. The study therefore substantially extends these previous reports by testing a modified rehabilitation intervention delivered in a larger and more representative population in a clinical trial that was adequately powered to detect a reduction in readmissions at 12 months.

Hospitalisation for AECRD is an important event in the natural history of disability, which in turn can be ameliorated by pulmonary rehabilitation. However, the current trial suggests that the acute admission is not the time to enrol patients in a progressive, rehabilitation process, which may be beyond the capabilities of many subjects in this situation. The results suggest that beyond low intensity mobilisation that characterises in-hospital physiotherapy practice, efforts at progressive rehabilitation should be deferred until the patient has left hospital. Once recovery from the acute event is underway, the hospital admission can be used to allow rest and recuperation and to constructively review other aspects of chronic disease management such as drug therapy, deploying community and social support and providing end of life care for those that need it.

In summary I report the largest clinical trial to date of an early, tailored rehabilitation intervention aimed at enhancing recovery and reducing re-hospitalisation in patients with acute exacerbations of Chronic Respiratory Disease. The lack of impact re-hospitalisation and the observation of an increased mortality at 12 months in the intervention group suggests caution is needed before implementing such programmes during the immediate recovery from acute illness.

# *Chapter Four*

# The effects of an early rehabilitation intervention on exercise performance, quadriceps strength and health related quality of life

## *4.1 Introduction*

Chronic Obstructive Pulmonary Disease (COPD) and other Chronic Respiratory Diseases are a major cause of morbidity and mortality worldwide, with dyspnoea and exercise intolerance among the predominant symptoms. Pulmonary Rehabilitation (PR) is recommended to all symptomatic patients with COPD, for which the primary improvements are those within exercise capacity and health status, including symptoms of dyspnoea.

Hospitalisation for an acute exacerbation of chronic respiratory disease has negative effects on physical performance and health status from which the patient may not fully recover[30, 121]. Treatment of the acute episode is predominantly targeted at improvement of ventilatory function with little attention paid to these wider systemic impacts. Consequently, physical performance and activity may be reduced for a prolonged period following hospitalisation.

The effects of hospitalisation for an acute exacerbation of chronic respiratory disease on physical fitness and skeletal muscle function may occur rapidly during the inpatient phase[29, 42] suggesting that a rehabilitation intervention delivered at the time of the acute illness might preserve physical function. This is supported by previous small scale trials of exercise based therapy during acute exacerbation of COPD, which have suggested such interventions are feasible and may be effective[166, 167, 200].

Chapter 3 investigated the effects of an early rehabilitation trial on health care utilisation. This chapter uses the same interventional randomised controlled trial but to investigate the effect of hospitalisation on physical function and health status and the effects of rehabilitation trial over 12 months. The study hypothesis was that hospitalisation for an exacerbation of chronic respiratory disease would result in a decline in physical performance and health status from which recovery would be incomplete and that a rehabilitation intervention delivered at the time of admission would ameliorate this decline compared with usual care.

## *4.2 Methods*

### *4.2.1 Study design and population*

Full description of study design and population is described in Chapter 3. At baseline measures of QMVC and health status were performed, as subjects were unable to perform other measures at time of admission due to acute illness. Repeat measures, including other measures detailed below, were performed at discharge, six weeks, three months and 12 months following

recruitment. Investigators were blinded to the randomisation group of the subjects. Timings of visits and measures are shown in figure 4.1.

### *4.2.2 Outcome Measures*

Detailed summary of the outcome measures are presented in Chapter 2.

#### *4.2.2.1Quadriceps Strength (QMVC)*

Quadriceps maximal voluntary contraction was measured at 90° fixed flexion of the right leg. The best of five contractions was used, measured as the mean force sustained for one second.

#### *4.2.2.2 Exercise performance*

Maximal and sub-maximal (endurance) exercise performance were measured using the incremental shuttle walk test (ISWT) and endurance shuttle walk test (ESWT) respectively. The ESWT walking speed was set at 85% predicted of discharge ISWT and kept at the same speed at other time points.

#### *4.2.2.3 Health related quality of life*

Health status was measured using the St George's Respiratory Questionnaire (SGRQ) and self-reported Chronic Respiratory Questionnaire (CRQ).

#### *4.2.2.4 Spirometry*

Spirometry was performed to BTS standards using a desktop spirometer (MicroLab, CareFusion).

### *4.2.3 Statistical analysis*

The primary outcome of the study was re-hospitalisation and presented in chapter 3. Baseline measures were compared using independent t-test and Mann-Whitney for parametric and non-parametric data respectively. Longitudinal changes in physiological outcomes were analysed using repeated measures analysis of variance (corrected for site). Bonferroni correction was applied for post-hoc analyses at 6 weeks and 3 months. For multiple imputation of the functional data (ISWT, ESWT, QMVC, SGRQ), 40 imputed datasets were calculated using chained equation with added constraints for minimum and maximum values. Observed data at all time points were used as predictors for missing data, as well as age, gender, and home oxygen use. Analyses using imputed data and observed data were compared to check that results were similar. Data were considered to be missing at random

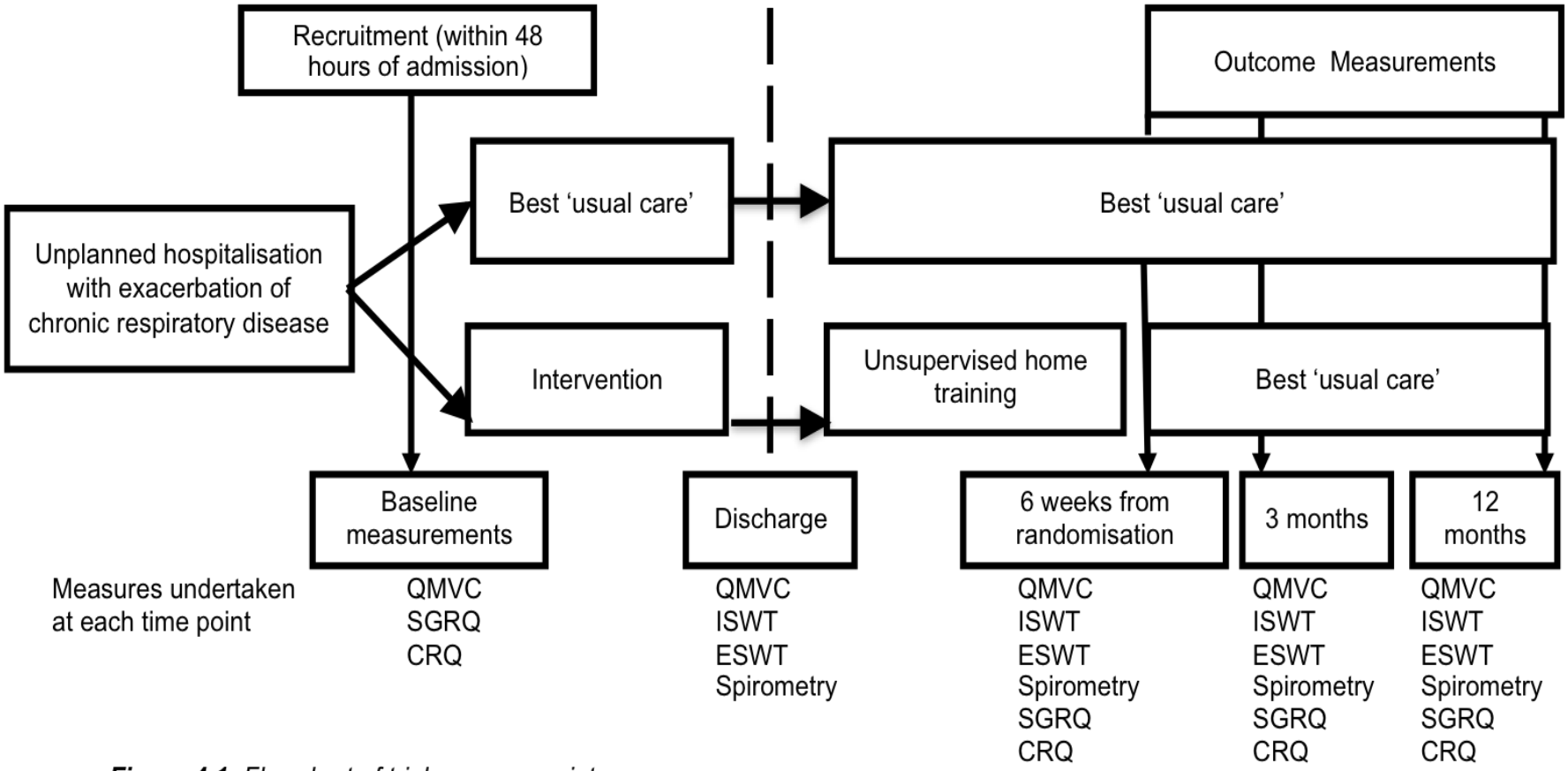



***Figure 4.1:*** *Flowchart of trial measure points,*

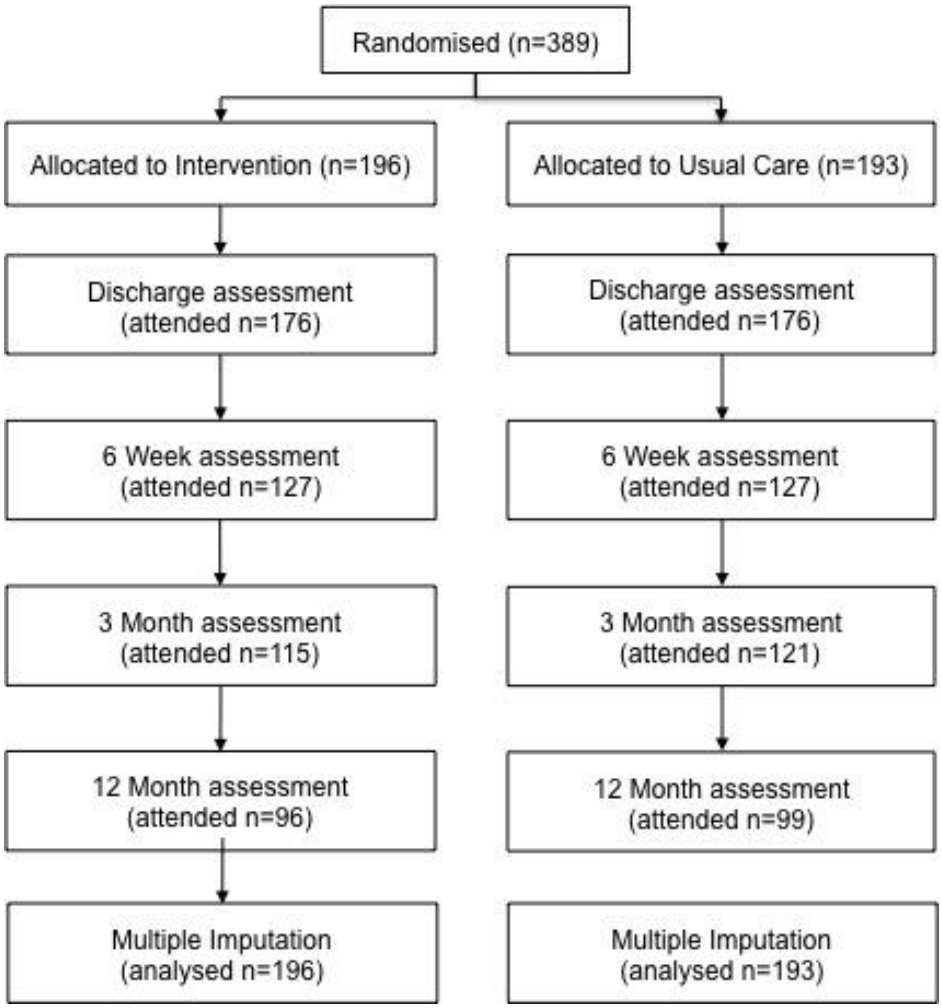
*QMVC- quadriceps maximal voluntary contraction, SGRQ- St George's Respiratory Questionnaire, CRQ- Chronic Respiratory Questionnaire, ISWT- incremental shuttle walk test, ESWT- Endurance shuttle walk test*

## *4.3 Results*

### *4.3.1 Attendance to Follow up*

In total 131 subjects (33.7%) attended all five assessment visits. Numbers attending each visit are shown in figure 4.2. In subjects that had not withdrawn or died, high symptom burden and perceived inability to come for assessment (despite taxi provision) was the commonest reason for non-attendance. Failure to attend a previous assessment was not an exclusion to subsequent visits.

***Figure 4.2**: Flowchart of subjects attending follow-up functional assessments*



### *4.3.2 Multiple Imputation Comparison*

The original data and imputed data are presented in table 4.1. Reduced means at 12 months were seen in the imputed data for ISWT and ESWT ($p<0.05$).

***Table 4.1**: Comparison of original data and imputed data. Significant differences were seen at 12months for ISWT and ESWT*

| Measure | Original | | Imputed | |
|---|---|---|---|---|
| | Mean | SEM | Mean | SEM |
| ISWT (m) | | | | |
| Discharge | 99 | 5 | 98 | 5 |
| 6 Weeks | 151 | 7 | 138 | 6 |
| 3 Months | 152 | 8 | 143 | 7 |
| 12 Months | 169 | 9 | 137 | 8 |
| ESWT (s) | | | | |
| Discharge | 131 | 7 | 128 | 7 |
| 6 Weeks | 233 | 16 | 218 | 15 |
| 3 Months | 268 | 20 | 254 | 20 |
| 12 Months | 276 | 24 | 217 | 28 |
| QMVC (kg) | | | | |
| Baseline | 13.12 | 0.37 | 13.09 | 0.37 |
| Discharge | 13.92 | 0.4 | 13.86 | 0.38 |
| 6 Weeks | 14.64 | 0.53 | 14.03 | 0.46 |
| 3 Months | 14.45 | 0.56 | 13.85 | 0.48 |
| 12 Months | 15.38 | 0.64 | 14.56 | 0.56 |

### *4.3.3 Baseline Measures*

Baseline characteristics and demographics are presented in chapter 3 (table 3.1). Baseline and discharge measures were similar in both groups (table 4.2). Subjects had considerable disability at baseline with a QMVC of 40% compared to a stable COPD population (compared with data from chapter 6) and a mean age-corrected ISWT of 15.5% predicted compared with a healthy population[203].

***Table 4.2*** *Measures of physical performance, health status and lung function at time of hospitalisation*

| | Usual Care | | Intervention | | p value |
|---|---|---|---|---|---|
| | Mean | SEM | Mean | SEM | |
| Exercise Performance | | | | | |
| ISWT (m) Discharge | 102 | 7 | 94 | 6 | 0.388 |
| ESWT (s) Discharge | 132 | 11 | 124 | 9 | 0.552 |
| QMVC (kg) Baseline | 13.3 | 0.6 | 12.0 | 0.5 | 0.540 |
| QMVC (kg) Discharge | 14.0 | 0.6 | 13.8 | 0.5 | 0.798 |
| Chronic Respiratory Questionnaire | | | | | |
| CRQ- Dyspnoea | 2.18 | 0.09 | 2.31 | 0.08 | 0.294 |
| CRQ- Emotion | 3.38 | 0.10 | 3.61 | 0.10 | 0.112 |
| CRQ- Fatigue | 2.59 | 0.09 | 2.60 | 0.09 | 0.910 |
| CRQ- Mastery | 3.08 | 0.10 | 3.24 | 0.10 | 0.277 |
| St George's Respiratory Questionnaire | | | | | |
| SGRQ- Symptoms | 73.23 | 1.51 | 73.14 | 1.46 | 0.965 |
| SGRQ- Activity | 81.72 | 1.26 | 82.05 | 1.12 | 0.844 |
| SGRQ- Impact | 54.70 | 1.25 | 54.59 | 1.33 | 0.952 |
| SGRQ- Total | 66.00 | 1.00 | 65.94 | 1.03 | 0.964 |
| Lung Function | | | | | |
| $FEV_1$ (L) | 1.01 | 0.03 | 0.94 | 0.03 | 0.118 |
| $FEV_1$ (% predicted) | 45.6% | 1.5 | 42.5% | 1.4 | 0.175 |
| $FEV_1$/FVC | 51.9% | 1.2 | 49.6% | 1.2 | 0.133 |

### *4.3.4 Exercise Performance*

Significant improvements in functional performance were observed during the follow-up period in both groups with the largest change seen in the first six weeks following the index admission (Fig. 4.2 and table 4.3). No statistically significant between group differences in these measures was observed at 12 months. ESWT was significantly higher in the ER group at six weeks (p = 0.034) but not other time points during the follow-up (figure 4.2b).

***Table 4.3*** *Means of physical performance in the 12 months following hospitalisation. No significant difference was seen between groups except in ESWT at 6 weeks. ISWT- incremental shuttle walk test, ESWT- endurance shuttle walk test, QMVC- quadriceps maximal voluntary contraction.*

| | Usual Care | | Intervention | |
|---|---|---|---|---|
| | Mean | SEM | Mean | SEM |
| ISWT (m) | | | | |
| Discharge | 102 | 7 | 94 | 6 |
| 6 Weeks | 140 | 8 | 135 | 8 |
| 3 Months | 149 | 9 | 138 | 9 |
| 12 Months | 146 | 11 | 129 | 9 |
| ESWT (s) | | | | |
| Discharge | 132 | 11 | 124 | 9 |
| 6 Weeks | 203 | 20 | 233 | 21 |
| 3 Months | 252 | 27 | 257 | 28 |
| 12 Months | 197 | 35 | 237 | 33 |
| QMVC (kg) | | | | |
| Baseline | 13.3 | 0.6 | 12.0 | 0.5 |
| Discharge | 14.0 | 0.6 | 13.8 | 0.5 |
| 6 Weeks | 14.0 | 0.7 | 14.0 | 0.6 |
| 3 Months | 14.0 | 0.7 | 13.7 | 0.6 |
| 12 Months | 14.6 | 0.7 | 14.6 | 0.7 |

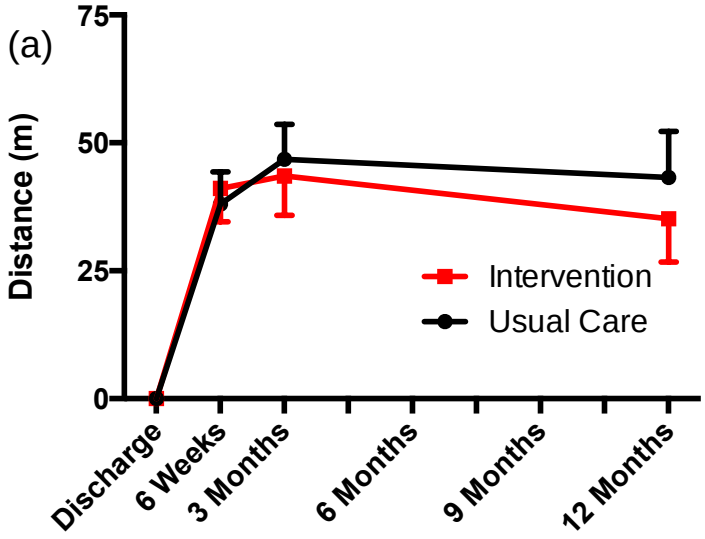
***Figure 4.3**: Change from baseline in physical performance. Values are mean ±SEM*

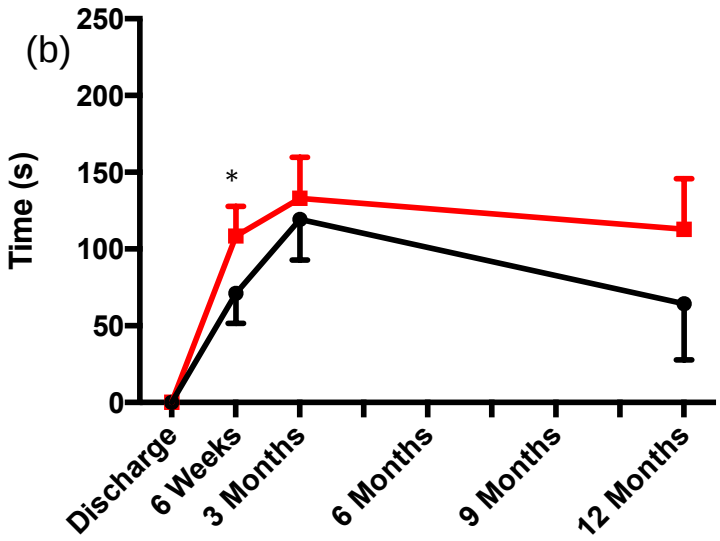
*(a) Incremental shuttle walk test*

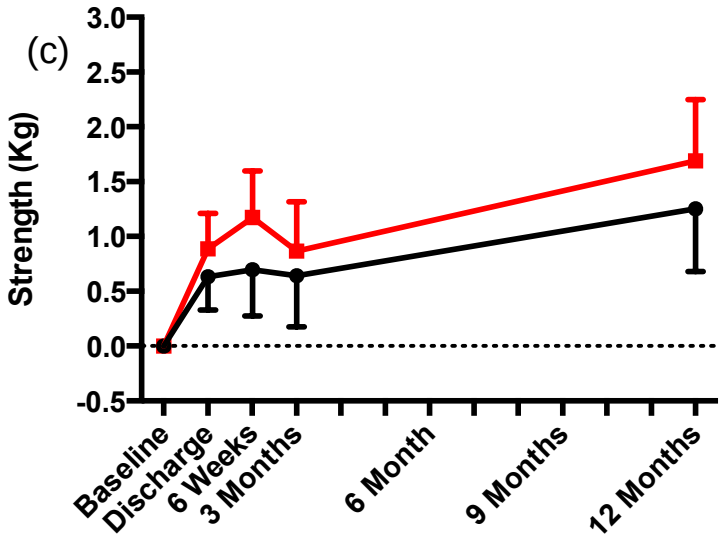
*(b) Endurance shuttle walk test*

*(c) quadriceps maximal voluntary contraction. Both groups had significant improvement at all time points from baseline.*

**Significant difference between groups (p=0.034)*

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### *4.3.5 Health Related Quality of Life*

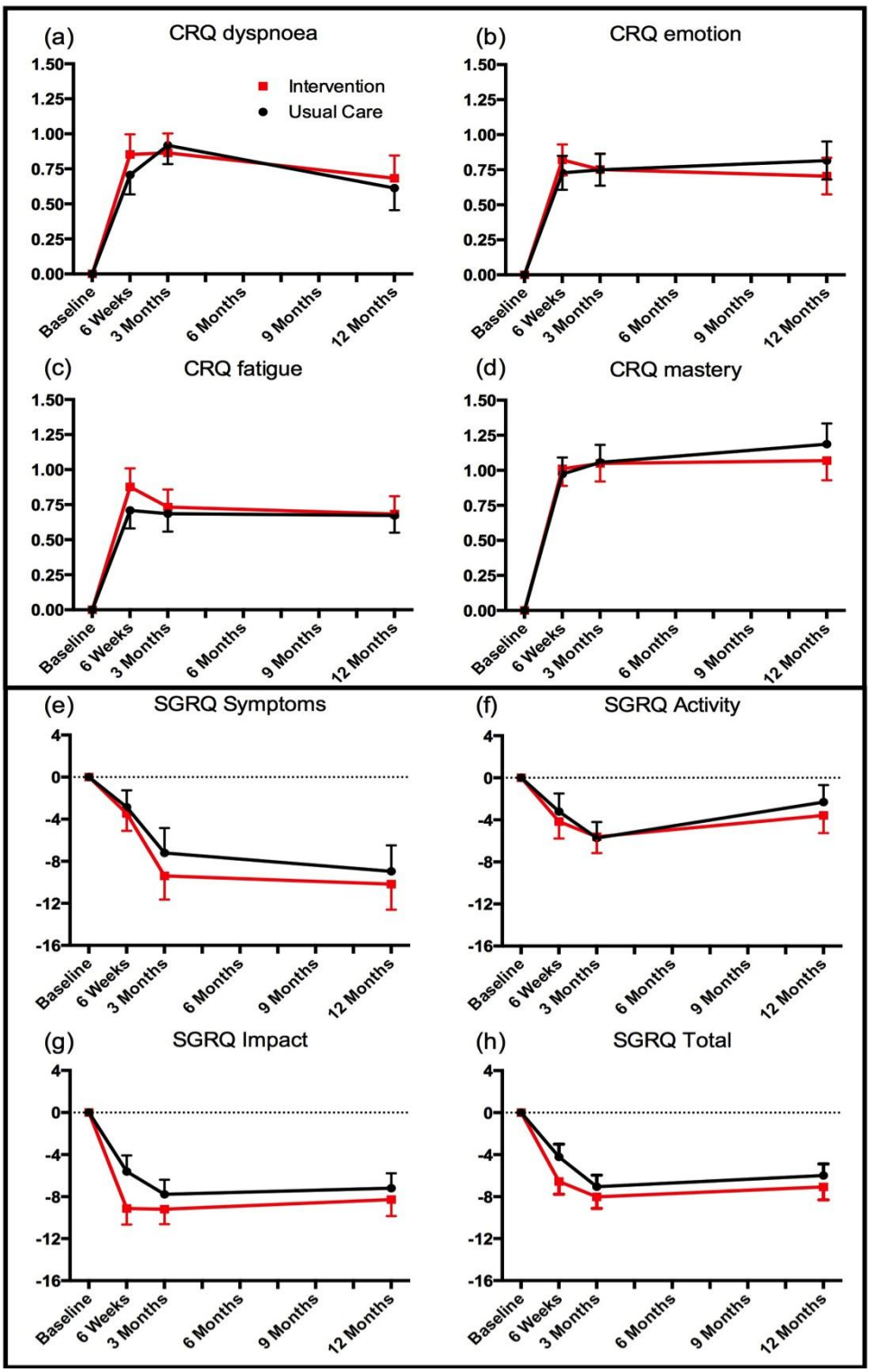
Large clinical and statistically significant improvement in health status was seen in both groups for CRQ and SGRQ. Improvements were principally in the recovery phase of the first six weeks, though further improvement occurred to three months for the SGRQ (table 4.5, table 4.6 and figure 4.4). No significant difference was seen between groups at any time points, or domains.

***Tables 4.5 and 4.6:*** *Means of physical performance in the 12 months following hospitalisation for Chronic Respiratory Questionnaire and St George's Respiratory Questionnaire. No significant difference was seen between groups at any time points.*

| | Usual Care | | Intervention | |
|---|---|---|---|---|
| | Mean | SEM | Mean | SEM |
| Chronic Respiratory Questionnaire (CRQ) | | | | |
| Dyspnoea | | | | |
| Baseline | 2.18 | 0.09 | 2.31 | 0.08 |
| 6 Weeks | 2.89 | 0.13 | 3.16 | 0.13 |
| 3 Months | 3.10 | 0.12 | 3.17 | 0.12 |
| 12 Months | 2.80 | 0.14 | 2.99 | 0.15 |
| Emotion | | | | |
| Baseline | 3.38 | 0.10 | 3.61 | 0.10 |
| 6 Weeks | 4.11 | 0.11 | 4.43 | 0.11 |
| 3 Months | 4.13 | 0.11 | 4.36 | 0.12 |
| 12 Months | 4.20 | 0.12 | 4.32 | 0.12 |
| Fatigue | | | | |
| Baseline | 2.59 | 0.09 | 2.60 | 0.09 |
| 6 Weeks | 3.30 | 0.12 | 3.48 | 0.12 |
| 3 Months | 3.27 | 0.11 | 3.33 | 0.12 |
| 12 Months | 3.26 | 0.12 | 3.28 | 0.11 |
| Mastery | | | | |
| Baseline | 3.08 | 0.10 | 3.24 | 0.10 |
| 6 Weeks | 4.06 | 0.12 | 4.25 | 0.12 |
| 3 Months | 4.14 | 0.12 | 4.29 | 0.12 |
| 12 Months | 4.27 | 0.13 | 4.31 | 0.13 |

| | Usual Care | | Intervention | |
|---|---|---|---|---|
| | Mean | SEM | Mean | SEM |
| St George's Respiratory Questionnaire (SGRQ) | | | | |
| Symptoms | | | | |
| Baseline | 73.23 | 1.51 | 73.14 | 1.46 |
| 6 Weeks | 70.37 | 1.53 | 69.68 | 1.55 |
| 3 Months | 66.02 | 2.32 | 63.74 | 2.11 |
| 12 Months | 64.27 | 2.22 | 62.96 | 2.19 |
| Activity | | | | |
| Baseline | 81.72 | 1.26 | 82.05 | 1.12 |
| 6 Weeks | 78.50 | 1.60 | 77.9 | 1.51 |
| 3 Months | 76.00 | 1.33 | 76.44 | 1.33 |
| 12 Months | 79.41 | 1.34 | 78.47 | 1.45 |
| Impact | | | | |
| Baseline | 54.70 | 1.25 | 54.59 | 1.33 |
| 6 Weeks | 49.10 | 1.51 | 45.45 | 1.45 |
| 3 Months | 46.92 | 1.32 | 45.39 | 1.27 |
| 12 Months | 47.51 | 1.14 | 46.31 | 1.30 |
| Total | | | | |
| Baseline | 66.00 | 1.00 | 65.94 | 1.03 |
| 6 Weeks | 61.78 | 1.27 | 59.39 | 1.22 |
| 3 Months | 58.96 | 1.07 | 57.92 | 1.02 |
| 12 Months | 60.02 | 0.97 | 58.87 | 1.08 |

***Figure 4.4**: Change from baseline in the four domains of the Chronic Respiratory Questionnaire (a-d) and St George's Respiratory Questionnaire (e-h). Values are mean ± SEM.*



### *4.3.6 Lung Function*

Significant improvements were seen at all time points compared with baseline in $FEV_1$. Figure 4.6 shows change in $FEV_1$percent predicted from baseline in both groups. No significant difference was seen between groups (data not imputed).

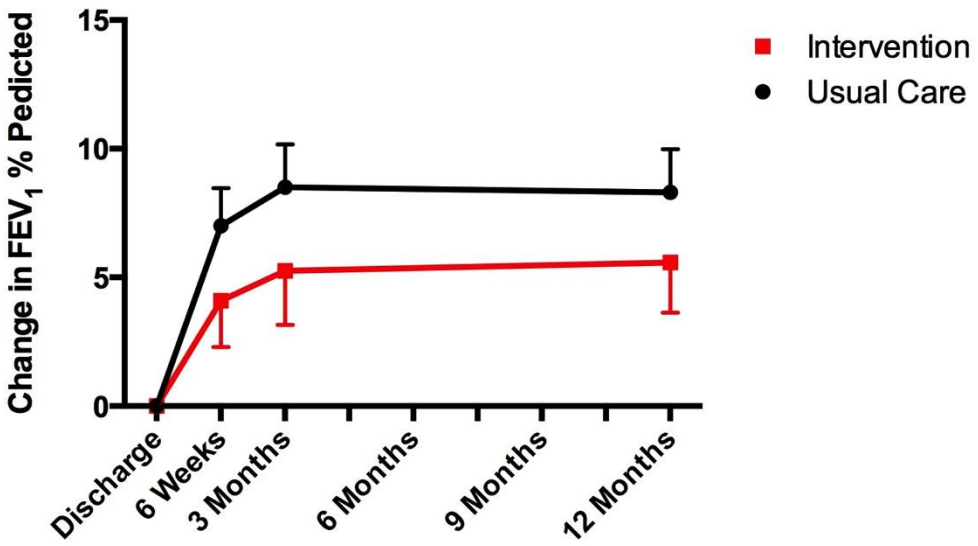



***Figure 4.6****: Change from baseline in forced expiratory volume in one second ($FEV_1$). Values are mean ± SEM.*

### *4.3.7 Non Readmitted Subjects*

An additional analysis in those subjects who were not readmitted during the follow-up period was conducted (n=133), to account for the functional insult of further hospitalisation. Significant improvements from baseline were seen in all measures in the early rehabilitation group (all $p<0.05$). Functional improvement was seen in the usual care group, but this was not statistically significant by 12 months for ESWT, QMVC or SGRQ activity (figure 4.7 and figure 4.8). No significant difference was seen between groups, except for ESWT at 6 weeks ($p = 0.021$) with a trend at 12 months ($p = 0.07$). However, compared with the ITT analysis there was a trend towards a difference in physical performance favouring the early rehabilitation group.

***Figure 4.7**: Change from baseline in physical performance in non-readmitted subjects. Values are mean ±SEM*

*(a) Incremental shuttle walk test*

*(b) Endurance shuttle walk test*

*(c) quadriceps maximal voluntary contraction. Both groups had significant improvement at all time points from baseline.*

**Significant difference between groups (p=0.034)*

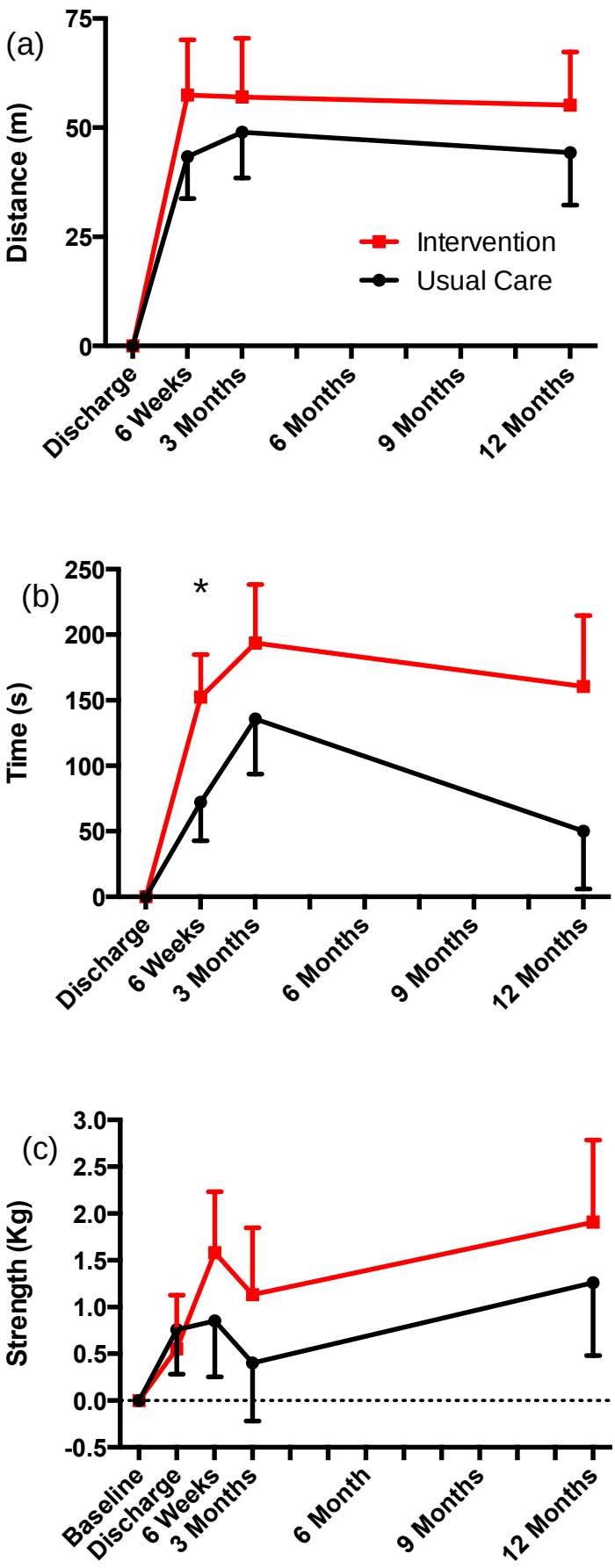
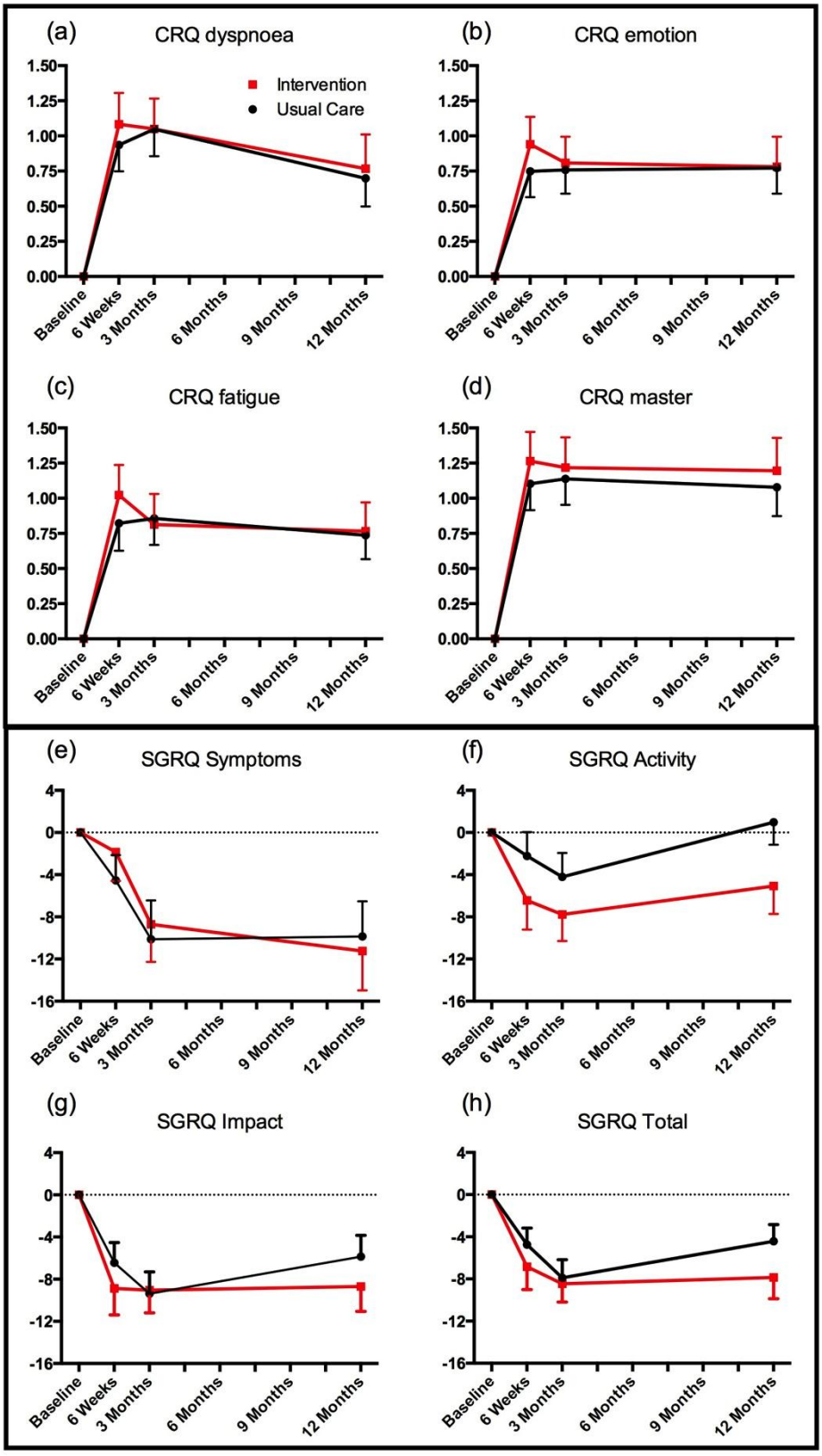


***Figure 4.8:*** *Change from baseline in the four domains of the Chronic Respiratory Questionnaire (a-d) and St George's Respiratory Questionnaire (e-h) for non-admitted subjects. Values are mean ± SEM.*



### *4.4 Discussion*

The data I present in this chapter suggest there was significant recovery of muscle strength, walking performance and health status following hospitalisation for an exacerbation of chronic disease. The early rehabilitation intervention did not augment this recovery, with the exception of a faster recovery of ESWT at six weeks.

The approach was informed by previous observational studies in COPD suggesting negative short term effects of hospitalisation on muscle strength. Spruit *et al* reported that muscle strength was lower in patients who had been admitted with and acute exacerbation of COPD and importantly that muscle strength declined over the subsequent 5 days during the hospital stay [42]. In a study comparing early post discharge PR with usual care Man *et al* showed that PR resulted in significant improvements in exercise performance but importantly, there was limited improvement seen in the control group [122]. This suggests that natural recovery following the event is limited. Additionally, in a longitudinal cohort study Donaldson *et al[121]* reported that symptoms had not returned to baseline 35 days after the onset of an exacerbation and that at this time point more patients were restricted to their homes compared with pre-exacerbation. This is important because low physical activity has been shown to be related to the risk of subsequent hospitalisation with AECOPD[30, 33]. Data on physical activity are not presented in this thesis but it is likely that improvements in physical performance are mediated through an increase in day to day activity. In contrast these previous reports, in the current trial significant within group improvements in muscle strength, field walking performance and health status were observed in both treatment

groups in the three months after discharge. Although improvement was observed in the current trial, we recognise that because subjects were recruited at the point of hospitalisation, return to pre-admission levels of health and fitness may have been incomplete. Other differences with these previous reports may reside in the nature of standard hospital care and thresholds for admission in different health systems which may have affected the acuity of the illness and therefore the trajectory of recovery.

The lack of additional functional improvement in the active ER group may be because the intervention was insufficiently intense to provide additional benefits over and above that delivered by current standard re-ablement by ward physiotherapists. This is probably limited both by the limited exercise intensity that can be undertaken by patients during the acute illness and recovery and potentially also by incomplete adherence to the exercise protocol once the subject had been discharged from hospital.

Interestingly, the analysis of physical performance in the subgroup of patients who were not re-admitted, indicated enhanced gains in performance in the intervention group that were sustained over the subsequent year (albeit not statistically significant). This might indicate that benefits from the intervention are conferred as long as the process is not disrupted by further unplanned hospitalisation, which results in further physical insult and interrupts maintenance of daily activity.

We acknowledge some limitations in this analysis. The attendance rates during the follow-up period were low, though unsurprising given the frailty of this population. There may have been a healthy survivor effect in subjects who attended follow-up visits (“sicker” patients were more likely to drop out)

which might explain some of the improvements in recorded outcomes. The reduction in mean values for the imputed data at 12 months also suggests this was the case, and imputation has helped correct for this.

In summary recovery in physical performance and health status occurred following unscheduled admission for exacerbation of chronic respiratory disease which was not meaningfully affected by the ER intervention.

# *Chapter Five*

# Lower Limb Muscle Mass Predicts Re-hospitalisation following admission for Acute Exacerbations of Chronic Respiratory Disease

## *5.1 Introduction*

Hospitalisation for exacerbations of Chronic Obstructive Pulmonary Disease (COPD) and other Chronic Respiratory Diseases (CRD) are recognised as important events in longer term natural history of these diseases. Admission for AECOPD is associated with worse health status, and higher risk of death and subsequent readmission but predicting exacerbations from measurements taken in the stable state has proved difficult with only previous exacerbation being found to be a reliable identifier of those at risk of subsequent events[110]. Readmission following an index hospitalisation is a common clinical problem and has been reported to be related to self reported physical activity[33]. Population studies have suggested that this risk increases exponentially with subsequent re-admissions[112] although it is unclear whether this pattern can be reliably applied to individual patients[204]. This suggests that systemic manifestations of COPD such as skeletal muscle dysfunction may be key mediators of the risk of subsequent hospitalisation. In

support of this, muscle strength and mass have been reported to predict risk of death independently from lung function impairment[18, 26]. However, these studies assessed subjects in the stable state rather than a hospitalised population who are at greater risk. Measurements of muscle function during the acute episode are challenging, particularly those that require voluntary effort. A bedside measurement of muscle mass may therefore allow assessment of muscle dysfunction during the acute episode that might permit risk stratification of future outcome.

A number of imaging modalities can be used to assess whole body and regional muscle mass including MRI, CT and DEXA. However, these cannot be performed at the bedside, incur significant expense and involve radiation exposure which renders them impractical for use in the acute setting. Bio-electrical impedance is a simple technique that could be performed at the bedside but is significantly affected by alterations in hydration status and cannot reliably detect changes in lower limb muscle mass. Ultrasound assessment of quadriceps muscle mass has previously been validated in COPD in the stable setting and can be easily performed in the acute setting at the bedside. [205, 206].

In this chapter I test the hypothesis that measurements of lower limb muscle function would predict re-admission in the subsequent 12 months. This hypothesis was investigated by analysing outcomes in a subgroup of subjects participating in the clinical trial described in chapters 3 and 4 who had measurements of lower limb muscle mass (using bedside US) and muscle strength at recruitment.

## *5.2 Methods*

This was a sub-study of the early rehabilitation randomised controlled trial presented in Chapters 3 and 4. Recruitment, inclusion and exclusion criteria are presented in Chapter 3. As the primary outcome, hospital readmissions, and other secondary outcomes were negative, the two groups were collapsed to allow a cohort analysis to test the chapter hypotheses.

### *5.2.1 Study population*

$Q_{csa}$ measures using ultrasound were conducted at one site (Glenfield Hospital, Leicester), conducted at the same time as the other baseline measures (Chapter 4).

### *5.2.2 Outcome measures*

Outcome measures previously presented were performed as described in chapters 2, 3 and 4.

#### *5.2.2.1 Quadriceps cross-sectional area ($Q_{csa}$)*

Cross sectional area of a single portion of the quadriceps, rectus femoris, was measured using B mode ultrasound (Hitachi). Full methodology of the ultrasound technique is described in chapter 2. Briefly, cross sectional measures were taken at midpoint of the thigh (half-way between the greater trochanter and knee) using a linear probe. 3 measures were taken at time of recruitment and the mean taken. Measures were performed by three investigators (NG, TH-D, LT).

#### *5.2.2.2 Statistical analysis*

Hospitalisation in the follow up year was used as the main outcome measure in this study (binary outcome of hospitalised or not hospitalised). Statistical analysis was conducted using STATA SE version 13 (Statacorp, USA)). Factors associated with hospitalisation were identified by univariate model by logistic regression. Factors tested were any baseline characteristic or outcome measure tested during the index admission. Multivariate analysis with the selected factors identified from the univariate analysis were conducted with binary logistic regression using a stepwise approach, offset by exposure time (time to death). All analyses used randomisation group as co-variate. Factors were subdivided by ROC curve and compared. Hospitalisation and mortality were compared using both chi-squared and cox regression. Total number of hospital days were compared using chi squared. Finally the clinical characteristics of the two groups identified were compared using independent t test and Mann-Whitney for parametric and non-parametric continuous data as appropriate. Categorical measures were compared using chi-squared.

## *5.3 Results*

### *5.3.1 Baseline characteristics and readmission*

A total of 191 subjects underwent ultrasound of the $Q_{csa}$ at baseline and were included in the analysis. Baseline characteristics and measures are shown in table 5.1. 121 (63.4%) of the subjects were readmitted in the year following their index admission. Mean time to readmission was 121 days (SD 106).

***Table 5.1**: Clinical characteristics of the subjects at the one site (Glenfield Hospital, Leicester)*

| Variable | Mean | SD |
|---|---|---|
| Age (years) | 71.6 | 9.1 |
| BMI ($kg/m^2$) | 26.0 | 6.0 |
| Gender (% Male) | 45.6% | |
| MRC Grade when stable | | |
| 3 | 34.1% | |
| 4 | 48.1% | |
| 5 | 17.8% | |
| Smoking | | |
| Current | 22.1% | |
| Ex | 70.0% | |
| Never | 7.9% | |
| | | |
| Pack years | 46.0 | 35.9 |
| Home oxygen use (%) | 28.3% | |
| No co-morbidities (median) | 2 | IQR |
| Hospitalised in previous year | 52.4% | |
| Co-habitation | | |
| Alone | 38.6% | |
| Spouse | 51.3% | |
| Family | 7.4% | |
| Other | 2.7% | |
| CRQ | | |
| Dyspnoea | 2.03 | 0.97 |
| Emotion | 3.26 | 1.26 |
| Fatigue | 2.31 | 1.03 |
| Mastery | 2.95 | 1.24 |
| SGRQ | | |
| Symptoms | 76.59 | 18.14 |
| Activity | 87.16 | 11.77 |
| Impact | 57.95 | 18.51 |
| Total | 70.06 | 14.01 |
| Physical Measures | | |
| QMVC (kg) | 15.5 | 7.1 |
| Quads thickness (mm) | 20.10 | 6.14 |
| Quads Cross sectional area ($cm^2$) | 4.76 | 1.41 |
| Heart rate (bpm) | 85.9 | 17.8 |
| ISWT (m) | 109 | 86 |
| ESWT (s) | 123 | 128 |
| $FEV_1$ on discharge (L) | 0.97 | 0.44 |
| $FEV_1$ % predicted (%) | 44 | 19 |
| $FEV_1$/FVC (%) | 53 | 15 |

*5.3.2 Factors associated with hospitalisation*

In the univariate logistic regression analysis of all available in-hospital assessments the risk of hospitalisation was calculated. Factors significantly associated with readmission were MRC grade, home oxygen use, quadriceps cross sectional area and previous hospitalisation (table 5.2).

***Table 5.2:*** *Factors associated with re-hospitalisation. Odds ratios (OR) are shown for each separate variable. Significant variables are shown in bold.*

| Variable | OR | 95% CI | | p |
|---|---|---|---|---|
| Age (years) | 1.03 | 0.99 | 1.06 | 0.137 |
| Gender (female) | 1.03 | 0.55 | 1.92 | 0.923 |
| BMI ($kg/m^2$) | 0.97 | 0.92 | 1.02 | 0.266 |
| Lives with (spouse) | 0.60 | 0.30 | 1.18 | 0.141 |
| **MRC baseline** | **2.94** | **1.78** | **4.85** | **<0.001** |
| Main diagnosis (ILD) | 1.12 | 0.30 | 4.15 | 0.863 |
| Smoking (yes) | 0.37 | 0.09 | 1.49 | 0.163 |
| Pack years | 1.00 | 0.99 | 1.01 | 0.444 |
| **LTOT** | **3.34** | **1.53** | **7.27** | **0.002** |
| QMVC(kg) | 0.97 | 0.93 | 1.01 | 0.192 |
| **Quadriceps thickness (mm)** | **0.93** | **0.89** | **0.98** | **0.008** |
| **Quadriceps CSA ($cm^2$)** | **0.75** | **0.60** | **0.93** | **0.011** |
| ISWT (m) | 1.00 | 0.99 | 1.00 | 0.177 |
| ESWT (s) | 1.00 | 1.00 | 1.00 | 0.380 |
| $FEV_1$ on discharge (L) | 0.53 | 0.25 | 1.133 | 0.101 |
| No of co-morbidities | 0.82 | 0.65 | 1.04 | 0.107 |
| Initial LOHS (days) | 0.98 | 0.93 | 1.03 | 0.426 |
| **Previous hospitalisation in last 12 months** | **2.09** | **1.44** | **3.02** | **<0.001** |
| Treatment allocation (intervention) | 1.20 | 0.65 | 2.23 | 0.558 |

The significant factors from the univariate analysis were put into a multivariate model using a stepwise approach. Independent factors associated with further hospitalisation were MRC grade, quadriceps cross-sectional area and previous hospitalisation. Home oxygen use was not significantly associated (p=0.197). Odds ratios are shown in table 5.3

***Table 5.3:*** *Multivariate analysis of variables significantly predictive of hospitalisation in the 12 months following measurement*

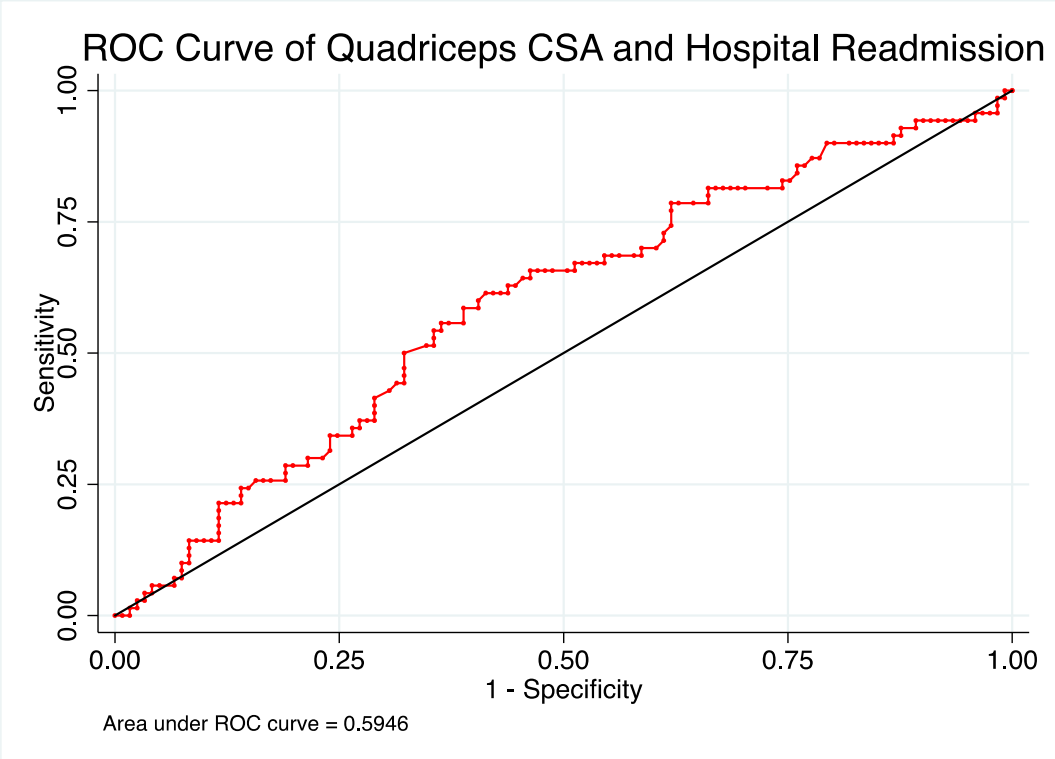
| Variable | OR | 95% CI | | p |
|---|---|---|---|---|
| MRC Grade | 2.52 | 1.52 | 4.19 | <0.001 |
| Admitted in previous year | 2.25 | 1.15 | 4.41 | 0.018 |
| Quadriceps cross sectional area | 0.77 | 0.61 | 0.98 | 0.031 |

*5.3.3 Identification of $Q_{csa}$ cut-off point*

Sensitivity and specificity for predicting hospitalisation using $Q_{csa}$ was calculated using a receiver operator characteristic (ROC) curve (figure 5.1). The area under ROC curve (95% CI) for $Q_{csa}$ and hospital readmission was 0.59 (0.51-0.68). Using the ROC curve to determine the $Q_{csa}$ threshold a cut-off of 4.79cm$^2$ was determined. Sensitivity for this point was 60.0% and specificity of 59.5%, correctly classifying 60% of subjects.

The cohort was divided into two groups (1) Smaller muscle group- defined as $Q_{csa}$<4.79cm$^2$ and (2) Larger muscle group- defined as $Q_{csa}$ ≥4.79cm$^2$. 100 (52%) subjects were in the smaller muscle group and 91 (48%) in the larger.

***Figure 5.1**: Receiver operator characteristic (ROC) curve for quadriceps cross sectional area and hospital readmission. Area under the curve= 0.59.*



*5.3.4 Multivariate analysis using Qcsa cut-off*

Multivariate analysis was repeated, but using the binary $Q_{csa}$ cut off, rather than as a continuous variable. The larger muscle size (≥4.79cm2) was used as the reference value. Again, home oxygen use was not significantly associated with hospitalisation. Results are shown in table 5.4

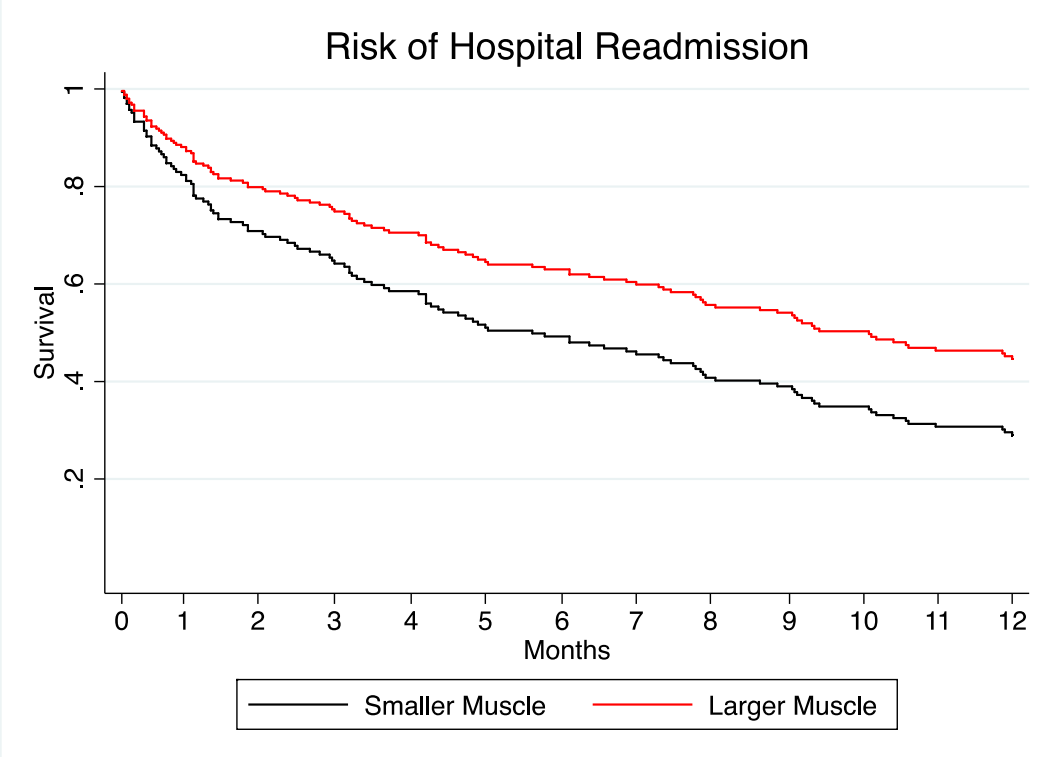
***Table 5.4:*** *Repeat multivariate analysis using the calculated $Q_{csa}$ cut off as caluculated from ROC curve as a predictor.*

| Variable | OR | 95% CI | | p |
|---|---|---|---|---|
| MRC Grade | 2.51 | 1.51 | 4.17 | <0.001 |
| Admitted in previous year | 2.31 | 1.18 | 4.54 | 0.014 |
| Small $Q_{csa}$ (<4.79cm$^2$) | 2.46 | 1.26 | 4.78 | 0.008 |

*5.3.5 Risk of Hospitalisation*

The proportions of patients readmitted in one year were 72% in the small muscle group and 53% in the large muscle group (p=0.009). Risk of hospitalisation using cox regression was significantly higher in the smaller muscle group (OR 1.60, 95% CI 1.11-2.32, p=0.013) and is shown in figure 5.2.

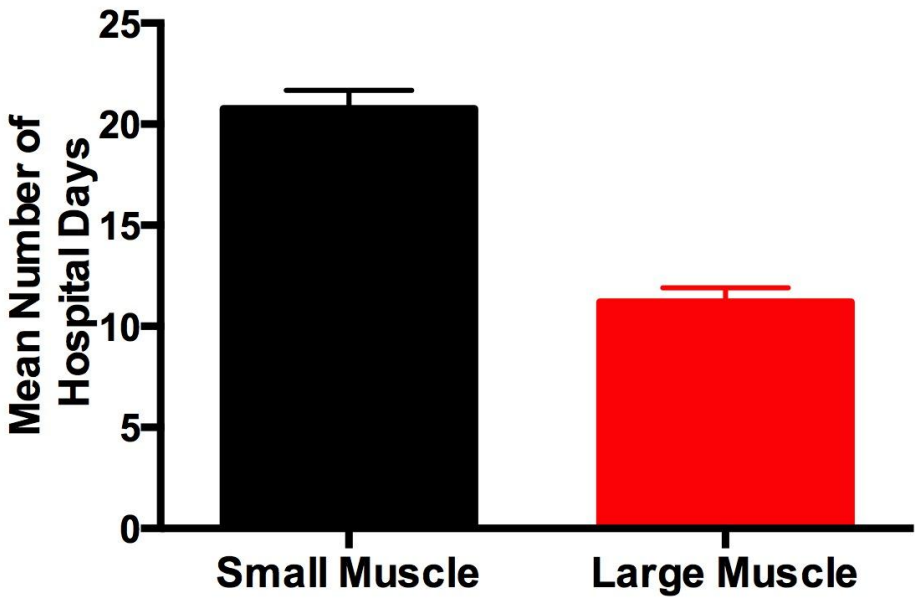
***Figure 5.2**: Cox regression curve of risk of hospitalisation for the smaller muscle ($Q_{csa}$<4.79cm$^2$) and larger muscle groups ($Q_{csa}$ ≥4.79cm$^2$). Significant difference is present at 12 months (p=0.013). Co-variates in regression curve are MRC grade, hospitalisation in previous one year, and early rehabilitation intervention*



*5.3.6 Number of Hospital Days*

The number of hospital days in the year following the original admission was significantly higher in the smaller muscle group (p=0.005) with 20.8 (SD 29.7) days per subject in the smaller muscle group and 11.20 (SD 20.5) in the larger muscle group (figure 5.3).

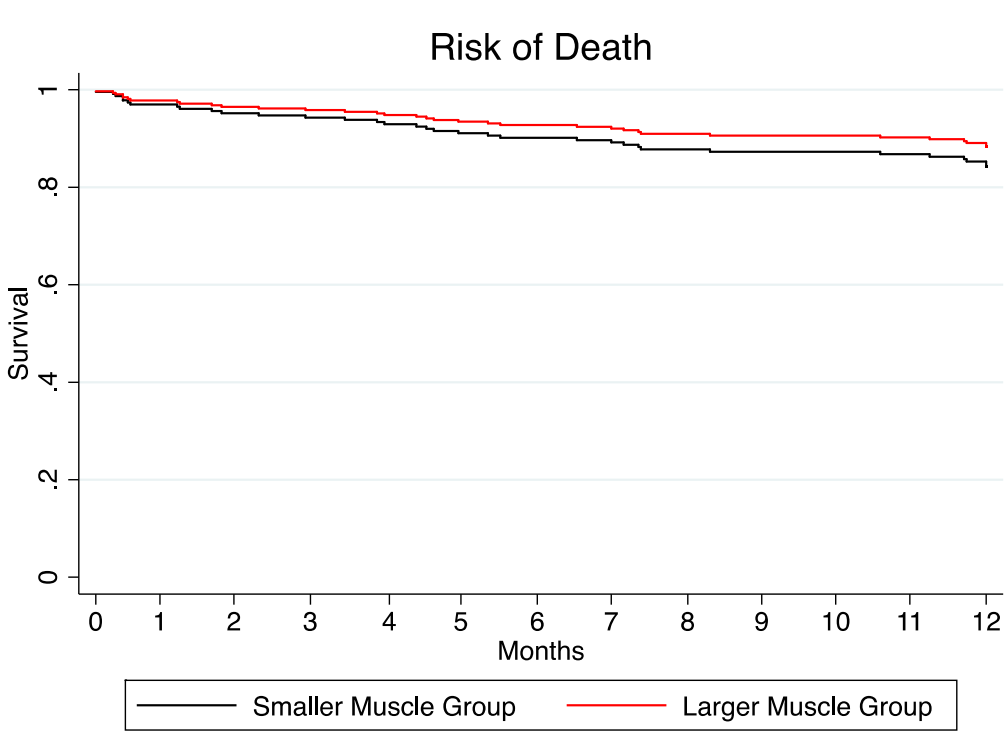
***Figure 5.3:*** *Mean number of days spent in hospital in the year following the index admission and ultrasound measurement for the smaller muscle ($Q_{csa}$<4.79cm$^2$) and larger muscle groups ($Q_{csa}$ ≥4.79cm$^2$). Error bars are 95% Poisson confidence intervals)*



*5.3.7Mortality*

22 (22%) of the smaller muscle group died compared with 13 (14%) of the larger muscle group. No statistically difference was noted in mortality (OR 1.42, 95% CI 0.63-3.20, p=0.403).

***Figure 5.4:*** *Cox regression curve of risk of mortality for the smaller muscle ($Q_{csa}$<4.79cm$^2$) and larger muscle groups ($Q_{csa}$ ≥4.79cm$^2$). No significant difference was seen at 12 months (p=0.403). Co-variates in regression curve are MRC grade, hospitalisation in previous one year, and early rehabilitation intervention*



*5.3.8 Clinical characteristics*

Baseline characteristics and demographics were compared between the larger and smaller Qcsa groups (table 5.5). Subjects with smaller Qcsa were more likely have a lower BMI and weight, be weaker, have a worse ESWT performance, have more severe airflow obstruction, be female and live alone. There was no difference between randomisation groups and presence of quadriceps wasting (usual care 53%, early rehabilitation 52%, p=0.841).

***Table 5.5:*** *Comparison of clinical characteristics of the smaller muscle ($Q_{csa}$<4.79cm$^2$) and larger muscle groups ($Q_{csa}$ ≥4.79cm$^2$). Significant differences are shown in bold.*

| Variable | Smaller Muscle ($Q_{csa}$<4.79cm$^2$) | | Larger Muscle ($Q_{csa}$≥4.79cm$^2$) | | p |
|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | |
| Age (years) | 72.5 | 9.7 | 70.5 | 8.3 | 0.127 |
| **Weight (kg)** | **63.9** | **15.5** | **76.7** | **17.3** | **<0.001** |
| **BMI (kg/m$^2$)** | **24.4** | **5.5** | **27.6** | **6.1** | **<0.001** |
| **QMVC (kg)** | **12.8** | **6.3** | **18.5** | **6.8** | **<0.001** |
| **Quadriceps thickness (mm)** | **17.1** | **5.2** | **23.3** | **5.4** | **<0.001** |
| ISWT (m) | 99.5 | 85.4 | 120.5 | 84.9 | 0.121 |
| **ESWT (s)** | **102** | **89** | **146** | **110** | **0.032** |
| Sats (%) | 92.9 | 3.3 | 92.5 | 91.8 | 0.374 |
| Heart Rate (bpm) | 87 | 14 | 91 | 13 | 0.052 |
| **$FEV_1$(L)** | **0.86** | **0.37** | **1.09** | **0.49** | **0.001** |
| $FEV_1$(% predicted) | 43.4 | 19.2 | 45.5 | 18.7 | 0.488 |
| MRC dyspnoea grade | 4 | 3-4 | 4 | 3-4 | 0.173 |
| Number of co-morbidities (median) | 2 | 1-3 | 2 | 1-3 | 0.580 |
| Index LOHS (days) | 6 | 3-10 | 5 | 3-8 | 0.148 |
| **Gender (% male)** | **37%** | | **55%** | | **0.013** |
| **Lives with (% alone)** | **46%** | | **31%** | | **0.012** |
| Principal diagnosis (% COPD) | 82% | | 79% | | 0.780 |
| Previously admitted (% yes) | 56% | | 48% | | 0.291 |
| Admitted ≥2 in previous year | 29% | | 19% | | 0.096 |

*5.3.9 Effect of early rehabilitation intervention in different muscle groups.*

The effects of the early rehabilitation were tested in the sub-groups of smaller $Q_{csa}$ and larger $Q_{csa}$. For the smaller muscle group 34/52 (65%) and 38/48 (79%) were readmitted in the usual care and early rehabilitation groups respectively (HR 1.28, 95% CI 0.81-2.03, p=0.288). For the larger muscle group 27/46 (59%) and 22/45 (49%) were readmitted in the usual care and early rehabilitation groups respectively (HR 0.74, 95%CI 0.43-1.30, p=0.301). Cumulative incidence of readmissions in both groups is shown in figure 5.5. No difference was seen in number of admissions or number of hospital days for the unadjusted analysis, but a significant reduction in favour of the intervention group was seen for the analysis adjusted for co-variates (table 5.6).

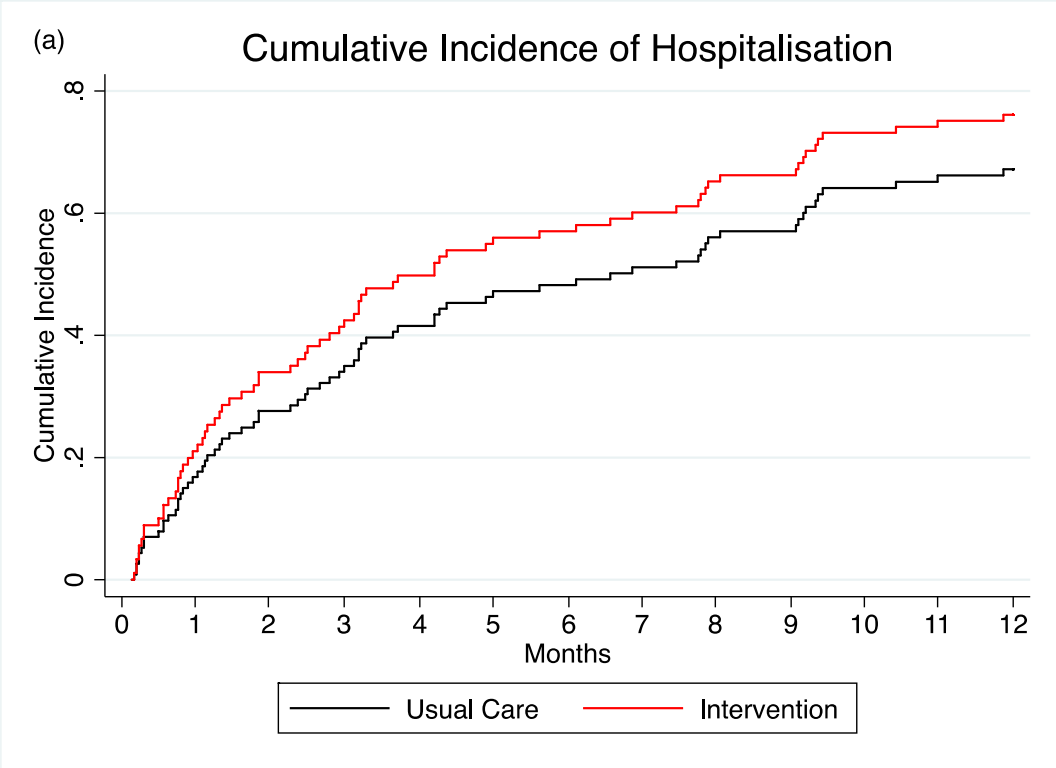
***Table 5.6*** *Health care utilisation. Comparison of number of hospital admissions per patient and hospital days per patient in the 12 months following admission for the small and large muscle groups as defined by rectus femoris cross sectional area. All data are intention to treat. Analyses are shown both unadjusted and adjusted for co-variates. Incident rate ratio is relative to the usual care group and offset for time exposed (time to death).*

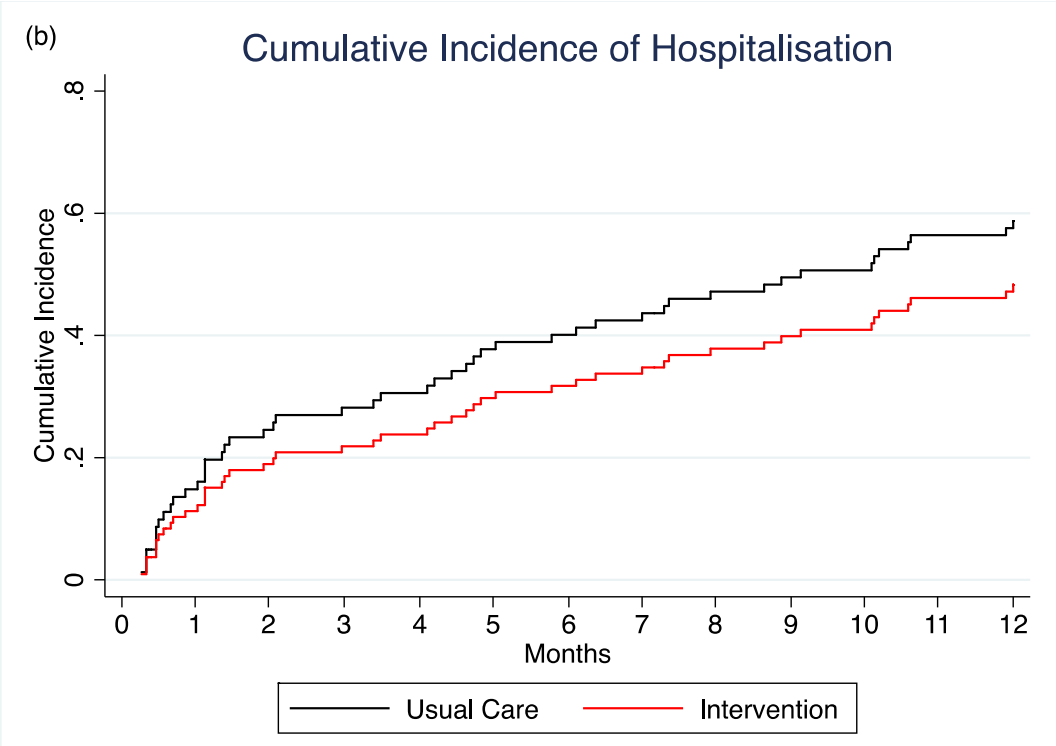
| | Usual Care | Intervention | Unadjusted | | | Adjusted for co-variates[$] | | |
|---|---|---|---|---|---|---|---|---|
| | Mean (SD) | Mean (SD) | IRR | 95% CI | p | IRR | 95% CI | p |
| Hospital admissions | | | | | | | | |
| Small muscle group | 2.15 (2.55) | 1.58 (1.50) | 0.76 | 0.47-1.23 | 0.262 | 0.92 | 0.56-1.50 | 0.731 |
| Large muscle group | 1.78 (2.29) | 1.33 (2.20) | 0.74 | 0.38-1.41 | 0.358 | 0.49 | 0.27-0.93 | 0.024 |
| Number of Hospital days | | | | | | | | |
| Small muscle group | 38 (39) | 20 (20) | 0.81 | 0.40-1.65 | 0.567 | 0.96 | 0.41-2.22 | 0.918 |
| Large muscle group | 23 (28) | 18 (18) | 0.51 | 0.20-1.29 | 0.157 | 0.27 | 0.10-0.73 | 0.010 |

[$]adjusted for site, age, diagnosis, previous hospital admissions, quadriceps strength at baseline, MRC grade, number of co-morbidities
IRR: Incident Rate Ratio

**Figur**

**e 5.5** Cumulative incidence of readmission to hospital using competing risks regression in the (a) smaller muscle group (<4.79cm$^2$), p=0.288 and (b) larger muscle group (≥4.79cm$^2$), p=0.301



*5.4 Discussion*

In this chapter I have investigated the hypothesis that indices of muscle function measured during hospitalisation are associated with the risk of re-admission over the subsequent 12 months. $Q_{csa}$ was independently predictive of re-admission and in a multivariate model remained significantly associated with this risk alongside MRC scale and previous hospitalisation. Post-hoc analysis of the ER intervention suggested that, when corrected for co-variates, there was a response in favour of the intervention group in patients with larger muscle size.

$Q_{csa}$ measurement was used as a marker of muscle mass in this analysis. This technique has been previously validated against strength[205] and DEXA[207] in COPD populations and has practical utility in the acute setting because it is independent of patient effort and can be performed at the bedside. $Q_{csa}$ has previously been shown to be related to quadriceps strength and physical activity in stable COPD[22, 206], and more recently been used to demonstrate progressive wasting in the intensive care environment[120]. It is likely to offer a more sensitive and reliable measure of muscle mass than other potential bedside measures such as bio-electrical impendence analysis which may not be able to detect regional loss of muscle mass and is subject to variation due to shifts in hydration status which will be more important during the acute illness. Muscle strength can also be performed during the acute illness but did not significantly influence readmission rate possibly because the volitional component of the assessment of strength was affected by the acute illness.

A threshold for reduced $Q_{csa}$ was identified using ROC analysis. Subjects in the smaller muscle group were more likely to be re-admitted (as expected) but also had more days in hospital over the subsequent 12 months. The small muscle group was characterised by worse lung function, walking performance and muscle strength which might explain the differences in re-admission rate although these factors were not significant in the multivariate regression analysis. Unsurprisingly there were more females in the small muscle group but this did not account for the findings when the analysis was adjusted for sex. Allocation to the active ER group did not affect the outcome of the analysis when unadjusted. However, post-hoc analysis- using the same co-variates as described in chapter 3- showed a significant reduction in hospitalisation and number of hospital days in the intervention group. This is of importance as measurement of quadriceps mass may allow stratification for targeted rehabilitation interventions. Patients with small muscle and increased frailty may be too frail to respond to an exercise based intervention and other therapies, such as palliative care, may be warranted.

We observed a 46% difference in the mean number of hospital days between the smaller and larger muscle groups. This proportionally larger difference in hospital days than number of hospital admissions (16% difference between groups) suggests that skeletal muscle dysfunction is not only important for admission to hospital but also the severity and duration of the admission. This is in keeping with Griffiths et al observation of a decrease in hospital days, but not admission following pulmonary rehabilitation[155].

There was no statistical difference in mortality between the smaller muscle and larger muscle groups, though the absolute difference was 8% in favour of

the larger muscle group. It is likely that this study is underpowered for this measure and further research would be of benefit, especially as other studies on advanced COPD have previously identified mortality and skeletal muscle dysfunction, though not necessary muscle atrophy, to be closer associated than lung function[18].

Previous studies have demonstrated that in the stable state measures of muscle mass are predictive of mortality[18, 26] but this is the first to report the effect on hospitalisation although muscle strength has been shown to have a negative association with healthcare utilisation[19] and mortality[18] in the stable state. Risk stratification for hospital admission is of considerable interest because of the burden and cost of unscheduled hospitalisation to patients and health care systems. However, predicting exacerbations of COPD per se in the stable state is difficult with a large cohort study finding that the only significant predictive factor was frequency of previous exacerbations[110]. Assessing this risk during an index hospitalisation is relevant because the episode represents an opportunity to identify and provide interventions that might modify this risk such as pulmonary rehabilitation or allow prioritisation of the provision of social or palliative care. The findings support other reports that suggest that self reported levels of physical activity predict re-admission after an index hospitalisation[33]. Other studies have reported factors predicting short term outcomes from unscheduled hospitalisation but have focused on routinely collected clinical measurements (including MRC score and previous hospitalisation which are included in the current analysis) which may assist medical teams with the management of the acute episode but might miss important patient centred

measures that allow risk stratification such as muscle mass and function because they are not routinely recorded[115].

Limitations to the analysis described in this chapter are acknowledged. Although the data were collected prospectively, it is a secondary, subgroup analysis of a clinical trial and risk stratification was not the purpose of the investigation. In any multivariate analysis, limitations are posed by the range of measures that are available It is possible that reduced $Q_{csa}$ is a surrogate for general “frailty” in this population that would be better captured using other measures such as the Short Physical Performance Battery or the 4m Gait Speed. This is supported by the observation that MRC grade was significant in the multivariate model and that the small muscle group had poorer walking performance and muscle strength. Whilst the factors associated with readmission were significant the overall predictive ability of the three identified factors remained poor ($r^2$= 0.08). This is likely to reflect the multiple physical, psychological and social complexities around hospitalisation in chronic disease. The analysis included a variety of exacerbations of chronic respiratory disease which raises questions about the applicability of the findings to specific disease populations. However, the majority had COPD and it is likely that the non-pulmonary manifestations of the condition that are the focus of this investigation are common to a wide range of primary chronic lung diseases. Indeed, it could be argued that this is a strength of the approach because considerable overlap exists between these entities in terms of lung pathophysiology.

Hospitalisation for exacerbation of chronic respiratory disease is a major cause of morbidity and mortality in the developed world and incurs substantial

healthcare costs. Reliable stratification of the subsequent risk of unscheduled admission would be a significant advance in the management of individual patients and in the planning of acute respiratory services. In this chapter I have shown that muscle mass can be assessed at the bedside during the acute episode using US and that this outcome is associated with subsequent risk of readmission. This measure has a potential role as a marker of future hospitalisation and may be used as a risk stratification tool. This is likely to be the result of a composite of a number of underlying processes adversely affecting patients, resulting in hospital readmission.

# *Chapter Six*

# The Effects of Neuromuscular Electrical Stimulation on the Quadriceps in COPD

## *6.1 Introduction*

Impaired skeletal muscle function is an important contributor to exercise limitation in COPD and an adverse prognostic indicator, independent of lung function[18, 19]. Given that the pulmonary pathophysiology is largely irreversible, interventions targeting the skeletal muscles are appealing. The efficacy of pulmonary rehabilitation in the stable state is unequivocally established and mediated in part through improvements in skeletal muscle function[156]. However, whole body exercise training may be impractical in some situations, such as patients with severe ventilatory limitation or during acute exacerbations. The latter is particularly important as the exacerbation represents a period of acute risk to the skeletal muscles because of the convergence of several potential adverse factors including immobilisation, systemic inflammation, hypoxia, and the use of therapies such as systemic corticosteroids. Non-volitional training techniques such as neuromuscular electrical stimulation (NMES) may represent a training modality that is suited to this task, as it provides a training effect to the muscle without stressing the ventilator system. Early clinical studies of NMES in advanced COPD have shown that quadriceps NMES may be effective despite eliciting low

contraction intensities[172, 173] and it can be adapted for the acute clinical setting[167] or in the recovery period[177, 180]. However, physiological adaptation to NMES, in comparison with other training modalities, such as strength training are less well understood. Recent evidence has suggested a similar clinical response to resistance training[176] but the mechanisms underpinning these adaptations are poorly understood[178].

In this chapter I describe a study which aims to address these gaps in knowledge by comparing the functional response (quadriceps mass and strength) to NMES applied over 6 weeks in one lower limb compared with the contralateral untrained limb. A matched cohort of patients undertook single leg voluntary resistance training in the same design as a comparator. The primary purpose of the study was the investigation of intramuscular adaptation using muscle biopsy samples taken at serial time points during the intervention. Muscle sample analysis is ongoing and not presented in this thesis.

## *6.2 Methods*

### *6.2.1 Study design*

This was a prospective, parallel group, study of single leg training. Subjects were randomly allocated to either single leg NMES or single leg resistance training (1:1 randomisation) and underwent six weeks training. The leg trained was randomised to either dominant or non-dominant leg (1:1 randomisation). Ethical approval was received from West Midlands Research Ethics Committee- clinical trial of an investigational medicinal device (10/H1208/73).

### *6.2.2 Study population*

Stable patients with a diagnosis of COPD were recruited from respiratory outpatient clinics and those referred for pulmonary rehabilitation at University Hospitals of Leicester. Inclusion criteria were those with a confirmed diagnosis of COPD, significant functional disability (MRC dyspnoea grade ≥3), no exacerbation within the preceding six weeks and not undergone pulmonary rehabilitation within the previous year. Exclusion criteria included subjects on long-term oral corticosteroids, anticoagulation e.g. warfarin (as muscle biopsies were performed), long-term oxygen therapy, and co-morbid conditions preventing exercise training.

### *6.2.3 Intervention protocols*

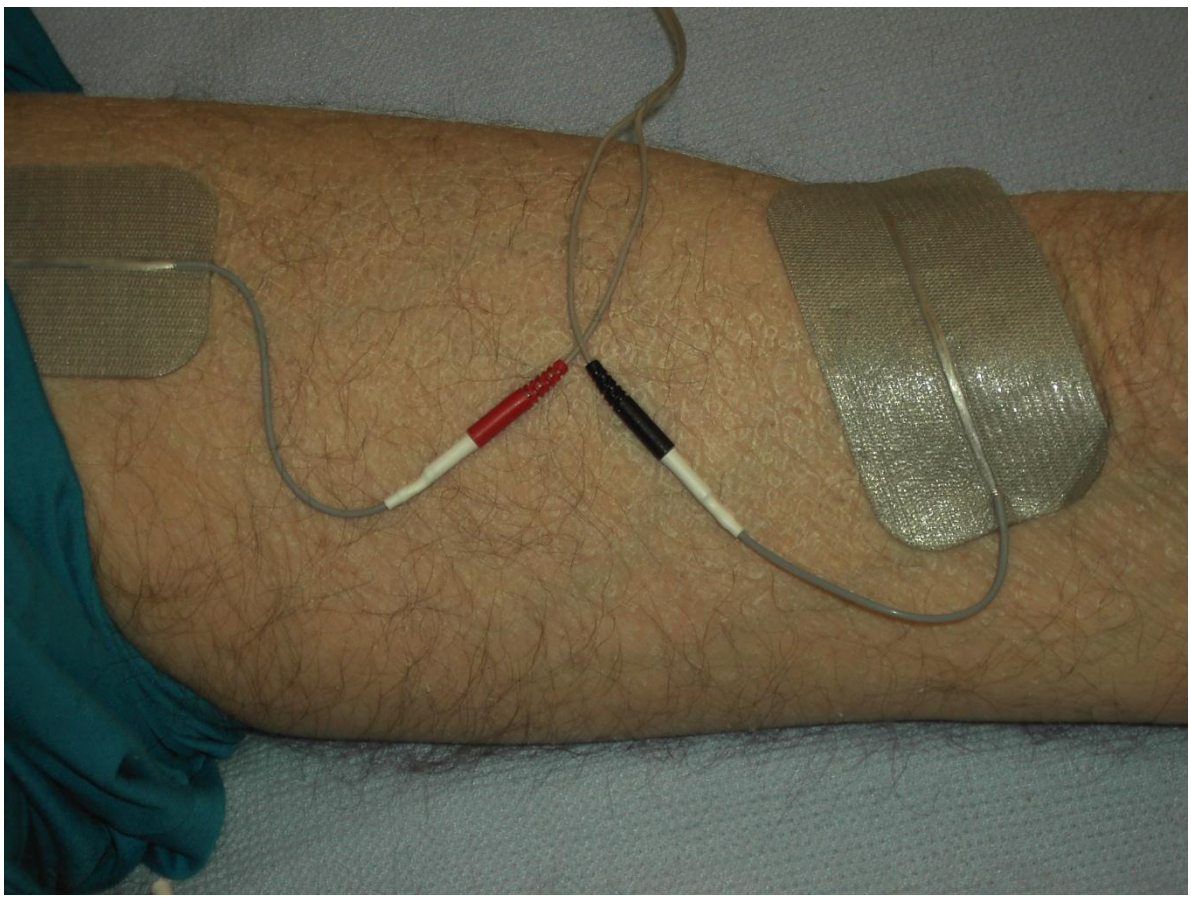
Heart rate, oxygen saturations, BORG breathlessness score and perceived exertion score were recorded pre and post every training session.

NMES (Empi 300pv, USA) was performed on the quadriceps at a frequency of 50Hz for 30 minutes in three supervised and two home sessions per week using intermittent stimulation (15s:5s on:off, 300μs band width, ramp period 2s). Amplitude was maximally titrated to subject tolerability and progressed throughout the study. Electrodes were placed on the quadriceps as shown in figure 6.1. Subjects were positioned with the knee extended and supported on a plinth.

Resistance training was performed 3 times per week, comprising of 5 sets of 30 maximal knee extensions at 180°/second, using an isokinetic dynamometer (Cybex II Norm: CSMi, Stoughton, USA). Each set was separated by one minute's rest, and included 30 repetitions of passive warm

up and warm down manoeuvres. Manoeuvres were performed with the knee at 90° at rest, extending to 180°, with encouragement by a member of the investigating team. This training regimen has previously been demonstrated to result in significant increases in leg muscle mass and function in subjects with COPD[50].

***Figure 6.1:*** *Positioning of NMES pads on quadriceps over the muscle belly on the lateral aspect proximally and lateral aspect distally*



### *6.2.4 Outcome measures*

Full descriptions of the outcome measures are covered in chapter 2. Measures were performed on both legs sequentially. Strength measures were performed a minimum of three days apart from the cardiopulmonary exercise test, to ensure recovery. In addition to the measures described bilateral vastus lateralis muscle biopsies were taken at baseline, 24 hours after the first training session and 24 hours after the final training session.

#### *6.2.4.1 Baseline measures*

Height, weight, fat-free mass index (FFMI), spirometry, and maximal exercise performance using cycle ergometry were performed at baseline. Muscle wasting was defined as FFMI <15 kg/m$^2$ for females and <16 kg/m$^2$ for males

#### *6.2.4.2 Thigh mass*

Thigh lean mass was measured, as region of interest, using DEXA (Lunar Prodigy Advance, GE Healthcare, UK).

#### *6.2.4.3 Quadriceps strength*

Isometric strength (QMVC) was measured with the knee at 90° fixed flexion. Six maximal contractions were performed with 30 seconds rest between manoeuvres. Vocal encouragement and visual feedback were provided. QMVC was captured using a load cell and data acquisition unit (Micro1401 and Spike2 software, CED, UK).

#### *6.2.4.4 Rectus femoris cross sectional area*

Ultrasound (Hitachi) was used to measure mid-thigh rectus femoris cross sectional area ($Q_{csa}$). Mid-point was taken as half the distance between mid point of greater trochanter on the femur to the knee joint. Cross sectional area was measured as described in chapter 2 and by Seymour et al[205].

#### *6.2.4.5 Quadriceps thickness*

Ultrasound of the quadriceps was used to measure quadriceps thickness ($Q_{thick}$). This was defined as the vertical distance from the top of rectus femoris to the base of rectus intermedius. Minimal pressure with the ultrasound probe was applied, allowing visualisation but preventing compression of the muscles. Three measures were taken and the mean calculated.

### *6.2.5 Statistical Analysis*

The study was powered to detect a difference in thigh mass of 4.8% (power 80%, alpha 0.05). This was based on the change seen using a similar resistance training protocol within the department[50]. This would require 13 patients to detect a difference. Allowing for a 25% drop out rate we planned to recruit 17 in each group.

Baseline characteristics were compared using independent t tests, Mann-Whitney and chi squared for parametric, non-parametric and categorical data respectively. Correlations were calculated using Pearson's correlation coefficient. Pre and post within- leg comparisons were made using paired t-tests. Changes between trained and untrained limb were compared using two-

way repeated measures ANOVA. Progression of training was measured using repeated measures ANOVA. The different training modalities were not compared, as the study was not adequately powered to detect a difference or equivalence (>100 subjects would be required). Effect size between trained and untrained limbs was measured using Cohen's d.

## *6.3 Results*

37 subjects were recruited. 20 subjects were randomised to the NMES group, of which16 completed (80%). 17 subjects were randomised to the resistance training group, of which 13 completed (76%).

### *6.3.1 Baseline characteristics*

Baseline demographics and characteristics of those that completed are described in table 6.1. Characteristics of subjects allocated to the different training modalities were not significantly different. Significant correlation coefficients for all measures of muscle function and size were seen at baseline (table 6.2, $p<0.01$)

### *6.3.2 Training progression*

There was significant progression in training intensity in both the NMES and resistance training groups (figure 6.2). Mean amplitude of the first and last NMES sessions were 42mA and 75mA respectively ($p=0.001$). For the resistance training group mean peak work for the first and last sessions were 958J and 1299J ($p=0.002$).

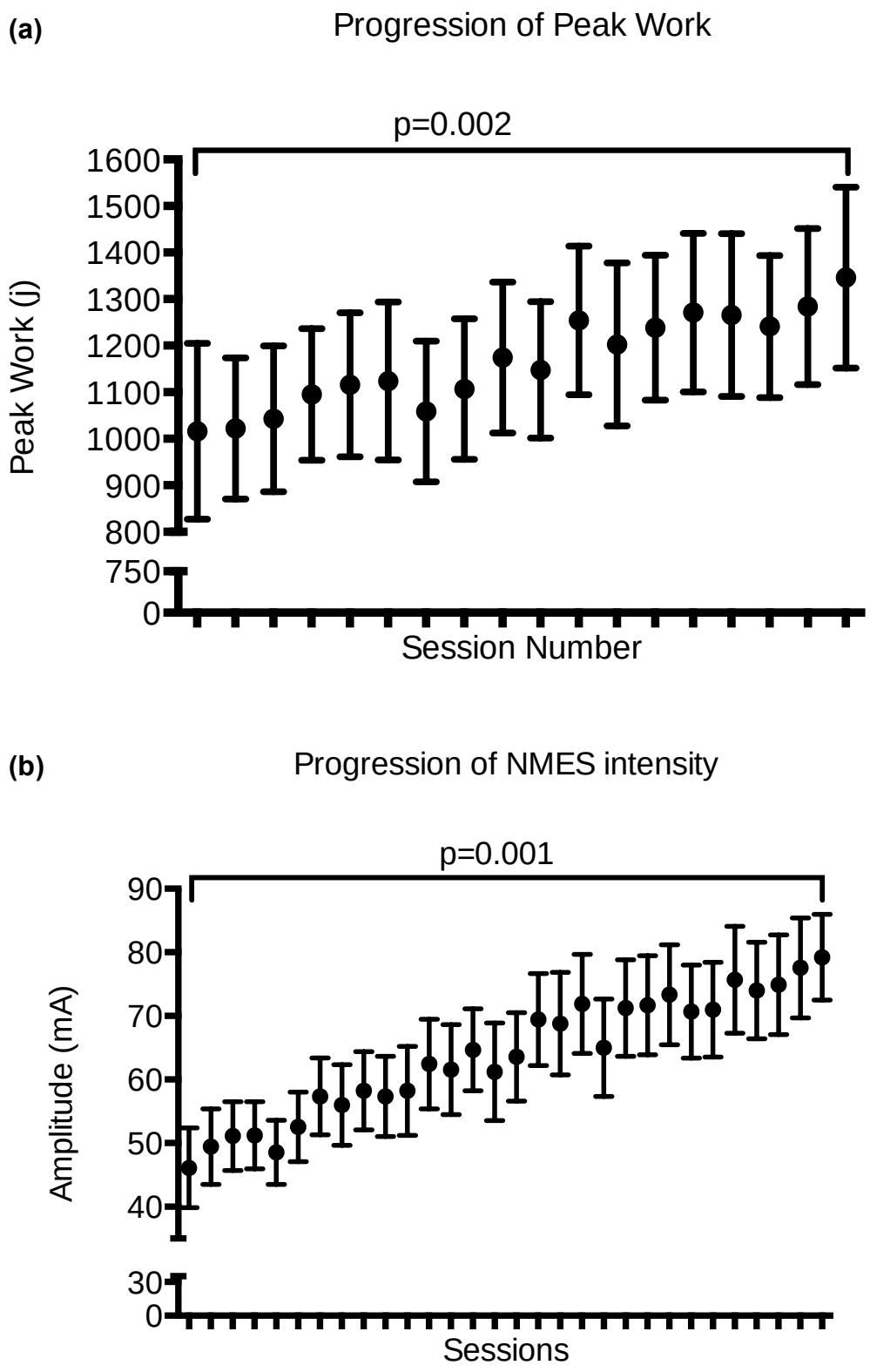
***Table 6.1:*** *Baseline demographics and characteristics of study completers.*

| | NMES (n=16) | | Resistance Training (n=13) | |
|---|---|---|---|---|
| | Mean | SD | Mean | SD |
| Age (years) | 65 | 9 | 70 | 11 |
| Gender (M:F) | 8:8 | | 9:4 | |
| MRC grade | 3.5 | IQR 3-5 | 3 | IQR 3-4 |
| BMI ($Kg/m^2$) | 26.5 | 5.2 | 27.1 | 5.4 |
| FFMI ($Kg/m^2$) | 17.0 | 1.8 | 18.0 | 2.6 |
| Muscle wasted (%) | 1 | 6% | 2 | 15% |
| Current smokers | 2 | 13% | 3 | 23% |
| Pack years | 43 | 22 | 54 | 32 |
| $FEV_1$ (L) | 1.11 | 0.40 | 1.34 | 0.38 |
| $FEV_1$ % predicted | 49.9 | 22.0 | 56.2 | 14.0 |
| $FEV_1$/FVC | 43.6 | 10.3 | 49.6 | 9.2 |
| SpO2 (%) | 95 | 2 | 94 | 2 |
| HR (bpm) | 85 | 16 | 80 | 11 |
| $VO_{2peak}$ (L/min) | 0.81 | 0.28 | 0.95 | 0.29 |
| $VO_{2peak}$ (W) | 58 | 18 | 63 | 23 |
| Thigh lean mass (g) | | | | |
| Training limb | 3509 | 776 | 3813 | 1056 |
| Control limb | 3482 | 776 | 3758 | 1095 |
| QMVC (N) | | | | |
| Training limb | 321 | 98 | 333 | 108 |
| Control limb | 325 | 85 | 308 | 112 |
| $Q_{csa}$ ($cm^2$) | | | | |
| Training limb | 5.04 | 1.72 | 4.69 | 1.81 |
| Control limb | 4.94 | 1.49 | 4.55 | 1.58 |
| $Q_{thick}$ (mm) | | | | |
| Training limb | 22.4 | 6.2 | 23.1 | 7.8 |
| Control limb | 22.8 | 6.0 | 23.1 | 8.9 |

***Table 6.2:*** *Correlation coefficients for baseline functional measures. Significant correlations were seen for all measures ($p<0.01$)*

| | DEXA trained | DEXA untrained | US thick trained | US thick untrained | Qcsa trained | Qcsa untrained | QMVC trained | QMVC untrained |
|---|---|---|---|---|---|---|---|---|
| DEXA trained | 1 | | | | | | | |
| DEXA untrained | 0.9858 | 1 | | | | | | |
| $Q_{thick}$ trained | 0.7542 | 0.7571 | 1 | | | | | |
| $US_{thick}$ untrained | 0.6905 | 0.7062 | 0.9553 | 1 | | | | |
| $Q_{csa}$ trained | 0.5998 | 0.5694 | 0.6809 | 0.6502 | 1 | | | |
| $Q_{csa}$ untrained | 0.5696 | 0.5483 | 0.6801 | 0.6905 | 0.9394 | 1 | | |
| QMVC trained | 0.7632 | 0.7299 | 0.6305 | 0.605 | 0.5307 | 0.4988 | 1 | |
| QMVC untrained | 0.784 | 0.7998 | 0.6256 | 0.6329 | 0.4805 | 0.4889 | 0.8616 | 1 |

***Figure 6.2:*** *Training progression for both groups. (a) mean peak work for the 18 sessions in the resistance training group. (b) mean amplitude for the 30 NMES sessions. Error bars are ±1 SD*



### *6.3.3 Muscle Mass*

Significant changes in thigh mass were seen in the training limbs, but not the untrained limbs, in both the NMES and resistance training groups. Mean thigh mass in the training limb for the NMES group increased from 3509g (SD 776) to 3592g (SD 750) and from 3813g (SD 1056) to 3927g (SD1073) in the resistance training group. Individual subject values are shown in figure 6.3. When accounting for change in the control limb there was a trend for improvement in the resistance training group (p=0.056), but not the NMES group (p=0.185). A medium effect size was seen in the resistant training group but only a small effect size for NMES (table 6.2). Change in thigh mass expressed as percent are shown in figure 6.7a.

### *6.3.4 Muscle Strength (QMVC)*

No significant difference in QMVC was seen pre and post training for either modality in the training limb, though with a trend for an increase in NMES (p=0.067). Mean QMVC in the training limb pre and post intervention for the NMES group was 321N (SD 24) and 337N (SD 21) respectively. In the resistance training group QMVC was 333N (SD 30) and 340N (SD 29) pre and post. Individual subject values are shown in figure 6.4. When accounting for change in the control limb a significant difference was seen in the NMES group (p=0.024) but not in the resistance training group (p=0.144), though a similar effect size was seen in both groups (table 6.2). Change in QMVC expressed as percent are shown in figure 6.7b.

***Figure 6.3:*** *Thigh mass (g) pre and post intervention in the trained and untrained limbs for the (a) NMES group and (b) Resistance training group.*

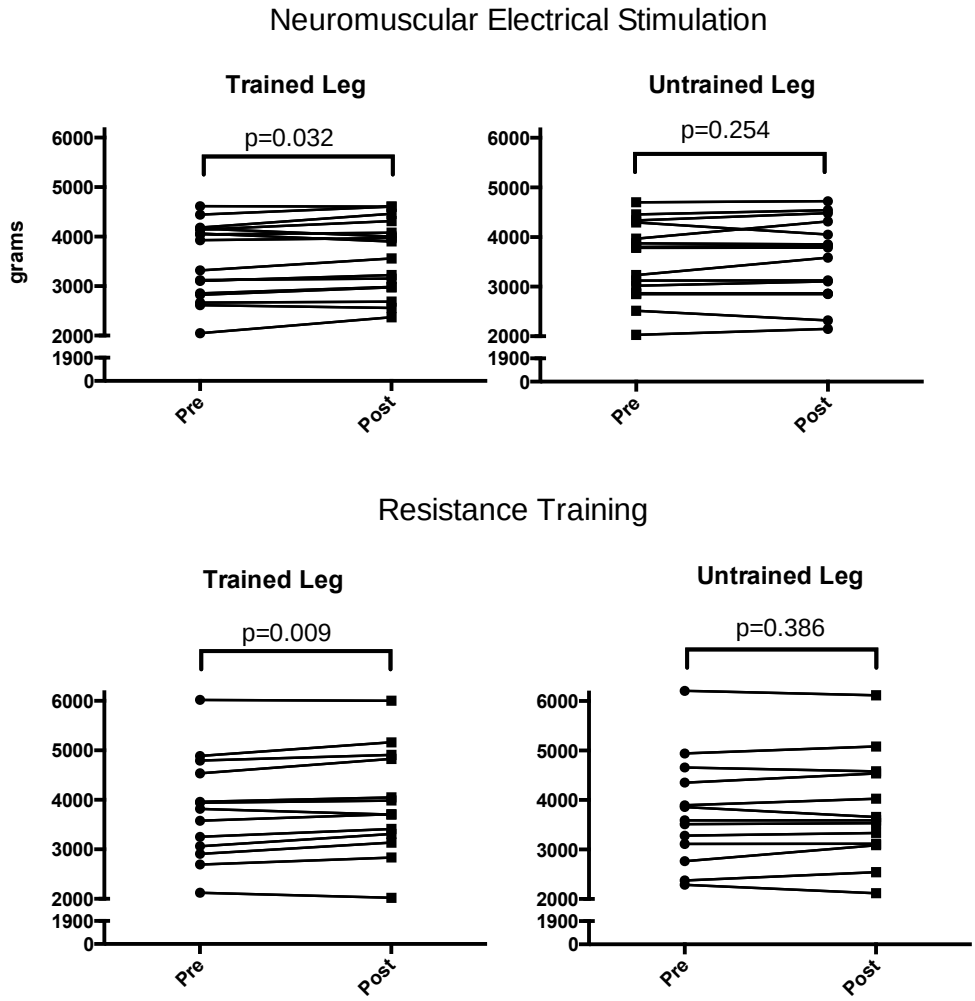
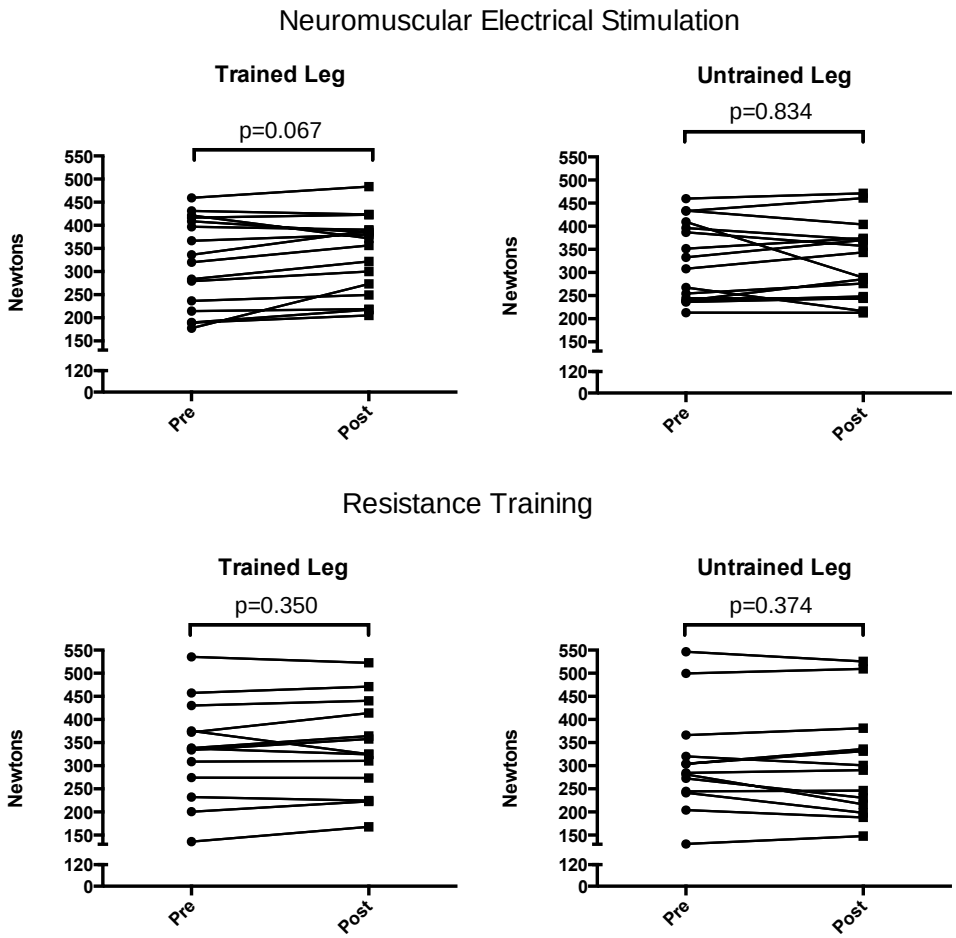


***Figure 6.4:*** *Quadriceps strength (N) pre and post intervention in the trained and untrained limbs for the (a) NMES group and (b) Resistance training group*



### *6.3.5 Muscle Cross sectional area ($Q_{csa}$)*

$Q_{csa}$ was significantly increased in the training limb for both intervention modalities (NMES $p<0.001$, resistance training $p=0.003$) following training. Mean $Q_{csa}$ for the NMES training limb increased from 5.04cm$^2$ (SD 1.72) to 5.91cm$^2$ (SD 1.76). In the resistance training group $Q_{csa}$ was 4.69cm$^2$ (SD1.81) and 5.39cm$^2$ (SD 1.66) pre and post. Individual subject values are shown in figure 6.5. When accounting for change in the control limb significant improvements in the trained limb were seen for both modalities (NMES $p<0.001$, resistance training $p=0.001$), Effect sizes were large for both groups, though higher for the NMES group (table 6.2). Change in $Q_{csa}$ expressed as percent are shown in figure 6.7c.

### *6.3.6 Muscle Thickness ($Q_{thick}$)*

$Q_{thick}$ significantly increased in the training limb for both intervention modalities (NMES $p=0.007$, resistance training $p=0.002$). Mean $Q_{thick}$ pre and post training was 22.4mm (SD 1.5) and 24.4mm (SD 1.4) for the NMES group and 23.1mm (SD 2.2) and 25.4mm (SD 1.9) for the resistance training group. Individual subject values are shown in figure 6.6. When accounting for change in the control limb significant increases were seen in both groups (NMES 0.002, resistance training $p<0.001$). Effect sizes were large with both groups and comparable with $Q_{csa}$ for the resistance training group (table 6.2). Change in $Q_{thick}$ expressed as percent are shown in figure 6.7d.

***Figure 6.5:*** *$Q_{csa}$ ($cm^2$) pre and post intervention in the trained and untrained limbs for the (a) NMES group and (b) Resistance training group.*

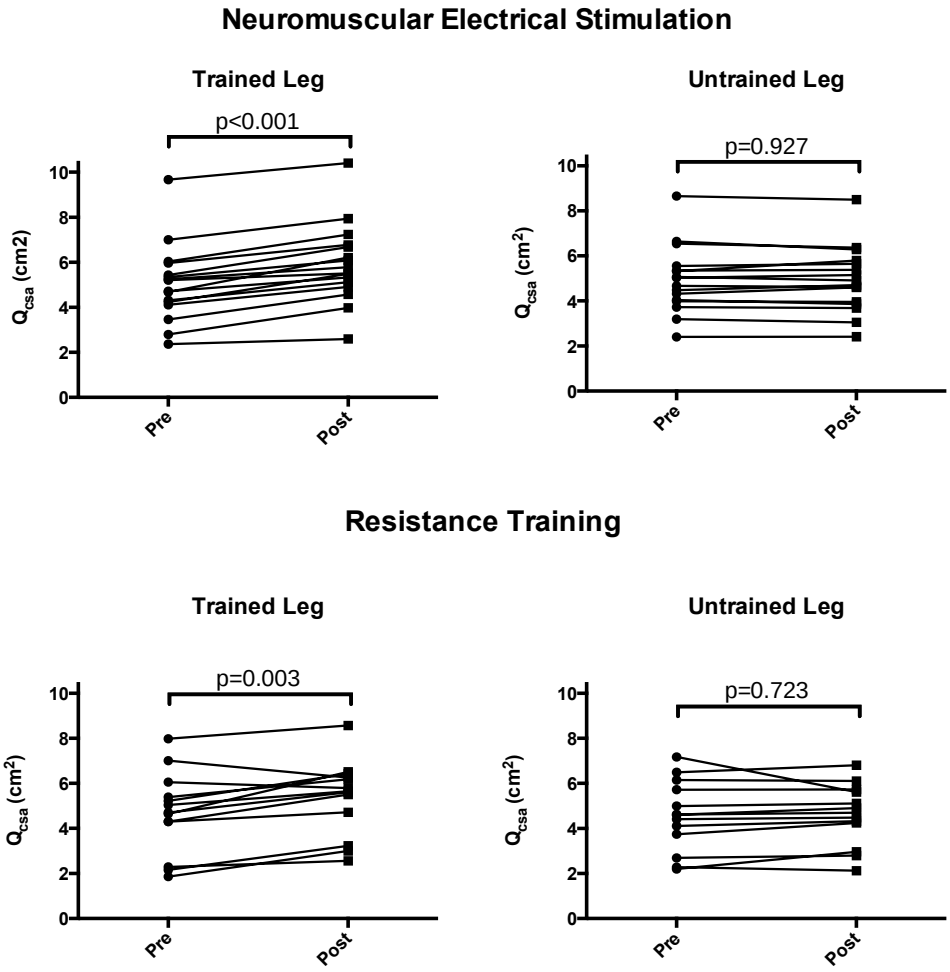


***Figure 6.6:*** *$Q_{csa}$ ($cm^2$) pre and post intervention in the trained and untrained limbs for the (a) NMES group and (b) Resistance training group.*

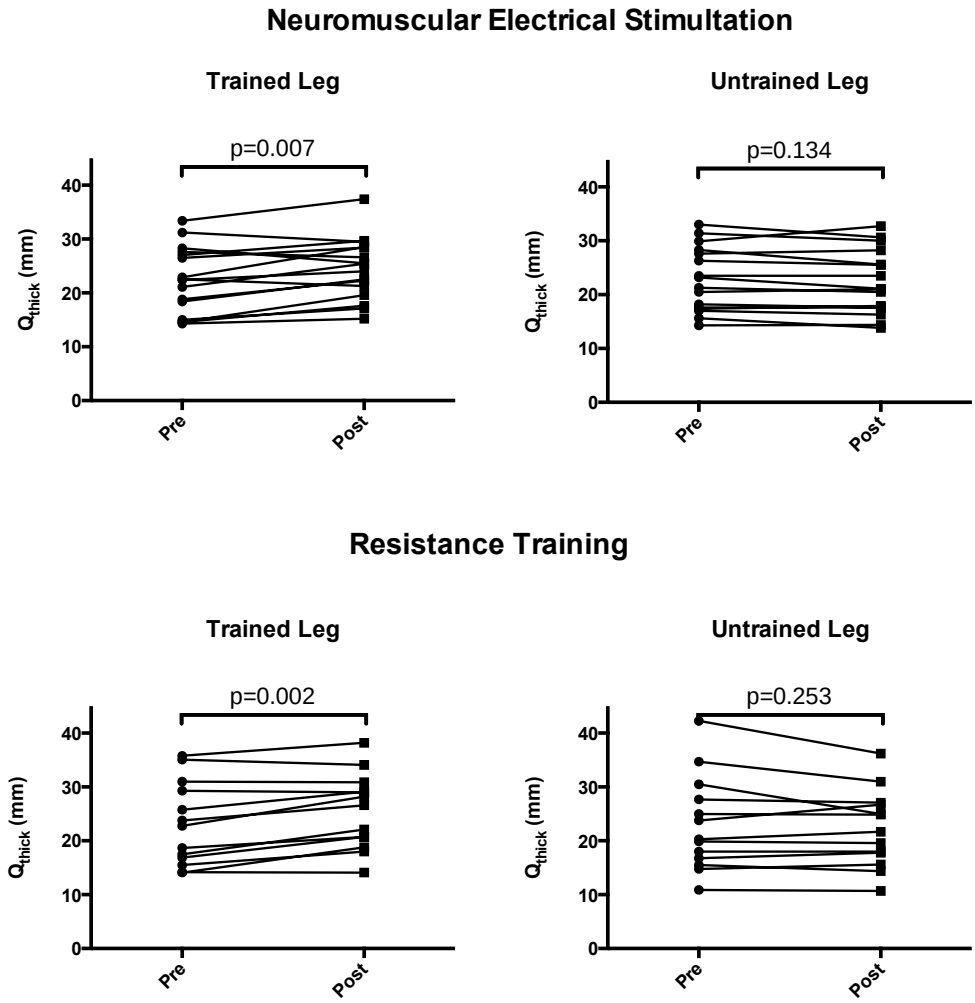


***Figure 6.7*** *(next page)  Percent change following training in the trained and untrained limbs for both training modalities. Changes are shown for measures (a) Thigh mass (g), (b) Quadriceps strength (N), (c) Rectus femoris cross sectional area ($cm^2$), (d) Quadriceps thickness (mm). Error bars are ±1SEM. P values represent 2 way repeated measures ANOVA showing the combined effects of time and control limb.*

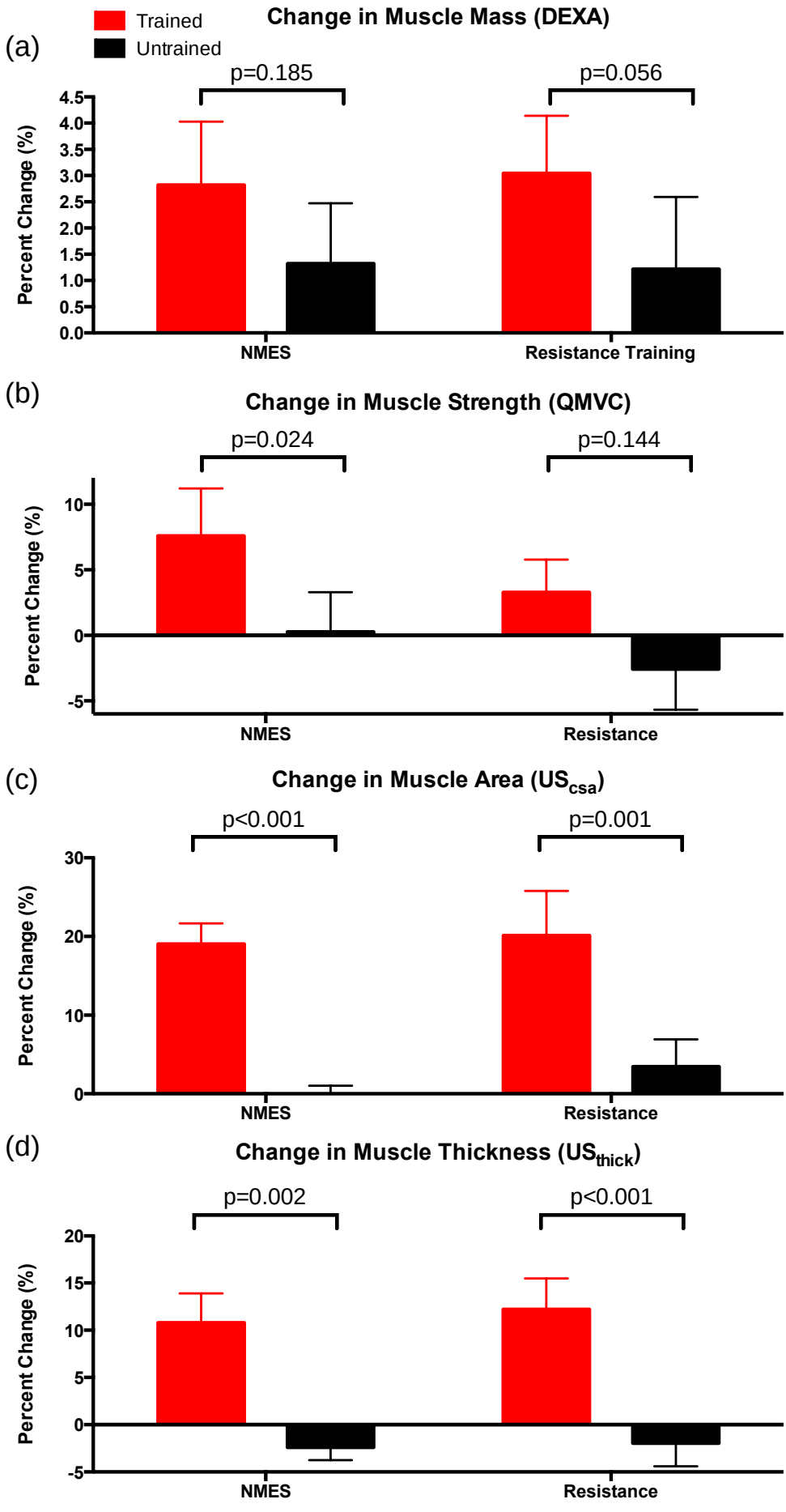

(a)
Trained
Untrained
Change in Muscle Mass (DEXA)
p=0.185
p=0.056
Percent Change (%)
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
NMES
Resistance Training
(b)
Change in Muscle Strength (QMVC)
p=0.024
p=0.144
Percent Change (%)
10
5
0
-5
NMES
Resistance
(c)
Change in Muscle Area (US$_{csa}$)
p<0.001
p=0.001
Percent Change (%)
30
20
10
0
NMES
Resistance
(d)
Change in Muscle Thickness (US$_{thick}$)
p=0.002
p<0.001
Percent Change (%)
20
15
10
5
0
-5
NMES
Resistance

***Table 6.3:*** *Effect size (Cohen's d) measures comparing trained and untrained limbs for the two training modalities*

| | NMES | Resistance Training |
|---|---|---|
| DEXA | 0.25 | 0.54 |
| QMVC | 0.49 | 0.52 |
| $Q_{csa}$ | 2.99 | 1.04 |
| $Q_{thick}$ | 1.25 | 1.33 |

## *6.4 Discussion*

In this chapter I have presented the effects of unilateral NMES on the quadriceps in COPD, alongside changes from resistance training. Significant changes in muscle size were seen in the trained limb for both training modalities. A differential response was seen depending on the outcome measure used. Ultrasound, using either rectus femoris cross sectional area or quadriceps thickness, appeared more sensitive to change.

In this chapter different measures of muscle function and size have been used. All measures were highly significantly correlated at baseline, but different changes in relative size and effect size were seen. Ultrasound, using either cross sectional area or thickness, showed greater magnitudes of change than regional thigh mass using DEXA. This is not surprising, as DEXA measures whole thigh mass, which includes the untrained hamstrings, which is unlikely to change with muscle specific training. Within the quadriceps itself alterations in muscle may also be regional. Mid thigh measures of rectus femoris may be more sensitive to change than the other muscle in the quadriceps, though this is unknown. Thigh mass, quadriceps thickness and rectus femoris also cannot be directly prepared as there constitute different

aspects of the quadriceps, which are not directly proportional to each other, i.e. changes in mass is related to muscle volume, not area.

The lack of change in quadriceps maximal voluntary contraction is surprising, given the changes seen in other measures, and progression in training intensity seen in both NMES and resistance training. Strength was assessed by means of an isometric test. Neither training modality, however, is specific for this measure. The resistance training comprised isokinetic training, so changes in isometric strength may be less pronounced. Other explanations are possible and discussed in the limitations below.

Interest in NMES as a training modality in COPD has been of interest for the past 10 years[172, 173]. Two systematic reviews have concluded that NMES is likely to improve strength in COPD[174, 175], though most of the individual trials do not achieve statistical significance. My findings are in keeping with these observations. Only one other study, published recently, has included a different training modality, as presented in this chapter[176]. This study by Sillen et al, had a resistance training group alongside 2 NMES training groups, of different NMES frequencies. Similarly to the study presented here they were not powered to compare resistance training and NMES, but observed similar benefits in the higher, 75Hz frequency NMES and resistance training group. No change was observed with the lower, 15 Hz frequency. In a different study thigh cross sectional area was noted to increase by approximately 6% using CT following quadriceps and calf NMES, though a proportionally larger increase in endurance performance was seen, rather than strength[178]. My findings also echo this study, though there is variation in the magnitude of change. This study by Vivodtzev et al, also performed

muscle biopsies, though the only effects seen were a shift from a catabolic to anabolic state.

There are a number of limitations to the study presented in this chapter. Firstly, the study was designed to provide the platform for investigation of the mechanistic processes underpinning NMES. This is continuing work and discussed further in chapter 7.

The measurement of the quadriceps using ultrasound has a number of advantages, but the technique has not yet been refined to be considered alongside the gold standards of MRI or CT. Two aspects of the technique should mean acknowledgement of caution in interpretation of the results. Firstly, the operator was not blinded to the training limb, which could potentially cause bias. Secondly, the position of the ultrasound probe is operator dependent and small changes in the angle the probe is held can alter cross sectional measures, though this can be minimized by visual feedback of the image. If these limitations can be overcome then ultrasound represents an easy, clinical measure that can be used in the acute setting[120].

Measures of strength were performed on a purpose build rig that has been extensively used in young, healthy subjects. However, COPD patients are more frail and it was noted during testing that some patients reported the test to be uncomfortable. While any discomfort was addressed, it is possible that factors other than maximal muscle contraction may have limited the performance.

Finally, the sample size was based on changes seen in quadriceps mass following a similar resistance training regime, and may have been underpowered. However, this was based on two-legged training, where cross-

education may result, when improvements are seen in an untrained leg when the other leg is trained.

This study, along with previous research, suggests that NMES has potential to be used on its own as a training modality. However, the benefits of NMES are confined to the training muscle and do not confer the benefits of whole body exercise. This means that interventions, such as those used in pulmonary rehabilitation, are likely to be of greater benefit. This echoes the findings of inspiratory muscle training, which improves dyspnoea but confers no benefit over pulmonary rehabilitation. NMES therefore has to identify its niche in clinical practice. This may be in patients who decline pulmonary rehabilitation, but are willing to use NMES at home. Some anticipatory caution needs to be had here; as if a patient lacks the motivation to undergo conventional pulmonary rehabilitation they may be less likely to progress NMES intensity. More likely the role of NMES may be in the acute setting, such as used in the early rehabilitation trial described in chapters 3 and 4. Here, where patients are very breathless and fatigued, NMES has potential benefit over conventional training, as it is both independent of effort and ventilatory limitation.

In conclusion NMES and resistance training show similar magnitudes of change following six weeks of single leg training. These improvements suggest that NMES, as a single intervention, may be a useful modality for quadriceps training in COPD, potentially in the acute setting. Ultrasound is a valid measure of muscle bulk, and sensitive to change following a training intervention.

# *Chapter Seven*

# Conclusions and Future Work

## *7.1 Introduction*

The aim of this thesis was to investigate the effects of hospitalisation and acute exacerbations of chronic respiratory disease on skeletal muscle dysfunction and assess if this could be ameliorated by a tailored early rehabilitation programme.

I have reported two intervention studies within this thesis; one a large RCT of an early rehabilitation intervention versus usual care and the functional results of another comprising single leg NMES, alongside a resistance training cohort. The early rehabilitation study was powered to detect a difference in future hospital readmissions, with functional performance outcomes also measured for the twelve month follow up period.

## *7.2 Summary of findings*

Chapters 3 described the health care utilisation of early rehabilitation versus usual care. No difference in readmission to hospital was seen or in number of hospital days for both intention to treat and per protocol analyses. Similarly no significant difference in number of hospital days spent in hospital in the subsequent year was seen. The study was adequately powered and a larger than expected proportion of patients were readmitted than expected (60%

versus 40%). This is the largest study within the field of peri-exacerbation pulmonary rehabilitation to date, capturing 233 patients readmitted and 599 total hospitalisations over two sites. It's findings, however, are in contradiction to several previous studies of post exacerbation pulmonary rehabilitation and the conclusions of the Cochrane review.

Unexpectedly, an increased mortality was seen at one year in the intervention group, only seen late on in the follow up period. It seems difficult to attribute this mortality difference to the intervention when it is so separated in time between cause and effect. However, this was observed in a randomised controlled trial, so cannot be dismissed. A number of possible explanations exist, including subtle case mix differences but also potentially adversely affecting behavioral change, or influencing patients to not take up pulmonary rehabilitation in the stable state, which is of proven benefit. This data, and another study by Fan et al[202], would strongly favour the need for a data monitoring committee for future work

Chapter 4 presented the functional outcomes measured at five time points over 12 months from the early rehabilitation trial. Large improvements were seen in physical performance, but this was mirrored in the usual care group, with the only difference in groups shown in the ESWT at six weeks. While there appeared to be some difference in those that were not readmitted, i.e. not re-exposed to the impact of a severe hospitalisation and readmission, this was not statistically significant.

The baseline measures of physical performance and quadriceps strength were striking in the overall weakness and disability of the patient cohort. Patients were considerable more limited than other studies of both pulmonary

rehabilitation and exacerbation cohorts, who tend to be treated as outpatients in the community. This questions whether this advanced frailty may render much of the population unsuitable for exercise rehabilitation interventions Significant natural recovery in the non-intervention group was unexpected. Previous data have suggested that improvements in quadriceps strength and exercise performance are not seen, or at least delayed, following hospitalisation in COPD[42, 122, 166]. Timing of measures and cohort characteristics make comparison with other trials difficult. It should also be considered that the non-intervention group received usual care, which consisted of ward based mobility assessment and advice, and this low level of intervention may be enough to account for the improvements seen.

Identification of factors that influence hospital readmission was the subject of chapter 5. Using a sub-group of the cohort from the early rehabilitation trial a measure of skeletal muscle dysfunction, quadriceps cross sectional area was independently associated with risk of hospital readmission, along with MRC dyspneoa grade and previous hospitalisation. The measure of quadriceps was done using bedside ultrasound. While this technique has been used previously this is the largest trial to date in chronic respiratory disease. The technique itself has benefit in that it can be conducted in the acute setting, where voluntary measures such as strength may be more difficult.

Predicting hospital readmission and mortality have been the subject of multiple studies and unsurprisingly the factors identifies depend on the measurements taken and the cohorts characteristics. This study, however, represents the importance of skeletal muscle dysfunction when considering the hospitalised population. It may also measure something different than

other scores such as the DECAF[115]. The DECAF score predicts inpatient hospital mortality so is likely to be linked to the severity of the admitting illness. Measures, such as rectus femoris cross sectional area are likely to represent a measure of the underlying patient condition, more like stable state MRC score or lung function. When considering the impact of an exacerbation a composite of the severity of the acute illness and the underlying condition should be taken into account.

In chapter 6 one aspect of the intervention from the early rehabilitation trial was studied in more detail. Neuromuscular electrical stimulation. This was performed on a single leg, allowing within subject comparison. It was also conducted alongside a resistance training group. Similar magnitudes of change were seen in the NMES and resistance for all measures, suggesting similar benefits to resistance training. Both were associated with significant increases from baseline in measures of mass and size, though not strength. NMES as a single intervention does appear to be effective as an intervention, and similarly akin to resistance training, providing intensity and progression can be maintained, to be considered as a training modality that could be used in the acute setting.

A number of limitations exist for the measures as discussed in chapter 6, but the apparent increased sensitivity of ultrasound as a measure of quadriceps change makes it an attractive tool for outcome measures. This also echoes previous data from the group[83]. Further work, as considered below, on refining the technique and ensuring quality control, is required before it could be used as a primary outcome measure.

### *7.3 Study limitations*

The main limitation of this thesis is around the intervention in the early rehabilitation trial. The question remains whether this was “intervention failure” or “failure to intervene”. As described in chapter one exercise training requires muscle overload and the intervention in this trial was unsupervised. Objective measures of the quantity and intensity for the outpatient part of the trial (on average 88% of the intervention period) was unknown, and therefore whether patients achieved the necessary training is also unknown. There are a number of potential explanations for this. Immediately post exacerbation patients will be more symptomatic and therefore less inclined or motivated to exercise. The other is that, overall, this group is too frail to participate effectively in an exercise based intervention. This is a realistic possibility as patients were much weaker than patients typically seen in the outpatient setting and also three-quarters were MRC dyspnoea grade 5 at time of exacerbation. There is some support of this in the stable COPD literature, as those housebound with MRC dyspnoea grade 5 do not obtain the same benefits as others[208].

For the NMES study a number of limitations exist around the measurements and sample size, as discussed in chapter 6. However the main limitation is not being able to link the functional changes to the mechanistic ones that underpin NMES. This is important as NMES stimulates muscle in a different mechanism to other training modalities as it bypasses Hennerman’s size principle. Understanding these differences may help allow the application of NMES into clinical practice, and maximize potential benefit. However, the NMES study was conducted in the stable population, and some caution may

be required when considering changes in the acute setting, where inflammation, hypoxia and corticosteroid therapy are different.

### *7.4 Future questions*

Post exacerbation pulmonary rehabilitation is recommended by national and international guidelines[146] and there is much focus in facilitating this in clinical practice. However, it is now known that the majority of patients refuse or are unable to attend[165]. The early rehabilitation trial presented in this thesis represents an important piece of additional knowledge that brining forward the timing will not work. It also raises questions around the general suitability of patients who are hospitalised for rehabilitation programmes. However, it does not mean that a line can be drawn through the area of peri-exacerbation rehabilitation for chronic respiratory disease. The question remains whether a modified rehabilitation intervention could be applied to a smaller sub-group of patients, which may be more intensive in nature.

In the past few years there has been much focus in the wider academic respiratory community around phenotyping of patients and the development of targeted therapy. A risk stratification approach, identifying potential responders to a rehabilitation therapy may therefore represent a better strategy for improving patient outcome.

The results from chapter 5 support this hypothesis, where the suggestion that those with a larger rectus femoris cross sectional area may respond to early rehabilitation. In reality this may already be echoed in post-exacerbation pulmonary rehabilitation where less than 10% of COPD patients hospitalised manage to complete the programme[165].

Identification of the non-responders may also be of benefit, as alternative strategies could be targeted to this cohort as well. These patients may well represent those that have progressed too far in the natural history of disease and disease modifying therapies not effective. More symptomatic guided therapy and pro-active palliative care may be more appropriate, improving patient outcome. This kind of strategy has already been trialed in the cancer populations with success[85].

One of the major aims of the NMES study was to explore the underlying mechanisms associated with this training modality. A considerable body of future work is planned for the muscle samples obtained during the study. Bilateral quadriceps biopsies were taken at three time points- baseline, 24 hours post first training session and 24 hours following the final training session. The samples have undergone immunohistochemistry to measure muscle fibre type and size, investigate the intramuscular inflammatory processes and muscle myogenesis including satellite cell activity. In addition further frozen samples are being analysed using gene array and networking techniques comparing the acute effects of NMES as a training modality compared to resistance training.

Ultrasound cross sectional area, similar to the early rehabilitation trial, was used in the NMES study. The sensitivity to change of ultrasound makes it an attractive tool as non-invasive and radiation free measure of the quadriceps. However, a number of methodological issues need to be addressed. Firstly, blinding and identification of the same plane of image is needed for longitudinal work. This could be solved by using anatomical landmarks from the ultrasound and the use of 3 dimensional (3D) volumetric scanning. In the

NMES study 3D scans of rectus femoris were taken at the same time as the 2D images (Flock of Birds, Hitachi). From these images muscle volume can be calculated, but also cross sectional area can be measured from set distances from landmarks such as tendon insertion to the muscle. This would address both blinding and variations in image. These data are currently being analysed, but proof of concept exists as changes in rectus femoris volume following resistance training using this technique within the unit are currently under peer review in a chronic kidney disease population.

### *7.5 Concluding remarks*

Severe exacerbations of chronic respiratory disease and hospitalisations undoubtedly mark a huge event in the course of patients' disease. I have demonstrated in this thesis that an intervention proven to be of considerable benefit in both the stable state, and later on in the recovery phase, is not efficacious when delivered at the time of hospitalisation.

The findings of the early rehabilitation trial may be the result of a number of factors but the overall frailty of this patient group is significant and suggests that future intervention studies should be aimed at those with rehabilitation potential. What the composition of a further rehabilitation programme in the acute setting would constitute remains to be identified. NMES certainly appears to be a modality of training suited to this environment, and increased nutritional input possibly including testosterone may be appropriate. One of the key times, however, will be to target the immediately post discharge phase, when most patients are too unwell to attend formal classes but close supervision of exercise is required to ensure maximal gain. Here, modern

technological approaches may be attractive, allowing health professionals "virtual supervision" of patients within their own home.

Addressing the adverse effects of exacerbations and hospital acquired disability is paramount to the management of advanced chronic respiratory disease, and the targeting of it's systemic effects, in particular skeletal muscle dysfunction remains appealing. However, the hospitalised population is frail and therapy must be tailored to individuals to minimize harm in addition to accelerating recovery and preventing future events.

# *Appendix 1*

# Patient Information Sheets

# and Consent Forms

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# Can rehabilitation delivered immediately on hospitalisation for an acute exacerbation of chronic respiratory disease improve long term health outcomes?
# "The REACH Trial"
# (Version 4 16/11/2010- GH)

Principal Investigator: Dr Neil Greening

Co- Researchers: Theresa Harvey-Dunstan
Dr Michael Steiner
Johanna Williams
Emma Chaplin
Laura Turner
Linzy Houchen

You may contact: Dr Neil Greening
0116 258 3652

This study is funded by Collaboration for Leadership in Allied Health Research and Care (CLAHRC).

You are being invited to take part in a research study, which is being conducted by the pulmonary rehabilitation team. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part. Thank you for reading this information.

## 1. What is the purpose of the study?

Patients with chronic respiratory disease (CRD) experience exacerbations or worsening of their symptoms which sometimes requires a hospital admission. Evidence strongly suggests that exacerbations cause levels of physical activity to decline and also increases the chance of readmission to hospital. Pulmonary rehabilitation has been proven to be beneficial for patients with stable CRD and improves levels of physical activity. However, we currently do not know the effects (on physical functioning, psychological state and long term health outcomes) of starting a rehabilitation programme immediately on hospitalisation for an acute exacerbation of CRD. This study is needed in

order to tell us whether or not an acute programme of rehabilitation during an exacerbation might be effective in improving patient care.

## 2. Why have I been chosen?

You have been identified by the team looking after you as a potential suitable participant for the study, because you have been admitted with a diagnosis of chronic respiratory disease (such as COPD, bronchiectasis or chronic asthma). We currently offer pulmonary rehabilitation as an outpatient to patients who have been in hospital with an exacerbation but would like to know if rehabilitation started immediately on admission to hospital will improve long term health outcomes. This will help us develop and improve our future services.

## 3. Do I have to take part?

It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive.

## 4. What will happen to me if I take part?

Once you have agreed to take part in the research you will be visited by a member of the research team. You will have an opportunity to ask any questions you may have, and you will be asked to sign a consent form to confirm your participation. With your permission we will also contact your consultant to check that they are agreeable to your participation. We don't know how effective starting the rehabilitation immediately on hospitalisation will be in improving long term health outcomes. To find out we need to make comparisons between the different approaches. We therefore put people into two groups. One group receives standard 'best usual care' and the other receives early rehabilitation (intervention). The results are compared to see if one approach is better than the other. To try to make sure the groups are the same to start with, each participant is put into a group by chance (randomly). There is a 50/50 chance of being allocated to either group.

Following baseline tests (see section 5 for explanation of tests) and randomisation, patients assigned to the standard care group will receive 'best usual care' from the medical and the multi-disciplinary teams managing them (such as physiotherapy and dietetics). Patients assigned to the rehabilitation (intervention) group will commence daily rehabilitation comprising an individually prescribed, progressive exercise programme and self management education advice. This will take place within 48 hours of admission.

Participants will be followed up for 12 months from the point of discharge from hospital. Outcomes will be measured on admission (baseline), discharge from hospital (or within 72 hours of discharge if discharge occurs over a weekend

or is arranged very quickly), six weeks (from the point of entry to the study), three months and 12 months (from date of discharge from hospital).

## 5. What do I have to do?

**Assessments**
You will be asked to complete the following assessments, regardless of which group you are allocated to. These will happen when you first start the study, just before discharge from hospital (or within 72 hours of discharge), 6 weeks after discharge, at 3 months and at 1 year.

Lung Function (Spirometry)
You will be asked to blow into a machine as hard as you can three times.

Exercise Performance
You will be asked to walk between two points at a set pace until you need to stop.

Muscle Strength
The strength of your thigh muscle will be measured using a strain gauge. This involves you sitting on a chair and extending your leg which is attached to a strap. An ultrasound scan will also be carried out to measure the amount of muscle in your thigh. This scan is painless and you will be asked to lie on a couch for a few minutes. By using a small amount of gel, an ultrasound probe is placed over the front of your thigh and some pictures will be taken.

Physical Activity Monitoring
Physical activity during your hospital admission will be recorded for the entire duration of the hospital stay using a portable, light weight activity monitor worn on the upper arm. You will then have the activity monitor at home on 2 other occasion (at 3 months and 12 months) for four days at a time.

Blood Test
At each visit we will also obtain a small blood sample from a forearm vein.

Health Status Questionnaires
You will be asked to complete some questionnaires about your health status. This will give us a guide to how breathlessness affects your daily life.

Muscle Biopsy
A small piece of muscle will be taken from the thigh. To perform the muscle biopsy, local anaesthesia is used to numb the area and a small needle is inserted through the skin into the thigh muscle. This will also include a DEXA scan. This scan measures the amount of muscle, fat and bone in your body. It is painless and requires you to lie flat for a few seconds. You will have 4 muscle biopsies and DEXA scans in total: at entry to the study, at 6 weeks, 3 months and 12 months. If you do not wish to have the biopsy it is possible to opt out of this and still take part in the rest of the study.

Discussion Group

At 12 months you will be asked if you would like to take part in a discussion group so that we can find out your experiences and feelings about your time in hospital and subsequent progress once home.

**Standard care group**
If you are assigned to the standard care group you will receive 'best usual care' from the medical and multidisciplinary teams managing you. Discharge and follow up management will be made by the clinical team at the acute hospital and then your GP as per usual.

**Intervention group**
If you are assigned to the rehabilitation (intervention) group, muscle strength exercise training will initially consist of using a muscle stimulation unit. This device produces a tingling sensation which is not uncomfortable and is designed to keep your muscles active during your hospital stay. We would ask that you place the pads on each thigh for 30 minutes a day for the duration of your hospital stay. You will have daily rehabilitation comprising an individually prescribed, progressive exercise programme. This will include upper and lower limb strength training as well as walking and self management education advice started within 48 hours of admission.

Once discharged home, you will receive fortnightly telephone calls from the rehabilitation team to offer support and encouragement. We will also check that you are progressing with the rehabilitation and to answer any queries that you might have.

## 6. What are the possible disadvantages and risks of taking part?

There are minimal identified risks to taking part in this research.

All participants in both groups will have blood samples at various time points. There may be minor discomfort at the site where the needle is inserted. All blood samples will be taken by a doctor or fully trained health professional.

The muscle biopsy is mildly uncomfortable and your thigh may ache for a day after the biopsy. If needed we can provide painkillers for you. There is a very small risk that the site of biopsy could bleed or become infected. All biopsies will be performed by a doctor who has been trained and has experience of the muscle biopsy procedure.

The DEXA scan involves a very small exposure to x-rays. This is much less than the amount involved in having a chest x-ray. A greater exposure would occur naturally from the environment if you were to take a two week holiday in Cornwall.

We appreciate that the wearing of an activity monitor might be a slight inconvenience for some patients. However, they are very light and we have used these monitors in recent research studies and have been very well tolerated by patients.

You will be asked to make three additional visits to hospital over a 12 month period. This is a potential inconvenience but in our experience, most patients are happy to attend. Travel expenses will be reimbursed or a taxi provided for these visits.

## 7. What are the possible benefits of taking part?

It is hoped that we may find that the rehabilitation intervention will benefit patients in terms of improved muscle strength, improved physical activity levels and will experience fewer readmissions to hospital. We would also hope that taking part in the research may help your understanding of the recovery process following an exacerbation. The study will inform both present and future pulmonary rehabilitation services therefore benefiting all CRD patients.

## 8. What if something goes wrong?

If you are harmed by taking part in this research project, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for a legal action but you may have to pay for it. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms would be available to you. Advice can also be sought from the Patient Advice and Liaison Service (PALS).

## 9. Will my taking part in this study be kept confidential?

All information that is collected about you during the course of the research will be kept strictly confidential. We will inform your GP that you are taking part in the study. Any information about you, which leaves the hospital, will have your name and address removed so that you cannot be recognised from it. Participants will not be identified in any subsequent written material; for example, numbers will be used to refer to participants' names. Results will be reported in such a way that completely preserves confidentiality.

## 10. What will happen to the results of the research study?

The results of this study will be circulated in medical journals, professional publications and presentations made at relevant conferences. Results will be reported in such a way that preserves confidentiality. You will receive a summary of the results.

11. **Who is organising and funding the research?**

This study is being funded by National Institute for Health Research (www.nihr.ac.uk) as part of the Collaboration for Leadership in Allied Health Research and Care (CLAHRC) in Leicestershire, Northamptonshire and Rutland (LNR).

12. **Who has reviewed the study?**

All research that involves NHS patients or staff, information from NHS medical records or uses NHS premises or facilities must be approved by an NHS Research Ethics Committee before it goes ahead. Approval does not guarantee that you will not come to any harm if you take part. However, approval means that the committee is satisfied that your rights will be respected, that any risks have been reduced to a minimum and balanced against possible benefits and that you have been given sufficient information on which to make an informed decision.

13. **Contact for Further Information**

If you have any concerns or other questions about this study or the way in which it has been carried out, you should contact the principal researcher Neil Greening – tel: 0116 2502762.

For further information please contact

Dr Neil Greening
Clinical Research Fellow
University Hospitals of Leicester NHS Trust
Glenfield Hospital
Groby Road
Leicester
LE3 9QP
0116 258 3652

Thank you for reading this information leaflet

## In Summary

**What is the purpose of the study?**
This study is needed in order to tell us whether or not an acute programme of rehabilitation during an exacerbation of chronic respiratory disease might be effective in improving patient care.

**Why have I been chosen?**
You have been identified by the team looking after you as a potentially suitable participant for the study.

**Do I have to take part?**
It is up to you to decide whether or not to take part.

**What will happen to me if I take part?**
You will be put in a group of either 'best usual care' or 'early rehabilitation', to see if one approach is better than the other.

**'Best usual care' group**
If you are assigned to the standard care group you will receive 'best usual care' from the medical and multidisciplinary teams managing you.

**'Early rehabilitation' group**
If you are assigned to the rehabilitation (intervention) group, you will receive:

- 30 min per day of muscle stimulation whilst in hospital
- Daily rehabilitation an individually prescribed exercise programme
- Fortnightly telephone calls from the rehabilitation team to offer support and encouragement for 6 weeks

**What do I have to do?**
You will be asked to complete the following assessments. These will happen on 4 occasions in the next year and includes:

- Lung Function (Spirometry)
- Exercise Performance
- Muscle Strength
- Physical Activity Monitoring
- Blood Test
- Health Status Questionnaires
- Muscle Biopsy & DEXA
- Discussion Group

**What are the possible disadvantages and risks of taking part?**
There are minimal identified risks to taking part in this research.

- You will have blood taken, which may cause minor discomfort.
- The muscle biopsy is mildly uncomfortable and has a very small risk that the site could bleed or become infected.
- The DEXA scan involves a very small exposure to x-rays.
- Wearing an activity monitor might be a slight inconvenience for some patients, but is usually very well tolerated by patients.
- There will be 3 additional visits to hospital over a year. Travel expenses will be reimbursed or a taxi provided for these visits.

**What are the possible benefits of taking part?**
It is hoped that we may find that the rehabilitation intervention will benefit patients. We would also hope that taking part in the research may help your understanding of the recovery process following an exacerbation.

**Will my taking part in this study be kept confidential?**
All information that is collected about you during the course of the research will be kept strictly confidential. We will inform your GP that you are taking part in the study.

University Hospitals of Leicester NHS
NHS Trust

**CLAHRC Rehabilitation Theme**

Participant Identification Number for this trial: _____

# Consent Form

## Can rehabilitation delivered immediately on hospitalisation for an acute exacerbation of chronic respiratory disease improve long term health outcomes?

Principal Investigator: Dr Neil Greening

Co-Researchers: Dr Michael Steiner
Johanna Williams
Theresa Harvey-Dunstan
Emma Chaplin
Laura Turner
Linzy Houchen

**Please initial box**

1. I confirm that I have read and understand the information sheet dated 16/11/2010 (version 4) for the above study and have had the opportunity to ask questions. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐
3. I understand that sections of any of my medical notes may be looked at by responsible individuals from regulatory authorities where it is relevant to my taking part in the research. I give permission for these individuals to have access to my records. ☐
4. I agree to take part in the above study. ☐
5. I agree to the muscle biopsy and DEXA scan section of the study ☐
6. I would like to be considered to take part in the group discussions at the end of the year. ☐
7. I agree to my GP being informed of my participation in this study. ☐

_____ _____ _____
Name of Patient Date Patient Signature

_____ _____ _____
Name of Researcher Date Researcher Signature

1 for patient; 1 for researcher; 1 to be kept with hospital notes

University Hospitals of Leicester NHS
NHS Trust
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# Patient Information Sheet

## "The Effects of Neuromuscular Electrical Stimulation on Quadriceps Muscle"

Principal Investigator: Dr Neil Greening

Co- Researchers: Ms Lorna Webb
Mrs Carolyn Sandland
Dr Michael Steiner

You may contact: Dr Neil Greening
01162502762

We would like to invite you to take part in our research study. Before you decide we would like you to understand why the research is being done and what it would involve for you. **One of our team will go through the information sheet with you and answer any questions you have.** We'd suggest this should take about 10 minutes.

Talk to others about the study if you wish. Ask us if there is anything that is not clear.

### 1. What is the purpose of the study?

Patients with chronic obstructive pulmonary disease (COPD) often have weak muscles, particularly muscles of the legs. Exercise training and strength training have been proven to be beneficial in the symptoms of COPD. However, this is not always practical, and other therapies to improve muscle strength have been developed. Neuromuscular electrical stimulation (NMES) is a new treatment. Whilst it has been shown to improve strength, it is not known how this improvement comes about. This study aims to further understand how NMES works.

### 2. Why have I been chosen?

You have been identified by the team looking after you as a potential suitable participant for the study. This is because you have COPD and this limits how far you can walk. You may have been identified either by your hospital doctor looking after you or by the pulmonary rehabilitation team at Glenfield. In total around 50 people will be invited to take part.

## 3. Do I have to take part?

It is up to you to decide to join the study. We will describe the study and go through the information sheet. If you agree to take part, we will then ask you to sign a consent form. You are free to withdraw at any time, without giving a reason. This would not affect the standard of care you receive.

## 4. What will happen to me if I take part?

The purpose of this research study is to compare 2 different types of leg exercise training. The groups are selected by a computer, which has no information about the individual (i.e. by chance).

In order to find out what the effects of these treatments are, you will be asked to attend the hospital for additional assessments before the start of the exercise programme and at the end.

You will be involved in the study for around 7 weeks. You would come to Glenfield Hospital 3 times a week.

**Exercise Programme** There will be 2 different types of training session, for which you will randomly receive one (which will be the same type throughout your involvement in the study). These are resistance training or neuromuscular electrical stimulation. Only one leg does the training so that we can compare the changes against the leg that does not train. The exercise programme will last for 6 weeks with three visits per week.

a. Resistance training. You will be asked to exercise one leg on a piece of equipment called a “Cybex”. This will involve extending your leg as hard as you can on the Cybex. We will ask you to do this 15 to 30 times (called “repetitions”). There will be up to five bouts of these repetitions. You will be able to rest between these bouts. Resistance training will take place 3 times per week at Glenfield Hospital.

b. Neuromuscular electrical stimulation. You will be asked to exercise one leg using neuromuscular electrical stimulation. 2 pads are placed on one of your thighs. A small current of electricity is passed through this, which causes the muscle to work. This would be on intermittently for 30 minutes. This is similar to both TENS machines and the devices advertised on TV to give you a flatter stomach. Neuromuscular electrical stimulation will be performed under supervised conditions 3 times per week at Glenfield Hospital and in 2 unsupervised sessions at home.

**Assessment Visits**

Visit 1. During this visit the study will be discussed with you and a medical history will be taken. You will be asked to perform breathing tests, which involves blowing down a tube. We will also ask you to have a practice run at your exercise programme

Visit 2. You will be asked to perform a test to measure strength in your thigh muscle. This involves sitting in a chair and extending your leg as hard as you can for a few seconds against resistance. During the strength test we will measure the electrical signals that your nerves are sending to your leg muscles using an EMG recorder. The EMG recorder works by attaching some sticky pads to the skin over your thigh muscles which send the information along small cables to a recording device.

You will also have a MRI scan and a DEXA scan. A MRI is scan of your thigh muscles (quadriceps) which takes about 20 minutes. It gives us a very accurate picture of your muscles. You would be lying down as the machine collects the information. The scan involves no radiation and is safe. A DEXA scan measures the amount of muscle, fat and bone in your body. It is painless and requires you to lie flat for a few seconds. You will also go on a exercise bicycle to test your fitness.

The exercise programme will start one to two weeks after visit 2.

Visit 3 On the first day you attend for the exercise programme we will take a small piece of muscle (approximately the size of a pin head) from your thigh. To perform the muscle biopsy, local anaesthesia is used to numb the area and a small needle is inserted through the skin into the thigh muscle. You will also have an ultrasound scan to measure the amount of muscle in your thigh. A blood test will be taken at the same time as the muscle biopsy. Your first exercise session of the programme will be performed after these tests.

Visit 4 The day after your first exercise session we will take another muscle biopsy from your thigh. We will also take another blood test.

The exercise training sessions will then continue 3 times per week for a total of 6 weeks. Visits for training sessions will normally last for about 45minutes.

Visit 5 On the day of your final exercise session we will repeat the MRI scan.

Visit 6 We will ask you to attend the day after your final exercise session, where we will take another muscle biopsy, repeat the ultrasound and DEXA scans and repeat the tests of muscle strength and EMG activity.

**5. Expenses**

We appreciate that you will be visiting the hospital on a number of occasions. We will pay for any travel and arrange taxis for you, or refund the cost for petrol and parking tickets.

**6. What will I have to do?**

Other than the training outlined above and assessment visits you will not have to make any changes to your lifestyle.

**7. What are the possible benefits of taking part?**

We would expect you to benefit from improvements in muscle strength as a result of the exercise programme, although this may not occur in all participants. We hope the information we get from this study will be helpful in understanding the problem of muscle wasting in patients with COPD and help develop treatments for this problem.

**8. What are the possible disadvantages and risks of taking part?**

The muscle biopsy is mildly uncomfortable and your thigh may ache for a day after the biopsy. If needed we can provide painkillers for you. There is a very small risk that the site of biopsy could bleed or become infected. All biopsies will be performed by a doctor who has been trained and has experience of the muscle biopsy procedure.

The DEXA scan involves a very small exposure to x-rays. This is a fraction of the dose involved in having a standard chest X-ray.

Although the training is only for one leg, it should not cause a limp or have any other effect on your ability to walk.

**9. What will happen to the samples that I have donated?**

The samples will be processed and securely stored at Glenfield Hospital by the research team. Some of the analysis will take place after the study has been completed and samples may be stored for up to five years. The samples you donate will not be tested for genetic diseases or other conditions. If you do not complete the whole study we will still use the samples that you have donated up to that point.

**10. What happens when the research study stops?**

The results of this study will be circulated in medical journals, professional publications and presentations made at relevant conferences. Results will be reported in such a way that preserves confidentiality. You will receive a summary of the results.

**11. What if there is a problem?**

If you are harmed by taking part in this research project, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for a legal action but you may have to pay for it. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms would be available to you. Advice can also be sought from the Patient Advice and Liaison Service (PALS).

**12. Will my taking part in this study be kept confidential?**

All information that is collected about you during the course of the research will be kept strictly confidential. We will inform your GP that you are taking part in the study. Any information about you, which leaves the hospital,

will have your name and address removed so that you cannot be recognised from it. Participants will not be identified in any subsequent written material; for example, numbers will be used to refer to participants' names. Results will be reported in such a way that completely preserves confidentiality.

**13. Who is organising and funding the research?**

This study is being funded by National Institute for Health Research (www.nihr.ac.uk) as part of the Collaboration for Leadership in Allied Health Research and Care (CLAHRC) in Leicestershire, Northamptonshire and Rutland (LNR).

**14. Contact for Further Information**

If you have any concerns or other questions about this study or the way in which it has been carried out, you should contact the principal researcher Neil Greening (0116 250 2762)

University Hospitals of Leicester NHS
NHS Trust

**CLAHRC Rehabilitation Theme**

Participant Identification Number: _____

## Consent Form

## "The Effects of Neuromuscular Electrical Stimulation on Quadriceps Muscle"

Principal Investigator: Dr Neil Greening

Co- Researchers: Lorna Webb
Caroline Sandland
Dr Michael Steiner

**Initial**

5. I confirm that I have read and understand the information sheet dated 05/01/11 (version 3) for the above study and have had the opportunity to ask questions. ☐
6. I understand that my participation is voluntary and I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐
7. I agree to donate as a gift a sample of tissue for research in the above project. ☐
8. We would like your permission to inform your GP of your participation in this study ☐
9. I understand that sections of any of my medical notes may be looked at by responsible individuals from regulatory authorities. I give permission for these individuals to have access to my records? ☐
10. Do you agree to take part in this study? ☐ Yes ☐ No

_____ _____ _____
Name of Patient Date Patient Signature

_____ _____ _____
Name of Researcher Date Researcher Signature

1 for patient; 1 for researcher; 1 to be kept with hospital notes

# *Appendix 2*

# BORG Exertion Score

## Rating of Perceived Exertion (RPE) Category Scale

| | |
|---|---|
| 6 | |
| 7 | Very, very light |
| 8 | |
| 9 | Very light |
| 10 | |
| 11 | Fairly light |
| 12 | |
| 13 | Somewhat hard |
| 14 | |
| 15 | Hard |
| 16 | |
| 17 | Very hard |
| 18 | |
| 19 | Very, very hard |
| 20 | |

# *Appendix 3*

## Reason for Termination of Shuttle Walk Tests

1) Chest pain
2) Speed
3) Joint pain
4) Leg fatigue
5) Other
6) Shortness of breath
7) Test complete

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