Enhancement of Cellular Adaptation to Physical Training in Chronic Obstructive Pulmonary Disease.
A Randomised Placebo Controlled Trial of Creatine Supplementation.

Thesis submitted for the degree of
Doctor of Medicine
at the University of Leicester

by

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June 2008
Declaration

I hereby declare that this thesis is my own work and that, to the best of my knowledge and belief, it contains no material that has been previously submitted or accepted for a higher degree award or written by another person.

Except where assistance has been acknowledged, the work described in this thesis was performed by myself during a period of research in the Department of Respiratory Medicine and Pulmonary Rehabilitation, Glenfield Hospital, Leicester. Emma Vincent oversaw pulmonary rehabilitation and the pulmonary rehabilitation team assisted with assessments and shuttle walk tests. Cardio-pulmonary exercise tests were carried out by myself and Melina Hall. Louise Sewell gave assistance during the biopsy procedure.

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Sarah Jane Deacon

20th May 2008
Acknowledgements

I am very grateful for all the support, patience and encouragement I have been given by my supervisor Professor Mike Morgan.

I am thankful for the invaluable support and enthusiasm Emma Vincent provided in ensuring pulmonary rehabilitation ran smoothly during the creatine supplementation trial. I would like to thank Professor Sally Singh and members of the pulmonary rehabilitation team: Louise Sewell, Rachael Collier and Jo Williams, for supporting me and allowing me into their department to complete this work.

The main body of work in this thesis was supported by a project grant from the British Lung Foundation. The Cybex reproducibility study was supported by a pump-priming grant from the University Hospitals of Leicester NHS Trust. Without this financial support this thesis would not have been possible. Thank you to Dr Mick Steiner for advice while writing grant applications and developing this project. I am grateful for the donation of the creatine, provided by Degussa AG, Germany.

Many thanks to Professor Paul Greenhaff for his collaboration, overseeing the laboratory analysis of muscle biopsy samples, performed by John Fox, and helping me to understand muscle physiology. I am appreciative of statistical advice given by Dr John Bankhart, at the Trent Institute for Health Services Research.

I am grateful for technical support and advice given by Richard Walton and Steve Wimpress on cardio-pulmonary exercise testing and to Melina Hall who assisted with exercise tests. The hospital pharmacy, especially Melanie and reception, was invaluable in dispensing supplements; packaged and randomised by Novalabs, Leicester, UK.

A big thank you to my work colleagues in the exercise laboratory, especially Rachael Evans and Lori Calvert for their support, chat and coffee.

Finally, I would like to thank my wonderful family, husband James and children, Benjamin and Jessica, for their constant support, love and patience while I wrote this thesis.
Abstract

Introduction: Chronic Obstructive Pulmonary Disease (COPD) is the commonest cause of disability due to lung disease in the UK. Skeletal muscle strength and bulk are reduced and have an impact on quality of life, survival and utilisation of health care resources. Improving physical performance is an important therapeutic goal and exercise training during pulmonary rehabilitation (PR) can reverse some of these effects.

Dietary creatine supplementation (CrS) has been shown to augment high-intensity exercise training in athletes and healthy elderly, thereby increasing muscle mass. Uptake is increased by exercise and is likely to be most beneficial when combined with training. Previous small studies looking at the effects of CrS during PR in subjects with COPD have shown conflicting results.

Hypothesis: CrS in association with aerobic exercise and resistance training will usefully augment the benefits of pulmonary rehabilitation.

Methods: This hypothesis was tested by a randomised double blind, placebo-controlled, parallel group trial of CrS during PR in patients with COPD (Chapters 4-6). One hundred subjects with COPD (mean (SD) age 68.2 (8.2) years, FEV₁ 44.0 (19.6) percent predicted) were randomised to receive creatine (22g/day loading for 5-days, maintenance 3.76g/d throughout PR) or placebo (lactose) supplements during 7-weeks of PR encompassing aerobic and resistance exercises. Baseline, post-loading and post-rehabilitation measurements included pulmonary function, body composition, peripheral muscle strength and functional performance (shuttle walking tests and cycle ergometry).

A protocol was developed for testing isokinetic strength in subjects with COPD, using a Cybex II dynamometer (Chapter 3). This included exploration of the
characteristics and reliability of isokinetic and isometric peripheral muscle strength measurements.

Peripheral muscle dysfunction contributes to exercise intolerance in COPD but our understanding about the metabolic adaptations in peripheral skeletal muscle during exercise is limited. A volunteer subgroup (n = 44) had quadriceps muscle biopsies in order to examine the changes in muscle metabolite concentrations, as a result of CrS during PR (Chapter 6).

Main Results: Eighty subjects completed the trial (38 creatine, 42 placebo). All outcome measures significantly improved after PR. There were no significant differences between groups post PR [mean (SD) change incremental shuttle walk distance 84 (79) m creatine vs. 83.8 (60) m placebo; p = 1.0, knee extensor work 19.2 (16) Nm creatine vs. 19.5 (17) Nm placebo; p = 0.9]. Muscle biopsies showed evidence of creatine uptake, although levels were not maintained over the 7-weeks of PR.

Conclusions: This thesis describes a large randomised, placebo-controlled trial, which demonstrates that CrS does not augment the substantial training effects of multidisciplinary PR for patients with COPD.
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Publications

Original Papers


Abstracts


SJ Deacon, SJ Singh & MD Morgan. Peripheral Muscle Isokinetic Strength in Chronic Obstructive Pulmonary Disease (COPD) is Variable over a 7-Week Period. *Am J Respir Crit Care Med* 2004; 169(7):A901.


SJ Deacon, MC Steiner, SJ Singh, and MDL Morgan. Can laboratory exercise tests predict the outcome of physical training in patients with severe COPD? *ERJ* 2002; 20(supp 38):19S.
## Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADP</td>
<td>Adenosine di-phosphate</td>
</tr>
<tr>
<td>AMP</td>
<td>Adenosine mono-phosphate</td>
</tr>
<tr>
<td>ATP</td>
<td>Adenosine tri-phosphate</td>
</tr>
<tr>
<td>ATS</td>
<td>American thoracic society</td>
</tr>
<tr>
<td>BIA</td>
<td>Bioelectrical impedance analysis</td>
</tr>
<tr>
<td>BMI</td>
<td>Body mass index</td>
</tr>
<tr>
<td>BS</td>
<td>Borg score</td>
</tr>
<tr>
<td>BTS</td>
<td>British Thoracic Society</td>
</tr>
<tr>
<td>BW</td>
<td>Body weight (mass)</td>
</tr>
<tr>
<td>CHF</td>
<td>Chronic heart failure</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence intervals</td>
</tr>
<tr>
<td>CT</td>
<td>Computerized tomography</td>
</tr>
<tr>
<td>COPD</td>
<td>Chronic Obstructive Pulmonary Disease</td>
</tr>
<tr>
<td>Cr</td>
<td>Creatine</td>
</tr>
<tr>
<td>CRQ-SR</td>
<td>Self-reported chronic respiratory questionnaire</td>
</tr>
<tr>
<td>CSA</td>
<td>Cross-sectional area</td>
</tr>
<tr>
<td>d·wk⁻¹</td>
<td>Days per week</td>
</tr>
<tr>
<td>DEXA</td>
<td>Dual energy x-ray absorptiometry</td>
</tr>
<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
</tr>
<tr>
<td>ERS</td>
<td>European Respiratory Society</td>
</tr>
<tr>
<td>ESWT</td>
<td>Endurance shuttle walk test</td>
</tr>
<tr>
<td>FEV₁</td>
<td>Forced expiratory volume in one second</td>
</tr>
<tr>
<td>FFM</td>
<td>Fat free mass</td>
</tr>
<tr>
<td>FFMI</td>
<td>Fat free mass index</td>
</tr>
<tr>
<td>FM</td>
<td>Fat mass</td>
</tr>
<tr>
<td>FVC</td>
<td>Forced vital capacity</td>
</tr>
<tr>
<td>g·d⁻¹</td>
<td>Grams per day</td>
</tr>
<tr>
<td>GOLD</td>
<td>Global Initiative for Chronic Obstructive Lung Disease</td>
</tr>
<tr>
<td>HADS</td>
<td>Hospital anxiety and depression scale</td>
</tr>
<tr>
<td>HR</td>
<td>Heart rate</td>
</tr>
<tr>
<td>HRQL</td>
<td>Health related quality of life</td>
</tr>
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</table>
### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMP</td>
<td>Ionosine monophosphate</td>
</tr>
<tr>
<td>ISWT</td>
<td>Incremental shuttle walk test</td>
</tr>
<tr>
<td>J</td>
<td>Joules</td>
</tr>
<tr>
<td>KE</td>
<td>Knee extension</td>
</tr>
<tr>
<td>Kg</td>
<td>Kilograms</td>
</tr>
<tr>
<td>mmol/kg dmm</td>
<td>Millimoles per kilogram of dry mater mass (weight)</td>
</tr>
<tr>
<td>MRC</td>
<td>Medical Research Council</td>
</tr>
<tr>
<td>MRS</td>
<td>Magnetic resonance spectroscopy</td>
</tr>
<tr>
<td>NICE</td>
<td>National Institute for Health and Clinical Excellence</td>
</tr>
<tr>
<td>Nm</td>
<td>Newton meters</td>
</tr>
<tr>
<td>1-RM</td>
<td>One-repetition maximum</td>
</tr>
<tr>
<td>PCr</td>
<td>Phosphocreatine</td>
</tr>
<tr>
<td>PE</td>
<td>Perceived exertion score</td>
</tr>
<tr>
<td>PFSDQ-M</td>
<td>Pulmonary functional status and dyspnoea questionnaire-modified</td>
</tr>
<tr>
<td>Pi</td>
<td>Inorganic phosphate</td>
</tr>
<tr>
<td>PMD</td>
<td>Peripheral muscle dysfunction</td>
</tr>
<tr>
<td>PR</td>
<td>Pulmonary rehabilitation</td>
</tr>
<tr>
<td>PT</td>
<td>Peak torque</td>
</tr>
<tr>
<td>ROM</td>
<td>Range of motion</td>
</tr>
<tr>
<td>RT</td>
<td>Resistance (strength) training</td>
</tr>
<tr>
<td>SaO₂</td>
<td>Oxygen saturation</td>
</tr>
<tr>
<td>6-MWD</td>
<td>6-minute walk distance</td>
</tr>
<tr>
<td>SD</td>
<td>Standard deviation</td>
</tr>
<tr>
<td>SEM</td>
<td>Standard error of the mean</td>
</tr>
<tr>
<td>SEₘ</td>
<td>Standard error of the measurement</td>
</tr>
<tr>
<td>SF-36</td>
<td>Short form-36</td>
</tr>
<tr>
<td>TCA cycle</td>
<td>Tricarboxylic acid cycle</td>
</tr>
<tr>
<td>TCr</td>
<td>Total creatine</td>
</tr>
<tr>
<td>[TCr]</td>
<td>Muscle total creatine concentration</td>
</tr>
<tr>
<td>TW</td>
<td>Total work</td>
</tr>
<tr>
<td>VO₂peak</td>
<td>Peak oxygen uptake</td>
</tr>
<tr>
<td>VO₂max</td>
<td>Maximal oxygen uptake</td>
</tr>
<tr>
<td>WR</td>
<td>Workrate</td>
</tr>
</tbody>
</table>
Chapter 1. Background and Literature Review

Introduction

The main aim of this thesis was to explore a particular performance-enhancing therapy in patients with chronic obstructive pulmonary disease (COPD). The impact of creatine monohydrate supplementation, during exercise training in the context of pulmonary rehabilitation, was investigated using a randomised placebo-controlled trial, described in Chapter 4. General methodology is described in Chapter 2. Results are presented in Chapters 4 to 6. Chapter 3 explores the reproducibility of isokinetic dynamometry as a measure of dynamic muscle performance in subjects with COPD, while developing an isokinetic testing protocol. A discussion of the overall results and conclusions from this thesis can be found in Chapter 7.

Chapter 1 is divided into three sections. Section 1.1 introduces COPD, describes healthy muscle function and reviews the literature and current evidence supporting the importance of peripheral muscle dysfunction in COPD. Section 1.2 describes current techniques available to assess performance in subjects with COPD; Section 1.3 explores therapeutic interventions available to enhance physical performance in this population, focusing on pulmonary rehabilitation and creatine monohydrate supplementation as an ergogenic aid.
1.1. Chronic obstructive pulmonary disease and peripheral muscle dysfunction

1.1.1. Chronic obstructive pulmonary disease (COPD)

Introduction

Chronic obstructive pulmonary disease (COPD), characterised by poorly reversible progressive airflow obstruction, is often associated with an abnormal inflammatory response in the lungs to noxious particles or gas, primarily cigarette smoke [Celli BR et al, 2004b; GOLD 2007, 2007]. COPD was initially defined as two components; chronic bronchitis coexisting with emphysema [Ciba Guest Symposium, 1959]. Chronic bronchitis clinically describes the presence of chronic cough with excessive sputum production most days, for at least 3 months per year, for more than 2 years. Emphysema is defined pathologically as the permanent, abnormal distension of air spaces (alveoli) distal to the terminal bronchiole with destruction of the alveolar walls [Honig EG et al, 1997]. The term COPD now encompasses chronic bronchitis, emphysema, chronic obstructive airway disease and chronic airways limitation.

Brief History of COPD

The word "catarrh" was used to describe the symptoms of chronic cough and mucus hyper-secretion associated with chronic bronchitis by Badham in 1814. Laënnec, who dissected lungs from patients whom he had previously examined, later described the emphysematous component of COPD [Petty TL, 2006]. He described the bronchus, "filled with mucous fluid" and hyperinflation, "the lungs do not collapse".
The spirometer, invented in 1846 by John Hutchinson, became fundamental to making the diagnosis and managing COPD [Petty TL, 2006]. The importance of history and physical examination were recognised in 1944 when Ronald Christie described "dyspnoea on exertion, of insidious onset...in a patient who has some physical signs of emphysema together with chronic bronchitis" [Petty TL, 2006]. Treatment was first contemplated in the text, *Pulmonary emphysema*, edited by Barach and Bickerman in 1956. Fletcher documented the association of smoking tobacco with the accelerated decline in FEV$_1$ and recognised that smoking cessation slowed the rate of decline to a rate approaching that of age-matched non-smokers [Fletcher C *et al.*, 1977; Peto R *et al.*, 1983].

The past 10 years have seen numerous guidelines published on the assessment and management of patients with COPD. The British Thoracic Society (BTS) published the first UK guidelines in 1997 [BTS guidelines, 1997]. The Global Initiative for Chronic Obstructive Lung Disease (GOLD), published by the World Health Organisation in 2002, increased awareness of COPD around the globe, providing a new classification of disease severity based on FEV$_1$ (forced expiratory volume in one second) [GOLD 2007, 2007; Pauwels RA *et al.*, 2001] (table 1.1). The National Institute for Health and Clinical Excellence (NICE) provided evidence based guidelines for making the diagnosis and to aid treatment at different stages of disease [Kerstjens HA, 2004; NICE, 2004]. The American Thoracic Society (ATS) and European Respiratory Society (ERS) then updated their guidelines, highlighting the increasing importance of COPD as a health problem, the growing impact on society and focused on advances made in the pathogenesis and management of the disease over the past decade [Celli BR, 2004b].
Chapter 1.1.1  Chronic obstructive pulmonary disease

**GOLD spirometric classification**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Spirometric classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I: Mild</td>
<td>FEV₁/FVC ≤ 0.70</td>
</tr>
<tr>
<td></td>
<td>FEV₁ ≥ 80% predicted</td>
</tr>
<tr>
<td>Stage II: Moderate</td>
<td>FEV₁/FVC ≤ 0.70</td>
</tr>
<tr>
<td></td>
<td>50% ≤ FEV₁ &lt; 80% predicted</td>
</tr>
<tr>
<td>Stage III: Severe</td>
<td>FEV₁/FVC ≤ 0.70</td>
</tr>
<tr>
<td></td>
<td>30% ≤ FEV₁ &lt; 50% predicted</td>
</tr>
<tr>
<td>Stage IV: Very Severe</td>
<td>FEV₁/FVC ≤ 0.70</td>
</tr>
<tr>
<td></td>
<td>FEV₁ &lt; 30% predicted or FEV₁ &lt; 50% predicted plus chronic respiratory failure.</td>
</tr>
</tbody>
</table>

**Table 1.1: GOLD spirometric classification of COPD severity.**

Simple spirometric classification of disease severity divided into four stages based on post-bronchodilator FEV₁, recommended by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) [Celli BR, 2004b; GOLD 2007, 2007]. Spirometry is essential for diagnosis and provides a useful description of the severity of pathological changes in COPD. Specific spirometric cut-points are used for purposes of simplicity: these cut-points have not been clinically validated. **Abbreviations:** FEV₁, forced expiratory volume in one second (percent predicted); FVC, forced vital capacity. Respiratory failure is defined as arterial partial pressure of oxygen (PaO₂) less than 8.0 kPa (60 mm Hg) with or without arterial partial pressure of CO₂ (PaCO₂) greater than 6.7 kPa (50 mm Hg) while breathing air at sea level.
Chapter 1.1.1  Chronic obstructive pulmonary disease

COPD today

The most recent guidelines define COPD as;

"a preventable and treatable disease with some significant extra-pulmonary effects that may contribute to the severity in individual patients. Its pulmonary component is characterized by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lung to noxious particles or gases." [GOLD 2007, 2007]

Airflow obstruction is defined as reduction in FEV₁ and FEV₁/FVC ratio (FVC, forced vital capacity), such that FEV₁ < 80% predicted and FEV₁/FVC < 0.7 [NICE, 2004]. Spirometric classification (tables 1.1 & 1.2), arterial blood gases, body mass index, timed walking distance, quadriceps strength and the patients sensation of dyspnoea, all determine disease severity and can predict health status and mortality [Celli BR, 2004b; Celli BR et al, 2004a; Swallow EB et al, 2007b].

<table>
<thead>
<tr>
<th>NICE spirometric classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severity</td>
</tr>
<tr>
<td>Mild airflow obstruction</td>
</tr>
<tr>
<td>Moderate airflow obstruction</td>
</tr>
<tr>
<td>Severe airflow obstruction</td>
</tr>
</tbody>
</table>

Table 1.2: NICE assessment of severity of airflow obstruction.
The severity of airflow obstruction assessed according to the reduction in forced expiratory volume in one second (FEV₁) as a percentage of the predicted value, described by the NICE guidelines [NICE, 2004].
Chapter 1.1.1 Chronic obstructive pulmonary disease

Symptoms may not be reported by 44% of people with severe airflow limitation [Mannino DM et al, 2000]. The diagnosis of COPD should be considered in any patient with symptoms of:

- chronic cough
- sputum production
- exertional breathlessness (dyspnoea)
- or history of exposure to disease risk factors.

COPD is a leading cause of morbidity and mortality worldwide, resulting in substantial and increasing economic and social burden [Celli BR, 2004b; GOLD 2007, 2007]. In 2004, nearly 900,000 people in the UK were diagnosed as having COPD and a further 450,000 were thought to be living with undiagnosed disease [NICE, 2004]. Population ageing means COPD, as a cause of chronic disability, is expected to increase worldwide in the next three decades [Murray CJ et al, 1997a].

Although smoking is believed to be responsible for over 95% of cases, only 10-20% of chronic heavy smokers develop COPD and COPD occurs in people who never smoke [Sandford AJ et al, 1997]. Other risk factors include occupational exposures, socioeconomic status and genetic predisposition [BTS guidelines, 1997; Celli BR, 2004b]. COPD is the leading respiratory disease causing lost work days within the EU, 1 in 8 emergency hospital admissions and 30,000 deaths in the UK each year [NICE, 2004]. It is expected to be the third biggest killer in the world by 2020 [Celli BR, 2004b; Murray CJ et al, 1997b; Petty TL, 2006].
Management of COPD

COPD is the commonest cause of disability due to lung disease in the UK. Peripheral muscle weakness is common and may predict mortality [Swallow EB, 2007b]. Patients become disabled by their inability to carry out activities of daily living because of exercise intolerance, leading to social isolation, depression and dependence, with an increased burden on carers (figure 1.1). Lung damage in COPD is irreversible and smoking cessation is most important in preventing further damage. Inhaled therapies, such as bronchodilators, can control symptoms and improve exercise capacity and corticosteroids can decrease exacerbation frequency in patients with an FEV₁ ≤ 50% and ≥ 2 exacerbations per year [NICE, 2004]. Unfortunately, therapy aimed at improving lung function frequently fails to meet patients' needs. Quality of life, emotional and social difficulties are addressed through pulmonary rehabilitation programmes. The combination of exercise training, education, psychosocial/behavioural intervention and nutritional therapy, aim to restore independence and functioning within the community. Pulmonary rehabilitation will be discussed in greater detail later (Section 1.3.1). NICE guidelines state that:

"Pulmonary rehabilitation should be offered to all patients who consider themselves functionally disabled by COPD (usually MRC grade 3 and above)" [NICE, 2004].

COPD is now recognised as a systemic illness effecting nutritional status, causing muscle wasting and depression [Fabbri LM et al, 2007]. Patients with only mild disease may have significant cardiovascular physiological impairments leading to exercise intolerance and deconditioning. This awareness has led to great deal of research into understanding the metabolic and musculoskeletal consequences of the disease, which are addressed later (1.1.3) [Petty TL, 2006].
Figure 1.1: Spiral of disease progression.
Schematic diagram showing the spiral of disease for COPD. Dyspnoea leads to reduced activity and deconditioning, causing further symptoms at lower levels of activity and resulting in disability.
1.1.2. The structure and function of healthy skeletal muscle.

Introduction

This section describes the structure of healthy skeletal muscle and the pathways by which energy, in the form of adenosine triphosphate (ATP), is replenished during muscular activity. An understanding of normal muscle function is required before the nature of peripheral muscle dysfunction in COPD is considered.

Skeletal Muscle Ultrastructure

Skeletal or striated muscle makes up the bulk of the body's musculature and is responsible for voluntary movements during daily activities. Individual muscles are composed of parallel bundles of multinucleate muscle fibres, each consisting of a syncytium of myofibrils (fused muscle cells), bound by an electrically excitable plasma membrane, the sarcolemma. Myofibrils comprise two kinds of protein filaments (myofilaments), thick myosin filaments and thin actin filaments, which overlap to give a striated appearance (figure 1.2). Myofibrils are segmented into functional units, sarcomeres, and immersed in a cytosol, the sarcoplasm, which is rich in glycogen, ATP, phosphocreatine, mitochondria and enzymes [Maughan R et al, 1997; Stryer L, 1988].

A single central nerve ending innervates each muscle fibre across a special synapse, the motor end plate. When an impulse causes propagation of an action potential along a nerve fibre, a neurotransmitter, acetylcholine, is released from the nerve ending. This activates muscle cell membrane receptors, transmitting electrical excitation along the sarcolemma and down T-tubules, releasing calcium from the sarcoplasmic reticulum (SR), leading to a sequence of events known as excitation-contraction coupling.
Chapter 1.1.2 Healthy skeletal muscle

Figure 1.2: Schematic diagram of the structure of a myofibril in striated muscle.
Individual muscles are composed of parallel bundles of multinucleate muscle fibres, each consisting of a syncytium of myofibrils. Myofibrils are segmented into functional units, sarcomeres, consisting of two kinds of protein filaments (myofilaments). Thick filaments, primarily myosin, each with 2 globular heads with ATPase activity and thin filaments, formed of actin molecules, overlap giving muscle fibres a striated appearance under light microscope. Six thin filaments encircle each thick filament. I band, only thin filaments; H zone of A band, only thick filaments, anchored by Z line.

Calcium, released from the SR, binds to troponin on the actin filament. This causes a conformational change, exposing a binding site, which interacts with globular myosin heads to form actomyosin. Myosin heads have ATPase enzyme activity, providing free energy, which drives muscular contractions. As ATP is hydrolysed (figure 1.3), cross-bridge formation between the thick and thin filaments causes them to slide past each other, reducing sarcomere length. Cyclical formation and dissociation of actomyosin produces a smooth continuous contraction, as the muscle shortens, force is generated [Maughan R, 1997; Stryer L, 1988].
Chapter 1.1.2 Healthy skeletal muscle

Muscle Fibre Types

Muscle fibres can be differentiated according to their speed of shortening and relaxation. The slower the force is generated, the less powerful the performance of the contraction. "Fast" fibres contract quickly, producing rapid movement, but at relatively high metabolic cost. Human skeletal muscle fibres are categorised histochemically according to the myosin heavy chain isoform present, which determines their physiological and metabolic characteristics (table 1.3). [Gosker HR et al, 2000; Maughan R, 1997; Spangenburg EE et al, 2003].

<table>
<thead>
<tr>
<th>Myosin heavy chain</th>
<th>Type I</th>
<th>Type II subtypes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human gene</td>
<td>MYH7</td>
<td>MYH2</td>
</tr>
<tr>
<td>Average percentage in human Vastus Lateralis muscle</td>
<td>40%</td>
<td>30%</td>
</tr>
<tr>
<td>Anatomical colour</td>
<td>Red</td>
<td>Red</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Aerobic (oxidative)</td>
<td>Aerobic/Anaerobic</td>
</tr>
<tr>
<td>Contractile velocity</td>
<td>Slow</td>
<td>Moderately fast</td>
</tr>
<tr>
<td>Fibre CSA</td>
<td>Small</td>
<td>Medium</td>
</tr>
<tr>
<td>Endurance</td>
<td>High</td>
<td>Medium</td>
</tr>
<tr>
<td>Fatigue resistance</td>
<td>High</td>
<td>Fairly high</td>
</tr>
<tr>
<td>Tension generated</td>
<td>Low</td>
<td>Medium</td>
</tr>
<tr>
<td>Mitochondrial density</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Capillary density</td>
<td>High</td>
<td>Intermediate</td>
</tr>
</tbody>
</table>

Table 1.3: Characteristics of human fibre types.

Abbreviations: MYH, myosin heavy chain; CSA, cross-sectional area. Adapted from [Maughan R, 1997; Spangenburg EE, 2003].
Energy Metabolism

All cells use ATP as an immediate energy source for metabolic processes. Energy is liberated as phosphate is enzymatically removed from ATP in a reversible reaction catalysed by adenylate kinase (figure 1.3). ATP stores are limited and can only sustain 2-seconds of maximal contraction. In order to sustain high power output ATP must be regenerated. Pathways involved in the resynthesis of ATP include anaerobic metabolism; the glycolytic and phosphagen systems and aerobic metabolism; oxidative phosphorylation (figure 1.4) [Maughan R, 1997].

\[ \text{ATP} + \text{H}_2\text{O} \rightleftharpoons \text{ADP} + \text{P}_i + \text{H}^+ \]

*Adenylate kinase*

**Figure 1.3**: Schematic diagram showing the hydrolysis of adenosine triphosphate. Diagram to show the chemical reaction of adenosine triphosphate (ATP) hydrolysis, catalysed by adenylate kinase, forming adenosine diphosphate (ADP), inorganic phosphate (P_i) and free hydrogen (H^+).

Anaerobic Metabolism

Phosphagen system

Phosphocreatine (PCr) hydrolysis contributes to ATP resynthesis during the initial seconds of exercise. PCr transports a phosphate molecule from mitochondrial ATP into the cytoplasm for phosphorylation of ADP. The splitting of PCr releases energy which drives phosphorylation, buffering the rapid accumulation of ADP and protons produced by ATP hydrolysis (figure 1.5) [Maughan R, 1997; Persky AM et al, 2001; Tarnopolsky MA, 2000a].
Chapter 1.1.2 Healthy skeletal muscle

Figure 1.4: Cellular energy metabolism.
Schematic diagram showing aerobic and anaerobic pathways, within the muscle cell cytoplasm and mitochondria, involved in the resynthesis of ATP during muscle contractions. Pathways described in more detail within text. Resynthesis of PCr occurs within the inter-mitochondrial space during recovery periods. Abbreviations: ATP, adenosine triphosphate; ADP, adenosine diphosphate; PCr, phosphocreatine; Cr, creatine; TCA, tricarboxylic acid; H₂O, water; CO₂, carbon dioxide; CK, creatine kinase (c, cytoplasmic; m, mitochondrial). NADH (nicotinamide adenine dinucleotides) and FADH₂ (flavin adenine dinucleotides) each contain a pair of electrons and therefore have high energy transfer potential.
PCr + ADP + H⁺ \rightarrow \text{Creatine + ATP}

Cytosolic creatine kinase

Figure 1.5: Schematic diagram of hydrolysis of phosphocreatine (PCr).
Diagram to show the chemical reaction of phosphocreatine (PCr) hydrolysis within the cytoplasm, catalysed by creatine kinase. Hydrolysis involving free hydrogen (H⁺) causes the transfer of phosphate to adenosine diphosphate (ADP) forming adenosine triphosphate (ATP). PCr has a higher phosphate-group transfer potential than ATP, which means the free energy of PCr hydrolysis is greater than ATP leading to the rapid transfer of phosphate from PCr to ADP to reform ATP. Momentary rise in ADP concentration is the primary stimulus to PCr hydrolysis via this reaction.

The creatine kinase reaction is reversible following exercise. Cellular concentrations of ATP, ADP and creatine (Cr) can influence the resynthesis of PCr. Free Cr is transported into the inter-mitochondrial space where mitochondrial creatine kinase catalyses PCr resynthesis [Maughan R, 1997; Persky AM, 2001; Tarnopolsky MA, 2000a]. Hydrogen ions (H⁺) are potent inhibitors of creatine kinase therefore low muscle pH; low oxygen (O₂) tension or reduced blood flow can impair PCr resynthesis after exercise.

PCr is stored in the cytosol of resting skeletal muscle at concentrations of 70-80 mmol/kg dmm. The ATP-PCr system provides energy at high rates during maximal exercise, but only for a few seconds before PCr stores are emptied. Dietary creatine supplementation might be beneficial by increasing Cr and PCr intracellular concentrations, extending ATP production beyond its normal 3-6 seconds of availability, theoretically supplying immediate energy required to continue acceleration during a sprint or to generate increased muscle force [Gilliam JD et al, 2000; Paddon-Jones D et al, 2004; Preen D et al, 2003]. Creatine may also
regulate glycolysis and stimulate muscle protein synthesis [Volek JS et al, 1999]. Creatine monohydrate supplementation is discussed in more detail later (1.3.3).

Glycolytic system

In high-intensity exercise, the majority of energy demand is met by energy released during carbohydrate breakdown (intramuscular glycogen or blood glucose). The availability of carbohydrate as fuel commonly limits performance. The initial steps of carbohydrate degradation, anaerobic glycolysis, are a sequence of reactions that convert glucose into pyruvate. In low-intensity exercise, pyruvate enters mitochondria and is oxidised by oxygen-dependent systems (oxidative phosphorylation, explained below). In more intense exercise, pyruvate is removed by conversion to lactate (glycolytic metabolism), producing ATP (2 molecules per glucose and 3 molecules per glycogen molecule). The glycolytic system, activated at the onset of exercise, produces energy more slowly than the phosphagen system, but has a greater capacity [Maughan R, 1997].

Aerobic Metabolism

In the presence of O₂, pyruvate and the breakdown products from lipid and protein catabolism enter mitochondria and are converted into a common metabolite, Acetyl-Coenzyme A. This molecule enters the final aerobic pathway, the tricarboxylic acid (TCA/Krebs) cycle and is degraded forming carbon dioxide (CO₂) and H⁺. The electron transport chain transfers H⁺ to O₂ to form water, driving oxidative phosphorylation and the resynthesis of ATP from ADP. One glucose molecule produces 38 molecules of ATP [Maughan R, 1997; Stryer L, 1988].

Energy production during high-intensity exercise

Submaximal steady-state exercise is achieved by the mitochondrial oxidation of carbohydrate and lipid stores, regenerating ATP. However, during high-intensity exercise the slow activation and rate of energy delivery of oxidative phosphorylation cannot meet the initial energy requirements and anaerobic metabolism becomes the dominant system of ATP resynthesis [Maughan R, 1997].
Chapter 1.1.2  
Healthy skeletal muscle

Anaerobic activation of energy delivery via the ATP-PCr system is instantaneous. PCr degradation is at its maximum within 2-seconds of the initiation of contraction, declining after only 1.3-seconds, buffering the lag in provision of ATP from glycolysis. Anaerobic glycolysis reaches maximum rates after 5-seconds and by 30-seconds, ATP resynthesis is double that from PCr degradation, but results in high muscle-lactate concentrations. Muscle glycogen stores are broken down rapidly, supplying energy for maximum-intensity effort for 20-second to 5-minutes. Oxidative metabolism becomes progressively more important as the duration of exercise increases [Maughan R, 1997].

The phosphagens are the major source of energy during short durations of high-intensity exercise (<15 seconds) and stores are commonly completely degraded. During intermittent, repeated bouts of exercise with rest periods, rates of PCr hydrolysis decline. This is related to the extent of PCr resynthesis during rest periods, limiting anaerobic ATP resynthesis during the next exercise bout. Resting PCr and glycogen concentrations are higher in Type II fibres (PCr 10-20 mmol higher than type I) but PCr resynthesis rate is significantly lower during initial recovery, which can adversely affect further performance. Intense contractions result in higher rates of glycogenolysis and PCr degradation in these fibres [Maughan R, 1997].

Muscular Changes in the Healthy Elderly

Sarcopenia

Sarcopenia, defined as age-related loss of skeletal muscle mass, strength and quality, is characterised by neurogenic, metabolic and morphological changes. These include loss of muscle fibres, altered contractility, changes in protein synthesis and diminished myofibrillar regeneration [Brouwer B et al, 2004]. It accounts for: age-related decreases in basal metabolic rate and muscle strength; increased risk of falls; reduced mobility and function, reducing independence and quality of life [Evans WJ, 1999].

Muscle mass is the major determinant of age and sex-related differences in strength [Evans WJ, 1999]. Muscle strength decreases by 30-40% between 30-80 years of age and correlates well with reduced muscle mass [Celli BR, 2004b]. After 50 years of age, muscle mass declines by 6% and strength by 12-14% per decade [Brouwer B, 2004]. Quadriceps muscle isometric and dynamic strength increase until the age of 30, begins to decrease after 50 and decline dramatically after 70 years of age [Position stand, 1998]. A strong relationship between quadriceps strength and walking speed in subjects over 86 years of age has been made [Fiatarone MA et al, 1990].

Strength relies on fibre composition, recruitment of motor units and the type of muscle action. Muscle mass is influenced by cellular remodelling and protein synthesis, both influenced by highly independent intrinsic (physiological) and extrinsic (health and lifestyle) factors (figure 1.6) [Brouwer B, 2004].

Intrinsic factors

Degenerative changes have been demonstrated showing a reduction in the number of functional motor units innervating muscles by 40-50% after 60 years of age, in association with a 47% reduction in maximal isometric contraction of the elbow flexors [Charette SL et al, 1991]. Age-related loss of motorneurons preferentially affects the larger, fast twitch type II fibres, which decrease from an average of 60% to below 30% after 80 years of age and is directly related to age-related decreases in strength [Position stand, 1998]. Protein synthesis declines in the elderly, reducing myofibrillar and mitochondrial protein production, contributing to muscle wasting and reduced oxidative and endurance capacity in aging muscle [Brouwer B, 2004].
Chapter 1.1.2 Healthy skeletal muscle

1.1.3. The nature of peripheral skeletal muscle dysfunction in COPD

Peripheral Muscle Weakness

Historically, the Inability to do the work of breathing, dynamic hyperinflation and limitations in gas exchange have been thought to be the principal factors in ventilatory muscle weakness. However, pulmonary function may improve with exercise training, and most lung transplant recipients have reduced exercise capacity [Levy et al., 1999]. Several studies have observed that symptoms during exercise are predominantly normal controls [Kvile, 1992].

Figure 1.6: Intrinsic and extrinsic factors contributing to age-related declines in muscle strength and mass.

The reciprocal relationship between intrinsic and extrinsic factors which contribute to age-related declines in muscle strength and loss of muscle mass [Brouwer B, 2004].

Extrinsic factors

Nutrition and protein intake are strongly linked to muscle mass and strength. Inactivity and deteriorating health status further depress muscle protein metabolism and cell regeneration and can increase protein degradation, leading to disuse atrophy. Disuse atrophy is initially associated with type I fibres but rapidly involves all fibre types [Gosker HR et al, 2002a]. Disuse and malnutrition are potentially preventable and reversible.
1.1.3. The nature of peripheral skeletal muscle dysfunction in COPD

Peripheral Muscle Weakness

Historically, the inability to increase pulmonary ventilation due to the work of breathing, dynamic hyperinflation and limitations in gas exchange, have been thought to be the principal determinants of exercise intolerance [ATS, 1999; Gallagher CG, 1994; O'Donnell DE, 1994]. Impairment in lung function however poorly predicts exercise capacity [Wasserman K et al, 1989]. Pulmonary function may improve with medication but this does not clearly benefit exercise capacity and most lung transplant recipients, with normalised lung function, still have reduced exercise capacity [Levy RD et al, 1993; Maltais F et al, 2000a].

Several studies have observed that symptoms limiting exercise are predominantly leg effort, or fatigue, and exertional dyspnoea [Hamilton AL et al, 1995; Killian KJ et al, 1992a; Maltais F, 2000a]. Leg effort during cycle ergometry is perceived to be the main exercise-limiting symptom in 40-45% of patients with COPD. Dyspnoea limited exercise more frequently (26%) in subjects with severe COPD (FEV₁ ≤ 40%) while symptom limitation was similar in subjects with mild-moderate COPD to normal controls [Killian KJ, 1992a].

Peripheral muscle weakness, commonly observed in patients with COPD, is increasingly recognised as an exercise-limiting factor and is associated with increased utilisation of health care services [Decramer M et al, 1997]. Quadriceps strength is reduced by 30% in patients with moderate-severe COPD and may predict mortality [Maltais F, 2000a; Swallow EB, 2007b]. Positive correlations have been shown between quadriceps strength and peak exercise capacity and improvements in quality of life occur after strength training [Gosselink R et al, 1996; Hamilton AL, 1995; Simpson K et al, 1992]. There is a large volume of evidence
indicating that peripheral skeletal muscle dysfunction (PMD), characterised by muscle atrophy, weakness and low oxidative capacity, is related to exercise intolerance, poor quality of life and reduced survival in patients with COPD. The evidence suggests that impaired functional capacity due to PMD, increases metabolic demands on the lungs during exercise, thereby limiting exercise performance [ATS, 1999].

This chapter has described the disability encountered by subjects with COPD due to deconditioning (1.1.1). Reversible age-related changes in healthy muscle structure and function have been described and the concept of strength training introduced (1.1.2). Understanding the cause and distribution of muscle weakness would be beneficial in designing rehabilitation programs for patients with COPD. This section explores the evidence for PMD, causal mechanisms, distribution, and consequences in patients with COPD.

Peripheral Skeletal Muscle Dysfunction

Structural Alterations

Reduced muscle mass
Peripheral muscle wasting is present in an estimated 30% of subjects with COPD and is associated with muscle weakness, poor exercise tolerance and predicts mortality independent of lung function [Maltais F, 2000a]. Indirect estimates, using bioelectrical impedance analysis, report reduced fat-free mass (FFM) in patients with COPD [Schols AM et al, 1991b]. Using direct measures, computed tomography demonstrates a 30% reduction in thigh muscle cross-sectional area (CSA) and magnetic resonance imaging (MRS) shows a significantly smaller calf muscle CSA (13%) in patients with COPD compared to healthy age-matched controls [Bernard S et al, 1998; Wuyam B et al, 1992]. Muscle fibres from COPD subjects often have a smaller CSA than controls, proportional to the reduction in mid-thigh CSA [Whittom F et al, 1998]. Fibre atrophy, mainly confined to type Ila/IIX
and IIx fibres in moderate COPD, correlates with weight loss and reduction in percent predicted FEV₁ [ATS, 1999; Gosker HR et al, 2002b; Gosker HR et al, 2007].

Quadriceps strength to mid-thigh CSA ratios are similar in COPD and normal subjects, supporting the idea that muscle atrophy contributes to muscle weakness [Bernard S, 1998]. Malnutrition, physical inactivity and the use of corticosteroids potentially contribute to muscle fibre atrophy [Gosker HR, 2002a]. However, the loss of strength may be out of proportion to loss of muscle mass in patients exposed to systemic steroids suggesting muscle function may be altered without causing muscle atrophy [Decramer M et al, 1994]. Disuse atrophy initially causes atrophy in type I fibres in the elderly and therefore, disuse alone cannot explain fibre type IIx atrophy [Gosker HR, 2002a].

**Shift in fibre composition, Type I → IIx**

Metabolic capacity is determined by skeletal muscle fibre type profile, assessed using classical histochemical fibre typing techniques and myosin heavy-chain isoform expression analysis. Muscle biopsy sampling allows a detailed assessment of morphological and biochemical indices and the vastus lateralis muscle of the quadriceps femoris is most commonly studied in COPD [Coggan AR, 1995].

A reduced proportion of type I fibres (17-29% in COPD versus 45-50% in normal subjects), with a reciprocal increase in type IIx fibres (13%) has been shown, most marked in patients with advanced airflow obstruction [Gosker HR, 2007; Jakobsson P et al, 1990; Maltais F et al, 1999; Whittom F, 1998]. Fibre shift has functional consequences in the affected skeletal muscle as it is accompanied by reduced oxidative and increased glycolytic capacity, resulting in loss of fatigue resistance and reduced muscle endurance [Gosker HR, 2002b]. This change probably contributes to decreased exercise tolerance, as muscle fatigue is often the exercise-limiting factor.
Reduced capillarity

Muscle capillarity is an important component of skeletal muscle oxidative capacity [Mador MJ et al, 2001a]. Electron microscopy studies have shown a 53% reduction in the number of capillaries per unit surface area in the vastus lateralis of patients with COPD compared to age-matched controls. Significantly reduced numbers of capillaries in contact with type I and IIa fibres and decreased mitochondrial volume density probably contribute to altered oxidative capacity in peripheral skeletal muscles [Gosker HR, 2000; Whittom F, 1998].

Altered Muscle Metabolism

Abnormal oxidative metabolism

Fibre shift is accompanied by reduced oxidative metabolism, demonstrated by a reduction in oxidative enzyme capacity in needle biopsy muscle samples from patients with COPD compared to controls [Jakobsson P et al, 1995; Maltais F et al, 1996b]. Low oxidative capacity is related to the proportion of type I fibres but a reduction in oxidative enzyme activity is also present within type II fibres [Gosker HR, 2002b]. Citrate synthase (involved in the TCA cycle) and 3-hydroxyacyl coenzyme A dehydrogenase (involved in β-oxidation of fatty acids) are both significantly reduced. There appear to be no differences in glycolytic enzymes with the exception of phosphofructokinase (regulatory enzyme for glycolysis), which was significantly increased in one group of COPD patients [Jakobsson P, 1995].

Muscle energy metabolism

Direct and non-invasive assessment of skeletal muscle energy metabolism at rest and during exercise has been possible using 31P-nuclear magnetic resonance [Gosker HR, 2000]. Studies show low intracellular pH, reduced PCr and ATP content and increased lactate and ionosine monophosphate (IMP) concentrations in resting vastus lateralis muscle, in keeping with impaired energy metabolism in COPD subjects [Fiaccadori E et al, 1987; Jakobsson P, 1990; Maltais F, 2000a; Pouw EM et al, 1998].
Chapter 1.1.3 Peripheral skeletal muscle dysfunction

Intracellular ratios of inorganic phosphate (Pi) to PCr and ADP to ATP are closely related and a measure of mitochondrial phosphorylation potential. Increased Pi:PCr ratio and low intracellular pH during exercise, indicate impaired oxidative phosphorylation and ATP resynthesis, suggesting higher dependence on anaerobic glycolysis during contraction [Mador MJ, 2001a; Maltais F et al, 2000b]. Higher ratios are associated with significant elevated IMP concentrations, a deamination product of adenosine monophosphate (AMP), reflecting an imbalance between ATP utilisation and resynthesis and reduced oxidative capacity [Pouw EM, 1998].

Rates of PCr breakdown and resynthesis are an indirect measure of oxidative phosphorylation [ATS, 1999]. Greater PCr breakdown and slower resynthesis, seen in patients with COPD, suggests less efficient re-phosphorylation [ATS, 1999; Sala E et al, 1999; Wuyam B, 1992]. PCr levels are lower in vastus lateralis muscle biopsies from patients with COPD than in healthy subjects [Fiaccadori E, 1987]. Findings in our department have shown that resting muscle PCr levels correlate with the incremental shuttle walking distance [Steiner MC et al, 2000a]. This would suggest a role for PCr in determining maximal walking performance. It has been shown that exercise induces a significant decline in ATP concentrations in muscle and this is abolished after exercise training [Steiner MC et al, 2001]. These findings offer further support that oxidative metabolism is impaired in COPD.

Lactic acidosis

Lactate is produced when mitochondrial oxygen delivery becomes inadequate in exercising muscle [Casaburi R, 2001]. Lactate concentrations increase at lower levels of work in patients with COPD. This reduces muscle pH and may influence exercise intolerance [Casaburi R et al, 1991; Maltais F et al, 1998]. Oxygen delivery to the leg does not appear to be impaired during submaximal exercise. This suggests that an intrinsic muscle abnormality, such as reduced oxidative
capacity and early activation of anaerobic glycolysis, may lead to increased lactate [Casaburi R, 1991; Maltais F, 1998].

Mechanisms of Peripheral Skeletal Muscle Dysfunction

The evidence above supports the existence of PMD contributing to exercise intolerance in COPD. There remains some debate however over the mechanisms responsible and whether COPD is associated with a specific myopathy or the muscle dysfunction is a consequence of the disease itself. Myopathy, or intrinsic muscle change, implies a pathological condition. Different mechanisms such as steroid use; hypoxaemia; acidosis and chronic inflammation, may contribute to functional changes which are only partially reversible [Couillard A et al, 2005]. The cause of PMD is multifactorial and both local and systemic factors have been implicated. These factors will be reviewed in the remainder of this section.

Aging

Muscle changes associated with aging were described earlier (1.1.2) and include reduced muscle mass; strength and proportions of type II fibres (with preservation of type I fibres) and lower oxidative capacity [Maltais F, 2000a]. Reduced proportions of type I fibres associated with COPD however are abnormal compared to age-matched healthy individuals. The aging process cannot be solely accountable for the change in fibre proportions seen in PMD.

Deconditioning

Patients with COPD develop a sedentary lifestyle to avoid dyspnoea, leading to a vicious cycle of deconditioning, increasing symptoms at lower activity levels and further reductions in physical activity (figure 1.1). Inactivity, or detraining, seems an obvious cause for the structural and functional changes seen in PMD [Franssen FM et al, 2002; Maltais F, 2000a]. Reduced peripheral muscle endurance and strength are also potentially reversible with physical training [Casaburi R et al, 1997].
Structural changes associated with COPD show heterogeneity in different muscle groups. Upper extremity muscles perform activities of daily living and act as accessory inspiratory muscles. They often show preserved strength relative to lower extremities muscles [Gosselink R et al, 2000]. Adductor pollicis strength is often preserved in patients with stable COPD, who show significant quadriceps muscle weakness [Man WD et al, 2003b]. While supporting the inactivity and subsequent disuse atrophy theory, there are differences between these muscle groups that suggest other factors are involved. The adductor pollicis, a distal muscle of the thumb, is principally composed of type I fibres, while the quadriceps, a proximal leg muscle, consists of 43% type I and 57% type II fibres [Man WD et al, 2005]. Significant reductions in quadriceps compared to abdominal expiratory muscle strength more strongly supports inactivity and muscle deconditioning as local factors contributing to muscle dysfunction. Both muscle groups are proximal with similar fibre type distribution.

Reduced activity may be the primary mechanism of PMD, but this alone is not sufficient to explain all muscle changes [Maltais F, 2000a]. Disuse induces about a one-third reduction in the proportion of type I fibres in the vastus lateralis of healthy sedentary subjects, compared to a two-third reduction in patients with COPD and atrophy occurs in both type I and II fibres in severe COPD [Gosker HR, 2000; Gosker HR, 2002b; Gosker HR, 2007]. These differences suggest the presence of intrinsic muscle disease or myopathy [Couillard A, 2005].

Nutrition

Poor nutritional state, weight loss and decreased FFM are recognised in over 25% of patients with COPD and appear to be determinants of exercise tolerance [Berton E et al, 2001; Engelen MP et al, 1994; Schols AM et al, 1991b; Serres I et al, 1998]. Prolonged malnutrition itself can reduce muscle strength and endurance due to fibre atrophy and decreased muscle mass [Mador MJ, 2001a]. Energy-producing processes may be unable to meet metabolic demands and reductions in
intracellular ATP turnover and decreased PCr concentrations lead to an early switch to anaerobic glycolysis [Berton E, 2001].

Muscle wasting, resulting from an imbalance between energy requirements and caloric intake, is predominantly loss of fat mass. Decreased calorie intake is related to increased severity of airflow obstruction [Schols AM et al, 1991a]. Appetite may be influenced by symptoms, dyspnoea and fatigue, or by systemic inflammation, mediated by an appetite-regulating hormone, leptin [Gosker HR, 2000]. Weight loss however, can occur despite normal dietary intake. Elevated resting energy expenditure (REE), often observed in patients with COPD, may increase metabolic demands [Gea JG et al, 2001; Gosker HR, 2000; Schols AM, 1991a].

Only modest improvements in body weight, muscle mass and strength have been observed with nutritional supplementation, suggesting that negative energy balance is not the only mechanism causing muscle wasting and dysfunction [Gea JG, 2001; Maltais F, 2000a; Steiner MC et al, 2003]. Loss of FFM and a greater atrophy of type II fibres may be due to disorders of protein metabolism [ATS, 1999; Mador MJ, 2001a].

Systemic inflammation and oxidative stress
Low-grade, chronic systemic inflammation may intensify oxidative stress and contribute to the pathogenesis of PMD in COPD. Circulating markers of systemic inflammation, tumour necrosis factor alpha (TNFα) and interleukin-8 (IL-8), are evident in patients with a high REE and low FFM [Jagoe RT et al, 2003]. An association between TNFα and weight loss in patients with COPD has been shown [Berton E, 2001]. During an acute exacerbation, the inflammatory response increases muscle proteolysis, supplying amino acids for the synthesis of acute phase proteins. IL-8 levels are inversely related to quadriceps strength and increased IL-6 levels are associated with radiological evidence of quadriceps
muscle wasting and reduced lean body mass in COPD [Debigare R et al, 2003; Eid AA et al, 2001; Spruit MA et al, 2003].

Reactive oxygen species (ROS), or free radicals, are produced during inflammation and exercise. Overgeneration of ROS can overwhelm antioxidant capacity and lead to oxidative stress, damaging cell components. Increased plasma concentrations of ROS, combined with reduced antioxidant capacity due to disuse, chronic hypoxia and reduced oxidative capacity in patients with COPD, may lead to muscle protein degradation and impaired muscle function [ATS, 1999; Berton E, 2001; Couillard A, 2005]. Oral antioxidant supplementation with N-acetylcysteine improves quadriceps endurance in COPD, supporting a role for exercise-induced oxidative stress reducing endurance in these individuals [Koechlin C et al, 2004].

Corticosteroids
Pharmacological intervention in COPD may contribute to existing skeletal abnormalities. Short courses of corticosteroids can induce myopathic changes and average daily dose significantly correlates with quadriceps weakness [Decramer M, 1994]. Patients with COPD, receiving low dose steroids over six months, have shown significant reductions in quadriceps strength and associated muscle atrophy [Bernard S, 1998].

"Steroid-induced myopathy", characterised by muscle weakness, type I and IIx fibre atrophy and increased glycolytic enzyme activity, is usually a subtle myopathy but can present as severe proximal myopathy and rhabdomyolysis [Serres I, 1998]. Steroids may down regulate insulin growth factor 1 (IGF-1) expression, leading to reduced protein synthesis and increased proteolysis [Gea JG, 2001]. Fibre atrophy may be compounded by malnutrition and patients with steroid-induced myopathy have a lower BMI and reduced survival compared to control patients with COPD [ATS, 1999; Decramer M et al, 1996]. How long myopathic changes persist once systemic steroids are stopped is unknown.
Hypoxaemia, hypercapnia and acidosis

Hypoxaemia (low blood oxygen levels) may be involved in the development of PMD, particularly in patients with low resting oxygen saturations or repeated desaturation [Maltais F et al, 2001]. A positive correlation between arterial partial pressure of oxygen (PaO₂) and percentage of type I fibres in vastus lateralis muscle in patients with COPD is reported [Jakobsson P, 1990]. Hypoxaemia increases cell vulnerability to oxidative stress, reduces ATP production and protein synthesis and may activate calcium-dependent proteolysis, adversely affecting muscle performance [Gea JG, 2001; Jagoe RT, 2003].

Acute or chronic respiratory insufficiency in patients with COPD frequently presents with hypercapnia. This contributes to intracellular acidosis which effects cellular energy metabolism, reducing ATP and PCr muscle concentrations and may enhance muscle proteolysis [ATS, 1999; Jagoe RT, 2003]. These changes are temporary and reversible after therapeutic interventions.

Hormones

IGF-1 is the principle mediator of growth hormone (GH) and androgenic steroid (testosterone) action which stimulate muscle growth and development by enhancing protein synthesis and inhibiting proteolysis [Berton E, 2001]. Low testosterone levels in elderly men and women have been linked to muscle weakness and atrophy. Substantially reduced levels of IGF-1 and testosterone have been identified in patients with COPD, which may affect muscle size and mass [Casaburi R, 2001].

Clinical Consequences of Peripheral Muscle Dysfunction

Strength (the capacity of the muscle to develop maximal force) and endurance (the capacity to maintain a certain force over time, thus resisting fatigue) determine muscle performance [Berton E, 2001]. Loss of either results in muscle weakness and impaired performance. Psychological factors such as anxiety, fear of dyspnoea
and poor motivation may contribute to exercise intolerance in COPD but PMD plays a major role by reducing muscle strength and endurance.

**Peripheral muscle strength**


**Peripheral muscle endurance**

A significant reduction in quadriceps endurance has been identified in patients with COPD [Mador MJ, 2001a; Serres I, 1998]. Low-intensity endurance muscle training can significantly improve limb muscle and whole-body endurance (walking) performance, suggesting a link between peripheral skeletal muscle function and exercise capacity [Clark CJ et al, 1996].

Despite correlations between peripheral muscle strength and performance in COPD, reduced endurance seems to be the dominant factor limiting peripheral muscle exercise, supported by the sense of leg effort given as one of the main reasons for stopping exercise [Belman MJ, 1993; Gosselink R, 1996; Hamilton AL, 1995; Killian KJ, 1992a]. Early lactic acidosis in exercising muscles contributes to muscle fatigue [Maltais F, 1996b; Maltais F, 1999].
1.2. Assessing Physical Performance

Introduction

Peripheral muscle weakness is commonly observed in patients with COPD. The evidence for peripheral muscle dysfunction and the clinical consequences leading to impaired performance have been discussed (1.1.3). Assessments of function and performance are important in determining disability and examining the effects of interventions intended to improve exercise capacity. Functional outcome assessments include subjective symptoms, health status questionnaires and exercise testing. Exercise testing includes measurements of whole body performance (maximal or endurance capacity) or the performance of individual, or groups of, muscles (muscular strength). Testing can be carried out in the laboratory or, more commonly, in the field. This section discusses the modalities of clinical exercise testing commonly used when assessing patients with COPD. Tests used during the conduct of this thesis are described in the general methods (Chapter 2).

1.2.1. Whole Body Exercise Testing

Whole body exercise testing provides an objective measure of a patients' work capacity. Laboratory exercise tests are the "gold standard", providing physiological measurements of cardiac and ventilatory work, but are not good predictors of daily physical function. Field tests, such as walking assessments, may reflect functional performance more relevant to every day life. Submaximal and maximal tests may be conducted both in the laboratory and the field. Choice depends on the availability of trained staff and equipment, the purpose of the test and the response variables required.
Laboratory Exercise Tests

Laboratory exercise testing using a cycle ergometer or treadmill allows the collection of physiological data (ventilation, gas exchange, oxygen saturations (pulse oximetry, $\text{SaO}_2$), heart rate, blood pressure), in addition to workrate achieved. Minute ventilation ($V_e$) and tidal volume are measured via a mouthpiece or mask and breath-by-breath analysis provides information about gas exchange, oxygen consumption or uptake ($\text{VO}_2$) and carbon dioxide production ($\text{VCO}_2$). Further information can be extrapolated from these measurements such as the respiratory exchange ratio ($\text{RER} = \frac{\text{VO}_2}{\text{VCO}_2}$), oxygen pulse and anaerobic threshold [Cooper CB et al, 2001]. Ratings of breathlessness and fatigue, using visual analogue scales or Borg scales for dyspnoea and perceived exertion, help identify factors limiting exercise performance [Borg GA, 1982].

In healthy individuals $\text{VO}_2$ rises steadily with workrate and attains a plateau, representing maximal aerobic capacity ($\text{VO}_2\text{max}$). This seldom occurs in patients with COPD who have a ventilatory limitation and whose lungs are unable to meet the demand for increased ventilation. The highest $\text{VO}_2$ achieved is termed $\text{VO}_2\text{peak}$ [Jones NL et al, 1982].

Laboratory exercise testing offers better control over the environment and subject but it is not always available, as it requires sophisticated and expensive equipment. Cycle ergometry has advantages over the treadmill for patients with severe lung disease. It provides a reasonably safe, stable exercise platform to measure workrate, while utilising a smaller muscle mass. Unfortunately however, cycling is often an unfamiliar exercise and can be intimidating to the patient. Frail or elderly patients with severe cardiac or pulmonary disease may become exhausted early and therefore, underestimating exercise capacity.
Symptom limited maximal incremental testing
Maximal exercise tests define the upper limit of physical performance: what the subject is capable of achieving. Subjects exercise for as long as possible until symptomatic or subjective limitation. This is a highly effort-dependent test involving physiological data collection, which includes gas exchange and allows aerobic capacity (VO₂max) to be measured [Cooper CB, 2001].

Submaximal endurance testing
Submaximal constant rate tests, performed at a percentage of VO₂peak, determine exercise endurance and repeated testing can assess improvements after treatment. This is particularly useful in patients with a ventilatory limitation to maximal exercise as this limitation is rarely reversed [Morgan MD, 1999].

Field Exercise Tests
Field exercise tests were developed to assess “functional exercise capacity” without needing fixed laboratory equipment [Steele B, 1996]. They are often cheap, simple performance measures of maximal or endurance capacity, commonly assessing walking ability. This is a familiar activity and testing requires minimal equipment.

Self-paced endurance tests
The corridor walking test was first introduced in 1976 [McGavin CR et al, 1976]. The 2-, 6- and 12-minute walk tests (MWD) are highly reproducible and correlate well with each other, the latter two tests are popular in patients with COPD [Butland RJ et al, 1982]. Patients are asked to walk for as long as possible and are allowed to rest and restart walking during the test. Distance or time walked is recorded.

These tests are not standardised and the subject determines pacing. They can be affected by motivation and mood, making it difficult to compare tests. Simple encouragement can improve performance during the 6-MWD by 30.5 meters [Guyatt GH et al, 1984]. A learning effect is common, with increasing distances
Chapter 1.2.1 Whole body exercise testing

walked through repeated trials, and three or more tests are necessary to achieve reproducible results [Knox AJ et al, 1988; Steele B, 1996].

The advantages are that they assess the subjects' ability to perform an every day activity. Walking tests show better correlation with self-reported daily physical functioning than maximal incremental cycle tests [Steele B, 1996]. Walking distance however, may not be limited in mild cardiopulmonary disease and self-paced tests can underestimate subjects' performance [Morgan MD, 1999; Steele B, 1996].

Shuttle walk tests

The incremental shuttle-walking test (ISWT) and endurance shuttle-walking test (ESWT) are standardised, externally paced field exercise tests, developed to measure maximal and endurance performance in patients with COPD [Revill SM et al, 1999; Singh SJ et al, 1992]. The subject is required to walk up and down a 10-meter course with walking speed dictated by a recorded audio signal. The influences of encouragement and patient motivation are reduced and tests are highly reproducible, requiring only one practice walk. The ISWT and ESWT have been extensively used in pulmonary rehabilitation and are sensitive to this intervention [Griffiths TL et al, 2000; Revill SM, 1999; Singh SJ, 1992]

The ISWT increases workload progressively and therefore, the cardiovascular stress is similar for all subjects. Monitoring heart rate, SaO₂ and rating breathlessness and perceived exertion while performing the test add substantial data. Prediction of VO₂peak is not the primary goal for field tests. While a portable device can be used to measure oxygen consumption and ventilation, VO₂peak can be estimated using prediction equations [Appendix I] [Singh SJ et al, 1994].
1.2.2. Assessing Muscular Strength

Muscle strength refers to a muscle's maximum force-generating capacity and is defined as the peak force (Newtons, N) or torque (Newton-meters, Nm) developed during a maximal contraction under a given set of conditions [Abernethy P et al, 1995]. Methods for assessing strength, utilising simple weights or sophisticated laboratory-based equipment such as a dynamometer, can be divided into voluntary and non-voluntary techniques. Firstly, an understanding of types of muscular contraction is required.

Types of Muscular Contractions

Muscle structure was described earlier (1.1.2). The word “contract” means to draw together or to shorten. A muscular contraction is when muscle fibres generate tension within themselves, leading to either the muscle shortening, remaining the same length or lengthening, known as concentric, isometric or eccentric contractions respectively [Isokinetics Explained, 2008]. Most movements occur around a joint axis.

Concentric contraction

Concentric contractions (meaning “towards the middle”) are the most common form of muscle action during dynamic activities. A muscle shortens once tension within the muscle is sufficient to overcome resistance, moving body segments towards each other. This action is dependent on one end of the muscle having more stability than the opposite end.

Eccentric contraction

Eccentric contractions (meaning “away from the middle”) occur when external resistance exceeds muscle force and the muscle acts as a brake or resistive force. The muscle lengthens while tension develops. In reality the muscle is not actually lengthening but returning to its normal resting length after shortening. Dynamic movements, such as walking down stairs or sitting down, involve eccentric actions.
Eccentric motions produced on dynamometers are usually long and through a full range of motion (ROM) unlike the short, rapid eccentric motions often produced during daily activities [Chan KM et al, 1996].

**Isometric (static) contraction**

Isometric contractions (meaning “equal length”) occur when a muscle attempts to shorten but cannot overcome external resistance, for example, against an immovable object. There is no muscle lengthening, shortening or joint movement.

**Isotonic contraction**

Isotonic literally means, “equal tension” and commonly describes concentric and eccentric muscle actions. Tension remains constant as the muscle shortens or lengthens but the speed of movement is variable. Weightlifting tasks are often described as isotonic. “Isoinertial” literally means constantly resistant to motion, and may more accurately describe the constant external loading associated with weightlifting tasks [Abernethy P, 1995].

**Volitional Assessment of Muscle Strength**

Volitional assessments rely on the contractile properties of the muscle and are effort-dependent, relying on subject motivation and cooperation. Measurements may therefore over estimate muscle weakness.

**Isometric assessment**

Isometric strength is the maximal voluntary contraction (MVC) that can be developed against an immovable object, without change in joint angle. Measurements can be obtained using portable hand-held dynamometers or strain gauges or more complex machines. Isometric assessment is a highly controlled measurement with high test-retest reliability but it is not a dynamic measure and isometric activity is rare in daily life [Abernethy P, 1995; Bassey EJ, 1997; Singh SJ, 1992].
1-Repetition Maximum assessment

Maximum isoinertial strength, or one-repetition maximum (1-RM), is a dynamic measurement often employed to assess muscular strength. It involves concentric and eccentric muscle actions, but only the concentric phase of the action evaluates the 1-RM. The 1-RM is the maximum weight (resistance) lifted once through a complete ROM of a particular exercise. A trial-and-error approach is used as the weight lifted is increased in increments, with a 2 to 3 minute rest between attempts, until the maximum weight is achieved. This measurement bears little resemblance to daily activities in terms of posture, pattern or speed of movement and is limited by the skill and experience of the individual. Inexperienced subjects however should achieve their 1-RM by the sixth trial [Abernethy P, 1995].

Isokinetic assessment

Literally translated, isokinetic means movement at a constant speed. Isokinetic assessments involve the measurement of torque through a ROM in which the limb is moving at a constant angular velocity. Isokinetic dynamometers allow a complete profile of performance for major muscle groups with the advantage that reliable and objective measurements are easily achieved. Isokinetic tests are reported to have high test-retest reliability but there is evidence to suggest that learning can improve results and reliability should be established for a given population [Abernethy P, 1995]. Isokinetic measurements and the reproducibility of the measurement are discussed in more detail in Chapter 3. Detailed descriptions of the outcome parameters can be found in Appendix VII.

Non-volitional Assessment of Muscle Strength

Volitional assessments may not always be practical or suitable for patient populations, such as during a hospital admission and may give sub-maximal measurements despite well-motivated subjects. Skeletal muscle is controlled by electrical impulses conducted via motor neurons to the motor end plate. Depolarisation of the nerve cell membrane initiates an action potential that
generates a muscular contraction (1.1.2). Non-volitional techniques have been developed to stimulate nerves supramaximally, causing a single impulse to be conducted down the nerve, resulting in a twitch contraction and subsequent relaxation of the muscle [Man WD et al, 2004a]. This laboratory-based measurement requires specialist equipment and expertise.

**Electrical nerve stimulation**

An external electrical current; applied through skin surface electrodes, a needle or implanted electrode, stimulates the nerve. The stimulus through surface electrodes is often large and stimulates sensory nerve ending in the skin, causing pain. Alternative techniques are often more invasive. Electrical stimulation has not been adopted for routine clinical assessment of muscle strength due to discomfort, poor reproducibility and difficulty in reliably achieving supramaximal stimulation [Man WD, 2004a]. Electrical stimulation of the femoral nerve, supplying the quadriceps muscle, is possible, but is technically difficult and reproducibility is poor.

**Magnetic nerve stimulation**

Magnetic stimulation creates intense, rapidly changing magnetic fields that penetrate clothing, soft tissue and bone to reach deep nerves, initiating an electrical current and subsequent depolarisation of the nerve cell membrane and consequently, muscle contraction [Man WD, 2004a]. This technique activates large nerve fibres and therefore, does not cause pain. It is easier to perform, produces supramaximal stimulation and is more suitable for clinical purposes.

Magnetic stimulation of the femoral nerve has been used to measure quadriceps isometric twitch force [Polkey MI et al, 1996]. Twitch quadriceps tension is measured with the knee flexed via an inextensible ankle strap connected to a transducer. Quadriceps contractility in patients with COPD, using magnetic stimulation, has shown that the quadriceps is \(\sim 30\%\) weaker than healthy elderly [Man WD, 2003b; Man WD et al, 2003a].
Skeletal muscle fatigue, defined as the loss of force generating capacity, has been implicated as the factor limiting exercise tolerance in patients with COPD [Saey D et al, 2003]. Magnetic stimulation has demonstrated a decrease in quadriceps fatigue following pulmonary rehabilitation in patients with COPD [Mador MJ et al, 2001b].
1.3. Enhancing Physical Performance

Introduction

Section 1.1.1 explained how muscle weakness and reduced exercise capacity render patients with COPD disabled. Patients reduce levels of activity to avoid exertional dyspnoea, leading to loss of independence, social isolation and depression. Few therapies are effective for COPD and despite optimal pharmacological treatment, many patients experience functional impairment. Muscle weakness and reduced exercise capacity are associated with increased utilisation of health care resources and mortality [Decramer M, 1997].

The nature and causes of peripheral muscle dysfunction (PMD) associated with COPD have been discussed (1.1.3). Aiming therapeutic treatments at reversing PMD could potentially improve exercise capacity and peripheral muscle strength. Given that deconditioning is one of the principal causes of PMD exercise training is the logical first step to improving physical performance. This section introduces the role of exercise training, in the form of pulmonary rehabilitation, focusing on resistance training (1.3.1). Strategies employed (1.3.2) in an attempt to enhance performance and improve training outcomes, which include nutritional supplementation, oxygen, hormones, drugs and in particular, creatine (1.3.3), will then be evaluated.
1.3.1. Exercise Training

Pulmonary Rehabilitation

Pulmonary rehabilitation (PR) is a multidisciplinary programme of care for patients with chronic respiratory impairment [NICE, 2004]. PR programmes have become well established over the years, their primary goal being to restore patients to their highest level of independent function [Celli BR, 2004b; Nici L et al, 2006; Ries AL et al, 2007]. A definition recently published focuses on three important features; multidisciplinary programmes, individual patient needs and attention to physical and social function;

"Pulmonary rehabilitation is an evidence-based, multidisciplinary, and comprehensive intervention for patients with chronic respiratory diseases who are symptomatic and often have decreased daily life activities. Integrated into the individualized treatment of the patient, pulmonary rehabilitation is designed to reduce symptoms, optimize functional status, increase participation, and reduce health-care costs through stabilizing or reversing systemic manifestations of the disease. Comprehensive pulmonary rehabilitation programs include patient assessment, exercise training, education, and psychosocial support."

[Nici L, 2006]

PR effectively improves health-related quality of life (HRQL), dyspnoea, leg fatigue and functional and maximum exercise capacity in patients with COPD [Celli BR, 2004b; Lacasse Y et al, 2002; Mador MJ, 2001b; Ries AL et al, 1995; Ries AL, 2007]. Improvements in HRQL are often seen without clinically significant improvements in exercise capacity [Troosters T et al, 2005]. Introducing outpatient PR to standard therapy is cost effective, reducing usage of health care services
Chapter 1.3.1 Exercise Training

[Garcia-Aymerich J et al, 2003; Griffiths TL, 2000; Griffiths TL et al, 2001; NICE, 2004]. Rehabilitation should be considered for all patients, particularly those with moderate disease: GOLD stage II with either reduced exercise tolerance and limitations in daily activities or breathlessness equivalent to MRC dyspnoea grade 3 [GOLD 2007, 2007; NICE, 2004]. Selection based on age, disability, smoking status or oxygen usage is not justified [BTS Statement, 2001]. Common restrictions to participation in PR are: co-morbidities limiting safe or efficient exercise; poor motivation; geography and transport.

Exercise training is an essential component of PR, improving fitness in an otherwise sedentary group by reducing fear of exercise and breathlessness. The principal objectives are to tackle the systemic consequences of COPD contributing to exercise intolerance. Training programs must overcome patient limitations and provide a sufficient stimulus to induce physiological adaptations in skeletal muscle to reverse the effects of PMD and deconditioning [Troosters T, 2005]. Physical benefits are generally restricted to the mode of exercise training employed, namely endurance (or aerobic) and resistance (or strength) training.

Endurance (Aerobic) Training

Endurance, the ability to sustain physical activity over time, is essential for everyday tasks such as walking, climbing stairs, housework and gardening [Morgan MDL et al, 2001; Steiner MC, 2004]. Endurance exercise, traditionally employed to increase cardiovascular fitness, improves health status and increases life expectancy. Guidelines suggest healthy elderly should exercise 3-5 days per week, for 20-30 minutes, at an intensity of 40-85% VO2peak [Position stand, 1998].

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Performance is improved through enhancement of skeletal muscle energy metabolism; increased oxidative enzyme concentrations, capillary density, fibre size and reduced exercise induced lactic acidosis, improving muscle strength [ATS, 1999; Maltais F, 1996a; Sala E, 1999; Whittom F, 1998].

Patients with COPD, exercised at low intensities, fail to show changes in muscle oxidative enzyme activity [Belman MJ et al, 1981]. Higher workloads can be sustained however and high-intensity training is feasible (60-80% VO$_2$peak), [Casaburi R, 1991; Casaburi R, 1997; Maltais F, 1996a; Maltais F et al, 1997]. These exercise intensities are sufficient to cause adaptations in exercising muscle, improving muscle function and exercise tolerance more effectively. $^{31}$P-MRS studies of quadriceps muscle following PR show improved cellular bioenergetics, reduced Pi:PCr ratio, increased intracellular pH and faster PCr recovery, consistent with improved mitochondrial oxidative capacity [Sala E, 1999]. Quadriceps muscle twitch force measurements, during supramaximal magnetic stimulation of the femoral nerve have demonstrated increased fatigue resistance following endurance-based training [Mador MJ, 2001b].

Interval training

Although high-intensity training is often well tolerated, an alternative strategy is interval training, alternating high-intensity exercise with short intervals of rest or low-intensity. Interval training can elicit substantial training effects with reduced ventilatory requirements and dyspnoea scores, improving measures of exercise tolerance and HRQL, comparable to continuous training [Arnardottir RH et al, 2007; Puhan MA et al, 2006; Spruit MA et al, 2007; Vogiatzis I et al, 2002]. Increases in peak oxygen consumption and work rate, reduced lactate accumulation and PCr recovery time and significant peripheral muscle adaptations increasing oxidative capacity have been observed [Ambrosino N et al, 2004; Vogiatzis I et al, 2005].
Programme length

Optimal intensity, frequency and length of an exercise programme remain undetermined. Programmes lasting six months can produce significantly greater results (although small) and better long-term effects compared to shorter interventions, but this is not always practical [Guell R et al, 2000; Troosters T et al, 2000; Troosters T, 2005]. Improvements in exercise capacity and health status, gained after one 8-week programme, were maintained for six months but not sustained at one year, compared to another where benefits of 8-weeks endurance training extended to one year [Bestall JC et al, 2003; Griffiths TL, 2000; Singh SJ et al, 1998]. Four weeks of supervised PR are comparable to 7-weeks at equivalent time points [Sewell L et al, 2006]. Magnitude and extent of physiological improvements are larger after supervised compared to non-supervised training [Puente-Maestu L et al, 2000]. Recommendation in the UK is 6-12 weeks of physical exercise, disease education and social interventions for patients with COPD [NICE, 2004].

Generic versus task specific training

The extent of muscle weakness in upper and lower limbs differs in patients with COPD. Upper extremity muscles are involved in many activities of daily living, which are often intermittent and relieved by rest periods, but patients frequently report limitations [ATS, 1999]. Proximal arm muscle weakness has been shown to be more prominent than forearm muscle weakness [Bernard S, 1998; Gosselink R, 2000]. It has been suggested that activities of lower limbs are more impaired, supported by greater reductions in quadriceps than handgrip muscle strength [Gosselink R, 1996].

Exercise limitation usually begins with impairment of ambulation therefore training programmes traditionally focus on lower extremity muscles, alone or in combination with arm or respiratory muscle training [Bourjeily G et al, 2000]. The benefits of physical training are often task specific. Lower extremity training
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(treadmill, free walking, cycling, stair climbing) is associated with improvements in functional performance and exercise tolerance, while upper extremity training improves arm muscle endurance and sense of well being [Bourjeily G, 2000; Ries AL, 2007]. Benefits achieved during PR translate into improved domestic function but individualised, goal-directed PR does not offer any advantages over simple generic exercise [Sewell L et al, 2005].

Resistance (Strength) Training

Endurance exercise in patients with COPD is often terminated prematurely due to ventilatory limitation and it is suggested that at peak exercise a significant metabolic reserve is present [Richardson RS et al, 1999; Troosters T, 2004]. A high prevalence of muscle weakness contributes to exercise intolerance and muscle bulk and quadriceps strength are predictors of survival and utilisation of health care resources [ATS, 1999; Decramer M, 1997; Marquis K et al, 2002; Swallow EB, 2007b]. Endurance-training has little effect on muscle weakness or atrophy and reduced type I fibre proportions remain unchanged after 12-weeks of endurance training [Gosselink R, 1996; Hamilton AL, 1995; Whittom F, 1998].

Endurance tasks require repetitive actions over time while strength tasks require explosive short-term performance. Strength-related tasks such as balance, raising from a chair or washing hair become more relevant to patients as they become weaker. Progressive resistance training (RT) describes training where the resistance against which a muscle generates force is progressively increased over time [Evans WJ, 1999]. RT causes less exercise-related dyspnoea therefore, could potentially be better tolerated and restore both muscle mass and strength more than endurance training in patients with COPD [Simpson K, 1992]. The benefits of RT are becoming apparent and the addition of RT to PR programmes is recommended [Ries AL, 2007].
Resistance training in the elderly

Sarcopenia and muscle weakness, exacerbated by inactivity, are prevalent in the aging population (1.1.2) and exercise can reverse these effects. RT is recommended by the American College of Sports Medicine as an important component of any fitness program, especially in the elderly [Position stand, 1998]. RT is well tolerated by the healthy elderly, increasing muscle mass, reducing fat mass and improving strength and mobility [Casaburi R, 2001; Fiatarone MA, 1990; Fiatarone MA et al, 1994; Position stand, 1998]. Given an adequate training stimulus, greater or similar strength gains are achieved compared to young individuals [Frontera WR et al, 1988; Frontera WR et al, 1990]. Training can induce hypertrophy of type I and II muscle fibres and have significant metabolic benefits, improving muscle oxidative capacity [Frontera WR, 1988; Jubrias SA et al, 2001; Pyka G et al, 1994]. Additional benefits include increased bone density, fall prevention, promotion of weight loss and improvements in glucose tolerance and blood lipid profiles [Evans WJ, 1999; Kraemer WJ et al, 2002; Nelson ME et al, 1994; Vincent KR et al, 2002]. The adaptations associated with RT are discussed below.

Muscular adaptations in healthy elderly with resistance training

Neuromuscular recruitment

Early physiological adaptations in response to RT are primarily neural factors or neuromuscular recruitment [Brouwer B, 2004; Sale DG, 1988]. Significant strength gains (17-37%) have been achieved in the elderly after training, but only modest increases in muscle CSA [Brouwer B, 2004; Fiatarone MA, 1990]. Strength gains have been reported before hypertrophy occurs, with no direct relationship between the degree of hypertrophy and strength gains [Fiatarone MA, 1990].

Muscle fibre hypertrophy

High-intensity RT programs clearly promote muscle fibre hypertrophy of the quadriceps muscle in elderly men and women. Significant increases in quadriceps
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CSA (10-12%), using computed tomography or MRS, following 6-12 weeks high-intensity training are accompanied by improvements in dynamic muscle strength [Fiatarone MA, 1990; Frontera WR, 1988; Tracy BL et al, 1999]. Muscle biopsies from the vastus lateralis have shown: hypertrophy of type I and II muscle fibres (33.5 and 27.6% respectively); fibre conversion increasing Ila and decreasing IIX fibres; and non-significant increases in capillary to fibre ratios following progressive RT [Charette SL, 1991; Ferketich AK et al, 1998; Frontera WR, 1988; Hagerman FC et al, 2000; Pyka G, 1994; Whittom F, 1998]. Training response appears most marked in the first 8-weeks and 95% of total strength can occur within 15-weeks [Pyka G, 1994]. Protein synthesis increases, consistent with satellite cell proliferation and the production of muscle proteins [Brouwer B, 2004]. Lower-intensity RT does not produce such significant changes in muscle hypertrophy, despite increase in quadriceps strength [Aniansson A et al, 1981].

Muscle energetics

Adaptations of muscle energetics during exercise in the elderly have been studied using 31P-MRS and muscle biopsies [Jubrias SA, 2001]. Endurance and RT over 24-weeks both significantly improved quadriceps muscle oxidative capacity, indicated by faster PCr recovery. Increases were greatest in the RT group (57% vs. 31%) who also demonstrated structural changes: greater muscle size and a rise in mitochondrial volume density. RT alone can improve maximal aerobic (oxidative) capacity (VO2max) [Frontera WR, 1990; Hagerman FC, 2000]. This adaptation differs from the reduced oxidative capacity typically seen in the young.

Fat-free mass

FFM, consisting of bone, skeletal muscle and water, generally decreases and fat mass (FM) increases with age [Hagerman FC, 2000]. Body fat deposition in the elderly is preferentially in the trunk and is independently associated with coronary heart disease and related to mortality [Treuth MS et al, 1994]. High-intensity RT (85-90% 1-RM) for 16-weeks can decrease FM in the legs, arms and trunk (measured by DEXA), demonstrated by a significant decrease in percentage body mass.
mass (3%) and a non-significant increase in FFM, accompanied by significant gains in maximal dynamic strength and a reduction in serum lipids [Hagerman FC, 2000].

Guidelines for prescribing resistance training

Training-related variables to consider when developing resistance-training programmes include; type of exercise, intensity, repetitions, sets, frequency, duration and progression [Kraemer WJ, 2002]. Recommendations for improving muscular strength and hypertrophy in older adults suggest slow to moderate lifting velocity exercises, using 60-80% 1-RM loads, 8-12 repetitions for 1-3 sets per exercise, with 1-2 minute rest between sets [Willoughby DS, 2001].

Type of exercise

Training adaptations are usually specific to the training mode adopted therefore effective RT should be directed at muscle groups important in everyday activities and target specific training goals [Kraemer WJ, 2002]. Dynamic repetitions, commonly utilised, involve concentric and eccentric muscle actions. Eccentric actions are more efficient and less metabolically demanding, producing greater force per unit muscle size and therefore hypertrophy, but result in more delayed onset muscle soreness. Isometric muscle actions play a secondary role.

Intensity (load or resistance)

Load prescription, the weight or resistance moved during exercise, is set using a standard test, the one-repetition maximum (1-RM). 1-RM is the maximum weight lifted once through the full ROM of an exercise. A mean training intensity of 60% 1-RM can increase dynamic muscular strength in untrained individuals [Kraemer WJ, 2002; Rhea MR et al, 2003]. Older individuals can tolerate up to 85% 1-RM [Willoughby DS, 2001]. Moderate loading allows proper learning of technique and reduces musculoskeletal injury.
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Repetitions per set
A repetition is one complete cycle of exercise, lifting and lowering a load through a full ROM. Each repetition at slow-moderate velocity should allow 2-3 seconds to lift (concentric contraction) and 4-6 seconds to lower (eccentric contraction) [Evans WJ, 1999; Willoughby DS, 2001]. The number of repetitions performed continuously, creating a set, varies with training experience, phase of training and goals. High-intensity RT, causing muscular fatigue after 8-12 repetitions, has dramatic effects at all ages.

Sets per exercise
In untrained individuals, 3-set training programs elicit greater strength gains than single-set protocols [Rhea MR, 2003]. Rest periods, recovery time between sets, vary between 15 seconds and 2-4 minutes.

Frequency
Frequency represents the number of training sessions per week. An initial frequency of three days per week (d·wk\(^{-1}\)) is effective in untrained individuals, followed by an effective maintenance frequency of 1-2 d·wk\(^{-1}\) [Kraemer WJ, 2002; Rhea MR, 2003]. Limiting each session to 20-45 minutes reduces injury and fatigue.

Training volume
Training volume, or total work, is the total number of repetitions performed per session multiplied by the resistance used [Kraemer WJ, 2002]. Untrained individuals are more sensitive to increases in volume than trained populations [Rhea MR, 2003].

Duration
In untrained individuals RT increases muscular strength by approximately 40% over periods ranging from 4-weeks to 2-years [Kraemer WJ, 2002]. RT, performed 2-3 d·wk\(^{-1}\) for at least 6-weeks, has consistently produced strength gains in all ages, including the elderly [Fiatarone MA, 1990; Frontera WR et al, 2003].
Changes in muscular strength occur early; producing strength gains within the first 4-8 weeks of training.

**Progression**

Progression refers to the gradual increase of stress placed upon the body in order to overload the neuromuscular system sufficiently to increase muscular fitness as individuals become accustomed to training [Kraemer WJ, 2002]. This involves the manipulation of variables every 2-3 weeks: increasing load, number of repetitions, volume and rest periods or in combination.

**Safety issues**

Safe, biomechanical lifting technique is a major concern. Correct lifting involves proper breathing (inhaling before a lift, exhaling during the lift and inhaling while lowering the weight) to avoid breathe-holding (Valsalva manoeuvre) and to minimise cardiovascular stress. Free weights allow exercises to mimic movements required for a specific task. Weight-lifting machines however, are easy to use and regarded safer as stabilisation limits movement about specific joints during contractions. Large muscle group and multiple-joint exercises should be performed before small muscle group and single-joint exercises.

**Resistance training in COPD**

A decrease in proportions of type IIx fibres with an increase in type IIa fibres, hypertrophy of both fibre types I and II and more efficient neuromuscular coupling are reported following RT in patients with COPD [ATS, 1999; Casaburi R, 2001; Clark CJ, 1996; Frontera WR, 1988]. Muscular adaptations only occur if the muscle is sufficiently stressed. Training smaller muscle groups can reduce the total work performed while sufficiently stressing peripheral muscles, inducing a training effect in people who would be ventilatory limited during whole body exercises. Single leg exercise can stress muscles more effectively than two-legged exercise and improve aerobic capacity [Dolmage TE et al, 2008; Richardson RS, 1999]. Successful training programmes are not necessarily determined by strength gains.

**Resistance training alone**

Compared to no training, weight-lifting for 8-weeks can increase strength measurements by 30%, improve motivation, quality of life and benefit whole body performance, significantly improving submaximal exercise tolerance in patients with COPD [Simpson K, 1992; Spruit MA et al, 2002]. Low-intensity peripheral muscle conditioning using isotonic exercises, which are simple and easy to perform at home, can improve treadmill walking and individual muscle endurance [Clark CJ, 1996].

**Resistance training combined with aerobic training**

Resistance exercises are well tolerated and as an adjunct to endurance training, diversify training sessions, maintaining patient interest and motivation [Bernard S et al, 1999; O'Shea SD et al, 2004]. Combined endurance and strength training programs have had variable effects on strength and endurance outcomes. Bernard et al found that combined training restored muscle strength and bulk to a greater extent, but did not improve aerobic function over changes seen with endurance training alone [Bernard S, 1999]. A 12-week study of resistance, endurance or combined training showed increased endurance in all groups, with improvements in breathlessness score and CRQ dyspnoea dimension [Ortega F et al, 2002]. Despite specificity of response to training mode, modest crossover effects occur [Ortega F, 2002; Spruit MA, 2002]. Combined training showed improvements in strength and endurance measures comparable to individual training modalities, suggesting this to be an optimal training strategy.

RT has successfully been added to endurance training regimes without impairing endurance-training response. Improvements in quadriceps muscle strength
(23.6%) after 8-weeks of combined training however, did not translate into additional improvement in HRQL, exercise performance or quadriceps fatigability [Mador MJ et al, 2004]. Another study of combined training, but for 12-weeks, improved lower limb muscle strength (36%) but also increased lean body mass (5%), 12-MWD and improved three of eight activity-of-daily living tasks compared to endurance training alone [Panton LB et al, 2004].

Prescribing resistance training in COPD
Training durations for patients with COPD have ranged between 8-12 weeks, with at least three sessions per week. Intensity has ranged from 32-85% 1-RM, with variable combinations of sets and repetitions, 1-3 sets comprising 10-12 repetitions. Significant effects have been seen with modest numbers of repetitions (3 sets of 8 repetitions) in patients with COPD, congestive heart failure and in healthy elderly [Jubrias SA, 2001; Pu CT et al, 2001; Spruit MA, 2002].

Varying degrees of dyspnoea and/or oxyhaemoglobin desaturation make it difficult to establish the ideal rest interval between sets for patients with COPD. One-minute rest interval might be attempted but in practice, longer periods of 2-3 minutes may be necessary to maintain adequate oxygen saturation (SaO₂). Diaphragmatic and pursed lip breathing may help maintain saturation levels (SaO₂ >90%) while exercising.
1.3.2. Specific Strategies to Increase Training Intensity

Introduction

Low and high-intensity endurance training yield improvements in quality of life and reduce symptoms in patients with COPD but physiological training effects are greatest with high-intensity training [Casaburi R, 1991; Goldstein RS, 1994; Griffiths TL, 2000; Ries AL, 1995; Spruit MA, 2002]. Patients with COPD can tolerate high-intensity training but this can be difficult to maintain [Maltais F, 1996b; Spruit MA, 2002]. Strategies, described below, have therefore been employed to allow patients to tolerate higher exercise intensities with the aim of achieving a greater training effect.

Inhaled Therapies

Bronchodilation

Improvements in ventilatory mechanics could enhance exercise training, by allowing longer high-intensity training periods. Long-acting inhaled bronchodilators such as salmeterol and tiotropium are beneficial in patients with COPD, reducing lung hyperinflation and exertional dyspnoea and improving symptom-limited exercise tolerance [Man WD et al, 2004b; O'Donnell DE et al, 2004]. Optimal pharmacological treatment should include a long-acting inhaled bronchodilator before commencement of PR [Spruit MA, 2007].

Tiotropium, combined with PR, can improve treadmill walking endurance time, producing clinically meaningful improvements in dyspnoea and health status for at least three months and increase patients self-reported participation in physical activities outside of PR [Casaburi R et al, 2005; Kesten S et al, 2008]. Nebulised
Chapter 1.3.2 Strategies to increase training intensity

ipratropium also significantly improves endurance time but not in patients with quadriceps muscle contractile fatigue [Saey D, 2003].

Oxygen supplementation

Chronic hypoxaemia is common in patients with COPD and may adversely affect skeletal muscle function. Acute oxygen administration can improve maximal exercise performance by reducing perceptions of dyspnoea, minute ventilation and leg fatigue during exercise [ATS, 1999; Maltais F, 1996b; Payen JF et al, 1993; Ries AL, 2007; Rooyackers JM et al, 1997; Spruit MA, 2002]. Oxygen may improve peak exercise capacity by enhancing blood flow to exercising muscle, therefore oxygen delivery and uptake, improving muscle energetics and decreasing exercise-induced lactic acidosis [Gosker HR, 2000; Maltais F, 2001; Richardson RS, 1999]. Oxygen may also induce pulmonary vasodilatation, reducing exercise-induced pulmonary hypertension and improving right heart function [Maltais F, 2001; O'Donnell DE et al, 1997; Palange P et al, 2005; Payen JF, 1993; Richardson RS, 1999].

Supplemental oxygen, given to hypoxaemic patients during exercise can improve peripheral muscle oxidative metabolism, significantly reducing intramuscular Pi:PCr ratio and improving muscle pH [Maltais F, 1996b; Payen JF, 1993]. Long-term oxygen therapy over 6-9 months also increased resting PCr concentrations, without changing oxidative enzyme activity [Jakobsson P, 1990; Jakobsson P, 1995].

Oxygen administration is recommended for safety in patients with severe resting or exercise-induced hypoxaemia during PR [Ries AL, 2007; Steiner MC, 2004]. It would seem reasonable to assume training with supplemental oxygen would allow higher training intensities. Oxygen during low-intensity training however failed to produce additional benefits in exercise tolerance or health status in patients with severe COPD who experienced exercise hypoxaemia [Garrod R et al, 2000b; Rooyackers JM, 1997]. A small improvement in exertional dyspnoea followed
training with oxygen compared to room air [Garrod R, 2000b]. A randomised double-blind trial of supplemental oxygen, during exercise training in non-hypoxaemic patients, indicated that oxygen enabled high-intensity training, improving endurance capacity and HRQL significantly more than room air-training [Emtner M et al, 2003].

Supplemental oxygen during training does not necessarily provide a clinically relevant benefit. A recent review concluded that the evidence supporting oxygen supplementation during PR was limited [Nonoyama ML et al, 2007]. However, there is evidence to suggest high-intensity exercise is better tolerated with supplemental oxygen and there are trends towards improvements in HRQL and endurance exercise [Emtner M, 2003; Puhan MA et al, 2004].

**Helium-oxygen breathing**

Low-density gas mixtures lower airflow resistance, facilitating lung emptying, decreasing exercise-induced hyperinflation, relieving symptoms and improving exercise capacity [Palange P, 2005; Spruit MA, 2007]. Heliox breathing can increase exercise endurance time but has not yet been shown to improve exercise capacity following PR [Palange P et al, 2004; Puhan MA, 2004; Troosters T, 2005].

**Assisted Ventilation**

Non-invasive positive-pressure ventilation (NPPV) aims to unload respiratory muscles and increase oxygen availability during exercise. Overnight home NPPV during training periods significantly improves shuttle walking distance and produces greater improvements in HRQL [Garrod R et al, 2000a; Ries AL, 2007]. Improved quality of sleep, daytime gas levels and respiratory muscle function may lead to better peripheral muscle function. Proportional assist ventilation during exercise training, evaluated in two studies, showed no additional benefit [Puhan MA, 2004]. More recently, inspiratory pressure support as an adjunct to high-intensity cycle exercise improved cycle endurance time and shuttle walk distance...
compared to spontaneous breathing [Ries AL, 2007]. In selected severe patients, NPPV can improve exercise tolerance.

**Hormones**

Normal muscle growth and development is dependent on appropriate hormonal stimuli. Two major hormones act on muscle, growth hormone and testosterone.

**Growth hormone**

Growth hormone (GH), secreted by the pituitary gland, stimulates the liver to produce insulin-like growth factor (IGF) promoting muscle protein synthesis and increasing lean body weight [ATS, 1999; Ries AL, 2007]. GH administered to undernourished patients with severe COPD, during 3-weeks in-hospital PR, caused an increase in lean body mass without improving muscle strength or exercise tolerance [Burdet L et al, 1997; Ries AL, 2007].

**Anabolic steroids**

Anabolic androgenic steroids are a class of synthetic steroids related to the hormone testosterone and are sometimes used in sports and bodybuilding to enhance strength or physique. Androgen supplementation in COPD has shown modest improvements in muscle mass, without improving strength or endurance [Casaburi R, 2001; Jagoe RT, 2003; Yeh SS et al, 2002]. Low dose nandrolone, combined with nutritional supplementation during PR, improved lean body mass and respiratory muscle strength in men and women with COPD, with no adverse effects [Schols AM et al, 1995].

Testosterone levels decline with age and low levels are relatively common in patients with COPD, contributing to muscle atrophy and weakness [Mador MJ, 2001a; Spruit MA, 2007]. Testosterone replacement in hypogonadal men substantially increases muscle mass and strength [ATS, 1999; Casaburi R, 2001; Ries AL, 2007]. Significant increases in lean body mass and quadriceps muscle strength, but not whole-body exercise endurance, are amplified by concomitant RT
Chapter 1.3.2 Strategies to increase training intensity

[Casaburi R et al, 2004]. Endurance is less likely to respond to an intervention aimed at increasing muscle bulk and strength. Oxandrolone however, an anabolic agent that facilitates weight restoration, was associated with clinically significant increases in 6-MWD in men and women with COPD-associated weight loss [Yeh SS, 2002].

Concerns regarding testosterone replacement in the elderly: unmasking subclinical prostate cancer; increased high density lipoproteins levels; increased haematocrit; liver toxicity and aggressive behaviour; along with a lack of functional improvement, tend to temper enthusiasm for anabolic hormone supplementation in COPD [ATS, 1999].

Neuromuscular Electrical Stimulation

Neuromuscular electrical stimulation (NMES) uses surface electrodes to passively stimulate locomotor muscles without ventilatory distress. NMES is well tolerated and has been associated with increased muscle mass, strength and endurance in patients with congestive heart failure and may augment muscle performance in patients with severe COPD [Neder JA et al, 2002].

NMES improves lower limb muscle strength, whole body exercise capacity and breathlessness during activities of daily living (ADLs) in patients with severe COPD and also as a home-based therapy in advanced COPD [Bourjeily-Habr G et al, 2002; Neder JA, 2002]. Despite selective type II fibre hypertrophy 6-weeks high-frequency NMES was ineffective in enhancing muscle strength and walking capacity in moderately impaired COPD patients [Dal Corso S et al, 2007]. It is suggested that a concomitant volitional stimulus, such as RT, may be more effective than NMES alone. Both are well tolerated and lead to acceptable levels of dyspnoea and fatigue [Sillen MJ et al, 2008]. NMES combined with active limb mobilisation, independent of volitional exercise, can produce greater improvements in quadriceps isometric strength and dyspnoea during ADLs in severely
deconditioned, malnourished patients with COPD and during acute exacerbations [Ambrosino N, 2004; Vivodtzev I et al, 2006].

Supplementation

Nutritional supplementation


Nutritional supplementation combined with PR in underweight patients with COPD demonstrated significant weight gain, mainly attributed to increased fat mass. The addition of anabolic steroids resulted in increased lean body mass but no improvement in physical performance [Schols AM, 1995]. Exercise training combined with carbohydrate-rich nutritional supplements successfully increased energy intake and weight, resulting in significant greater improvement in shuttle walk performance in a subgroup of well-nourished patients with COPD (BMI >19kg/m²) [Steiner MC, 2003]. Supplementation may overcome a negative energy balance encountered during exercise training but there is insufficient evidence to support the routine use of nutritional supplementation [Puhan MA, 2004; Ries AL, 2007].

Polyunsaturated fatty acids

Polyunsaturated fatty acids (PUFA) are incorporated into cell membrane phospholipids and may modulate systemic inflammation and cytokine response [Gosker HR, 2000]. PUFA supplementation, combined with 8-weeks PR, improved
Chapter 1.3.2 Strategies to increase training intensity

functional capacity, peak exercise capacity and submaximal endurance time in patients with COPD. Improved exercise capacity may be due to increased oxidative capacity induced by PUFA [Broekhuizen R et al, 2005].

Creatine supplementation

Oral creatine supplementation (CrS) has been used as an ergogenic aid to enhance gains in muscle function and mass during exercise training in young and healthy elderly subjects [Chrusch MJ et al, 2001; Vandenberghe K et al, 1997]. The principal purpose of this thesis is to investigate the use of CrS as an adjunct to PR in patients with COPD. Creatine will therefore be discussed in greater detail in the remainder of this chapter.

1.3.3. Creatine as an Ergogenic Aid

Introduction

Creatine is a naturally occurring nitrogen compound found in animal products, meat and fish. A typical non-vegetarian daily diet contains ~1g of creatine. Normal body metabolism breaks down 1-2 grams per day (g·d⁻¹) into creatinine, excreted by the kidneys. Daily turnover is met by endogenous synthesis from amino acids, glycine, arginine and methionine, in the liver [Harris RC et al, 1992; Maughan R, 1997; Vandenberghe K, 1997]. Approximately 95% of body creatine content (120-140g for an average-sized 70kg male) is stored within skeletal muscle, the remainder in the heart, brain and testes [Balsom PD et al, 1994; Kraemer WJ et al, 1999; Persky AM, 2001]. Oral creatine is absorbed by the intestinal tract and transported by the blood stream to skeletal muscle. A sodium-dependent creatine transporter (CreaT) spanning the plasma membrane facilitates intracellular uptake. Muscle cells maintain a reversible equilibrium between free creatine (Cr) and phosphocreatine (PCr), catalysed by cytosolic creatine kinase [Wallimann T et al, 1992]. In resting muscle 60-70% of total creatine (TCr) content is stored in the form of high-energy PCr [Harris RC, 1992].
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Interests in oral creatine supplementation (CrS) increased in the early 1990s due to its potential to enhance exercise performance [Greenhaff PL et al, 1993; Harris RC, 1992]. PCr availability may be a limiting factor during intense, burst-type (anaerobic), exercise as it is the primary phosphate source in maintaining adenosine triphosphate (ATP) resynthesis [Hultman E et al, 1991; Mesa JL et al, 2002; Paddon-Jones D, 2004]. Athletes utilizing CrS as a nutritional ergogenic aid, enhance performance by increasing the phosphagen pool available for rapid resynthesis of ATP from ADP during periods of high ATP turnover (figure 1.4). It may also stimulate PCr resynthesis during recovery [Casey A et al, 1996; Juhn MS et al, 1998a]. Studies indicate that CrS (creatine monohydrate) enhances high-intensity short-term (strength-power) exercise, over short recovery periods but there is little evidence suggesting CrS enhances prolonged moderate-intensity (endurance) exercise performance [Casey A et al, 2000; Juhn MS, 1998a; Kraemer WJ, 1999; Tarnopolsky MA et al, 2000b].

Creatine Monohydrate Supplementation

Creatine supplementation is often in the form of creatine monohydrate (figure 1.7).

![Chemical structure of creatine monohydrate powder (Creapure™)](image)

The chemical name for Creatine is methyl guanidine-acetic acid. Chemical formula: $C_7H_7N_3O_2$·$H_2O$
Dietary supplementation of 20 grams per day (g·d⁻¹) over 5-7 days, typically utilised as a loading phase, increases intramuscular TCr concentration by 20-25%, approximately 20% accounted for by PCr [Casey A, 1996; Gilliam JD, 2000; Hultman E et al, 1996; Kreider RB, 2003; Maughan R, 1997]. The majority of uptake occurs during the initial days of supplementation with the greatest uptake in the first two days. Performing submaximal exercise during acute supplementation enhances TCr accumulation by 10%. Carbohydrate ingestion increases insulin concentrations, stimulating the CreaT transporter, augmenting intramuscular TCr retention [Green AL et al, 1996; Snow RJ et al, 2003]. High carbohydrate (90g) or combined carbohydrate (47g) and protein (50g) supplementation is required which can cause problems, such as reduced gastric motility. Greater increases in intramuscular TCr occurs in those with low initial concentrations (<120 mmol/kg dmm) and in middle-aged individuals [Maughan R, 1997; Smith SA et al, 1998; Tarnopolsky MA, 2000a]. Muscle TCr returns to baseline 4-weeks after acute supplementation but can remain elevated for a further week in meat-eaters [Hultman E, 1996; Lemon PW, 2002]. Skeletal muscles have a threshold for the amount of TCr stored and maximum concentrations are maintained with 2 g·d⁻¹ supplementation [Hultman E, 1996]. Typical maintenance regimes for CrS utilize 3-5 g·d⁻¹.

Creatine supplementation in the healthy

CrS is used worldwide to increase muscle performance [Graham AS et al, 1999]. It was estimated that 80% of athletes at the 1996 Summer Olympics in Atlanta used creatine [Paddon-Jones D, 2004]. Acute creatine loading (15-25 g·d⁻¹ for 4-6 days) enhances high-intensity, short-duration, intermittent exercise performance, increasing muscle bulk in healthy subjects [Greenhaff PL, 1995; Kreider RB, 2003]. Beneficial effects appear to be related to the extent of intramuscular creatine accumulation, with evidence that some subjects may be non-responders. Muscle biopsies following intense exercise show that CrS enhances PCr resynthesis in the first two minutes of recovery, but only in those individuals who increase muscle TCr >20 mmol/kg dmm after loading [Greenhaff PL et al, 1994; Greenhaff PL, 1995].
contrast, \(^{31}\)P-Nuclear MRS studies concluded that creatine loading did not facilitate PCr resynthesis during intermittent isometric muscle contractions despite improved performance [Vandenberghe K et al., 1999]. Enhanced ATP turnover due to increased PCr availability in type II muscle fibres rather than accelerated PCr resynthesis might contribute to the ergogenic effects of CrS [Casey A, 1996].

Activities that are repetitive or have high-energy output stress the PCr system and would probably benefit from CrS [Terjung RL et al., 2000]. There is evidence to suggest that acute high-dose CrS may improve maximal intermittent exercise performance but not single bout high-intensity or endurance exercise [Vandenberghe K, 1997]. This is not surprising, since the contribution of the PCr-ATP system decreases as the exercise duration increases but unfortunately there are inconsistencies.

Acute CrS (3-6 days) enhanced fatigue resistance during single 10-second bouts of maximal cycle exercise but showed no ergogenic effect on power output during single 30-second cycle bouts [Balsom PD et al., 1995; Odland LM et al., 1997]. Similarly, 5-days acute CrS improved endurance in young women but failed to reduce the decline in quadriceps isokinetic peak torque during endurance testing in men [Gilliam JD, 2000; Kambis KW et al., 2003]. Performance enhancement during short-duration repeated bouts of high-intensity exercise, such as isokinetic knee extensions (KE) separated by rest periods, has been more convincing [Gilliam JD, 2000; Greenhaff PL, 1993; Tarnopolsky MA, 2000a]. Performance has been enhanced in swimming, all-out cycling, sprinting, repeated jumping and resistance training (RT) [Juhn MS et al., 1998b].

Longer-term CrS during RT programs can improve body composition and muscular strength [Branch JD, 2003; Nissen SL et al., 2003]. CrS combined with 3-12 weeks RT in young men and women has been shown to increase FFM (60%); improve average lifting volumes; maximal muscle strength (20-25%) and total work performed and can delay onset of fatigue compared to placebo [Burke DG et al,
Chapter 1.3.3 Creatine as an ergogenic aid

2000; Vandenberghe K, 1997; Volek JS, 1999]. The major advantage of creatine may derive from improved training capacity.

It is hypothesized that Cr stimulates protein synthesis and muscle hypertrophy [Persky AM, 2001]. Protein synthesis may be stimulated by increased cellular swelling, due to the osmotic effects of Cr and resultant water retention, acting as an anabolic signal [Hultman E, 1996; Paddon-Jones D, 2004]. Muscle biopsies demonstrate type II muscle fibre hypertrophy and 31P-Nuclear MRS measurements show increased intramuscular TCr and PCr content after RT combined with CrS against placebo [Vandenberghe K, 1997; Volek JS, 1999].

Creatine supplementation in the elderly

Aging results in reduced muscle mass, strength and exercise performance (1.1.1) [Evans WJ, 1995; Fiatarone MA, 1994; Frontera WR et al, 2000]. Resting skeletal muscle TCr concentrations are 25% lower and PCr resynthesis rates are 22% slower after exercise in middle-aged compared to young subjects, which may contribute to declining performance [Brose A et al, 2003; Smith SA, 1998; Tarnopolsky M et al, 1999; Volek JS, 1999]. The implication that CrS can increase intramuscular TCr and PCr greatest in those with initial low concentrations and enhance high-intensity and strength performance in healthy individuals, suggests that CrS may benefit the elderly [Casey A, 1996; Tarnopolsky MA, 2000b]. There is also evidence to suggest that creatine reduces total plasma cholesterol and triglycerides [Persky AM, 2001].

Acute CrS (5-7 days) in males over 50 years of age has produced variable performance results. In middle-aged men, increased intramuscular PCr levels (30%) and resynthesis rates have been accompanied by improved resistance to fatigue [Smith SA, 1998]. Two small placebo controlled studies of older males (59-78 years) differed in their outcomes. Rawson et al showed no significant change in body composition, isometric elbow strength or isokinetic KE endurance, while Gotshalk et al showed significant improvements in body weight, FFM and muscle
performance (1-RM, isometric KE strength and lower-extremity functional capacity) [Gotshalk LA et al, 2002; Rawson ES et al, 2000]. Change in transporter density is associated with aging and decreased Cr uptake may explain the poorer response in the elderly [Persky AM, 2001].

Creatine supplementation and resistance training in the elderly

RT is the most effective non-pharmacological intervention in the elderly, partially reversing age-associated losses in muscle mass and strength, improving functional capacity and independence [Fiatarone MA, 1994; Frontera WR, 1988; Treuth MS, 1994]. Combining RT with CrS is effective in the young and may also be beneficial in the elderly.

A number of placebo-controlled trials of progressive RT combined with CrS have produced conflicting results. No additional increases in maximal dynamic strength or resistance to fatigue over placebo were seen after 7-weeks in elderly males and females (67-80 years) [Bermon S et al, 1998]. In contrast, 12-weeks of training in elderly men (60-84 yrs) enhanced muscle strength (1-RM) and endurance, lower body isokinetic power and lean body mass against placebo [Chrusch MJ, 2001]. No direct measurements of muscle fibre size, creatine content or functional outcomes were included. CrS during a 14-week whole-body RT programme in healthy men and women (>65 years) showed increases in muscle TCr of 27% compared to placebo [Brose A, 2003]. This was accompanied by increased FFM and improved isometric KE strength but not dynamic muscle strength (1-RM) or functional capacity. TCr increased more in men and intramuscular PCr only increased in men.

Longer-term CrS (5 g·d⁻¹ for 6-12 months) combined with moderate resistance and cardiorespiratory endurance training, failed to enhance physical fitness in older men (55-75 years) against placebo [Eijnde BO et al, 2003]. Static muscle strength improved in the initial three months but after six months, training effects irrespective of creatine were not enhanced. Maximal isometric KE strength; FFM;
Chapter 1.3.3 Creatine as an ergogenic aid

Body weight and maximal cycle ergometry results were similar to baseline. Muscle biopsies showed increased TCr, but not PCr or ATP with CrS.

**Creatine supplementation in disease**

Muscle immobilisation in young healthy subjects causes disuse atrophy and a 15% decrease in muscle PCr, which returns to baseline within 3-weeks of rehabilitation. CrS during muscle disuse negates this decrease and increases PCr by 12% during 3-weeks of rehabilitation [Hespel P et al, 2001]. Oral creatine may reduce the biochemical and structural deterioration of skeletal muscle during disuse, shortening the duration of rehabilitation.

**Neuromuscular disorders**

Muscle weakness and atrophy are common in neuromuscular disorders. Although reduced intramuscular PCr is observed in patients with mitochondrial cytopathies and inflammatory myopathies there are differences in basal muscle Cr and PCr content among disease states [Tarnopolsky M, 1999]. Short-term CrS increased body weight and measurements of handgrip, dorsiflexion and KE isokinetic and isometric strength in patients with neuromuscular disorders against placebo. In comparison, CrS in patients with hereditary motor sensory neuropathy showed no significant differences in body weight, FFM, maximal voluntary strength, endurance or functional tests [Doherty TJ et al, 2001].

**Muscular disorders**

Studies looking at 3-4 months CrS in boys with Duchenne and Becker Muscular Dystrophies have demonstrated increased: muscle strength (3-15%); resistance to fatigue and FFM. This may provide symptomatic relief but improvements in functional tasks and activities of daily living were not observed [Louis M et al, 2003; Persky AM, 2001; Tarnopolsky MA et al, 2004].
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Chronic heart failure

Patients with chronic heart failure (CHF) experience early exertional fatigue and skeletal muscle abnormalities are similar to those found in COPD patients. Short-term (10 days) CrS, in patients with CHF and low basal levels of creatine, significantly increased quadriceps muscle strength (5%) and endurance (10-20%) against placebo [Gordon A et al, 1995]. Improved skeletal muscle metabolism, with reductions in ammonia and lactate accumulation, accompanied by a significant increase in handgrip contractions until exhaustion, have been demonstrated following 5-days of CrS [Andrews R et al, 1998]. Both studies however were small (n = 17-20).

Chronic obstructive pulmonary disease

As explained (1.1.3), PCr levels are low in patients with COPD presenting a potential therapeutic target to improve physical performance [Fiaccadori E, 1987]. Creatine uptake is increased by exercise therefore combining CrS with physical training should augment any benefits [Terjung RL, 2000]. Two small studies looking at the effects of CrS in patients with COPD have been published [Faager G et al, 2006; Fuld JP et al, 2005].

A randomised, double blind, placebo-controlled trial of CrS in patients with moderate-severe COPD showed a significant increase in muscle performance, compared to placebo, after 2-weeks loading (15g·d⁻¹) and a further significant improvement following maintenance supplementation (5g·d⁻¹) combined with 8-weeks exercise training [Fuld JP, 2005]. Improvements were in lower limb strength and endurance and handgrip endurance, accompanied by an increase in body weight, predominantly FFM. No significant improvements in whole body functional performance, measured using the ISWT, ESWT and cycle ergometry, were seen after initial loading or training.

In contrast, Faager et al reported a negative RCT of CrS in similar subjects with COPD [Faager G, 2006]. CrS combined with 8-weeks predominantly aerobic based
PR showed no significant improvements in physical performance, measured using ESWT, against placebo. Only the creatine group showed significant improvement in ESWT after PR (296 seconds vs. 180 seconds, p=0.8), suggesting the effectiveness of PR alone was negligible. No improvements in HRQL measured using the St George's Respiratory questionnaire or changes in body weight following CrS were seen.

1.4. Summary

Patients with COPD are often disabled by their inability to carry out activities of daily living. Breathlessness during activities leads into a vicious cycle of inactivity, loss of muscle strength, further breathlessness and inactivity. Skeletal muscle bulk and strength predict peak exercise capacity and may predict mortality [ATS, 1999; Gosselink R, 1996; Swallow EB, 2007b]. Exercise limitation does not correlate with airway function and patients may complain of leg fatigue as much as breathlessness as their limiting symptom during cycling exercise [Killian KJ, 1992a; Levy RD, 1993]. Reduced exercise capacity shows only a weak relationship to lung function impairment and improving lung function, either by medication or lung transplantation, has no clear effect on exercise capacity [ATS, 1999; Wasserman K, 1989].

Loss of peripheral muscle mass and strength accompanies normal ageing but peripheral muscle dysfunction (PMD) is recognised as a major systemic effect associated with chronic lung disease and contributes towards disability [ATS, 1999]. PMD, characterised by a reduction of type 1 (slow twitch) muscle fibres, muscle atrophy, weakness, low oxidative capacity and early lactate production during exercise, is related to exercise intolerance, poor quality of life and reduced survival [Casaburi R, 1991; Maltais F, 1996b]. PCr breakdown, the principal source of energy during early muscular exercise, is greater while PCr resynthesis is slower in patients with COPD [Maughan R, 1997; Sala E, 1999].
Deconditioning is one of the principal causes of PMD and potentially reversible. [Casaburi R, 1997; Gosselink R et al, 1998; Levy RD, 1993; Maltais F, 1996b]. Exercise training is the logical step and the role of physical training in PR, particularly endurance exercise, is well-established and can improve exercise capacity, symptoms and quality of life. High-intensity RT is feasible and associated with significant gains in strength and muscle hypertrophy [Clark CJ, 1996; Griffiths TL, 2000; Griffiths TL, 2001; Lacasse Y et al, 1996; Ries AL, 2007].

Strategies have been employed to facilitate higher training intensities in an attempt to improve exercise tolerance and health status. Acute oxygen therapy; non-invasive ventilation; nutritional supplementation; growth hormone and anabolic steroids are just a few of the therapies utilized with little success. The cause of PMD is multifactorial therefore isolated therapeutic strategies are unlikely to completely resolve the problem. A global approach with correction of all possible contributing factors should provide a better chance of success.

Creatine supplementation (CrS) can increase muscle mass in healthy subjects by enhancing high-intensity exercise training. It is used by athletes to augment their performance and training [Greenhaff PL, 1995]. PCr availability can limit muscle performance during intense, fatiguing muscular contractions [Andrews R, 1998]. It is thought that creatine, in its phosphorylated form (PCr), enhances performance by increasing the phosphagen pool available for rapid resynthesis of ATP from ADP. This decreases recovery time and allows increased work during training.

Although studies out in the field have provided conflicting results the majority show that short-term creatine uptake into muscle is enhanced by endurance exercise and can improve high intensity, short duration performance in various athletic tasks [Kreider RB, 2003]. Combining creatine with adjunct physical training is therefore essential in increasing strength and power [Harris RC, 1992]. Dietary CrS combined with RT programmes in the elderly has been shown to have an
ergogenic effect enhancing: isometric muscle strength; lower body endurance and lean body mass, but not functional capacity [Brose A, 2003; Chrusch MJ, 2001].

There is evidence from biopsy studies that muscle PCr content is lower in patients with COPD compared to healthy age-matched subjects [Fiaccadori E, 1987]. In patients with COPD ISWT distance correlates with peripheral muscle resting PCr content and is related to quadriceps muscle strength [Steiner MC, 2000a; Steiner MC et al, 2000b; Steiner MC et al, 2005]. This could suggest a role for PCr in determining maximal walking performance and a potential therapeutic target to improve exercise performance.

Measurements of muscular strength are important in assessing disability and can be made using non-volitional and volitional techniques [Mador MJ, 2004]. Isometric or static muscular force is most commonly used but dynamic muscle performance provides a quantitative evaluation of physiological function [Gosselink R, 1996; Spruit MA, 2002]. Isokinetic strength assesses muscle tension generated throughout an entire range of joint motion at a constant angular velocity, giving a peak rotational force or torque. It is believed that isokinetic dynamic measurements may provide a more objective measure of strength.

Pharmaceutical manipulation, used to enhance physical performance in athletes, could be considered reasonable in patients with COPD. One study suggests that CrS increases FFM, health status, peripheral muscle strength and endurance but not exercise capacity in patients with COPD [Fuld JP, 2005]. However, as the accompanying editorial pointed out, this study was underpowered. The main body of this thesis (Chapters 4-6) describes a large randomised, double-blind, placebo-controlled trial of CrS conducted to test the hypothesis that CrS, in association with aerobic exercise combined with resistance training, will enhance the functional benefits of PR [Griffiths TL et al, 2005]. In addition, a protocol was developed to measure peripheral muscle strength in subjects with COPD using an isokinetic dynamometer.
Chapter 2. General Methods

Introduction

The main objective of this thesis was to explore whether creatine supplementation (CrS) can augment the clinical outcomes of pulmonary rehabilitation (PR) in subjects with COPD. In order to evaluate the impact of this intervention several outcome measures of physical performance and health status were used, which are described in this chapter. Methods sections in subsequent chapters (Chapters 3 to 6) refer back to this chapter.

Strength measurements are an important outcome measure and a role for isokinetic dynamometry was introduced in Section 1.2.2. Chapter 3 subsequently explores the potential use of isokinetic dynamometry as a measure of muscle performance in subjects with COPD and examines the reproducibility of measurements. The protocol used for testing reproducibility in Chapter 3 differed from that used for the main investigation and is described separately.

2.1. Spirometry

Spirometry was measured in the seated position to ARTP/BTS standards (Vitalograph Model R, Bucks, UK) [ARTP, 1994]. Subjects completed at least three acceptable maximal forced manoeuvres. Values, expressed as a percentage of predicted values, were calculated from ERS regression equations [Quanjer PH et al, 1993] [Appendix III].

2.2. Anthropometry

Body weight was measured in light clothing at each visit using digital scales (Seca, UK) to the nearest 100g. Height was measured in centimetres using a wall-mounted scale. Body mass index (BMI) was calculated as weight(kg)/height(m)^2.
2.3. Body Composition

Muscle wasting contributes to the pathogenesis of skeletal muscle weakness in COPD (1.1.3). Depletion of whole body fat-free mass (FFM), mainly muscle mass, is an important determinant of exercise performance in patients with severe COPD [Engelen MP, 1994; Schols AM, 1991b]. Body composition has also been shown to be a predictor of mortality [Marquis K, 2002; Slinde F et al, 2005].

Increasing muscle mass is an important therapeutic goal for rehabilitation, even more so in subjects taking CrS, making FFM an important measurement. Numerous methods are available for assessing body composition but many are unsuitable for clinical practice. Anthropometric methods, commonly used, underestimate fat mass (FM) in elderly subjects due to centralisation and internalisation of body fat, not reflected in skinfold thickness [Schols AM, 1991b]. Dual-energy X-ray absorptiometry (DEXA) has been validated and recommended as a suitable reference method but it is costly and requires sophisticated equipment. Bioelectrical impedance analysis (BIA) is a safe, non-invasive, reliable measurement that is rapid, inexpensive and portable and requires minimal subject cooperation.

Bioelectrical impedance analysis (BIA)

Non-invasive measurements of body fat, lean muscle mass and water content were made using a handheld bedside unit (BODYSTAT®1500; Bodystat Ltd, Douglas, Isle of Man, UK) to calculate bioelectrical impedance [Lukaski HC et al, 1985]. Subjects rested for 4-5 minutes in a semi-supine position before measurements were taken. All measurements for an individual subject were taken at approximately the same time of day. Four disposable, self-adhesive electrodes were placed on the dorsal surface of the right hand and foot. Electrodes were placed above the second metatarsal of the foot, midway between the medial and lateral malleolus of the ankle, above the second metacarpal of the hand and medial to the distal process of the ulna bone at the wrist. An electrical current, 500 micro
amps at a frequency of 50 KHz, was passed between the electrodes and impedance recorded.

Different prediction equations to calculate FFM from BIA measurements have been proposed for patients with chronic respiratory failure [Kyle UG et al, 1998; Pichard C et al, 1997]. Schols et al correlated BIA with deuterium-dilution and skinfold anthropometry and proposed a prediction equation specific for patients with severe COPD [Schols AM, 1991b]. This equation has since been refined to give sex-specific equations that show better agreement between BIA and DEXA [Steiner MC et al, 2002]. FFM was estimated from impedance measurements using these sex-specific equations [Appendix IV].

2.4. Whole Body Exercise Testing

Laboratory and field based measurements of whole body exercise performance were conducted on separate occasions with at least 24 hours between tests.

Field based measurements

Incremental shuttle walking test (ISWT)
The ISWT is a maximal, symptom-limited incremental field test [Singh SJ, 1992]. Subjects walked up and down the 10-meter course, defined by two cones, at a speed dictated by an audio signal, increasing in increments every minute. Either the subject, who is too tired or breathless to continue, or the operator determines the end of the test, if the subject fails to complete a shuttle in time (> 0.5 m away from cone). The total distance walked (meters) is recorded.

Endurance shuttle walking test (ESWT)
The ESWT is a standardised, open ended, externally paced, constant work rate field test of endurance capacity [Revill SM, 1999]. Subjects walk around the same 10 m course used for the ISWT at a constant speed, set by an audio signal, after a 2-minute warm-up. The speed is set at 85% of the individuals' predicted maximal
capacity (VO₂peak) achieved during the ISWT [Appendix I]. The total time, excluding warm-up, (seconds) is recorded.

**Laboratory based measurements**

**Incremental cycle ergometry**

Maximal, symptom-limited incremental exercise tests were performed on an electrically braked cycle ergometer (Ergoline er900, Germany). After 1-minute at rest, subjects pedalled at a constant speed of 40 revolutions per minute (rpm). After 2-minutes of unloaded cycling, the workload increased incrementally by 10 watts every minute. Standardised encouragement was used to ensure subjects continued cycling for as long as possible. Peak work (Watts) achieved and total exercise time (seconds) were recorded. Ventilation and gas exchange measurements were made using breath-by-breath analysis. Continuous ECG and oxygen saturation monitoring were performed and blood pressure was taken every minute. Breathlessness and perceived exertion scores were recorded at the end of the test using the modified Borg scale [Appendix XV] and reasons for terminating the test were documented.

2.5. **Peripheral Muscle Strength**

Dominant quadriceps isometric and dynamic isokinetic muscle strength and dominant biceps and triceps dynamic isokinetic muscle strength were measured using a Cybex II Norm dynamometer (CYBEX NORM™ Testing and Rehabilitation System, CYBEX® International, Inc. Ronkonkoma, New York). The dynamometer was calibrated regularly and settings were unchanged during the trial. Session data was gathered by the computer software (system version 2.0), which calculated the key values [Appendix VII, figure A.3].
Chapter 2 General Methods

Quadriceps muscle testing

Positioning for muscle testing
Subjects were seated with the backrest at $85^\circ$ and stabilised with straps across the chest, pelvis and mid-distal thigh (figure 2.1). Seat length and height was individualised for each patient. All settings were retained for all subsequent tests. An adjustable lever arm was attached, via a shin pad; to the leg proximal to the lateral malleolus (allowing full ankle dorsiflexion) and its axis of rotation aligned visually lateral to the lateral femoral epicondyle. The subjects’ arms were crossed over the chest to minimise upper torso movement and help isolate leg movement. Gravity correction to torque at $45^\circ$ (leg straight = $0^\circ$) was calculated by the computer software. Subjects were able to view their torque-moment curves during the familiarisation phase but no visual feedback was given during the test phase.

Isokinetic quadriceps protocol
Isokinetic strength was measured using a continuous concentric-eccentric contraction protocol at $60^\circ$/sec [Li RC et al, 1996]. Range of moment was set $10^\circ$ - $80^\circ$ of flexion (figure 2.1). Following a warm-up, a detailed explanation of the different contractions involved was given and a familiarisation session performed. This incorporated two sets of three submaximal continuous concentric-eccentric cycles followed by a maximal practice trial of five cycles. After a two-minute rest, the test was conducted, consisting of two trials of five cycles (figure 3.1). No pause occurred between concentric and eccentric contractions or the five cycles. A two-minute rest separated each trial.

Subjects were instructed to push as hard as possible straightening the leg, from knee flexion to extension (concentric phase - muscle shortening), and then to resist the lever arm bending the knee (eccentric phase - muscle lengthening while tension develops). Standardised strong verbal encouragement, “push hard to the top,” “resist all the way down,” was used throughout. Best overall peak torque (PT,
Figure 2.1: CYBEX NORM™ Testing and Rehabilitation System.

Subjects were seated with the backrest at 85° and stabilised with straps across the chest, pelvis and mid-distal thigh. **Pictures 1-3: Quadriceps muscle testing.** An adjustable lever arm was attached, via a shin pad; to the leg proximal to the lateral malleolus (allowing full ankle dorsiflexion) and its axis of rotation aligned visually lateral to the lateral femoral epicondyle. The subjects' arms were crossed over the chest to minimise upper torso movement and help isolate leg movement. Gravity correction to torque at 45° (leg straight = 0°) was calculated by the computer software. Subjects were able to view their torque-moment curves during the familiarisation phase but no visual feedback was given during the test phase. **Picture 4: Biceps and triceps muscle testing.** Arm positioned in extension. The chair and Cybex head were positioned parallel. With the subject seated, the adjustable lever arm attached to the Cybex head was positioned with the axis of rotation lateral to the elbow joint. A Velcro strap stabilised the upper arm while the subject held the handle proximally (range of movement 20 – 100°).
the maximum measurement obtained from each set of five isokinetic cycles) and total work were used for analysis.

Isometric quadriceps protocol
Isometric force was measured with the knee at an angle of 70° flexion. Two sets of three maximum voluntary isometric contractions were performed, with twenty seconds between contractions and two-minutes between sets. Subjects were instructed to push as hard as they could, in a controlled manner, for six seconds or until effort declined. Best overall force was used for analysis.

Biceps and triceps muscle testing

Isokinetic arm protocol
Dominant biceps and triceps muscle strength were measured in the same seated position as for the quadriceps measurements. A seated position for this measurement was devised because subjects had difficulty breathing while lying prone (figure 2.1). The chair and Cybex head were positioned parallel to each other and the footrest was attached to the chair. An adjustable lever arm, attached to the head of the Cybex, was positioned with the axis of rotation aligned visually lateral to the elbow joint with the subject holding a handle proximally. A Velcro strap held the upper arm close to the chair to prevent excessive movement during the measurements.

Isokinetic strength was measured using a continuous concentric-concentric contraction protocol at 120°/sec. Range of moment was set 20° - 100° of extension (full flexion = 0°). The familiarisation session incorporated two sets of three submaximal continuous concentric-concentric cycles followed by a maximal practice trial of five cycles. After a two-minute rest, the test was conducted, consisting of two trials of five cycles. No pause occurred between concentric contractions or the five cycles. A two-minute rest separated each trial.
Subjects were instructed to pull up and down as hard as possible while keeping their body and shoulders still. Standardised strong verbal encouragement, "pull hard to the top," "pull all the way down," was used throughout. Best overall peak torque and total work for biceps and triceps were used for analysis.

2.6. Health Status Assessment

Health status measures the impact of a disease and coexisting symptoms on an individual's life. Instruments used to assess health status include measures of health related quality of life (HRQL) and functional status. Quality of Life (QoL) assessments subjectively measure changes in physical, functional, mental and social health in order to evaluate the human and functional costs and benefits of an intervention [Testa MA et al, 1996]. This is of particular value when symptom control and the ability to carry out routine daily activities, rather than a cure, is the principle outcome. HRQL refers to distinct domains of health; physical, psychological and social domains, influenced by a person's experiences, beliefs, expectations and perceptions. It measures the impact an individual's health has on their ability to perform and enjoy activities of daily life [Curtis JR et al, 1994]. Each domain, measured separately using specific questions, can be measured by objective assessment of functioning and more subjective perceptions of health. Subjective perceptions and expectations translate the objective assessment into the actual QoL experienced.

HRQL is commonly assessed using health status questionnaires, which include general health and disease specific measures. Generic questionnaires assess a range of domains applicable to various health states, conditions or diseases in the general population. They are comparable between disease states but less likely to reflect specific problems experienced by patients with particular conditions. Some can also be used for cost-effectiveness analyses. Disease-specific questionnaires focus on domains most relevant to the disease or condition and characteristics most prevalent in subjects being studied. They are more sensitive to small changes
and therefore appropriate for clinical trials to evaluate specific therapeutic interventions.

Improving survival time is an important aim of treatment but reducing symptoms, increasing function and improving QoL are important goals for patients with COPD. Dyspnoea, fatigue, depression and anxiety are commonly reported. Dyspnoea is often considered the primary activity-limiting symptom [Lareau SC et al, 1999]. From the patients' perspective, the ability to remain active is often the most important outcome of medical care. "Functional status" is the patient's ability to perform at a normal level of functioning during activities of daily living [Curtis 1994]. Correlations between improvements in health status and exercise performance following PR are generally weak in patients with COPD [Guyatt GH et al, 1999]. Functional status can refer to the level of activity attained but for some is equivalent to physiological measures of airway function [Lareau SC et al, 1994].

This thesis is concerned with the effects of CrS as an adjunct therapy during PR. HRQL and functional status are therefore important outcome measures. Disease-specific and generic questionnaires were used to assess the HRQL effects during this intervention.

**Generic questionnaires**

**Hospital anxiety and depression scale (HADS)**

HADS was developed by Zigmond and Snaith [Zigmond AS et al, 1983] to identify 'caseness' (possible and probable) of anxiety disorders and depression among patients in non-psychiatric hospital clinics. It is a self-reported questionnaire with anxiety (A) and depression (D) subscales, each containing seven intermingled items. Scores range from 0 to 21 for each subscale, 0-7 is regarded as the normal range, 8-10 suggestive of anxiety or depression and >11 indicates probable presence of mood disorder. A pilot study in COPD populations found clinically relevant anxiety, indicated by high HADS scores, more common in patients with
severe COPD, a past history of anxiety or depression and females. Anxiety and total mood improved during inpatient rehabilitation [Dowson C et al, 2001].

**Short form-36 health survey (SF-36)**

The SF-36 is a self-administered general health status questionnaire shown to be responsive to changes due to PR [Brazier JE et al, 1992; Griffiths TL, 2000; Jones PW, 2001]. Its use is supported by studies involving group-level analysis [Ware JE, Jr. et al, 1992]. Physical and psychological dimensions are measured, generating eight distinct health status concept scores and one score measuring self-reported health transition, ranging from 0 to 100, where 100 indicates good health.

**Disease-specific questionnaire**

**Self-reported chronic respiratory questionnaire (CRQ-SR)**

The chronic respiratory questionnaire (CRQ), the most commonly used disease-specific questionnaire designed specifically for chronic lung disease, is consistently reported to be sensitive to change after PR and pharmacologic therapy. There is clear evidence showing validity of within-subject changes in health status [Guyatt GH et al, 1987; Guyatt GH, 1999; Lacasse Y, 1996]. The self-reported CRQ (CRQ-SR) was developed from the interviewer-led CRQ and allows patients to complete the questionnaire alone, in their own time [Guyatt GH, 1987; Williams JE et al, 2001].

The CRQ-SR includes 20 questions in four domains: dyspnoea, fatigue, emotional function, and mastery (feeling of being in control). The dyspnoea domain measures shortness of breath in five activities chosen by the individual as being important in daily living. Response options, presented as a seven-point scale, produce mean scores per domain [Appendix V]. The threshold for a clinically significant change per domain has been identified as 0.5 [Juniper EF et al, 1994].
Functional status questionnaire

Pulmonary functional status and dyspnoea questionnaire – modified version (PFSDQ-M)

The PFSDQ-M is a disease specific, self-reported questionnaire of functional status in patients with pulmonary disease [Appendix VI]. The PFSDQ was originally a 164-item survey developed as a clinical evaluation questionnaire for the assessment of both symptom and activity levels in patients with pulmonary impairment [Lareau SC, 1994]. The PFSDQ-M, a briefer version, is self-administered and consists of 40 items, measuring three domains: activity levels; dyspnoea and fatigue [Lareau SC et al, 1998]. As a health status measure it provides information about the day-to-day impact of pulmonary impairment on dyspnoea and functional abilities of the patient. It is reported to take seven minutes to complete on first testing and six minutes on repeat testing.

Subjects are encouraged to complete the PFSDQ-M without assistance in order to avoid errors based upon the perceptions/observations of other persons. General instructions are read to the subject explaining that the questionnaire asks for their evaluation of three areas, dyspnoea (shortness of breath), fatigue (tiredness) and activity levels with ten activities. There are five general questions about dyspnoea and fatigue followed by questions about their dyspnoea, fatigue, and activity levels in relation to the activities. If an activity is never performed, they are advised to tick: "has never been an activity".

Scores include a frequency score (how many times a month for dyspnoea and fatigue), general scores (how you feel Most Days during the past year, Today, and with Most Day to Day Activities for dyspnoea and fatigue), Total, Mean and Individual Activity Scores for all three components [Appendix VI]. A negative change in score represents an improvement in functional status.
2.7. Peripheral Muscle Biopsy

Muscle biopsies were obtained in a subgroup of volunteers from the non-dominant Vastus Lateralis (quadriceps) muscle at rest using the Bergström technique [Bergstrom`J, 1975]. Samples were taken at baseline, after supplement loading, 4-weeks into PR and after completion of PR.

Under aseptic conditions, local anaesthesia (Lignocaine 1%) was infiltrated into the skin, subcutaneous tissues and muscle fascial sheath midway between the patella and the greater trochanter. At baseline and after completion of PR two samples were taken to ensure adequate tissue was obtained for analysis. Only one sample was taken at other time points. A scalpel blade was used to make 5mm incisions through the skin and fascia. A Bergströme-Stille 5mm diameter needle (New Splint Ltd, UK) was introduced into the muscle. Under suction (using a 50ml syringe) and with simultaneously external compression of the leg by the hand to ensure muscle tissue entered the needle, the inner trochar of the needle cut the muscle sample. The needle was immediately frozen in liquid nitrogen.

Following the procedure pressure was applied to the biopsy site for at least five minutes. Butterfly sutures (steri-strips) were used to close the incisions and the wound was dressed with a clear dressing. A compression bandage was applied for 6-12 hours to stop any bleeding and reduce bruising.

Muscle samples were later removed from the needle in the laboratory and stored in liquid nitrogen. Biochemical analysis was not carried out by the author but performed at the Department of Biomedical Sciences, The University of Nottingham, under the supervision of Prof. Paul Greenhaff. Samples were freeze-dried; ground into powder and muscle tissue was separated from blood, connective tissue and fat. Analysis included creatine, total creatine and phosphocreatine, normalised for non-muscle constituents using adenosine triphosphate (ATP) [Harris RC, 1992]. Non-muscle contaminants such as blood, connective tissue and
fat, reduce ATP content in muscle. Results were therefore corrected using ATP, which reduces variation.

### 2.8. Conduct of randomised controlled trial

The following flow diagram outlines how the measurements described in this chapter were used during the conduct of the randomised, placebo-controlled, trial of creatine supplementation during PR, described in Chapters 4-6 of this thesis.
Chapter 3. The characteristics of peripheral muscle isokinetic strength measurements in chronic obstructive pulmonary disease.

Introduction

Muscular strength (for example of the quadriceps femoris) is defined as the maximal force generated by a specific or group of muscles. Different types of measurements, available to assess muscle performance in COPD, were discussed earlier (Chapter 1.2.2). Accurate and reliable methods of quantifying muscle strength are important for assessing disability and documenting improvements following training interventions. Isokinetic dynamometry is a laboratory-based, volitional measurement of dynamic muscle strength, which may provide a more objective measure of strength, representative of activities of daily living. It assesses muscle tension generated throughout an entire range of joint motion at a constant angular velocity, giving a peak rotational force or torque.

Despite substantial literature on dynamic muscle testing and the reproducibility of isokinetic measurements, there is no standardised testing protocol. Dynamic muscle strength is often reported as an outcome measure in COPD but there is sparse information regarding appropriate protocols and their reproducibility or reliability [Bernard S, 1999; Clark CJ et al, 2000; Franssen FM et al, 2004; Mador MJ, 2004]. There is little documentation of disease specific torque patterns.

This chapter first explores the background to isokinetic measurements and the potential use of isokinetic dynamometry as a measure of muscle strength. A validation study is then described which assesses the reproducibility of isokinetic
and isometric dynamometry measurements in subjects with COPD, using a Cybex II dynamometer, while developing a testing protocol. Short-term (1-week) and medium-term (6-weeks) test-retest reliability of quadriceps isokinetic strength (concentric and eccentric manoeuvres) were examined and compared to isometric measurements.

3.1. Background to Isokinetics

Isokinetic dynamometry has provided quantitative assessments of dynamic muscle performance for over 25 years. A dynamometer is a device used to measure muscular effort, force or torque and rotational speed (rpm), from which power can be calculated. The first speed-controlling device (CYBEX I) was patented in the USA by James Perrine in 1967. Further devices (Cybex II, LIDO, BIODEX, KIN-COM) and measurement modes were developed in the 1980's [Isokinetics Explained, 2008].

Isokinetic machines were initially found in universities and used by sports athletes. Clinicians soon realised that objective isokinetic testing allowed functional evaluation of the effects of an injury or condition on physical performance and allowed documentation of progress during treatment or rehabilitation. Increasing knowledge has led to a wider use of isokinetics measurements.

Isokinetic dynamometry allows dynamic muscle force to be measured against a controlled resistance at a constant angular velocity. After an initial acceleration phase, the preset angular velocity is reached and any muscular force applied to the lever arm that would correspond to an increase in speed, is absorbed by the device and recorded as resistance. The mechanical resistance from the muscle changes through the range of motion (ROM), as the maximum force varies according to the joint angle. The result is a constant speed with variable workload or accommodating resistance, proportional to the force applied by the subject [Dvir Z, 1995b; Isokinetics Explained, 2008]
Chapter 3

Isokinetic dynamometry in COPD

3.2. Reproducibility of Measurements

For a measurement to be meaningful and interpretable it must show reproducibility, sensitivity and validity. Reproducibility refers to the consistency of measurements, implying that under the same test conditions the outcome parameters will produce identical values. Some of the potential sources of error during isokinetic dynamometry testing are shown here (table 3.1) [further discussion Appendix VIII].

1. machine linked inconsistencies
   calibration, variation in velocity, gravitational forces & inertial forces

2. subject/patient linked variations
   limb dominance, familiarisation, motivation, time of day

3. testing procedure linked errors
   stabilisation, positioning for repeat measurements

4. protocol linked variations
   intercontraction pauses

5. examiner linked variations
   verbal encouragement

6. data processing linked factor
   smoothing, damping of signal from transducer

Table 3.1: Potential sources of error affecting the reproducibility of isokinetic dynamometry measurements.

Subject variations

Any factor liable to influence the performance of a subject is a potential source of error. These factors include: pain; fatigue; level of motivation and cooperation and are difficult to assess quantitatively. They should be considered and assessed for each individual before initiating testing. Within-test reproducibility is often an excellent indicator of motivation or cooperation, which is essential for retest reproducibility. Substantial variations in muscular performance occur with age, sex, body mass and activity levels; causing difficulties when making comparisons with a population database.
Chapter 3  

Isokinetic dynamometry in COPD

Effects of age and gender

Significantly higher peak torque (PT) has been shown in men aged 20-70 years, compared with age-matched women [Borges O, 1989]. Isokinetic and isometric torque decrease with age, with a significant decrease between 60-70 years. PT has been found to correlate significantly with body weight, height and body surface area.

Effects of aging on concentric and eccentric mode strength measurements have been looked at in untrained men (20-60 years) [Horstmann T et al, 1999]. Knee extensor PT was higher in eccentric and isometric modes. Concentric mode PT decreased with increasing angular velocity and showed negative correlations with age. It was concluded that the influence of muscle fibre loss and degeneration during aging has less influence on measurements in eccentric than concentric mode. High eccentric tensions may be maintained due to increased stiffness of the connective tissue.

Testing protocols

The test protocol is the most complex and least understood of the issues concerning reproducibility [Dvir Z, 1995a]. Selecting the optimal protocol from an infinite number of potential protocols is difficult. Testing procedures incorporated into protocols include:

1. unidirectional vs. bi-directional movement, e.g. extension only or extension followed by flexion ("reciprocal")
2. contraction mode, e.g. concentric contraction/s only or concentric-eccentric sequence
3. inter-contraction pause (if any and how long)
4. number of contraction cycles per set
5. inter-set pause
6. test-retest interval
Chapter 3 Isokinetic dynamometry in COPD

The testing protocol must be reliable, with low within-subject variation, so that changes in performance can be attributed to the study intervention [Montgomery LC et al, 1989]. It is important to minimise testing time and the number of observations required to obtain a predetermined level of measurement precision [Stratford PW et al, 1990]. Most strength testing protocols advocate using the mean (or maximal score) of 3-5 maximal contractions. Unfortunately, some subjects require more trials to reach optimal performance levels. It has been suggested that untrained individuals are less likely to reproduce performance measures compared to those involved in regular physical activity [Giles B et al, 1990]. Different test protocols are discussed in Appendix IX.

3.3. Use of Isokinetics in Disease

Isokinetic measurements have been used to assess peripheral muscle strength in COPD, chronic heart failure (CHF) and neurological disorders. Isokinetic muscle testing was first measured using hydraulic resistance before commercial dynamometers became available [Bernard S, 1998; Hamilton AL, 1995; Mador MJ, 2004]. Isokinetic dynamometry muscle testing has identified reduced skeletal muscle function in patients with COPD and associated this with utilisation of health services and steroid treatment [Decramer M, 1994; Decramer M, 1997; Franssen FM, 2004]. Isokinetic concentric PT and work have demonstrated increased muscle performance following resistance training programmes in patients with COPD and CHF [Clark CJ, 2000; Gordon A, 1995; Kongsgaard M et al, 2004]. Isokinetic cycle testing has also been developed to assess lower limb muscle function in patients with COPD [Haccoun C et al, 2002]. Isokinetic testing (Cybex II) has been shown to be reliable in assessing muscle strength after stroke and has demonstrated increased muscle strength in myasthenia gravis following resistance training combined with creatine supplementation [Pohl PS et al, 2000]. Despite the substantial use of dynamic muscle testing there is no standardised testing protocol.
3.4. Protocol Development for Isokinetic Dynamometry Measurements in COPD

Study Design

Dominant limb quadriceps muscle isometric and dynamic isokinetic strength were measured on three separate occasions on week one (session one), week two (session two) and week seven (session three), at approximately the same time of day. All subjects were inexperienced on the dynamometer and were not involved in an exercise programme between measurements.

Measurements

A detailed description of assessments is given in Chapter 2.

Exercise performance, using the incremental shuttle walk test (ISWT) [Singh SJ, 1992], spirometry [ARTP, 1994] and disease specific health status, using the Self Reported Chronic Respiratory Questionnaire (CRQ-SR) [Williams JE, 2001] were measured session one and three to ensure stability. Subjects were weighed each session.

Isokinetic and Isometric Testing

Positioning was as described in Chapter 2. For safety purposes, blood pressure, heart rate and pulse oximetry were recorded before and after each exercise during session one. Details of outcome parameters are given in Appendix VII.

Isokinetic quadriceps protocol

Isokinetic strength was measured using a continuous concentric-eccentric contraction protocol at 60°/sec [Li RC, 1996]. Slower speeds, 30-90°/sec, are comparable to velocities during functional activities such as comfortable walking or rising from a chair [Hsu AL et al, 2002]. Range of moment was set 10 - 80°.
Following a warm-up, a familiarisation session was performed which included a detailed explanation and two sets of three submaximal continuous concentric-eccentric contraction cycles. After a two-minute rest, the test was conducted, consisting of four trials of five cycles (figure 3.1). Five continuous contractions, maximises the chances that maximal strength occurs after the third contraction [Li RC, 1996]. No pause occurred between concentric and eccentric contractions or between cycles within a trial. A two-minute rest separated each trial. Standardised strong verbal encouragement, “push hard to the top,” “resist all the way down,” was used throughout. Best peak torque (PT) from each of the four trials was used for analysis.

**Isometric protocol**

Isometric force was measured at 70°. Two sets of three maximum voluntary isometric contractions were performed, with twenty seconds between contractions and two-minutes between sets. Subjects were instructed to push as hard as they could, in a controlled manner, for six seconds or until effort declined. Best force from each set of three contractions was used for analysis.

**Subjects**

Twelve subjects who met clinical and spirometric criteria for COPD, GOLD stage II - IV (10 male, 1 left-handed female, 56-80 years, mean [SD] percent predicted FEV₁ 41.5 [15.5]% ) were recruited from the PR waiting list [BTS guidelines, 1997]. Software problems associated with the Cybex dynamometer resulted in lost data for five subjects. This restricted the final analysis to data from seven subjects. Approval was obtained from Leicestershire Health Authority Research Ethics Committee.

**Statistical Analysis**

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS v11.0). Demographic variables are described as mean and standard deviations (SD), except for MRC dyspnoea scroe (median and Inter
Quartile Range). Paired students $t$-tests were used to assess stability of subjects between sessions and to compare PT within and across sessions. Statistically significance was accepted as $p < 0.05$. Mean (SD) PT or force was calculated for each isokinetic trial, concentric and eccentric measurements, and each isometric set respectively. To establish test-retest reliability, random-effects two-way analysis of variance was used to calculate intraclass correlation coefficients (ICC) using ICC (2, 1) [Appendix XI] [Shrout PE et al, 1979]. ICC, a relative reliability coefficient, measures the agreement between scores and is defined as the ratio of the variance between patients over total variance [de Winter AF et al, 2004]. High reliability is accepted as 0.70 to 0.89 and very high reliability, $\geq 0.90$ [Burdock EI et al, 1963].

Within-session reliability used results of peak torque from all four trials and between-session reliability used single best PT from trials 2 and 3, each session.

ICC gives no information on the disparity between measures. Standard error of the measurement ($SE_m$), or within-subject standard variation, is an absolute reliability coefficient that indicates the extent to which a score varies on repeated measurements. Calculated as the square root of the residual mean square, it represents the typical error in a measurement in the same units as the original measurement. $1.96SE_m$ is associated with a 95% confidence interval [Stratford PW, 2004]. Expressing the value as a percentage of the respective mean, typical percentage error, allows comparison of reliability between measurements [Hopkins WG, 2000].

Mean changes with standard error of the mean (SEM) are displayed graphically. Advice on statistical analysis was provided by the Trent Institute for Health Services Research.
Chapter 3  Isokinetic dynamometry in COPD

Figure 3.1: Schematic diagram of protocol used to test reliability of isokinetic dynamometry.

Diagram shows the continuous concentric-eccentric contraction protocol, at 60°/second, used for measuring quadriceps isokinetic muscle strength. After warm-up and familiarisation, four trials were performed, each consisting of five continuous concentric-eccentric contraction cycles and separated by two-minute rest. Maximum peak torque [Nm], the maximal value of the moment angular position curve or the best PT of five cycles within each trial, was recorded after each trial. I = One continuous concentric-eccentric cycle at 60°/sec. Abbreviations: PT, peak torque; Nm, Newton-meters; min, minutes.
Results

Patient Stability

Analysis was carried out using data from seven, right-hand dominant subjects (6 male) (table 3.2). There were no significant changes in exercise performance, spirometry or health status, except for a negative change in the emotion component of the CRQ-SR, between sessions one and three (table 3.3). There were no significant changes in heart rate, blood pressure or oxygen saturation from baseline during the exercises.

<table>
<thead>
<tr>
<th></th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>65.3 (7.6)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>74.3 (9.1)</td>
</tr>
<tr>
<td>Height, m</td>
<td>1.7 (0.05)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>26.1 (2.4)</td>
</tr>
<tr>
<td>ISWT, m</td>
<td>275.7 (157.6)</td>
</tr>
<tr>
<td>FEV₁, L</td>
<td>1.3 (0.3)</td>
</tr>
<tr>
<td>FEV₁, % predicted</td>
<td>47.5 (11.2)</td>
</tr>
<tr>
<td>MRC Dyspnoea Scale †</td>
<td>3.0 (3.4)</td>
</tr>
</tbody>
</table>

Table 3.2: Baseline characteristics for isokinetic dynamometry reliability.
Data presented as mean (SD), except MRC dyspnoea score, †median (Inter Quartile Range), n = 7. Abbreviations: Kg, kilograms; m, meters; BMI, body mass index; ISWT, incremental shuttle walk test (meters); FEV₁, forced expiratory volume in 1 second (litres); % predicted, percent predicted; MRC, Medical Research Council.
<table>
<thead>
<tr>
<th></th>
<th>Mean (SD)</th>
<th>Between Session</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Session 1</td>
<td>Session 3</td>
<td>Mean</td>
<td>(95% CI)</td>
</tr>
<tr>
<td>FEV₁, L</td>
<td>1.32 (0.29)</td>
<td>1.36 (0.23)</td>
<td>0.05</td>
<td>(-0.12, 0.21)</td>
</tr>
<tr>
<td>ISWT, m</td>
<td>275.7 (157.6)</td>
<td>272.9 (163.8)</td>
<td>-2.90</td>
<td>(-44.8, 39.1)</td>
</tr>
<tr>
<td>CRQ-SR†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>2.1 (0.7)</td>
<td>1.9 (0.6)</td>
<td>-0.23</td>
<td>(-0.7, 0.3)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>2.9 (0.6)</td>
<td>3.0 (0.7)</td>
<td>0.04</td>
<td>(-0.47, 0.54)</td>
</tr>
<tr>
<td>Emotion</td>
<td>4.2 (1.6)</td>
<td>3.7 (1.3)</td>
<td>-0.51</td>
<td>(-0.93, -0.09)</td>
</tr>
<tr>
<td>Mastery</td>
<td>3.9 (1.9)</td>
<td>3.1 (1.2)</td>
<td>-0.82</td>
<td>(-2.47, 0.82)</td>
</tr>
</tbody>
</table>

Table 3.3: Change in exercise performance, spirometry and health status.
Data presented as mean (SD) for sessions 1 and 3 and between session mean change (95% confidence intervals), n = 7. Between session difference for FEV₁ and ISWT, student paired t-test, for CRQ-SR, Wilcoxon Signed Ranks test. Statistically significant level *p<0.05. No intervention between sessions. Abbreviations: FEV₁, forced expiratory volume in 1 second (litres); ISWT, incremental shuttle walk test (meters); CRQ-SR, Chronic Respiratory Questionnaire-Self-Reported (four domains). A positive change signifies improvement in health status. The threshold for a clinically significant change for each domain has been identified as 0.5 [Juniper EF, 1994].
Isokinetic Measurements

Within-session reliability

Individual subject best isokinetic concentric PT after 5-cycles of concentric-eccentric quadriceps testing, from trials one to four, across three testing sessions are shown (figure 3.2). Mean (SEM) isokinetic concentric and eccentric PT for each trial are presented in figure 3.3.

There were no significant differences between trials within each session. Within session one, mean concentric PT showed greatest change between trials one and two. Mean percentage change (SD) between trials one and two, two and three and three and four, for concentric PT were 14.4% (25.6), 2.0% (37.4) and -6.0% (18.3) and for eccentric PT, -1.4% (10.1), 1.8% (17.1) and 6.7% (21.0) respectively.

Figure 3.2: Individual best peak torque for each trial during three testing sessions. Data presented as individual subject (n = 7) best isokinetic concentric peak torque (Nm) after 5-cycles of concentric-eccentric isokinetic quadriceps testing, from trials one to four, across three testing sessions; session 1 (week 1), 2 (week 2) and 3 (week 7). Abbreviations: Nm, Newton-meters.
Figure 3.3: Mean isokinetic concentric and eccentric quadriceps peak torque.
Data presented as mean (SEM) isokinetic peak torque (Nm) after 5-cycles of concentric-
eccentric isokinetic quadriceps testing during trials 1, 2, 3 and 4. Testing session 1
(week 1), 2 (week 2) and 3 (week 7). Concentric quadriceps (top graph), eccentric
quadriceps (bottom graph), n=7. Abbreviations: Nm, Newton-meters.
Intraclass Correlation Coefficient for within-session reliability

Within-session ICC ranged from 0.72 to 0.93 (table 3.4). SE\(_m\) ranged from 5.5 to 9.9 Nm (5.7 to 17.3 % of the mean) for concentric PT and 11.0 to 14.7 Nm (9.5 to 12.1 % of the mean) for eccentric PT.

<table>
<thead>
<tr>
<th></th>
<th>Concentric</th>
<th>Eccentric</th>
</tr>
</thead>
<tbody>
<tr>
<td>Session 1</td>
<td>0.72 (9.9)</td>
<td>0.73 (11.0)</td>
</tr>
<tr>
<td>Session 2</td>
<td>0.92 (5.5)</td>
<td>0.86 (14.7)</td>
</tr>
<tr>
<td>Session 3</td>
<td>0.93 (5.6)</td>
<td>0.90 (13.2)</td>
</tr>
</tbody>
</table>

Table 3.4: Isokinetic within-session reliability.

Data presented as ICC (SE\(_m\)) for quadriceps muscle concentric and eccentric isokinetic measurements with in each testing session; session 1 (week 1), 2 (week 2) and 3 (week 7). High reliability is accepted as 0.70 to 0.89. Abbreviations: ICC, Intraclass Correlation Coefficient; SE\(_m\), standard error of the measurement.

Number of trials required per session

Figure 3.4 shows the mean concentric PT using best PT from different combinations of trials. If only one trial at maximum effort is performed (trial 1) there is a significant improvement in best PT across sessions (figure 3.4a). Adding results from trial two (figure 3.4b) shows better reliability with no significant difference between sessions. The magnitude of change between session one and two is smaller. The same result is seen with the addition of trial three (figure 3.4c) and using all four trials (figure 3.4d). Discarding trial one each session (representing a maximal practice manoeuvre) and comparing best PT from trials two and three with best PT from trials two, three and four, concentric PT did not differ significantly. Results for eccentric PT were similar. It was therefore decided that further analysis for between session reliability would use best PT from trials two and three.
Figure 3.4: Mean concentric peak torque taken from different combinations of trials.

Mean (SEM) concentric peak torque using best peak torque taken from different combinations of trials (n=7), panel a) trial one only; panel b) trials one and two; panel c) trials one, two and three; panel d) all four trials. Testing session 1 (week 1), 2 (week 2) and 3 (week 7). Between session difference, paired student t-tests, significance level \( *p < 0.05 \). Abbreviations: Nm, Newton-meters.
Between-session reliability

Best PT from trials two and three each session was used to determine between session reliability. Mean isokinetic PT showed a steady improvement across sessions (figure 3.5). Mean (SD) differences between sessions for concentric PT were not statistically significant, sessions one to two, 13.1 (21.9) Nm, two to three, 7.7 (10.7) Nm. There was however, a significant difference session one to three, 20.9 Nm (19.3), p<0.03. There were significant differences for eccentric measurements between sessions two to three, 15.6 (15.0) Nm, p<0.03 and one to three, 37.9 (33.4) Nm, p<0.02.

Mean percentage change (SD) in PT between sessions were, one to two, 18.2% (31.5) and 19.7% (29.4) and two to three, 7.6% (10.4) and 14.5% (16.3), for concentric and eccentric PT respectively.

![Figure 3.5: Mean concentric and eccentric peak torque across testing sessions.](image)

Data presented as mean (SEM) quadriceps concentric and eccentric peak torque, using best peak torque from trials two and three (n=70, testing session 1 (week 1), 2 (week 2) and 3 (week 7). Between session difference, paired student t-tests, significance level *p < 0.05. Abbreviations: Nm, Newton-meters; SEM, standard error of the mean.
Intraclass Correlation Coefficient between-session reliability

Short-term reliability, sessions one to two (concentric and eccentric PT respectively), ICC was 0.36 and 0.50, SEm 15.5 and 20.6 Nm (17.3 and 17.2 % of the mean) and medium-term, sessions two to three, ICC was 0.84 and 0.88, SEm 7.6 and 20.6 Nm (7.6 and 7.7 % of the mean) (table 3.5).

<table>
<thead>
<tr>
<th>Isokinetic ICC (SEm)</th>
<th>Concentric</th>
<th>Eccentric</th>
</tr>
</thead>
<tbody>
<tr>
<td>Session 1 to 2</td>
<td>0.36 (15.5)</td>
<td>0.50 (20.6)</td>
</tr>
<tr>
<td>Session 2 to 3</td>
<td>0.84 (7.6)</td>
<td>0.88 (10.6)</td>
</tr>
</tbody>
</table>

Table 3.5: Isokinetic between-session reliability.
Data presented as ICC (SEm) for quadriceps muscle concentric and eccentric isokinetic measurements between testing sessions; session 1 (week 1), 2 (week 2) and 3 (week 7). High reliability is accepted as 0.70 to 0.89. Abbreviations: ICC, Intraclass Correlation Coefficient; SEm, standard error of the measurement.

Isometric Measurements

Within-session reliability
Isometric testing consisted of two sets of three contractions. Results from the second set were slightly better than the first but were not statistically significant. Mean best isometric force is shown (figure 3.6). Within-session ICC ranged from 0.83 to 0.97, SEm 3.3 to 9.6 Nm (2.5 to 7.9 % of the mean) (table 3.6).

Between-session reliability
ICC between sessions ranged from 0.93 to 0.94, SEm 4.6 to 6.3 Nm (3.5 to 4.8 % of the mean) (table 3.6). Isometric force showed no statistically significant difference between sessions. Mean (SD) difference between sessions one to two, 4.7 (6.5) Nm, mean percentage change, 4.4% (5.5).
Figure 3.6: Mean isometric peak force across testing sessions.
Data presented as mean (SEM) isometric peak force using best force from two sets of three maximal contractions (n = 7). Testing sessions; session 1 (week 1), 2 (week 2) and 3 (week 7). Abbreviations: Nm, Newton-meters; SEM, standard error of the mean.

<table>
<thead>
<tr>
<th></th>
<th>Isometric</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ICC (SEm)</td>
</tr>
<tr>
<td><strong>Within-Session</strong></td>
<td></td>
</tr>
<tr>
<td>Session 1</td>
<td>0.83 (9.6)</td>
</tr>
<tr>
<td>Session 2</td>
<td>0.97 (3.3)</td>
</tr>
<tr>
<td>Session 3</td>
<td>0.91 (7.8)</td>
</tr>
<tr>
<td><strong>Between-Session</strong></td>
<td></td>
</tr>
<tr>
<td>Session 1 to 2</td>
<td>0.94 (4.6)</td>
</tr>
<tr>
<td>Session 2 to 3</td>
<td>0.93 (6.3)</td>
</tr>
</tbody>
</table>

Table 3.6: Isokinetic and isometric within-session and between-session reliability.
Data presented as ICC (SEM) for quadriceps muscle isometric measurements (n = 7). High reliability is accepted as 0.70 to 0.89. Abbreviations: ICC, Intraclass Correlation Coefficient; SEm, standard error of the measurement.
Chapter 3 Isokinetic dynamometry in COPD

Discussion

The results described in this chapter show that measurements of quadriceps strength, using an isokinetic dynamometer, have high within-session test-retest reliability in subjects with COPD. However, isokinetic measurements do not appear stable across three testing sessions over 7-weeks, in contrast to isometric measurements that show high test-retest reliability. Low to moderate short-term reliability (sessions one to two) probably represents a learning phase, but reliability subsequently improved by session three. Isokinetic measurements demonstrate a longitudinal drift suggesting that caution should be used when reviewing results in the context of uncontrolled trials. A separate day familiarisation visit may be necessary to improve the accuracy of isokinetic testing.

Subjects with COPD are often frail and disabled therefore, muscle strength measurements need to minimise discomfort and limit fatigue. One repetition maximum (1-RM), isometric force and dynamic contractions against hydraulic resistance have all been used to assess performance following PR [Bernard S, 1999; Clark CJ, 2000; Franssen FM, 2004; Gosselink R, 1996; Mador MJ, 2004; Spruit MA, 2002]. The accuracy of isokinetic PT should make it ideal for examining dynamic change in muscle strength following an intervention [Li RC, 1996].

Within-session reliability

This chapter demonstrates high within-session reliability for isokinetic dynamometry and isometric strength. Isokinetic concentric strength however improved by 14.4% between trials one and two during session one. This may represent a learning effect. The familiarisation phase only incorporated submaximal practice cycles which are required to achieve consistency; reduce muscle strain and facilitate coordination of movements [Mathur S et al, 2004; Osternig LR, 1986; Quittan M et al, 2001]. Reports suggest that reliability improves if at least one maximal cycle is completed before test measurements are made [Mawdsley RH et al, 1982]. A test-retest reliability study of knee extensor (KE)
muscles concluded that two tests on separate occasions are required to accurately determine average PT [Frontera WR et al, 1993]. This is not always practical, especially with elderly subjects in the clinical setting. A study incorporating a same-session "learning phase" into a continuous concentric-eccentric protocol; three submaximal (50% effort) followed by three maximal contractions before true testing; reported good reliability across three sessions (ICC >0.90) [Steiner LA et al, 1993].

As this chapter explains, PT from trial one was discarded to signifying a maximal practice manoeuvre. The negative change by trial four probably represents fatigue. Comparisons between best PT from trials two and three, with best PT from trials two, three and four, showed no significant differences therefore trial four was discarded. Best PT from trials two and three was used for further analysis. A protocol for future isokinetic testing was therefore developed consisting of a familiarisation phase; comprising two submaximal trials (3 cycles each) and one maximal trial (5 cycles); followed by a testing phase of two maximal trials separated by 2-minutes rest.

**Short-term (1-week) reliability**

This chapter reports low to moderate short-term reliability, for isokinetic concentric quadriceps testing at 60°/sec, with improvements in PT of 18% (±31%) over two testing sessions 1-week apart. Although this improvement was not statistically significant, the clinical significance is unknown and may represent a further learning phase. Healthy subjects show various mean changes in quadriceps PT across testing sessions; 9.5% over 4-10 days; 13.7% across separate test days and 14% variation in average PT [Li RC, 1996; Steiner LA, 1993; Thorstensson A et al, 1976]. Variation in muscle performance (14-30%) can simply occur through repeated testing and does not necessarily constitute a significant improvement or deterioration in muscular performance [Li RC, 1996; Steiner LA, 1993; Thorstensson A, 1976]. Additional testing could increase reliability but this involves extra time and costs.
The short-term reliability reported here (ICC 0.36) differs from other studies. Similar protocols testing between-session KE strength in healthy populations report ICCs ranging 0.83 to >0.92 [Li RC, 1996; Montgomery LC, 1989; Stratford PW, 1990; Tredinnick TJ et al., 1988]. Care should be taken when comparing studies because ICC can be calculated using one measurement or the average of several measurements and is specific to the test, protocol and population [Shrout PE, 1979]. Factors such as interval between contractions and test sessions may also significantly affect the reliability of isokinetic performance [Keating JL et al, 1996; Mawdsley RH, 1982; Stratford PW, 1990].

Medium-term reliability
Despite high medium-term reliability, isokinetic measurements improved across testing sessions. This drift was not reflected in isometric measurements. A training effect is unlikely as sessions were 6-weeks apart. In order to confirm whether a gradual drift occurs or a plateau is reached reliability testing would require weekly measurements, resulting in a training effect. Additional strength measurements (1-RM) could have been used to confirm whether the improvements were true increases in strength. A learning effect may explain these improvements but subjects were not exposed to the dynamometer or training between sessions. The same equipment, testing conditions, tester and standardised testing procedure were used each session. Subjects were stable over the testing period and exercise performance did not alter. Changes in the CRQ-SR emotional component are probably explained by being involved in a clinical study.

Previous work
A previous study exploring short-term reliability of quadriceps strength in COPD subjects (Cybex II dynamometer, n = 10), concluded their protocol was safe and reliable over 7-days, reporting ICCs 0.85 and 0.96 at angular velocities 30°/sec and 90°/sec respectively [Mathur S, 2004]. Larger studies (n = 33-38) have established short-term reliability in patients with CHF (ICCs 0.88-0.99) [Quittan M, 2001; Selig SE et al, 2002]. One study recorded a 13 ± 21% increase in quadriceps strength.
over 1-week and recommended a familiarisation trial before testing [Selig SE, 2002]. They suggested neural adaptations occur in response to exercise after prolonged disuse, which contribute to increases in muscle strength.

**Eccentric muscle performance**

Eccentric muscle action is part of normal muscular activity: descending stairs, running, sitting down. When studying eccentric muscle action continuous concentric-eccentric protocols are frequently performed. They reflect physiological activities where different muscle actions are employed cyclically, rather than isolated concentric or eccentric actions [Bennett JG et al, 1986; Li RC, 1996]. Eccentric testing is unusual and differs from functional muscle use [Steiner LA, 1993]. Resisting the lever arm can inhibit maximal contraction but greater concentric contraction force is produced when proceeded by an eccentric contraction. Moderate to excellent reliability for eccentric quadriceps PT is reported for healthy elderly (ICCs 0.47-0.86) similar to the between-session reliability in the COPD subjects reported in this chapter [Tredinnick TJ, 1988].

**Isometric reliability**

Isometric short- and medium-term reliability was high in this COPD population. Little information is available on the test-retest reliability of isometric force. Isometric quadriceps force in CHF shows high test-retest reliability, ICC >0.90 [Quittan M, 2001]. Lower ICs (0.83-0.90) are reported in women with osteoarthritis of the knee [Wessel J, 1996]. High within-session (ICC 0.94) and 7-day (ICC 0.96) test-retest reliability for isometric force has been reported in COPD subjects [Mathur S, 2004].

**Sample size**

The small sample size (n = 7) is a limitation to this work. Subjects however represented a wide range of age (56-80 years) and disease severity (GOLD II-IV) and many measurements were conducted. Three time points across 7-weeks (PR duration) were observed. Larger numbers would probably provide a more robust
idea of how this outcome measure behaves and offer a legitimate protocol for this population.

**Biological variability**

A certain amount of biological variability accompanies all human performance. Measurements should be obtained efficiently, minimising testing time and observations required to obtain precision [Stratford PW, 1990]. Sufficient warm-up and familiarisation reduce fear of musculoskeletal injury through incorrect technique thereby avoiding submaximal torque production on initial testing. Visual feedback during testing is reported to improve human performance in healthy populations, but is not usual practice in patient populations [Dvir Z et al, 1996; Kellis E et al, 1996; Mathur S, 2004; Quittan M, 2001; Selig SE, 2002; Stratford PW, 1990]. Subjects were given visual feedback during familiarisation to ensure they understood and could perform both concentric and eccentric manoeuvres. This was not used during testing as it became distracting. This practice has been shown to be effective [Hobbel SL et al, 1993]. Subject motivation is harder to control, despite verbal encouragement during each test.

**Conclusion**

This chapter describes the short- and medium-term test-retest reliability of isokinetic dynamometry testing in subjects with COPD. Isometric measurements show high reliability but isokinetic measurements demonstrate a learning effect across 1-week, followed by longitudinal drift. Isokinetic dynamometry measurements should be viewed with some caution in the context of uncontrolled trials. Isometric assessments may be more reliable but bear little resemblance to the dynamic nature of most physical activities. The proposed protocol for future isokinetic testing incorporates a familiarisation phase; comprising two submaximal and one maximal trial (5 cycles); followed by a testing phase of two maximal trials separated by a two-minute rest. If isokinetic measurements were to be used as an outcome measure for an uncontrolled clinical trial however, a familiarisation visit on a separate day to the formal testing session would be recommended.
Chapter 4. Effects of creatine on performance measures.

Introduction

Chapter 1 outlined the causes and effects of peripheral muscle dysfunction in subjects with COPD (1.1.3) and how exercise training during pulmonary rehabilitation can improve performance (1.3.1). Means of augmenting this training effect were discussed (1.3.2). The impact of performance-enhancing therapy in COPD however, has received little attention. It has been suggested that creatine supplementation increases fat-free mass (FFM), health status, peripheral muscle strength and endurance but not exercise capacity in patients with COPD (1.3.3) [Fuld JP, 2005]. An accompanying editorial however, explained that this trial was underpowered [Griffiths TL, 2005].

The main objective of this thesis was to investigate whether creatine supplementation (CrS) can augment the clinical outcomes of pulmonary rehabilitation (PR) in subjects with COPD. A large randomised, double blind, placebo-controlled trial of CrS was conducted to test the hypothesis that CrS, in association with aerobic exercise and resistance training, will enhance the functional benefits of PR in subjects with COPD.
Chapter 4 Results of performance measures

Aim

To determine whether creatine supplementation enhances the clinical outcomes of combined aerobic and resistance training, in the form of pulmonary rehabilitation, in subjects with COPD.

The results of performance measures are described first (Chapter 4); changes in health and functional status are then described (Chapter 5) and finally, the cellular adaptations found in peripheral skeletal muscle, following this intervention are explored (Chapter 6).

Methods

Study Design

This was a randomised, double-blind, placebo-controlled, parallel group trial of CrS during PR. Subjects were tested at baseline, one week later post-loading with supplement and before commencing PR and within one week after completion of PR, at approximately the same time of day (figure 4.4). Baseline and post-PR shuttles were completed on separate days to other performance measures, with at least 24 hours rest. Cycle ergometry was not performed post-loading. Functional dyspnoea was assessed using the Medical Research Council (MRC) Dyspnoea Scale at baseline and post-PR [Appendix II].

Measurements

A detailed description of assessments is given in Chapter 2.

Spirometry

Spirometry was measured seated to ARTP/BTS standards (Vitalograph Model R) [ARTP, 1994].
Chapter 4 Results of performance measures

Body composition

Body composition was measured non-invasively using bioelectrical impedance (BODYSTAT®1500). Fat free mass was estimated using disease specific regression equations [Steiner MC, 2002].

Whole body exercise testing

Walking performance was measured using the incremental (ISWT), reproducible after one practice walk and endurance (ESWT) shuttle walking tests [Revill SM, 1999; Singh SJ, 1992]. Maximal, symptom limited incremental exercise tests were performed on a cycle ergometer.

Peripheral muscle performance

Dominant limb quadriceps, triceps and biceps dynamic isokinetic performance and quadriceps isometric strength were measured using a CYBEX® II Norm dynamometer. Isokinetic strength is described as the torque produced by a muscle group during maximal muscle action (concentric and/or eccentric) through a specified range of movement at a constant angular velocity of movement.

Lower limb isokinetic measurements used a continuous concentric-eccentric contraction protocol at \(60^\circ/sec\) [Li RC, 1996]. Isometric maximum voluntary contractions were performed with the knee at an angle of \(70^\circ\) flexion (leg straight = \(0^\circ\)). Upper limb isokinetic measurements used a continuous concentric-concentric contraction protocol at \(120^\circ/sec\). Analysis used peak work, torque or force and total work.

Subjects

All subjects referred to the Glenfield Hospital PR programme, who met clinical and spirometric criteria for COPD (FEV1/FVC ≤ 0.70), were approached for inclusion [BTS guidelines, 1997]. Subjects were excluded if over 85 years of age or unsuitable for the exercise component of the programme due to neuropsychiatric
or musculoskeletal disorders. Written informed consent was obtained [Appendix XII]. Approval was acquired from Leicestershire Health Authority Research Ethics Committee.

**Supplementation**

After baseline measurements, subjects were randomised to take creatine (creatine monohydrate, Degussa AG, Trostberg, Germany) or placebo (lactose, Novalabs, Leicester, UK) supplement, allocated in blocks of 20 from an independently prepared randomisation list and dispensed by the hospital pharmacy. Packaging was identical and powders had similar texture and appearance. Subjects loaded, four times a day for 5 days (5.58g creatine/6g lactose per dose), followed by daily maintenance during PR (3.76g creatine/4g lactose). Verbal and written instructions were given. Subjects were asked to take their supplement 30-minutes before training sessions or home exercises, dissolved in warm water and flavoured with orange juice, thereby adding carbohydrate to aid absorption [Appendix XIII]. Subjects were given 5-weeks supply at a time. Self-reported compliance sheets recorded time supplement was taken, any missed doses or adverse events [Appendix XIII]. If illness or holidays caused breaks from PR greater than 1-week, supplement was stopped and subjects reloaded over 3-days on return. All subjects, investigators and rehabilitation staff were blinded to supplement allocation. Unblinding occurred when the last subject completed their final assessment.

**Pulmonary Rehabilitation Programme**

Subjects participated in standard outpatient PR programme at Glenfield Hospital, enhanced with resistance training (RT) plus an additional one-hour RT session each week, for a total of 21-sessions over 7-weeks [Appendix XIV]. The PR programme consisted of twice-weekly supervised sessions incorporating 1-hour of combined endurance walking exercise and RT and 1-hour of education composed of topical seminars and discussions [Sewell L, 2006]. Each session incorporated a 5-minute general warm-up with stretching exercises.
Chapter 4

Results of performance measures

Aerobic training

Subjects were initially instructed to walk at a speed equal to 85% of the predicted VO₂ achieved during their initial ISWT. They were encouraged to walk for as long as possible at this speed and walking times increased progressively during the course of the programme. Speeds were checked weekly (figure 4.3). Subjects recorded total time (minutes, seconds) of continuous walking in a walking diary.

Resistance training

A research nurse supervised individually prescribed RT three times per week, exercising the major muscle groups; quadriceps, hamstrings, biceps, triceps and deltoids. Each session incorporated dynamic RT using gym equipment (Technogym, Gambettola (FC), Italy); leg extension (quadriceps) and leg curl (hamstrings) (figure 4.1) and two of the three sessions incorporated upper and lower body exercises using free weights. These exercises included; bicep curls and pull-ups for the upper limbs, step-ups and sitting-to-standing exercises for the lower limbs (figure 4.2).

During the first session, muscular strength was assessed to identify one-repetition maximum (1-RM). Resistance (weight lifted) was set at 80% 1-RM for lower limb and 70% 1-RM for upper limb exercises. Each exercise was performed for three sets of eight repetitions, with a 1-minute rest between sets [Position stand, 1998]. Subjects recorded weight lifted, number of repetitions achieved and Borg breathlessness (dyspnoea) and perceived exertion (PE) score at the end of each exercise in training logs [Appendix XV] [Borg GA, 1982]. Resistance was increased progressively once three sets were easily achieved or the Borg dyspnoea and PE scores declined. If scores were not declining after two weeks, training resistance was reassessed using the 12-RM technique. If twelve repetitions of a subjects training weight were completed, the resistance was increase for subsequent training sessions.
Chapter 4 Results of performance measures

Figure 4.1: Lower limb muscle resistance training exercises.

Pictures 1 & 2: Dynamic resistance training using gym equipment (Technogym, Italy), leg extension (quadriceps) and leg curl (hamstrings) exercises.

Pictures 3 & 4: Free weight resistance training exercises, sitting-to-standing (quadriceps) and step-ups (quadriceps and hamstrings).
Chapter 4 Results of performance measures

Figure 4.2: Upper limb muscle resistance training exercises.

*Pictures 1 & 2:* Free weight resistance training exercises; bicep curls (biceps), pull-ups (triceps & latissimus dorsi).

Figure 4.3: Aerobic exercise training.

Subjects were encouraged to walk for as long as possible at a speed equal to 85% of the predicted VO$_2$ achieved during their initial ISWT. The speed and walking times increased progressively during the course of the programme. Speeds were checked weekly.
Subjects were encouraged to walk every day and do one additional (unsupervised) free weight training session at home. Subjects who had no access to free-weights used plastic milk containers filled with the appropriate weight of water [Appendix XVI]. Subjects recorded visits to their GP, changes in medication or need for antibiotics or steroids in their training log.

**Statistical Analysis**

The primary outcome measure was the ISWT. The power calculation was made based on data available at the time, which suggested that a mean clinically important difference with standard PR was 48m [Singh SJ et al, 2002; Singh SJ et al, 2008]. Subjects who improved 30m above the mean clinically important difference reported better functional benefits therefore; the sample size was calculated (with 80% power) to ensure an additional 30m increase in ISWT performance would be detected in the creatine group, against placebo, assuming a 20% drop out rate from PR. In order to achieve this, the aim was to recruit 100 subjects, with 80 completing the trial, 40 in each group.

The purpose of this thesis was to determine if CrS could enhance the outcome of PR. The analysis was therefore confined to subjects who completed the course of PR. Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS, versions 11.0 - 14.0; Chicago, IL). Demographic variables are described as mean and standard deviation (SD), except gender. The overall effect of supplement plus rehabilitation was assessed using repeated measures ANOVA and effects of covariates on outcomes using univariate analysis.

Comparisons were made using paired (within-treatment effect) and unpaired (between-treatment effect) t-tests, with statistical significance set at p<0.05. Mann-Whitney tests were used for non-parametric data; MRC dyspnoea, Borg breathlessness and perceived exertion scores. Mean changes with standard error of the mean (SEM) are displayed graphically. Advice on statistical analysis was provided by the Trent Institute for Health Services Research.
Illnesses included acute exacerbation of COPD (AE COPD), heart failure, shingles, rheumatoid arthritis (RhA), leg ulcers, cellulitis and transient ischaemic attack (TIA).

Abbreviations: ISWT, incremental shuttle walk test; ESWT, endurance shuttle walk test; FFM, fat-free mass; CRQ-SR, chronic respiratory disease questionnaire; HADS, Hospital Anxiety and Depression Scale; PFSDQ-M, Pulmonary Functional Status Dyspnoea Questionnaire-Modified; SF-36, short form-36 questionnaire.
Chapter 4  Effects of creatine on performance measures

Results

Subjects and baseline characteristics

100 subjects participated and 80 completed the trial. Dropouts (8 placebo, 12 creatine) were mainly due to illness (figure 4.4) preventing completion of PR, two were lost to follow-up. There were two deaths in the creatine group (from pneumonia). Two creatine group subjects blamed the supplement for side effects (hair loss and stomach upset); both discontinued with supplementation but subsequently withdrew from rehabilitation. Baseline characteristics between dropouts and completers were not statistically different, except placebo dropouts had lower baseline functional performance (ISWT 137.5 (34.5) m vs. 223.8 (135.3) m, p < 0.01). There were no significant differences between dropouts and completers in gender split or supplementation (Chi squared 0.39, p = 0.53 and 1.0, p = 0.32 respectively).

Treatment groups were well matched at baseline in pulmonary function (table 4.1), muscle performance (table 4.2) and functional performance (field and laboratory based measurements) (table 4.3). There were significantly more men in the placebo group compared to the creatine group. The creatine group had higher BMI and a significantly higher fat mass (FM) at baseline. Females tended to have higher BMI and FM, but there were no statistically significant differences between genders within either group (p > 0.05).
## Table 4.1: Baseline characteristics of subjects completing trial.

Data presented as group mean (SD), except MRC Dyspnoea Score, median (Inter Quartile Range), for baseline characteristics, pulmonary function and body composition for creatine and placebo supplementation groups. Independent student's t-test used for between-group comparisons. Gender and medication usage analysed using ^2 Chi squared (gender Chi squared, 4.8). ^*MRC score analysed using non-parametric tests (Mann-Whitney test for between group comparisons). Statistical significance, ^*p < 0.05.

Abbreviations: PYHx, pack year history; MRC, Medical Research Council; FEV₁, forced expiratory volume in 1 second (litres per minute); FVC, forced vital capacity (litres); BMI, body mass index (weight/height^2); FFM, fat-free mass; FFMI, fat-free mass index.
Chapter 4

Results of performance measures

<table>
<thead>
<tr>
<th></th>
<th>Creatine</th>
<th>Placebo</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 38</td>
<td>n = 42</td>
<td>(2-tailed)</td>
</tr>
<tr>
<td>Lower Limb (Quadriceps) Muscle Performance</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isokinetic Concentric PT (Nm)</td>
<td>72.9 (28.0)</td>
<td>83.7 (32.2)</td>
<td>0.12</td>
</tr>
<tr>
<td>Isokinetic Eccentric PT (Nm)</td>
<td>113.1 (32.3)</td>
<td>119.8 (37.8)</td>
<td>0.40</td>
</tr>
<tr>
<td>Isometric Force (Nm)</td>
<td>108.1 (41.7)</td>
<td>121.4 (42.8)</td>
<td>0.16</td>
</tr>
<tr>
<td>Lower Limb (Quadriceps) Total Work</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isokinetic Concentric TW (J)</td>
<td>428.3 (195.2)</td>
<td>513.8 (236.2)</td>
<td>0.09</td>
</tr>
<tr>
<td>Isokinetic Eccentric TW (J)</td>
<td>586.7 (219.0)</td>
<td>651.0 (278.0)</td>
<td>0.26</td>
</tr>
<tr>
<td>Upper Limb Muscle Performance</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isokinetic Biceps PT (Nm)</td>
<td>22.7 (10.8)</td>
<td>24.8 (10.6)</td>
<td>0.39</td>
</tr>
<tr>
<td>Isokinetic Triceps PT (Nm)</td>
<td>31.3 (12.5)</td>
<td>34.0 (10.5)</td>
<td>0.32</td>
</tr>
<tr>
<td>Upper Limb Total Work</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isokinetic Biceps TW (J)</td>
<td>247.6 (140.7)</td>
<td>288.5 (141.0)</td>
<td>0.20</td>
</tr>
<tr>
<td>Isokinetic Triceps TW (J)</td>
<td>404.8 (187.0)</td>
<td>453.3 (173.4)</td>
<td>0.24</td>
</tr>
</tbody>
</table>

Table 4.2: Baseline muscle performance in subjects completing trial.

Baseline muscle performance measured on Cybex II dynamometer for lower limb (quadriceps) and upper limb (biceps and triceps) muscles. Data presented as group mean (SD) for creatine and placebo supplementation groups. Independent student's t-test used for between-group comparisons, no significant difference between treatment groups, p< 0.05. Abbreviations: PT, peak torque (peak work); Nm, Newton-meters; TW, total work; J, joules.
### Results of performance measures

<table>
<thead>
<tr>
<th>Shuttle Walking Tests</th>
<th>Creatine n = 38</th>
<th>Placebo n = 42</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISWT (meters)</td>
<td>208.7 (105.6)</td>
<td>223.8 (135.3)</td>
<td>0.58</td>
</tr>
<tr>
<td>SaO2 (%) rest</td>
<td>94.4 (2.3)</td>
<td>95.0 (2.4)</td>
<td>0.26</td>
</tr>
<tr>
<td>SaO2 (%) peak</td>
<td>88.2 (6.5)</td>
<td>89.8 (6.7)</td>
<td>0.29</td>
</tr>
<tr>
<td>Post Exercise BS†</td>
<td>5 (4, 5.5)</td>
<td>4 (4, 5)</td>
<td>0.19</td>
</tr>
<tr>
<td>Post Exercise PE†</td>
<td>15 (13, 17)</td>
<td>15 (13, 15.25)</td>
<td>0.18</td>
</tr>
<tr>
<td>ESWT (seconds)</td>
<td>161.0 (106.4)</td>
<td>182.3 (106.2)</td>
<td>0.37</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Incremental Cycle Ergometry</th>
<th>Creatine n = 36</th>
<th>Placebo n = 40</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak Work Rate (Watts)</td>
<td>49.2 (24.3)</td>
<td>54.4 (24.7)</td>
<td>0.36</td>
</tr>
<tr>
<td>Time to pWR (seconds)</td>
<td>289.9 (143.6)</td>
<td>330.7 (151.6)</td>
<td>0.23</td>
</tr>
<tr>
<td>VO2Peak (ml/kg/min)</td>
<td>11.4 (2.9)</td>
<td>12.7 (3.9)</td>
<td>0.34</td>
</tr>
<tr>
<td>VCO2Peak (ml/kg/min)</td>
<td>11.9 (3.4)</td>
<td>13.1 (4.7)</td>
<td>0.22</td>
</tr>
<tr>
<td>Peak VE (litres)</td>
<td>30.1 (10.49)</td>
<td>33.2 (13.8)</td>
<td>0.29</td>
</tr>
<tr>
<td>Peak RER</td>
<td>0.96 (0.07)</td>
<td>0.96 (0.09)</td>
<td>0.81</td>
</tr>
<tr>
<td>Post Exercise BS†</td>
<td>5 (4, 7)</td>
<td>5 (4, 7)</td>
<td>0.86</td>
</tr>
<tr>
<td>Post Exercise PE†</td>
<td>17 (15, 17)</td>
<td>17 (15.25, 17)</td>
<td>0.12</td>
</tr>
<tr>
<td>Resting Heart Rate (bpm)</td>
<td>83.9 (14.3)</td>
<td>83.6 (12.0)</td>
<td>0.90</td>
</tr>
<tr>
<td>Peak Heart Rate (bpm)</td>
<td>118.9 (16.1)</td>
<td>115.4 (20.7)</td>
<td>0.42</td>
</tr>
<tr>
<td>Percent Predicted Peak HR (%)</td>
<td>78.4 (12.2)</td>
<td>76.1 (13.0)</td>
<td>0.44</td>
</tr>
<tr>
<td>SaO2 (%) rest</td>
<td>94.5 (2.5)</td>
<td>94.7 (3.1)</td>
<td>0.73</td>
</tr>
<tr>
<td>SaO2 (%) peak</td>
<td>89.5 (5.8)</td>
<td>90.3 (6.9)</td>
<td>0.62</td>
</tr>
</tbody>
</table>

**Table 4.3: Baseline functional performance of subjects completing trial.**

Data for baseline shuttle walk tests and maximal incremental cycle exercise tests presented as group mean (SD), except Borg and perceived exertion scores, median (Inter Quartile Range), for creatine and placebo supplementation groups. *Mann-Whitney non-parametric test used for between group comparisons for BS and PE. Independent student’s t-test used for all other between-group comparisons, no significant difference between treatment groups, p < 0.05.

Within group comparisons (student t-tests), statistically significant differences from resting value within group; †p < 0.001. *Abbreviations: ISWT, incremental shuttle walk test; ESWT, endurance shuttle walk test; SaO2, Oxygen Saturations; BS, Borg Score; PE, Perceived Exertion Score WR, Workrate; VO2Peak, Peak Oxygen Uptake; VCO2Peak, Peak Carbon Dioxide Release; Peak VE, Peak Ventilation; RER, Respiratory Quotient; HR, heart rate; bpm, beats per minute.
Chapter 4  
Effects of creatine on performance measures

<table>
<thead>
<tr>
<th>Reason for stopping</th>
<th>Numbers of subjects reporting reason</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Creatine</td>
</tr>
<tr>
<td>Shortness of breath (SOB)</td>
<td>24</td>
</tr>
<tr>
<td>Leg fatigue</td>
<td>4</td>
</tr>
<tr>
<td>SOB + leg fatigue</td>
<td>5</td>
</tr>
<tr>
<td>Leg pain</td>
<td>1</td>
</tr>
<tr>
<td>General tiredness</td>
<td>2</td>
</tr>
<tr>
<td>Chest tightness</td>
<td>0</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>1</td>
</tr>
<tr>
<td>Panic due to mouth piece</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 4.4: Reasons given for discontinuing the incremental cycle test at baseline.

There were no significant differences between supplement groups in reasons reported for discontinuing incremental cycle testing (Chi squared 8.1, \( p = 0.52 \)).

Compliance

Compliance was monitored by supplement pot returns to pharmacy. Overall number of pots dispensed was 337, of which 261 (77.5%) were returned. Subjects who completed the trial were better in returning pots, 223/274 (81.4%) for completers compared to 25/63 (60.3%) for dropouts.

Self-reported compliance suggested that the majority of subjects took their supplement during the PR period and until final assessments were made. Subjects completing the trial documented 181 missed days, out of an approximate total of 5,537 supplement days, giving 96% compliance. There were no significant differences in number of missed days between groups (total days creatine 99, placebo 59, independent t-test, \( p = 0.2 \)). Seven subjects (3 creatine, 4 placebo) ran out or stopped taking supplement 2-10 days before final assessments. One subject failed to load correctly (placebo) but was compliant with supplementation during PR. Reloading occurred in six subjects, following infection (creatine 3, placebo 1) and holidays (creatine 1, placebo 1).
Supplements were generally taken in the mornings. Subjects had difficulty taking supplements thirty minutes before exercise classes held at the hospital due to travel. Hospital transport required subjects to be ready at least 2-hours before class.

**Loading with Supplement**

**Functional and muscle performance**

Loading with creatine and placebo resulted in minor but statistically significant improvements in functional and muscle performance within groups (table 4.5), except for eccentric isokinetic total work in both groups and eccentric quadriceps peak work (peak torque, PT), triceps and biceps total work (TW) in the creatine group. There were no statistically significant differences between treatment groups in functional performance or muscle performance.

**Set and sum total work**

Isokinetic work was measured during two sets of exercise each consisting of 5-continuous concentric-eccentric or concentric-concentric contractions, separated by a 2-minute rest period. Supplement loading had no significant effect on TW performed within each set of concentric quadriceps muscle contractions (figure 4.2a). The sum of TW performed (set one plus two) showed no statistically significant differences between treatment groups (table 4.5, figure 4.2b), except for triceps isokinetic TW (mean difference 38.4 J (95% CI 5.3 to 71.5), p 0.02).
### Chapter 4 Results of performance measures

<table>
<thead>
<tr>
<th>Functional Performance</th>
<th>Creatine Change (95% CI)</th>
<th>Placebo Change (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISWT (meters)</td>
<td>36.8 ** (17.6, 56.1)</td>
<td>24.3 ** (7.7, 40.9)</td>
</tr>
</tbody>
</table>

#### Lower Limb (Quadriceps) Muscle Performance

<table>
<thead>
<tr>
<th></th>
<th>Creatine</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isokinetic Concentric PT (Nm)</td>
<td>6.5 ** (3.1, 9.8)</td>
<td>9.9 ** (5.8, 14.1)</td>
</tr>
<tr>
<td>Isokinetic Eccentric PT (Nm)</td>
<td>3.5 (-2.0, 9.1)</td>
<td>9.6 ** (4.6, 14.6)</td>
</tr>
<tr>
<td>Isometric Force (Nm)</td>
<td>8.9 ** (4.1, 13.7)</td>
<td>10.0 ** (6.7, 13.2)</td>
</tr>
</tbody>
</table>

#### Lower Limb (Quadriceps) Total Work

<table>
<thead>
<tr>
<th></th>
<th>Creatine</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isokinetic Concentric TW (J)</td>
<td>76.2 ** (45.7, 106.8)</td>
<td>84.2 ** (52.0, 116.4)</td>
</tr>
<tr>
<td>Isokinetic Eccentric TW (J)</td>
<td>34.1 (-12.7, 80.8)</td>
<td>27.5 (-19.8, 74.7)</td>
</tr>
</tbody>
</table>

#### Upper Limb Muscle Performance

<table>
<thead>
<tr>
<th></th>
<th>Creatine</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isokinetic Biceps PT (Nm)</td>
<td>1.6 ** (0.5, 2.8)</td>
<td>1.9 ** (0.6, 3.2)</td>
</tr>
<tr>
<td>Isokinetic Triceps PT (Nm)</td>
<td>1.3 * (0.01, 2.6)</td>
<td>2.9 ** (1.3, 4.6)</td>
</tr>
</tbody>
</table>

#### Upper Limb Total Work

<table>
<thead>
<tr>
<th></th>
<th>Creatine</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isokinetic Biceps TW (J)</td>
<td>16.1 (-0.9, 33.0)</td>
<td>32.2 ** (14.4, 50.1)</td>
</tr>
<tr>
<td>Isokinetic Triceps TW (J)</td>
<td>14.3 (-9.2, 37.7)</td>
<td>52.7 ** † (28.8, 76.6)</td>
</tr>
</tbody>
</table>

Table 4.5: Change in functional and muscle performance from baseline after supplement loading.

Data presented as treatment group mean change (95% Confidence Interval) from baseline after supplement loading (creatine or placebo supplementation). Within-group comparisons made using paired student’s t-test, statistically significant differences (from baseline): *p<0.05, **p<0.01. Between-group comparisons made using independent student’s t-test, no significant difference between treatment groups except for triceps isokinetic total work, †p<0.05. Abbreviations: ISWT, incremental shuttle walk test; PT, peak torque (peak work); Nm, Newton-meters; TW, total work; J, joules.
Figure 4.5: Quadriceps muscle isokinetic total work at baseline and post-loading. 

**Panel a**: Set total work (set 1 and 2). **Panel b**: Sum total work (TW for set 1 plus 2).

Mean (SEM) total work (joules) for isokinetic concentric quadriceps muscle at baseline and post-loading with creatine (hashed bars) or placebo (clear bars) supplementation. **Abbreviations**: B, baseline; PL, post-loading. Each set consisted of 5-cycles of concentric-eccentric isokinetic manoeuvres. Set 1 and 2 separated by 2-minute rest period. No significance difference between sets within treatment groups (independent student t-test) at baseline or after supplement loading, p > 0.05. Significant difference from baseline within group (paired student t-test), **p < 0.001.
Body composition

The creatine group showed a significant increase in body weight, predominantly FFM, after loading (table 4.6). The placebo group also significantly increased FFM from baseline. There were no significant differences between groups (figure 4.6).

<table>
<thead>
<tr>
<th>Body Composition</th>
<th>Creatine Change (95% CI)</th>
<th>Placebo Change (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td>0.41 ** (0.17, 0.65)</td>
<td>0.29 (-0.003, 0.59)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>0.2 ** (0.06, 0.26)</td>
<td>0.09 * (0.005, 0.17)</td>
</tr>
<tr>
<td>FFM (kg)</td>
<td>1.10 ** (0.34, 1.85)</td>
<td>0.72 * (0.12, 1.32)</td>
</tr>
<tr>
<td>Fat Mass (kg)</td>
<td>-0.66 (-1.34, 0.02)</td>
<td>-0.40 (0.95, 0.16)</td>
</tr>
</tbody>
</table>

Table 4.6: Change in body composition from baseline after supplement loading.

Data presented as treatment group mean change (95% Confidence Interval) from baseline after supplement loading (creatine or placebo supplementation). Within-group comparisons made using paired student’s t-test, statistically significant differences (from baseline): *p < 0.05, **p < 0.01. Between-group comparisons made using independent student’s t-test, no significant difference between treatment groups, p > 0.05.

Abbreviations: BMI, body mass index; FFM, fat-free mass; kg, kilograms; m, metres.
Panel a

Figure 4.6 Change in body composition after supplement loading.

Panel a: Mean change (SEM) from baseline. Panel b: Mean (SD) value at baseline (shaded bars) and post-loading (unshaded bars). Post-loading with supplement, creatine (hashed bars) or placebo (clear bars). Comparisons made using paired student’s t-test for within-group difference after supplement loading. Statistically significant differences (from baseline), *p < 0.05, **p < 0.01. Independent student’s t-test used for between-group comparisons. Significant differences between treatment groups for fat mass at baseline and post-loading, †p < 0.05. Abbreviations: BM, body mass (weight); FFM, fat-free mass; FM, fat mass; kg, kilograms.
Maintenance Supplementation Combined with Pulmonary Rehabilitation

Functional performance

Functional performance significantly improved from baseline after rehabilitation in both groups (tables 4.7, 4.8 & 4.9, figures 4.7 & 4.8). CrS combined with rehabilitation resulted in no additional statistically significant improvements in whole body performance compared with rehabilitation alone.

Shuttle walking tests

Significant improvements in walking tests were seen after PR in both groups (table 4.7). Mean ISWT at baseline, after loading and PR are shown graphically (figure 4.7a). The creatine group showed a greater but non-significant percentage improvement in ISWT with loading and post-PR (32% vs. 14%, p 0.2 and 72% vs. 45%, p 0.2, respectively) (figure 4.7b). Univariate analyses were therefore performed, adjusting for covariates such as baseline concentric quadriceps work, gender and fat mass. Repeated measures ANOVA, including loading and maintenance phases and also adjusting for covariates, showed no overall effect on outcomes of rehabilitation with creatine against placebo (p = 0.7). Including the 98 subjects who completed the post-loading visit, did not alter this outcome; there were no statistically significant differences between groups.
Chapter 4

Results of performance measures

<table>
<thead>
<tr>
<th>Within group mean change after rehabilitation</th>
<th>Creatine</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change (95% CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shuttle Walking Tests</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ISWT (meters)</td>
<td>84.0 **</td>
<td>83.8 **</td>
</tr>
<tr>
<td></td>
<td>(58.0, 109.9)</td>
<td>(65.0, 102.6)</td>
</tr>
<tr>
<td>ESWT (seconds)</td>
<td>377.4 **</td>
<td>487.4 **</td>
</tr>
<tr>
<td></td>
<td>(248.6, 506.3)</td>
<td>(367.2, 607.6)</td>
</tr>
</tbody>
</table>

Table 4.7: Change in shuttle walking performance from baseline after pulmonary rehabilitation.

Data presented as treatment group mean change (95% Confidence Interval) from baseline after pulmonary rehabilitation (PR) with supplementation (creatine or placebo). Comparisons made from baseline, within-group difference (paired student's t-test), statistically significant differences, **p < 0.01. Between-group comparisons after PR (independent student's t-test), no significant differences, p > 0.05. Abbreviations: ISWT, incremental shuttle walk test; ESWT, endurance shuttle walk test.
Chapter 4  Results of performance measures

Panel a

Figure 4.7: Change in mean ISWT after supplement loading and pulmonary rehabilitation.

Panel a: Mean (SEM) ISWT. Panel b: Percentage change (SEM) from baseline. B, Baseline (pre-loading); PL, post-loading, PR, post-rehabilitation. Supplementation during pulmonary rehabilitation with creatine (red open squares, hashed bars) or placebo (blue closed triangles, clear bars). Significant improvements from baseline (paired student t-tests), ** p < 0.01. No significant difference between treatment groups (independent t-tests), p > 0.05. Abbreviations: ISWT, incremental shuttle walk test.
Maximal incremental cycle tests

Both groups showed statistically significant changes in exercise time to peak work rate from baseline (figure 4.8b). The placebo but not creatine group showed statistically significant changes in peak work rate, peak oxygen uptake and other gas exchange variables following PR compared to baseline variables (table 4.9, figure 4.8). There were small but significant decreases in perceived exertion score after the incremental cycle test in both groups following PR. The changes in saturation and heart rate after training were small and their clinical relevance is questionable. There were no statistically significant differences between treatment groups in incremental test variables following PR.

Leg pain or fatigue were reported on stopping the cycle test by 10 creatine and 11 placebo subjects at baseline, compared to 9 creatine and 13 placebo subjects after PR (tables 4.4 & 4.8) (no between group difference, Chi squared 0.16). There were no significant differences within groups between baseline and post-PR reporting (Chi squared creatine 0.94, placebo 0.96).

<table>
<thead>
<tr>
<th>Reason for stopping</th>
<th>Number of subjects reporting reason</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Creatine</td>
</tr>
<tr>
<td>Shortness of breath (SOB)</td>
<td>21</td>
</tr>
<tr>
<td>Leg fatigue</td>
<td>7</td>
</tr>
<tr>
<td>SOB + leg fatigue</td>
<td>0</td>
</tr>
<tr>
<td>Leg pain</td>
<td>2</td>
</tr>
<tr>
<td>Back pain</td>
<td>0</td>
</tr>
<tr>
<td>Discomfort of mouth piece</td>
<td>3</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>1</td>
</tr>
<tr>
<td>Dizziness</td>
<td>1</td>
</tr>
<tr>
<td>Anxiety</td>
<td>0</td>
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</tbody>
</table>

Table 4.8: Reasons given for discontinuing the incremental cycle test after pulmonary rehabilitation.
## Chapter 4

**Effects of creatine on performance measures**

### Table 4.9: Change in maximal incremental cycle test variables after pulmonary rehabilitation.

Data presented as treatment group mean change (95% Confidence Interval) from baseline after PR (baseline measurements subtracted from post-training measurements), except Borg and perceived exertion scores; median (Inter Quartile Range). Negative values denote a decrease in variable score. Student t-tests for within group comparisons and independent student’s t-test used for between-group comparisons, except for BS and PE. Non-parametric tests used, Mann-Whitney test for between group comparisons, Wilcoxon Signed Ranks Test for within-group change from baseline. Statistical significance differences from baseline within group, *p<0.05, **p<0.01. Statistically significant differences from resting value within group; †p < 0.001. No significant differences between treatment groups. *Abbreviations:* SaO₂, Oxygen Saturations; BS, Borg Score; PE, Perceived Exertion Score; WR, Work rate; VO₂Peak, Peak Oxygen Uptake; VCO₂Peak, Peak Carbon Dioxide Release; Peak VE, Peak Ventilation; RER, Respiratory Quotient; HR, heart rate; bpm, beats per minute.

<table>
<thead>
<tr>
<th></th>
<th>Creatine Change (95% CI)</th>
<th>Placebo Change (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Incremental Cycle Ergometry</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak Work Rate (Watts)</td>
<td>2.1 (-0.8, 4.9)</td>
<td>4.9* (0.9, 8.9)</td>
</tr>
<tr>
<td>Time to pWR (seconds)</td>
<td>15.4* (1.6, 29.3)</td>
<td>35.8** (10.1, 61.5)</td>
</tr>
<tr>
<td>VO₂Peak (ml/kg/min)</td>
<td>0.57 (-0.3, 1.4)</td>
<td>0.93* (0.04, 1.82)</td>
</tr>
<tr>
<td>VCO₂Peak (ml/kg/min)</td>
<td>-0.89 (-1.8, 0.004)</td>
<td>-1.18* (-2.16, -0.20)</td>
</tr>
<tr>
<td>Peak VE (litres)</td>
<td>0.72 (-1.01, 2.44)</td>
<td>2.40* (0.02, 4.78)</td>
</tr>
<tr>
<td>Peak RER</td>
<td>0.03** (0.02, 0.05)</td>
<td>0.02* (0.001, 0.043)</td>
</tr>
<tr>
<td>Peak Heart Rate (bpm)</td>
<td>-0.7† (-4.3, 2.9)</td>
<td>1.5† (-2.3, 5.2)</td>
</tr>
<tr>
<td>Peak SaO₂ (%)</td>
<td>-0.2† (-1.5, 1.1)</td>
<td>-0.3† (-1.5, 1.0)</td>
</tr>
<tr>
<td><strong>Median (IQR)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post Exercise BS†</td>
<td>5 (4, 7)</td>
<td>5 (4, 7)</td>
</tr>
<tr>
<td>Post Exercise PE†</td>
<td>15* (13, 17)</td>
<td>15** (15, 17)</td>
</tr>
</tbody>
</table>
Figure 4.8: Incremental cycle test variables after pulmonary rehabilitation.
Data presented as group mean (SD) at baseline (B) and post-pulmonary rehabilitation (PR) with supplementation (creatine, hashed bars or placebo, clear bars). **Panel a**: peak work rate (watts). **Panel b**: time to peak work rate (seconds). **Panel c**: peak oxygen uptake (mls/kg/min). Significant improvements from baseline (paired student t-tests), *p<0.05, **p<0.01. No significant difference between treatment groups (independent t-tests), p > 0.05. **Abbreviations**: VO₂ peak, peak oxygen uptake; pWR, peak work rate.
Muscle performance and total work

Resistance training
RT was well tolerated and progressive during the 21-sessions of PR (figure 4.9). Significant improvements were made in load lifted in both groups, with no significant differences between treatment groups. Mean 1-RM achieved to initiate training for lower limbs was 63.4% (range 33.3-85.7%).

Muscle performance
Muscle performance improved significantly from baseline after rehabilitation in both groups (table 4.10, figure 4.10). The placebo group made a significantly greater improvement in quadriceps eccentric peak work after PR (mean difference between groups (95% CI), 10.8 Nm (0.8 to 20.9), p < 0.05). CrS combined with rehabilitation resulted in no additional improvements in muscle performance compared with rehabilitation alone.

Set total work
The increase in quadriceps isokinetic concentric sum TW after PR was greatest for the creatine group (table 4.10) but not statistically significant. Following PR, TW achieved during the second set of isokinetic concentric exercise significantly increased in the creatine group (figure 4.10a) (mean (SD) TW set one; 296.9 (122.3) J, set two; 315.6 (128.3) J, p 0.007). The difference in TW between sets after PR compared to baseline showed no significant difference within or between treatment groups.

Isokinetic sum TW for quadriceps eccentric and triceps muscle groups significantly improved in the placebo group after PR (mean difference between groups (95% CI), 94.2 J (6.1 to 182.2), p 0.04 and 39.9 (3.6 to 76.1), p 0.03, respectively) (table 4.10, figure 4.10b).
Figure 4.9: Progression of training loads during pulmonary rehabilitation.

Data presented as mean load (kg) utilised for resistance training during pulmonary rehabilitation (PR) across training sessions (week), as recorded in training diaries. Supplementation during PR with creatine (red open squares) or placebo (blue closed triangles). Significant improvements from baseline (paired student t-tests), **p < 0.01.

Mean (SD) increase in load after PR from baseline: leg curl, 11 (7) kg and 11 (5) kg; leg extension, 10 (7) kg and 8.5 (5) kg, for CrS and placebo groups respectfully. Progression of training loads showed no significant differences between treatment groups at any time point (independent t-tests), p > 0.05. Abbreviations: kg, kilograms.
Chapter 4 Results of performance measures

<table>
<thead>
<tr>
<th></th>
<th>Creatine Change (95% CI)</th>
<th>Placebo Change (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Within group mean change after rehabilitation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>**</td>
<td>**</td>
</tr>
<tr>
<td><strong>Lower Limb (Quadriceps) Muscle Performance</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isokinetic Concentric PT (Nm)</td>
<td><strong>19.2</strong> (14.0, 24.3)</td>
<td><strong>19.5</strong> (14.2, 24.7)</td>
</tr>
<tr>
<td>Isokinetic Eccentric PT (Nm)</td>
<td><strong>15.5</strong> (8.9, 22.1)</td>
<td><strong>26.3</strong> <strong>†</strong> (18.7, 33.9)</td>
</tr>
<tr>
<td>Isometric Force (Nm)</td>
<td><strong>19.6</strong> (16.0, 23.3)</td>
<td><strong>23.1</strong> <strong>†</strong> (17.8, 28.4)</td>
</tr>
<tr>
<td><strong>Lower Limb (Quadriceps) Total Work</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isokinetic Concentric TW (J)</td>
<td><strong>191.9</strong> (146.8, 237.0)</td>
<td><strong>168.2</strong> <strong>†</strong> (129.8, 206.5)</td>
</tr>
<tr>
<td>Isokinetic Eccentric TW (J)</td>
<td><strong>126.7</strong> <strong>†</strong> (70.1, 183.4)</td>
<td><strong>220.9</strong> <strong>†</strong> (153.0, 288.7)</td>
</tr>
<tr>
<td><strong>Upper Limb Muscle Performance</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isokinetic Biceps PT (Nm)</td>
<td><strong>2.8</strong> <strong>†</strong> (0.9, 4.8)</td>
<td><strong>3.6</strong> <strong>†</strong> (1.9, 5.4)</td>
</tr>
<tr>
<td>Isokinetic Triceps PT (Nm)</td>
<td><strong>1.8</strong> <strong>†</strong> (0.3, 3.4)</td>
<td><strong>2.6</strong> <strong>†</strong> (1.0, 4.2)</td>
</tr>
<tr>
<td><strong>Upper Limb Total Work</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isokinetic Biceps TW (J)</td>
<td><strong>28.7</strong> <strong>†</strong> (7.7, 49.6)</td>
<td><strong>55.6</strong> <strong>†</strong> (32.9, 78.4)</td>
</tr>
<tr>
<td>Isokinetic Triceps TW (J)</td>
<td><strong>15.6</strong> <strong>†</strong> (-10.8, 42.0)</td>
<td><strong>55.4</strong> <strong>†</strong> (29.7, 81.1)</td>
</tr>
</tbody>
</table>

Table 4.10: Change in muscle performance from baseline after pulmonary rehabilitation.

Data presented as treatment group mean change (95% Confidence Interval) from baseline after pulmonary rehabilitation (PR) with supplementation (creatine or placebo). Comparisons made from baseline, within-group difference (paired student's t-test), statistically significant differences, *p < 0.05, **p < 0.01. Comparisons between groups, significant difference after PR (independent student's t-test), statistically significant differences, †p < 0.05. Abbreviations: PT, peak torque or work; Nm, Newton-meters; TW, total work; J, joules.
Figure 4.10: Quadriceps muscle isokinetic total work after pulmonary rehabilitation.

Panel a: Mean (SEM) set total work (joules) for isokinetic concentric quadriceps muscle (set 1 and 2) after pulmonary rehabilitation (PR). Panel b: Mean change (SEM) from baseline in sum (set one plus set two) total work (joules) after PR for isokinetic concentric and eccentric quadriceps muscles. Supplementation during PR with creatine (hashed bars) or placebo (clear bars). Two sets, each consisting of 5-cycles of concentric-eccentric isokinetic manoeuvres, separated by a two-minute rest period. Significant difference in TW achieved between sets in creatine group (paired student t-test), *p < 0.001. Comparisons of mean change in sum total work after PR, within group significant difference from baseline (paired student t-test), **p < 0.001, between groups significant difference after PR (independent t-test), †p < 0.05.
Predicted concentric peak torque

Predictive equations were used to calculate gender and age specific percent predicted values for concentric knee isokinetic strength at baseline and following PR (table 4.11) [Appendix X] [Neder JA et al, 1999]. Actual concentric quadriceps PT (but not percent predicted PT) showed significant differences between genders at baseline and post-PR within both treatment groups. Significant improvements from baseline following PR were seen with both measurements for both genders and treatment groups.

<table>
<thead>
<tr>
<th></th>
<th>Creatine</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td><strong>Concentric Quadriceps Peak Torque (Nm)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>91.0 (26.3)</td>
<td>54.8 (14.9)</td>
</tr>
<tr>
<td>Post PR</td>
<td>114.3 (31.1)</td>
<td>69.9 (16.7)</td>
</tr>
<tr>
<td><strong>Percent Predicted Concentric Quadriceps Peak Torque (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>62.0 (15.8)</td>
<td>61.2 (14.8)</td>
</tr>
<tr>
<td>Post PR</td>
<td>77.8 (19.0)</td>
<td>78.7 (19.0)</td>
</tr>
</tbody>
</table>

Table 4.11: Percent predicted values for concentric quadriceps peak torque.

Data presented as actual (Nm, Newton-metres) and percent predicted (% , percentage) values for concentric quadriceps peak torque (PT) at baseline and after pulmonary rehabilitation (PR) split by gender (males bold). Actual measured concentric quadriceps PT showed significant differences between genders within both treatment groups at baseline and post-PR, independent t-test, \( \text{***p < 0.001} \). There were no significant differences between genders when percent predicted values were evaluated. Actual and percent predicted concentric PT showed significant improvements from baseline following PR for both genders and treatment groups, paired student t-test, \( \text{**p < 0.001} \). There were no significant differences between treatment groups at any point (independent t-test, \( \text{p > 0.05} \).
Body composition

The creatine group significantly increased body weight, predominantly FFM, after rehabilitation but there were no significant differences in mean change after PR between treatment groups (table 4.12, figure 4.11, panel a). Increases in weight and BMI in the creatine group did not have any negative impact on performance.

<table>
<thead>
<tr>
<th>Body Composition</th>
<th>Creatine</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Change (95% CI)</td>
<td>Change (95% CI)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>0.76 **  (0.24, 1.28)</td>
<td>0.22  (-0.39, 0.83)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>0.30 **  (0.08, 0.52)</td>
<td>0.06  (0.15, 0.27)</td>
</tr>
<tr>
<td>FFM (kg)</td>
<td>0.92 *   (0.14, 1.69)</td>
<td>0.77  (-0.05, 1.60)</td>
</tr>
<tr>
<td>Fat Mass (kg)</td>
<td>-0.14  (-0.95, 0.67)</td>
<td>-0.47  (-1.28, 0.35)</td>
</tr>
</tbody>
</table>

Table 4.12: Change in body composition from baseline after pulmonary rehabilitation with supplementation.

Data presented as treatment group mean change (95% Confidence Interval) from baseline after supplement loading (creatine or placebo supplementation). Within-group comparisons made using paired student's t-test, statistically significant differences (from baseline): *p<0.05, **p<0.01. Between-group comparisons made using independent student's t-test, no significant difference between treatment groups, p > 0.05.

Abbreviations: BMI, body mass index; FFM, fat-free mass; kg, kilograms; m, metres.
Chapter 4  Effects of creatine on performance measures

Panel a

![Graph showing changes in body composition after pulmonary rehabilitation.](image)

**Panel a:** Mean change (SEM) from baseline. **Panel b:** Mean (SD) value at baseline (shaded bars) and after PR (unshaded bars). PR with supplement, creatine (hashed bars) or placebo (clear bars). Comparisons made using paired student's t-test for within-group difference after supplement loading. Statistically significant differences (from baseline), *p < 0.05, **p < 0.01. Independent student's t-test used for between-group comparisons. Significant differences between treatment groups for fat mass at baseline and after PR, 'p < 0.05. **Abbreviations:** PR, pulmonary rehabilitation; BM, body mass (weight); FFM, fat-free mass; FM, fat mass; kg, kilograms.
Chapter 4  Effects of creatine on performance measures

Discussion

The results described in this chapter show that CrS, as an adjunct therapy to well-conducted multidisciplinary PR for patients with COPD, does not significantly augment the training effect. This large, randomised, double-blind, placebo-controlled trial of CrS during PR, was powered to detect clinically important differences in functional performance [Griffiths TL, 2005]. Intended numbers of subjects were successfully recruited and completed the trial. Functional and muscle performance were measured using well-established, reproducible measurements.

Supplements were well tolerated with few adverse events. Gastrointestinal disturbances due to creatine have been reported anecdotally. Reports of nausea, vomiting or diarrhoea tend to be associated with high single doses of creatine [Persky AM, 2001]. Unsubstantiated reports of hair loss have been reported, mostly in men. Acute exacerbations and illness preventing the completion of rehabilitation were mainly responsible for dropouts and unrelated to supplement. Drop out rate from PR (20%) was as expected. Two deaths occurred in subjects taking creatine, considered not to be contributory to the cause of death (both pneumonia).

Baseline characteristics

Subjects appeared to be well matched at baseline except for gender and FM. The placebo group generally performed better at baseline but there were no statistically significant differences between treatment groups. There were significantly more men in the placebo group, which may account for better performance results. This could influence the outcome of the trial but analysis of variance using either gender or FM as a covariate showed no significant differences between treatment groups.

There were no significant differences in FFM or total body weight (BW) between groups. Baseline BMI was slightly higher, but nonsignificantly, in the creatine
mass, which was significantly higher compared to placebo. This may reflect the significantly higher number of women within the creatine group. Within group analysis however showed no statistically significant differences in BMI between genders. Baseline BW but not BMI showed positive correlations with baseline muscle performance.

**Loading with supplement**

**Functional and muscle performance**

All subjects benefited from 5-days supplement loading, with significant improvements in performance. No exercise training was undertaken during this time. Improvements in both treatment groups, with no significant differences between groups, are possibly due to learning and/or placebo effects. The ISWT is reproducible after a single practice walk, performed by all subjects before baseline measurements [Revill SM, 1999; Singh SJ, 1992]. To minimise learning effects during isokinetic dynamometry, familiarisation was incorporated into the warm-up prior to testing. Same-session familiarisation has been reported as adequate in reducing learning effects, achieving good reliability across testing sessions [Steiner LA, 1993]. Reproducibility data for the isokinetic testing protocol used for this trial showed moderate short-term and high medium-term reliability that should be adequate within a randomised controlled trial (Chapter 3). Non-volitional techniques would provide measurements of muscle function independent of subject motivation (1.2.2) but unfortunately these techniques were unavailable.

Acute creatine loading increases intramuscular PCr storage, thus replenishing ATP more efficiently and providing fuel for muscles to work longer before becoming fatigued, thereby increasing TW output. Strength only improves with increased muscle mass and would not be expected to increase following acute loading. Isokinetic work was measured during two sets of 5-cycles of manoeuvres, separated by a 2-minute recovery period. Creatine loading should help replenish ATP during recovery, increasing the amount of TW achieved in subsequent sets.
The creatine group did not perform any better in the second set compared to the placebo group following supplement loading.

**Body composition**

Gains in body mass, greatest following acute creatine loading, are thought to be a result of intramuscular water retention due to the osmotic action of creatine in the muscle compartment and the influence of increased water content on protein synthesis (1.3.3) [Branch JD, 2003; Hultman E, 1996]. Significant increases in BW, averaging 1 kg after 6-days of creatine loading, are demonstrated in young healthy subjects more often than in the elderly [Bermon S, 1998; Eijnde BO, 2003; Gilliam JD, 2000]. Creatine loading in this group of elderly subject with COPD produced significant increases in BW and FFM. These increases provide evidence to support the uptake of creatine into the muscle despite the fact that they were not significantly different to placebo.

**Maintenance supplementation combined with pulmonary rehabilitation**

**Functional and muscle performance**

PR is well established and effective in improving functional performance in patients with COPD (1.3.1). Mean improvements in ISWT of 52m have recently been shown [Sewell L, 2006]. This trial enhanced PR with individually prescribed, optimal RT, as described by the American College of Sports Medicine, in order to potentiate any effects of creatine during training [Position stand, 1998]. Mean improvements in ISWT after PR (~84m) were better than expected in both groups and probably attributed to closely supervised combined endurance and RT. High-intensity RT was well tolerated and the progression of training loads increased significantly for each group. The creatine group did not show any training advantage over placebo. RT could have a ceiling effect reached sooner with CrS, but this theory is not supported by the data. The impact of the enhanced exercise programme on the
training response may have simply overshadowed any effect creatine has on performance, especially in a group of significantly deconditioned subjects.

The creatine group showed evidence of better improvements in functional performance over placebo. The creatine group made larger, non-significant percentage improvements from baseline in ISWT after loading (32% vs. 14%) and PR (72% vs. 45%) and also in isokinetic PT after PR (29.9% vs. 26.7%). A greater improvement in quadriceps concentric isokinetic TW following PR was also evident in the creatine group although not significant against placebo. After PR the creatine group did achieve significantly greater set TW during the second set of quadriceps concentric isokinetic muscle testing compared to the first. The difference between sets however, was not significantly different when compared to baseline measurements. It is reported that TW is more reliable at faster speeds, as it can be harder to maintain maximum effort at slower speeds, resulting in poorer reliability compared to PT.

The placebo group showed significantly better eccentric quadriceps performance and TW after PR compared to the creatine group, which is difficult to explain. Eccentric manoeuvres are reported to be difficult for subjects to perform. The subject is required to resist the lever bar as it tries to flex the knee from an extended position. There were significantly more males in the placebo group whom certainly found this easier to master, which may explain the discrepancies with this outcome measure. The large, significant improvements in upper limb TW are also difficult to explain and may be a result of higher numbers of male subjects.

The placebo group showed significant improvements after PR in all incremental cycle ergometry variables, but there were no significant differences between treatment groups. It is not surprising that cycle ergometry improvements are small as the main form of aerobic training was walking. Subjects were encouraged to use the static bikes during class but only if they had completed supervised RT and walking exercises.
Chapter 4  

Results of performance measures

Recent publications suggest that the ESWT is more responsive than the 6-MWD for detecting changes in exercise performance following bronchodilation. Endurance testing, using constant workrate cycle ergometry, can be responsive to change in exercise tolerance following PR and correlates with improvements in health status [Laviolette L et al, 2008; Pepin V et al, 2007]. An accompanying editorial argued that walking tests are simple, more relevant to daily life and can avoid limitations due to muscle fatigue often found with cycling tests [Morgan MD et al, 2007]. The ESWT has also been shown to be sensitive to change after PR [Revill SM, 1999].

The outcome measures used in this trial were appropriate and sensitive enough to detect improvements following PR. Muscle strength has been shown to be related to incremental but not endurance shuttle walking performance [Steiner MC, 2005]. Subjects performed a large number of outcome measures, including ISWT and it was felt that measuring endurance using cycle ergometry was not necessary. The use of activity monitors to assess activity was considered but the number of visits and measurements involved became too complicated. Isokinetic dynamic measurements were used to identify any significant functional improvement relevant to activities of daily living.

Body composition
The creatine group showed significant increases in BW and FFM after PR combined with CrS but no significant differences against placebo. Intramuscular water retention may again be responsible for these small increases in weight. If increases in weight are a result of increased muscle mass due to the enhanced training effect of creatine this is not reflected in functional performance measures. Weight gain might be considered disadvantageous as it may curtail exercise performance, especially in weight bearing exercise such as walking. Changes in weight however, did not show any significant negative correlations with change in performance measures after loading or PR.
Conclusion

This large randomised, double blind, placebo-controlled trial provides evidence that as an adjunct therapy to well-conducted multidisciplinary PR for patients with COPD, CrS does not significantly augment the training effect. Changes in body composition are suggestive of creatine uptake into peripheral muscles. Results suggest a placebo or learning effect during supplement loading, with significant improvements in muscle strength and functional performance, before any physical training. Although this is essentially a negative trial it supports the extensive benefits of PR, showing excellent improvements in a variety of outcome measures including muscle strength and work and whole body functional performance. In conclusion, CrS does not significantly augment the substantial training effects of multidisciplinary PR for patients with COPD.
A randomised controlled trial of dietary creatine as an adjunct therapy to physical training in COPD

Chapter 5. Effects of creatine on health status assessments.

Introduction

Chapter 4 presented the primary outcomes and performance measures following a large randomised, double-blind, placebo-controlled trial (RCT) of creatine supplementation (CrS) conducted to test the hypothesis that CrS, in association with aerobic exercise and resistance training (RT), will enhance the functional benefits of pulmonary rehabilitation (PR) in subjects with COPD. Health status or health related quality of life (HRQL) measurements are a central feature of studies in COPD. Questionnaires are used to objectively measure the impact an individuals health has on their ability to perform and enjoy activities of daily life. A number of questionnaires are available to assess health status, broadly divided into generic and disease-specific measures (Chapter 2). Disease-specific measures may be more sensitive to small changes in HRQL. These instruments measure dyspnoea and activity but not changes in the ability to perform daily activities or functional status.

This chapter describes the results of HRQL and functional assessments completed during the RCT of CrS. It than examines the relationship of change in self-reported functional performance, using the Pulmonary Functional Status Dyspnoea
Chapter 5 Effects of creatine on health status assessments

Disease specific questionnaire

Self-Reported Chronic Respiratory Questionnaire (CRQ-SR)
CRQ-SR measures disease-specific health status [Appendix V][Williams JE, 2001]. Results are presented as mean scores per domain; dyspnoea, fatigue, emotion and mastery. The minimal clinically important difference for each domain has been identified as 0.5 [Juniper EF, 1994]. A positive change in score signifies improvement in health status.

Functional status questionnaire

Pulmonary Functional Status and Dyspnoea Questionnaire – modified version (PFSDQ-M)
PFSDQ-M is a disease specific, self-reported questionnaire of functional status in patients with pulmonary disease [Appendix VI]. It measures three domains; activity levels, dyspnoea and fatigue and provides information about the day-to-day impact of pulmonary impairment on dyspnoea and functional abilities of the patient [Lareau SC, 1998]. A negative change in score represents an improvement in functional status.

Measurement of walking performance; ISWT and ESWT and peripheral muscle performance; quadriceps dynamic isokinetic performance and isometric strength were used to examine the relationship between changes in self-reported functional performance and changes in measured exercise performance.

Statistical Analysis
Demographic variables are described as mean and standard deviation (SD) (SPSS, versions 11.0 - 14.0; Chicago, IL). Student t-tests (paired, within group differences; independent, between group differences) identified significant within group changes in performance measures after PR. Ordinal questionnaire data was analysed using non-parametric tests; Wilcoxon Signed Ranks tests for within-group
Chapter 5

Results of health status assessments

Whitney tests for differences between treatment groups after PR. Mean (SEM) changes are displayed graphically.

On examining the PFSDQ-M data, no significant differences were found between treatment groups. PFSDQ-M results were therefore pooled to examine the relationships between change in PFSDQ-M with measurements of exercise performance and quadriceps strength. Correlations between changes in PFSDQ-M scores and performance were identified using Spearman’s rank correlation coefficients. Scatter plots for change in PFSDQ-M mean scores against change in strength and exercise performance after PR were analysed.

Results

Subjects

The 80 subjects described in the previous chapter (Chapter 4, table 4.1) completed assessments. Treatment groups were well matched at baseline in all health and functional status assessments (tables 5.1, 5.3, 5.4 & 5.5).

Generic questionnaires

Hospital Anxiety and Depression Scale (HADS)

Mean HADS scores “suggest” the presence of anxiety in both groups prior to PR. Significant improvements were seen in anxiety and depression scores after rehabilitation in both treatment groups but there were no significant differences between groups (table 5.1). The presence of “probable” mood disorder indicated by HADS score reduced following PR (table 5.2).
Chapter 5  Results of health status assessments

<table>
<thead>
<tr>
<th></th>
<th>Baseline Mean (SD)</th>
<th>After PR Mean (SD)</th>
<th>Within group mean change after rehabilitation (95% CI)</th>
</tr>
</thead>
<tbody>
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<td><strong>Creatine supplementation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td>8.8 (4.0)</td>
<td>7.4 (3.9)</td>
<td>-1.2 * (-1.9, -0.5)</td>
</tr>
<tr>
<td>Depression</td>
<td>7.2 (3.9)</td>
<td>5.6 (3.2)</td>
<td>-1.2 ** (-1.9, -0.4)</td>
</tr>
<tr>
<td><strong>Placebo supplementation</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td>8.5 (3.8)</td>
<td>7.3 (4.2)</td>
<td>-1.3 ** (-2.5, -0.1)</td>
</tr>
<tr>
<td>Depression</td>
<td>6.8 (3.0)</td>
<td>5.6 (4.2)</td>
<td>-1.6 ** (-2.3, -0.9)</td>
</tr>
</tbody>
</table>

Table 5.1: HADS baseline scores and change after PR (generic health status)
Baseline data presented as mean (SD) for each treatment group (supplementation with creatine, n=36 or placebo, n=42). Comparisons made using non-parametric tests. There were no significant differences between treatment groups at baseline (Mann-Whitney Test), p > 0.05. Change from baseline after PR presented as treatment group mean change (95% Confidence Interval). Statistically significant differences for within-group change from baseline (Wilcoxon Signed Ranks Test); *p < 0.05, **p < 0.01. No significant differences between treatment groups after PR (Mann-Whitney Test), p > 0.05. *Abbreviations: PR, pulmonary rehabilitation; HADS, Hospital Anxiety and Depression Scale. Scores range from 0 to 21 for each subscale, 0-7 is regarded as the normal range, 8-10 suggestive of anxiety or depression and >11 indicates probable presence of mood disorder [Zigmond AS, 1983].
### Table 5.2: Caseness of anxiety and depression at baseline and after PR with supplementation.

Data presented as number of subjects (percentage, %) with none, suggested or probable anxiety or depression, based on HADS score at baseline and after pulmonary rehabilitation (PR), for each treatment group (supplementation with creatine, n=36 or placebo, n=42). Presence of mood disorder indicated by HADS score; none 0-7, suggested 8-10 and probable >11 [Zigmond AS, 1983]. Chi squared tests used to assess distribution of caseness, significant change after PR for placebo group only, Chi squared 34.4, p<0.001. No significant difference between treatment groups at baseline or after PR. **Abbreviations**: PR, pulmonary rehabilitation; HADS, Hospital Anxiety and Depression Scale.

<table>
<thead>
<tr>
<th></th>
<th>Baseline Subjects (%)</th>
<th>After PR Subjects (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Creatine supplementation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td></td>
<td></td>
</tr>
<tr>
<td>none</td>
<td>15 (41.7)</td>
<td>18 (50.0)</td>
</tr>
<tr>
<td>suggested</td>
<td>9 (25.0)</td>
<td>12 (33.3)</td>
</tr>
<tr>
<td>probable</td>
<td>12 (33.3)</td>
<td>6 (3.9)</td>
</tr>
<tr>
<td>Depression</td>
<td></td>
<td></td>
</tr>
<tr>
<td>none</td>
<td>22 (59.5)</td>
<td>27 (73.0)</td>
</tr>
<tr>
<td>suggested</td>
<td>8 (21.6)</td>
<td>9 (24.3)</td>
</tr>
<tr>
<td>probable</td>
<td>7 (18.9)</td>
<td>1 (2.7)</td>
</tr>
<tr>
<td><strong>Placebo supplementation</strong></td>
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<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td></td>
<td></td>
</tr>
<tr>
<td>none</td>
<td>19 (45.2)</td>
<td>27 (64.3)</td>
</tr>
<tr>
<td>suggested</td>
<td>11 (26.2)</td>
<td>9 (21.4)</td>
</tr>
<tr>
<td>probable</td>
<td>12 (28.6)</td>
<td>6 (14.3)</td>
</tr>
<tr>
<td>Depression</td>
<td></td>
<td></td>
</tr>
<tr>
<td>none</td>
<td>23 (54.8)</td>
<td>30 (71.4)</td>
</tr>
<tr>
<td>suggested</td>
<td>10 (23.8)</td>
<td>6 (14.3)</td>
</tr>
<tr>
<td>probable</td>
<td>9 (21.4)</td>
<td>6 (14.3)</td>
</tr>
</tbody>
</table>
Short Form-36 Health Survey

Significant improvements were seen in five of the nine domains in the creatine group and four in the placebo group after PR (table 5.3). Both groups improved in social functioning and change in general health. In addition, the creatine group improved in physical functioning, general mental health and general health perception and the placebo group improved in energy/vitality and bodily pain domains. The creatine group showed a nonsignificant mean negative change in role limitation due to physical problems. Change in general health status measured using the SF-36 showed no significant differences between groups after rehabilitation.
Chapter 5 Results of health status assessments

<table>
<thead>
<tr>
<th></th>
<th>Baseline Mean (SD)</th>
<th>After PR Mean (SD)</th>
<th>Within group mean change after rehabilitation Change (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Creatine supplementation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical Functioning</td>
<td>24.3 (15.8)</td>
<td>31.5 (17.5)</td>
<td>7.22 ** (2.57, 11.88)</td>
</tr>
<tr>
<td>RL - Physical Problems</td>
<td>21.4 (34.4)</td>
<td>20.7 (33.5)</td>
<td>-0.71 (-15.22, 13.79)</td>
</tr>
<tr>
<td>RL - Emotional Problems</td>
<td>49.5 (42.3)</td>
<td>50.5 (47.4)</td>
<td>0.95 (13.34, 15.25)</td>
</tr>
<tr>
<td>Social Functioning</td>
<td>60.4 (31.3)</td>
<td>70.3 (27.1)</td>
<td>9.91 * (1.73, 18.09)</td>
</tr>
<tr>
<td>General Mental Health</td>
<td>65.2 (19.3)</td>
<td>73.4 (19.7)</td>
<td>8.22 ** (3.83, 12.61)</td>
</tr>
<tr>
<td>Energy/Vitality</td>
<td>43.0 (21.8)</td>
<td>45.0 (19.5)</td>
<td>2.03 (-5.14, 9.19)</td>
</tr>
<tr>
<td>Bodily Pain</td>
<td>53.5 (28.6)</td>
<td>58.0 (26.5)</td>
<td>4.50 (-4.12, 13.12)</td>
</tr>
<tr>
<td>General Health Perception</td>
<td>27.1 (18.0)</td>
<td>31.1 (19.7)</td>
<td>3.94 * (-1.27, 9.16)</td>
</tr>
<tr>
<td>Change in Health</td>
<td>50.0 (11.8)</td>
<td>56.1 (14.9)</td>
<td>6.08 * (0.73, 11.43)</td>
</tr>
<tr>
<td><strong>Placebo supplementation</strong></td>
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<td></td>
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</tr>
<tr>
<td>Physical Functioning</td>
<td>27.0 (22.9)</td>
<td>33.1 (23.1)</td>
<td>6.10 (-0.26, 12.45)</td>
</tr>
<tr>
<td>RL - Physical Problems</td>
<td>20.7 (33.0)</td>
<td>31.7 (37.5)</td>
<td>10.98 (1.26, 23.21)</td>
</tr>
<tr>
<td>RL - Emotional Problems</td>
<td>50.8 (41.3)</td>
<td>60.8 (42.6)</td>
<td>10.00 (-4.72, 24.73)</td>
</tr>
<tr>
<td>Social Functioning</td>
<td>58.7 (31.5)</td>
<td>77.0 (24.2)</td>
<td>18.25 ** (12.19, 24.32)</td>
</tr>
<tr>
<td>General Mental Health</td>
<td>68.6 (16.1)</td>
<td>72.0 (18.5)</td>
<td>3.43 (-0.93, 7.79)</td>
</tr>
<tr>
<td>Energy/Vitality</td>
<td>43.4 (18.0)</td>
<td>52.4 (20.3)</td>
<td>9.02 ** (4.91, 13.14)</td>
</tr>
<tr>
<td>Bodily Pain</td>
<td>62.4 (28.2)</td>
<td>68.5 (25.9)</td>
<td>6.09 * (-0.89, 13.06)</td>
</tr>
<tr>
<td>General Health Perception</td>
<td>31.9 (16.6)</td>
<td>32.3 (19.6)</td>
<td>0.34 (-5.18, 5.87)</td>
</tr>
<tr>
<td>Change in Health</td>
<td>50.0 (11.0)</td>
<td>61.3 (22.2)</td>
<td>11.31 * (4.38, 18.24)</td>
</tr>
</tbody>
</table>

Table 5.3: SF-36 baseline scores and change after PR (generic health status)
Baseline data presented as mean (SD) for each treatment group (supplementation with creatine, n=37 or placebo, n=42). Comparisons made using non-parametric tests. There were no significant differences between treatment groups at baseline (Mann-Whitney Test), p > 0.05. Change from baseline after PR presented as treatment group mean change (95% Confidence Interval). Statistically significant differences for within-group change from baseline (Wilcoxon Signed Ranks Test); *p < 0.05, **p < 0.01. No significant differences between treatment groups after PR (Mann-Whitney Test), p > 0.05. Abbreviations: PR, pulmonary rehabilitation; SF-36, Short Form-36 Health Survey; RL, role limitation. Scores range from 0 to 100, where 100 indicates good health, a positive change after PR signifies improvement.
Chapter 5

Results of health status assessments

Disease specific questionnaire

Self-Reported Chronic Respiratory Questionnaire (CRQ-SR)

Disease-specific health status, measured using the CRQ-SR, showed statistical and clinically significant improvements in all domains following PR (table 5.4, figure 5.1). There were no significant differences between groups after rehabilitation.

![Figure 5.1: Mean change in CRQ-SR questionnaire after pulmonary rehabilitation. Data presented as treatment group mean change from baseline (SEM) after pulmonary rehabilitation (supplementation with creatine, n=37 or placebo, n=42). The horizontal line represents the minimal clinical important difference (MCID) of 0.5. Statistically significant differences for within-group change from baseline (Wilcoxon Signed Ranks Test); **p < 0.01. No significant differences between treatment groups after pulmonary rehabilitation (Mann-Whitney Test), p > 0.05. Abbreviations: CRQ-SR, Chronic Respiratory Questionnaire-Self Reported.](image-url)
Table 5.4: CRQ-SR baseline scores and change after PR (disease specific health status).

Baseline data presented as mean (SD) for each treatment group (supplementation with creatine, n=37 or placebo, n=42). Comparisons made using non-parametric tests. There were no significant differences between treatment groups at baseline (Mann-Whitney Test), p > 0.05. Change from baseline after PR presented as treatment group mean change (95% Confidence Interval). Statistically significant differences for within-group change from baseline (Wilcoxon Signed Ranks Test); *p < 0.05, **p < 0.01. No significant differences between treatment groups after PR (Mann-Whitney Test), p > 0.05. Abbreviations: PR; pulmonary rehabilitation, CRQ-SR, Self-Reported Chronic Respiratory Questionnaire. A positive change signifies improvement in health status. The threshold for a clinically significant change for each domain has been identified as 0.5 [Juniper EF, 1994].

<table>
<thead>
<tr>
<th></th>
<th>Baseline Mean (SD)</th>
<th>After PR Mean (SD)</th>
<th>Within group mean change after rehabilitation Change (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Creatine supplementation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>2.2 (0.8)</td>
<td>3.0 (1.0)</td>
<td>0.8 ** (0.5, 1.1)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3.3 (1.2)</td>
<td>4.2 (1.2)</td>
<td>0.8 ** (0.5, 1.2)</td>
</tr>
<tr>
<td>Emotion</td>
<td>4.2 (1.2)</td>
<td>4.9 (1.2)</td>
<td>0.8 ** (0.4, 1.2)</td>
</tr>
<tr>
<td>Mastery</td>
<td>4.1 (1.3)</td>
<td>4.9 (1.2)</td>
<td>0.8 ** (0.4, 1.2)</td>
</tr>
</tbody>
</table>

| **Placebo supplementation** |                    |                    |                                                          |
| Dyspnoea                  | 2.3 (0.9)          | 3.1 (1.1)          | 0.9 ** (0.6, 1.2)                                        |
| Fatigue                   | 3.6 (1.1)          | 4.5 (1.2)          | 0.8 ** (0.4, 1.2)                                        |
| Emotion                   | 4.2 (1.1)          | 5.1 (1.2)          | 0.8 ** (0.5, 1.1)                                        |
| Mastery                   | 4.4 (1.2)          | 5.0 (1.4)          | 0.7 ** (0.4, 1.0)                                        |
Chapter 5

Results of health status assessments

Functional status questionnaire

Pulmonary Functional Status and Dyspnoea Questionnaire – modified
version (PFSDQ-M)

Significant improvements in functional status following PR occurred in both groups
but no significant differences between groups after PR (table 5.5). The creatine
group showed significant improvement in general fatigue with Most Day to Day
Activities, all general dyspnoea scores and level of dyspnoea during activities (DA)
mean score. The placebo group showed significant improvement in general
dyspnoea scores; except dyspnoea today, all general fatigue scores, level of
fatigue (FA) and dyspnoea (DA) during activities and change in activities performed
(CA) mean scores.
## Chapter 5

### Results of health status assessments

<table>
<thead>
<tr>
<th></th>
<th>Baseline Mean (SD)</th>
<th>After PR Mean (SD)</th>
<th>Within group mean change after rehabilitation</th>
<th>Change (95% CI)</th>
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<tr>
<td><strong>Creatine supplementation</strong></td>
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<tr>
<td>General Dyspnoea Score</td>
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<tr>
<td>Dyspnoea Today</td>
<td>5.2 (1.8)</td>
<td>4.6 (2.0)</td>
<td>-0.59 *</td>
<td>(-1.18, 0.001)</td>
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<tr>
<td>Dyspnoea Most Days</td>
<td>6.4 (1.7)</td>
<td>5.6 (2.2)</td>
<td>-0.86 **</td>
<td>(-1.56, -0.15)</td>
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<td>Dyspnoea Day-to-Day</td>
<td>6.2 (1.6)</td>
<td>5.6 (1.7)</td>
<td>-0.59 *</td>
<td>(-1.15, -0.03)</td>
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<tr>
<td>General Fatigue Score</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue Today</td>
<td>4.7 (2.3)</td>
<td>4.3 (2.0)</td>
<td>-0.41</td>
<td>(-1.06, 0.23)</td>
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<tr>
<td>Fatigue Most Days</td>
<td>5.6 (2.0)</td>
<td>5.2 (2.0)</td>
<td>-0.39</td>
<td>(-0.89, 0.12)</td>
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<tr>
<td>Fatigue Day-to-Day</td>
<td>5.5 (1.7)</td>
<td>4.9 (1.7)</td>
<td>-0.64 **</td>
<td>(-1.07, 0.21)</td>
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<td>Dyspnoea Mean Score (DA)</td>
<td>3.5 (1.9)</td>
<td>3.1 (1.9)</td>
<td>-0.48 *</td>
<td>(-0.88, -0.08)</td>
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<tr>
<td>Fatigue Mean Score (FA)</td>
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<td>2.4 (1.9)</td>
<td>-0.45</td>
<td>(-0.88, -0.02)</td>
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<tr>
<td>Activity Mean Score (CA)</td>
<td>3.7 (2.1)</td>
<td>3.4 (2.2)</td>
<td>-0.33</td>
<td>(-0.80, 0.15)</td>
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<tr>
<td><strong>Placebo supplementation</strong></td>
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<td></td>
<td></td>
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<tr>
<td>General Dyspnoea Score</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnoea Today</td>
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<td>4.3 (1.9)</td>
<td>-0.42</td>
<td>(-1.0, 0.16)</td>
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<td>Dyspnoea Most Days</td>
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<td>5.4 (1.6)</td>
<td>-0.78 **</td>
<td>(-1.3, -0.29)</td>
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<td>Dyspnoea Day-to-Day</td>
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<td>5.2 (1.8)</td>
<td>-0.73 **</td>
<td>(-1.19, -0.27)</td>
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<tr>
<td>General Fatigue Score</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue Today</td>
<td>4.4 (2.1)</td>
<td>3.8 (2.0)</td>
<td>-0.66 *</td>
<td>(-1.27, -0.06)</td>
</tr>
<tr>
<td>Fatigue Most Days</td>
<td>5.2 (1.9)</td>
<td>4.7 (2.0)</td>
<td>-0.60 *</td>
<td>(-1.22, 0.02)</td>
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<tr>
<td>Fatigue Day-to-Day</td>
<td>5.3 (1.9)</td>
<td>4.6 (1.8)</td>
<td>-0.74 *</td>
<td>(-1.3, -0.18)</td>
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<tr>
<td>Dyspnoea Mean Score (DA)</td>
<td>3.6 (2.2)</td>
<td>3.1 (2.0)</td>
<td>-0.50 **</td>
<td>(-0.86, -0.15)</td>
</tr>
<tr>
<td>Fatigue Mean Score (FA)</td>
<td>3.1 (2.2)</td>
<td>2.7 (1.9)</td>
<td>-0.45 **</td>
<td>(-0.88, -0.01)</td>
</tr>
<tr>
<td>Activity Mean Score (CA)</td>
<td>3.7 (2.3)</td>
<td>2.9 (1.9)</td>
<td>-0.81 *</td>
<td>(-1.32, -0.29)</td>
</tr>
</tbody>
</table>

Table 5.5: PFSDQ-M baseline scores and change after PR (functional status).

Baseline data presented as mean (SD) for each treatment group (supplementation with creatine, n=38 or placebo, n=41). Comparisons made using non-parametric tests. There were no significant differences between treatment groups at baseline (Mann-Whitney Test), p > 0.05. Change from baseline after PR presented as treatment group mean change (95% Confidence Interval). Statistically significant differences for within-group change from baseline (Wilcoxon Signed Ranks Test); *p < 0.05, **p < 0.01. No significant differences between treatment groups after PR (Mann-Whitney Test), p > 0.05. **Abbreviations:** PR; pulmonary rehabilitation, PFSDQ-M, Pulmonary Functional Status and Dyspnoea Questionnaire – modified version; DA, dyspnea with activities; FA, fatigue with activities; CA, change in activities. A negative change in score represents an improvement in functional status.
PFSDQ-M correlations with functional performance

CrS did not enhance change in PFSDQ-M after PR against placebo (table 5.5) therefore; data was pooled to increase subject numbers for correlation analysis. Significant improvements in functional capacity, muscle performance and mean PFSDQ-M scores were seen after PR, beyond those usually achieved following standard PR (table 5.6). Spearman's rank correlation coefficients between post-PR change in PFSDQ-M mean scores and change in functional performance and strength showed weak, but statistically significant correlations for change in ESWT with change in mean activity and dyspnoea scores (table 5.7, figure 5.2). Correlations with performance were generally poor and the strongest correlations were with measures of endurance exercise (ESWT).
Chapter 5

Results of health status assessments

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Within group mean change after rehabilitation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Change (95% CI)</td>
</tr>
<tr>
<td><strong>Functional Capacity</strong></td>
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<td></td>
</tr>
<tr>
<td>ISWT (m)</td>
<td>216.6 (121.6)</td>
<td>83.9 ** (68.5, 99.3)</td>
</tr>
<tr>
<td>ESWT (sec)</td>
<td>172.2 (106.1)</td>
<td>435.1 ** (348.3, 522)</td>
</tr>
<tr>
<td><strong>Lower limb muscle performance (concentric quadricep)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isokinetic PT (Nm)</td>
<td>78.6 (30.5)</td>
<td>19.3 ** (15.7, 22.9)</td>
</tr>
<tr>
<td>Isometric Force (Nm)</td>
<td>115.1 (42.5)</td>
<td>21.5 ** (18.2, 24.7)</td>
</tr>
<tr>
<td><strong>Lower limb muscle total work (concentric quadricep)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isokinetic TW (J)</td>
<td>473.4 (222.2)</td>
<td>179.4 ** (150.6, 208.2)</td>
</tr>
<tr>
<td><strong>PFSDQ-M Mean Score</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnoea (DA)</td>
<td>3.6 (2.0)</td>
<td>-0.5 ** (-0.2, -0.8)</td>
</tr>
<tr>
<td>Fatigue (FA)</td>
<td>3.0 (2.1)</td>
<td>-0.5 ** (-0.2, -0.8)</td>
</tr>
<tr>
<td>Activity (CA)</td>
<td>3.7 (2.1)</td>
<td>-0.6 ** (-0.2, -0.9)</td>
</tr>
</tbody>
</table>

Table 5.6: Pooled results for functional capacity, muscle performance and PFSDQ-M mean scores.

Data presented as mean (SD) baseline values and mean change (95% Confidence Intervals) after PR for pooled data from 80 subjects who completed RCT of creatine supplementation. Comparisons made using paired student's t-test for within-group change, except for PFSDQ-M scores, non-parametric Wilcoxon signed ranks test. Statistically significant differences (from baseline): **p < 0.01. Abbreviations: PR; pulmonary rehabilitation, ISWT, incremental shuttle walk test (meters); ESWT, endurance shuttle walk test (seconds); PT, peak torque; Nm, Newton-meters; TW, total work; J, joules; PFSDQ-M, Pulmonary Functional Status and Dyspnoea Questionnaire – modified version; DA, dyspnoea with activities; FA, fatigue with activities; CA, change in activities. A negative change in score represents an improvement in functional status.
Chapter 5

Results of health status assessments

<table>
<thead>
<tr>
<th>Change PFSDQ-M Mean Score</th>
<th>Dyspnoea (DA)</th>
<th>Fatigue (FA)</th>
<th>Activity (CA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Functional performance</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change ISWT</td>
<td>-0.016</td>
<td>-0.019</td>
<td>-0.106</td>
</tr>
<tr>
<td>Change ESWT</td>
<td>-0.295 **</td>
<td>-0.157</td>
<td>-0.311 **</td>
</tr>
<tr>
<td>Lower limb muscle performance (quadriceps concentric)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change Isokinetic PT</td>
<td>0.053</td>
<td>0.004</td>
<td>0.178</td>
</tr>
<tr>
<td>Change Isometric Force</td>
<td>0.025</td>
<td>0.114</td>
<td>0.078</td>
</tr>
<tr>
<td>Change Total Work</td>
<td>0.086</td>
<td>-0.005</td>
<td>0.11</td>
</tr>
</tbody>
</table>

Table 5.7: Spearman's rank correlation coefficients between change in PFSDQ-M mean scores and change in functional performance after PR.

Spearman's rank correlation coefficients shown between change in PFSDQ-M activity, dyspnoea & fatigue mean scores and change in functional performance and strength. Statistical significance; **p < 0.01. Abbreviations: PFSDQ-M, Pulmonary Functional Status and Dyspnoea Questionnaire – modified version, domains; DA, dyspnoea with activities; FA, fatigue with activities; CA, change in activities; ISWT, incremental shuttle walk test; ESWT, endurance shuttle walk test; PT, peak torque.
Chapter 5 Results of health status assessments

Discussion

The results described in this chapter showed that PR, as an adjunct therapy to well-conducted multidisciplinary interventions for COPD, was not significantly augmented by the inclusion of PR for subjects with COPD. Improvement in quality of life was assessed using well-established, reproducible health status assessments. Significant improvements were seen in both groups following PR, but no significant difference was seen between treatment groups. Mean HADS scores showed that, despite cases of anxiety prior to PR, improved significantly in PR in both groups. "Probable" cases of anxiety and depression also decreased. Similar improvements were observed in the CRQ-SR and HADS. Changes in PFSDQ-M dyspnoea and fatigue domains showed variable improvements. Improvements in physical domains were seen in both groups: PFSDQ-M dyspnoea and daily and fatigue day-to-day and SF-36 change in health and social functioning.

If creative improvements in PFSDQ-M activity or fatigue domains were expected, but this was not shown. The creativeness of the PFSDQ-M domains for each domain of PFSDQ-M against change in exercise performance (ESWT) after PR. Abbreviations: PFSDQ-M, Pulmonary Functional Status and Dyspnoea Questionnaire - modified version; ESWT, endurance shuttle walk test (seconds). Spearman's rank correlation coefficient, r, **p<0.01.

Figure 5.2: Change in PFSDQ-M mean scores against change in ESWT after PR. Scatter plots show correlation of change in mean score for each domain of PFSDQ-M against change in exercise performance (ESWT) after PR.
Chapter 5  Effects of creatine on health status assessments

Discussion

The results described in this chapter show that CrS, as an adjunct therapy to well-conducted multidisciplinary PR for subjects with COPD, does not significantly augment improvements in quality of life. HRQL was assessed using well-established, reproducible health status questionnaires.

Significant improvements in health and functional status were seen in both groups following PR but no significant differences were seen between treatment groups. Mean HADS scores showed that "suggested" cases of anxiety prior to PR improved significantly after PR in both groups. "Probable" cases of anxiety and depression also decreased following PR. All domains in the CRQ-SR and HADS improved in both groups but domains in other questionnaires showed variable improvements. Improvements in the following domains were seen in both groups: PFSDQ-M dyspnoea domains (except dyspnoea today) and fatigue day-to-day and SF-36 change in health and social functioning.

If creatine improves muscle performance, significant improvements in PFSDQ-M activity or fatigue domains could be expected, but this was not shown. The creatine group nevertheless, did show a significant improvement in SF-36 change in physical functioning, role limitation due to physical problems and general health perception, not seen in the placebo group. The relationships between changes in health status and performance are not straightforward and the time course of changes in performance and adaptations to lifestyle following rehabilitation may differ [Green RH et al, 2001].

The aim of PR is to improve independence in subjects with lung disease and the principal aim of this RCT was to improve physical performance. The PFSDQ-M has had limited use but these results suggest that it can be used to describe changes in functional performance following PR in subjects with COPD [Lareau SC et al, 1996]. The improvements seen in PFSDQ-M scores suggest that subjects function
better during home activities after PR, but improvements are not enhanced by CrS. Statistically significant correlations were seen between change in ESWT and change in mean activity and dyspnoea PFSDQ-M scores after PR but the relationship is weak and therefore, not predictive.

**Conclusion**

HRQL assessments during this RCT trial of CrS showed excellent improvements in health status in subjects with COPD following PR. The PFSDQ-M also confirmed improvements in functional status. Creatine supplementation however, does not significantly augment the extensive benefits of PR. Improvements in maximal functional exercise capacity and muscle performance do not predict improvements in functional performance assessed using the PFSDQ-M.
A randomised controlled trial of dietary creatine as an adjunct therapy to physical training in COPD

Chapter 6. Cellular adaptations in peripheral skeletal muscle.

Introduction

Chapter 1 outlined the primary determinants of disability in chronic lung disease, namely peripheral skeletal muscle dysfunction (PMD) and loss of muscle strength and bulk (1.1.3) [ATS, 1999; Gosselink R, 1998]. The clinical benefits of exercise training alone in patients with COPD are well established and performance-enhancing therapies are receiving more attention (Section 1.3). One such therapy, creatine supplementation (CrS), is the main focus of this thesis (1.3.3). CrS combined with resistance training (RT) in the elderly has been shown to have an ergogenic effect enhancing muscle strength and lower body endurance [Brose A, 2003; Chrusch MJ, 2001]. Chapter 4 described the clinical outcomes (functional performance) of a randomised, double blind, placebo-controlled trial (RCT) of CrS during pulmonary rehabilitation (PR), enhanced with RT in subjects with COPD. CrS did not significantly augment the training effect. Understanding the metabolic adaptations in peripheral skeletal muscle during supplementation would help to interpret these results. This chapter describes the cellular adaptations, focusing on the change in concentrations of peripheral muscle metabolite concentrations, as a result of CrS during PR in a subgroup of subjects.
Chapter 6 Cellular adaptations

Methods

Study Design

A subgroup of subjects who participated in the RCT of CrS described in Chapter 4, volunteered to undergo quadriceps muscle sampling. Subjects, randomised to receive creatine or placebo supplementation, attended multidisciplinary outpatient PR for 21-session, over 7-weeks, comprising aerobic exercise with individually prescribed progressive dynamic RT [Sewell L, 2006].

Measurements

In addition to performance measures, detailed in Chapter 4, muscle biopsies were taken at rest on four occasions; at baseline before supplementation, 1-week after supplement loading, 4-weeks into the PR programme and after completion of PR and all outcome performance measures (figure 6.1).

Muscle Biopsy Samples

Muscle biopsies were obtained at rest from the vastus lateralis of the non-dominant leg using the Bergström technique with suction (Methods, Chapter 2) [Bergstrom J, 1975]. Muscle samples were analysed for creatine (Cr), total creatine (TCr) and phosphocreatine (PCr), normalised for non-muscle constituents using adenosine triphosphate (ATP), at the department of Biomedical Sciences, Nottingham [Harris RC, 1992]. Samples with <3mg of muscle tissues were too small for accurate measurements of metabolites and were discarded.
Chapter 6 Cellular adaptations

5 days loading with supplement

Pulmonary rehabilitation, 21 sessions with maintenance supplementation

48 hrs ▼

Muscle biopsy 1

48 hrs ▼ 4 weeks ▼

Muscle biopsy 2

Muscle biopsy 3

48 hrs ▼

Muscle biopsy 4

Recruitment & rehabilitation assessment

ISWT
ESWT
CRQ
SF-36

Baseline
Weight
Height
Spirometry
Isokinetic & isometric dynamometry
Incremental cycle

Post-loading
ISWT
Isokinetic & isometric dynamometry

Discharge
ISWT
ESWT
CRQ
SF-36
HAD

Post-PR
Weight
Spirometry
Isokinetic & isometric dynamometry
 Incremental cycle ergometry
PFSDQ

Figure 6.1: Study outline showing biopsy time points.

Biopsy time points during randomised, double-blind, placebo-controlled, parallel group trial of creatine supplementation during pulmonary rehabilitation in subjects with COPD. Abbreviations: ISWT, incremental shuttle walk test; ESWT, endurance shuttle walk test; FFM, fat-free mass; CRQ-SR, chronic respiratory disease questionnaire; HADS, Hospital Anxiety and Depression Scale; PFSDQ-M, Pulmonary Functional Status Dyspnoea Questionnaire-Modified; SF-36, short form-36 questionnaire; hrs, hours.
Statistical Analysis

Demographic variables are described as mean and standard deviation (SD) (SPSS, versions 11.0 - 14.0; Chicago, IL). Comparisons were made using paired (within-treatment effect) and unpaired (between-treatment effect) Student t-tests, with statistical significance, p<0.05. Mean changes with standard error of the mean (SEM) are displayed graphically. Correlations between changes in TCr concentrations and performance were identified using Pearson's correlation coefficients. Scatter plots were also analysed.

Results

Subjects

Forty-six subjects volunteered for muscle sampling, one subject dropped out first visit due to a needle phobia before any samples were taken. There were more dropouts in the creatine group but dropouts were from PR and not secondary to muscle sampling. Groups were well matched at baseline except for gender, FFM and isometric muscle performance (table 6.1).

Compliance

Compliance was monitored by supplement pot returns to pharmacy and showed 83 of the 103 pots dispensed were returned (80.6%) by the subjects used in the final biopsy analysis (n=29). Self-reported compliance showed documented missed supplement days as 57, out of a total number of 1,799 supplement days, giving 96.8% compliance. The active group did miss significantly more days than the placebo group (52 vs. 5 days, p<0.05). Five subjects (2 creatine, 3 placebo) ran out or stopped taking supplement 1-7 days before final biopsy. Reloading occurred in four subjects, following infection (2 creatine) and holidays (creatine 1, placebo 1).
## Table 6.1: Baseline characteristics of all volunteers who had muscle biopsies.

Data presented as mean (SD) for creatine and placebo supplementation groups (n=45). Student independent t-test used for between group differences, except gender, \(^\dagger\) Chi squared, statistical significance \(^*\)\text{p}<0.05, \(^{**}\text{p}<0.01. Abbreviations: Kg, kilograms; BMI, body mass index (weight/height\(^2\)); FFM, fat-free mass; FM, fat mass; FEV\(_1\), forced expiratory volume in 1 second (litres per minute); %, percent; FVC, forced vital capacity (litres); ISWT, incremental shuttle walk test; ESWT, endurance shuttle walk test; PT, peak torque; Nm, Newton-meters.
Biopsy Samples

There were no major complications, only mild discomfort and bruising. One subject required antibiotics due to erythema around the biopsy site. The biopsy procedure was not always successful in obtaining muscle for analysis (table 6.2), which was only evident in the laboratory while removing samples from the biopsy needles. Biopsy results from twenty-nine subjects were used in the final analysis. Groups were well matched at baseline except for gender (table 6.3). All measurements were non-significantly higher in the placebo group. There were five current smokers and one subject on daily steroids in the creatine group.

<table>
<thead>
<tr>
<th>Subjects biopsied</th>
<th>Samples sent for analysis</th>
<th>Samples providing a result</th>
<th>Samples suitable for analysis (&gt; 3mg)</th>
<th>Paired data*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>45</td>
<td>44</td>
<td>40</td>
<td>34</td>
</tr>
<tr>
<td>Post-Loading</td>
<td>42</td>
<td>40</td>
<td>33</td>
<td>25</td>
</tr>
<tr>
<td>4-weeks PR</td>
<td>33</td>
<td>29</td>
<td>26</td>
<td>23</td>
</tr>
<tr>
<td>Post-PR</td>
<td>30</td>
<td>30</td>
<td>25</td>
<td>19</td>
</tr>
</tbody>
</table>

Table 6.2: Numbers of biopsies samples taken and suitable for analysis.

Numbers of subjects biopsied, samples sent for analysis, results available from samples and samples giving viable results deemed suitable for the final analysis. Samples <3mg of muscle tissues were felt to be too small for accurate measurements of metabolites and were discarded. If the baseline sample was unsuitable for analysis the subject was removed from the analysis (10 subjects). No successful samples were obtained from one subject. *Paired data shows number of paired samples for either baseline to post-loading, baseline to mid-PR or baseline to post-PR. Abbreviations: PR, pulmonary rehabilitation.
<table>
<thead>
<tr>
<th></th>
<th>Creatine n = 16</th>
<th>Placebo n = 14</th>
<th>p (2-tailed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>68.9 (7.3)</td>
<td>67.9 (8.3)</td>
<td>0.73</td>
</tr>
<tr>
<td>Gender (males)†</td>
<td>9</td>
<td>13</td>
<td>0.04*</td>
</tr>
<tr>
<td>Pack Years Smoking History</td>
<td>53.6 (22.6)</td>
<td>62.7 (43.7)</td>
<td>0.48</td>
</tr>
<tr>
<td>Drop outs†</td>
<td>3</td>
<td>2</td>
<td>0.68</td>
</tr>
</tbody>
</table>

**Body Composition**

<table>
<thead>
<tr>
<th></th>
<th>Creatine</th>
<th>Placebo</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td>71.4 (14.4)</td>
<td>77.8 (18.2)</td>
<td>0.31</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.1 (6.9)</td>
<td>26.5 (5.8)</td>
<td>0.80</td>
</tr>
<tr>
<td>FFM (kg)</td>
<td>46.5 (8.7)</td>
<td>52.6 (7.5)</td>
<td>0.05</td>
</tr>
<tr>
<td>FM (kg)</td>
<td>24.9 (9.7)</td>
<td>25.4 (11.3)</td>
<td>0.91</td>
</tr>
</tbody>
</table>

**Pulmonary Function**

<table>
<thead>
<tr>
<th></th>
<th>Creatine</th>
<th>Placebo</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV₁ (l/min)</td>
<td>1.1 (0.6)</td>
<td>1.1 (0.4)</td>
<td>0.82</td>
</tr>
<tr>
<td>FEV₁ (% predicted)</td>
<td>45.9 (23.4)</td>
<td>39.6 (16.6)</td>
<td>0.41</td>
</tr>
<tr>
<td>FVC (l)</td>
<td>2.4 (1.0)</td>
<td>2.8 (0.6)</td>
<td>0.25</td>
</tr>
</tbody>
</table>

**Functional Performance**

<table>
<thead>
<tr>
<th></th>
<th>Creatine</th>
<th>Placebo</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISWT (meters)</td>
<td>231.3 (124.4)</td>
<td>287.1 (167.2)</td>
<td>0.32</td>
</tr>
<tr>
<td>ESWT (seconds)</td>
<td>160.3 (55.6)</td>
<td>168.3 (67.6)</td>
<td>0.75</td>
</tr>
</tbody>
</table>

**Quadriceps Concentric Muscle Performance**

<table>
<thead>
<tr>
<th></th>
<th>Creatine</th>
<th>Placebo</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isokinetic PT (Nm)</td>
<td>72.7 (34.0)</td>
<td>90.7 (40.2)</td>
<td>0.20</td>
</tr>
<tr>
<td>Isometric PT (Nm)</td>
<td>108.7 (42.6)</td>
<td>131.1 (42.4)</td>
<td>0.17</td>
</tr>
<tr>
<td>Total Work (joules)</td>
<td>437.3 (223.6)</td>
<td>600.1 (298.1)</td>
<td>0.11</td>
</tr>
</tbody>
</table>

Table 6.3: Baseline characteristics of subjects used for final biopsy analysis.

Data presented as mean (SD) for creatine and placebo supplementation groups (n=29). Student independent t-test used for between group differences, except gender, †Chi squared, statistical significance *p<0.05, **p<0.01. Abbreviations: Kg, kilograms; BMI, body mass index (weight/height^2); FFM, fat-free mass; FM, fat mass; FEV₁, forced expiratory volume in 1 second (litres per minute); %, percent; FVC, forced vital capacity (litres); ISWT, incremental shuttle walk test; ESWT, endurance shuttle walk test; PT, peak torque; Nm, Newton-meters.
Chapter 6

Cellular adaptations

Muscle ATP content

Muscle metabolite content was corrected for non-muscle constituents using ATP, which did not change significantly following PR (figure 6.2) [Harris RC, 1992].

Figure 6.2: ATP content for all viable muscle biopsy results.

Individual subject and mean (line) muscle adenosine triphosphate (ATP) content. Four biopsy points during the trial period; B, Baseline; PL, post-loading with supplement; MR, mid-rehabilitation (4-weeks); PR, post-rehabilitation. Pulmonary rehabilitation (PR) combined with supplementation; creatine (left, red open squares) or placebo (right, blue closed triangles). Mean change (SEM) ATP post-PR from baseline; creatine 0.9 (0.8) vs. placebo 1.4 (1.4); p = 0.8. Abbreviations: mmol/kg/dm, mmol per kg per dry matter weight.
Baseline metabolite content

Baseline correlations and gender differences

Baseline performance measures and biopsy results were available for thirty-four subjects. Baseline muscle metabolite content (table 6.4) did not show any strong correlations with performance at baseline or after PR.

<table>
<thead>
<tr>
<th></th>
<th>Mean (SD) muscle metabolite concentration (mmol/kg dmm)</th>
<th>Between groups p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Female n = 10</td>
<td>Male n = 24</td>
</tr>
<tr>
<td>Total Creatine</td>
<td>119.8 (20.4)</td>
<td>114.7 (17.8)</td>
</tr>
<tr>
<td>Creatine</td>
<td>65.4 (11.1)</td>
<td>65.5 (10.7)</td>
</tr>
<tr>
<td>Phosphocreatine</td>
<td>54.4 (12.2)</td>
<td>49.2 (9.7)</td>
</tr>
</tbody>
</table>

Table 6.4: Gender differences in muscle metabolite content at baseline.

Data presented as mean (Standard Deviation) values for muscle metabolite content for male and female groups (n=34) before supplementation. There were no statistical significance differences between groups in baseline metabolites (student independent t-test), p >0.05.
**Creatine Loading**

**Baseline to post-loading paired samples**

Nineteen paired baseline to post-loading biopsy results were analysed. Significant increases in TCr and Cr concentrations were seen after 5-days loading with creatine against placebo supplementation (Table 6.5, Figure 6.3a). Mean percentage change in muscle metabolites were all significantly higher after loading with creatine (Figure 6.3b). There were no significant differences in loading between genders.

<table>
<thead>
<tr>
<th>Mean (SD) metabolite content</th>
<th>Within group mean change post supplement loading</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>Post Loading</td>
</tr>
<tr>
<td>Creatine supplementation</td>
<td></td>
</tr>
<tr>
<td>Total creatine</td>
<td>107.9 (15.9)</td>
</tr>
<tr>
<td>Creatine</td>
<td>45.8 (8.2)</td>
</tr>
<tr>
<td>Phosphocreatine</td>
<td>62.1 (9.0)</td>
</tr>
<tr>
<td>Placebo supplementation</td>
<td></td>
</tr>
<tr>
<td>Total creatine</td>
<td>119.4 (20.9)</td>
</tr>
<tr>
<td>Creatine</td>
<td>50.5 (11.5)</td>
</tr>
<tr>
<td>Phosphocreatine</td>
<td>68.9 (12.8)</td>
</tr>
</tbody>
</table>

Table 6.5: Baseline and post-loading mean muscle metabolite content.

Data presented as mean (SD) muscle metabolite content at baseline and after loading and within group mean change (95% confidence intervals) from baseline, after loading with creatine (n=9) or placebo (n=10) supplementation. Significant differences within-group from baseline (paired Student t-test), **p <0.01. Significant differences between groups post-loading (independent Student t-test), †p <0.05; ††p <0.01.
Figure 6.3: Change in muscle metabolite content after supplement loading.
Data presented as mean (SEM) muscle metabolite content after supplement loading with creatine (hashed bars) or placebo (clear bars) (n=19). Panel a: mean change (mmol/kg dmm); Panel b: percentage change (%). Abbreviations: TCr, total creatine; Cr, free creatine; PCr, phosphocreatine. Significant difference within groups from baseline (paired student t-test), **p<0.01. Significant difference between groups (independent student t-test), †p<0.05.
Descriptive trends for muscle metabolite content

Descriptive trends for muscle metabolite content are shown using all available (unpaired) biopsy data (figure 6.4). Creatine loading produced initial increases in all metabolites. PCr levelled off mid-PR, while TCr and Cr declined. Metabolite concentrations drop towards, but did not reach baseline values post-PR. A small increase in muscle metabolites occurred following loading with placebo.

Numbers of viable biopsy samples available for analysis diminishes post-PR (figure 6.4a). Paired samples accessible for further analysis were small and limited interpretation. Only four subjects had results from all biopsy points (2 creatine, 2 placebo), which showed no significant trends in muscle metabolite content.
Chapter 6 Cellular adaptations

Figure 6.4: Descriptive trends for creatine metabolite muscle content.

**Panel a**: Individual subject (n=44) and mean (line) muscle metabolite content at each biopsy point. **Panel b**: Mean (SEM) muscle metabolite content. All available muscle sample data used at each biopsy point; B, Baseline; PL, post-loading; MR, mid-rehabilitation; PR, post-rehabilitation, with creatine (red open squares) or placebo (blue closed triangles) supplementation.
Creatine Combined with Pulmonary Rehabilitation

Baseline to post-pulmonary rehabilitation paired samples

Sixteen-paired baseline to post-PR biopsy results were analysed (male:female; 3:5 creatine, 7:1 placebo, Chi squared 0.04). Once loaded with supplement, subjects took a maintenance dose until after their final biopsy post-PR. Two creatine subjects admitted to stopping supplement 1-7 days before final biopsy. Results confirm muscle creatine metabolites were still present post-PR in subjects maintained with creatine but concentrations were not significantly higher compared to baseline or placebo group (figure 6.5). Nineteen-paired baseline to mid-PR biopsies showed significantly higher intramuscular retention of TCr within the creatine group 4-weeks into PR, compared to placebo and baseline (p < 0.05) (table 6.6).

Table 6.6: Percentage change in muscle metabolites from baseline with creatine supplementation.

Data presented as mean percentage change (SD) from baseline of intramuscular creatine metabolite content post-loading, 4-weeks into pulmonary rehabilitation (mid-PR) and after pulmonary rehabilitation (post-PR) combined with creatine supplementation. Data from paired biopsy samples therefore different subgroups of subjects. Between-group comparisons made using independent student’s t-test, significant difference against placebo, †p <0.05.
Panel a

Figure 6.5: Change in muscle metabolite content after pulmonary rehabilitation. Data presented as mean (SEM) change from baseline in muscle metabolite content after pulmonary rehabilitation with maintenance supplementation, creatine (hashed bars) or placebo (clear bars). **Panel a:** mean change (mmol/kg dmM); **Panel b:** percentage change (%). Within-group change from baseline, only significant difference for PCr (paired student $t$-test), $^* p < 0.05$. No significant differences between groups (independent student $t$-test), significance level $p < 0.05$. **Abbreviations:** TCr, total creatine; Cr, free creatine; PCr, phosphocreatine.
Relationship of TCr uptake in creatine supplemented group

Only one subject, who already had high muscle TCr, 130 mmol/kg dmm, did not increase muscle TCr concentration [$\text{[TCr]}$] after loading, (figure 6.6*). Muscle $\text{[TCr]}$ and $\text{[PCr]}$ increased greatest in subjects with lower initial muscle concentrations. (figure 6.7). Subjects with an initial $\text{[TCr]}$ <120 mmol/kg dmm showed a significantly larger uptake post-loading (figure 6.8).

![Figure 6.6](image)

**Figure 6.6: Muscle total creatine concentration in individual subjects at baseline and post-loading with creatine supplement.**

Data presented as individual subject (n = 9) baseline and post-loading muscle total creatine concentration after loading with creatine supplement, 5.58g creatine/6g lactose four times a day for 5 days. **Abbreviations:** [TCr], muscle total creatine concentration (mmol/kg dmm).
Figure 6.7: Muscle uptake of creatine during supplement loading in relation to baseline creatine metabolite concentration.

Data presented as individual subject (n = 9) baseline metabolite concentration (mmol/kg dmm) against change in concentration (95% confidence intervals) after loading with creatine supplement. Muscle total creatine concentration [TCr] (top) and phosphocreatine concentration [PCr] (bottom). Pearson's correlation coefficient (r); TCr shows stronger relationship, baseline [TCr] with change [TCr], -0.66, p=0.054.
Figure 6.8: Mean change in muscle total creatine after supplement loading, according to baseline concentration.

Data presented as mean change (SEM) in muscle TCr concentration according to baseline concentration, after supplement loading with creatine (hashed bars) or placebo (clear bars) (n=19). [TCr], muscle total creatine concentration (mmol/kg dmm), divided into baseline [TCr] <120 mmol/kg dmm and baseline [TCr] >120 mmol/kg dmm. Significant difference within groups from baseline (paired student t-test), **p<0.01. Significant difference between groups (independent student t-test), †p <0.05.
Responders to creatine loading

An increase in muscle [TCr] > 20 mmol/kg ddm after creatine loading (responders) was observed in eight subjects (2 placebo). There were no significant correlations between change in [TCr] after loading and change in performance after loading or PR (figures 6.9 & 6.10).

Figure 6.9: Change in total creatine post-loading against change in quadriceps total work after pulmonary rehabilitation.

Graph showing the relationship between change in intramuscular TCr concentration after loading and change in performance, quadriceps total work, following pulmonary rehabilitation (PR). Dotted line represents [TCr] 20 mmol/kg dmm, increase in intramuscular [TCr] > 20 mmol/kg dmm are associated with increased performance in healthy subjects. No significant correlations in either group, creatine (open squares) or placebo (closed triangles) supplementation. Abbreviations: [TCr], muscle total creatine concentration.
Figure 6.10: Change in performance after pulmonary rehabilitation in responders and non-responders to supplement loading.

Data represents change in performance after PR according to increase in muscle TCr concentration after loading with supplement, creatine (hashed bars) or placebo (clear bars). **Panel a:** change in ISWT (meters), **Panel b:** change in concentric quadriceps isokinetic total work (joules). **Abbreviations:** Responders (R), increase in [TCr] > 20mmol/kg dmm after loading; non-responders (NR), increase in [TCr] < 20mmol/kg dmm after loading with supplement; ISWT, incremental shuttle walk test; TW, total work; [TCr], muscle total creatine concentration.
Discussion

These results confirm significant uptake of creatine into peripheral skeletal muscle following loading with CrS against placebo in subjects with COPD. Intramuscular creatine retention during maintenance supplementation remained high 4-weeks into PR (mid-PR) but declined; almost reaching baseline levels following 7-weeks PR. Muscle sampling was well tolerated with no major complications but unfortunately did not always produce a muscle sample suitable for analysis. Small numbers were therefore available for data analysis. It was reasonable to use ATP to normalise for muscle metabolite content as this did not change significantly over the course of PR. An increase in ATP with training, could have explained the reduction in muscle TCr.

Baseline characteristics

Subjects, who volunteered to undergo muscle sampling tended to be male, were heavier with significantly greater FFM and had higher baseline performance. As a consequence, the placebo group had fewer female subjects, which resulted in better baseline performance. Baseline levels of creatine muscle metabolites were lower than age-matched healthy individuals (PCr 103.6 ± 5.7 [Eijnde BO, 2003]), as previously reported in subjects with COPD [Fiaccadori E, 1987; Jakobsson P, 1990].

Creatine loading

Acute CrS is reported to increase intramuscular TCr by approximately 20%, greatest in the first two days [Casey A, 1996; Gilliam JD, 2000; Hultman E, 1996; Maughan R, 1997]. Muscle biopsy samples have previously shown significant increases in intramuscular TCr and PCr (15-40%) after short-term loading (5-days, 20g·d⁻¹) [Kreider RB, 2003]. Significant mean percentage increases; TCr 46%, Cr 78% and PCr 22% demonstrated in this chapter, confirm sufficient muscle uptake after 5-days CrS (22.3g·d⁻¹) against placebo. The loading response was comparable to other groups (from 125 to 150 mmol/kg dmm) [Lemon PW, 2002].
Some individuals showed larger increases and significantly greater uptake occurred in subjects with lower baseline intramuscular TCr, <120 mmol/kg dmm, as described in the literature [Casey A, 1996; Harris RC, 1992; Tarnopolsky MA, 2000a].

Small, non-significant increases were seen in the placebo group. All subjects were given information about naturally occurring creatine and the benefits of supplementation in athletes. Diet and exercise were not monitored during the loading phase, which may explain the changes seen in the placebo group; in addition, there were small sample numbers, which can cause analysis errors.

**Creatine combined with pulmonary rehabilitation**

Samples available for analysis showed poor retention of muscle creatine over the PR period reflected by declining muscle concentrations mid- to post-PR. Following loading, the natural decline of creatine muscle content without supplementation is 28 days, longer in meat eaters [Hultman E, 1996; Lemon PW, 2002]. Compliance data suggests supplement was taken until after the final biopsy by all but two creatine subjects. They stopped CrS 1-7 days before their final biopsy which should have had limited effects on the results.

The natural decline of muscle creatine content would have coincided with the 4-week biopsy (mid-PR). The maintenance dose (3.76g·d⁻¹ creatine) may not have been sufficient to sustain muscle creatine levels in this population group. The nature of PMD associated with COPD (inflamed wasted muscle (1.1.3)) may alter transport mechanisms across cell membranes [Lemon PW, 2002]. Uptake into muscle cells is facilitated by a sodium-dependent creatine transporter (CreaT), which can be inhibited by tumour necrosis factor (TNF), commonly associated with PMD [Berton E, 2001; Jagoe RT, 2003]. Diuretics can also influence membrane transport by altering the sodium gradient. Cr uptake is modulated by the plasma membrane content of CreaT in rodents and uptake by oxidative fibres may be influenced more by changes in intracellular Cr concentrations [Brault JJ et al,
Chapter 6 Cellular adaptations

2003. These theories however, would not explain why successful loading is followed by poorer retention.

Intramuscular uptake is enhanced with prolonged, submaximal exercise training, especially if CrS occurs 30-minutes before exercise [Maughan R, 1997; Snow RJ, 2003]. Exercise intensity in this group may not have been a sufficient stimulus and the timing of supplementation in relation to exercise classes was difficult to control. Insulin can stimulate muscle creatine uptake and co-ingestion of carbohydrate with CrS has been shown to increase muscle TCr accumulation [Lemon PW, 2002; Snow RJ, 2003]. Creatine monohydrate powder was not mixed with carbohydrate for this trial, but subjects were instructed to take supplement dissolved in warm water flavoured with orange juice. The accumulation of intramuscular TCr however, suggests that the CrS protocol was adequate.

Responders to creatine loading

The beneficial effects of CrS appear to be related to the extent of muscle creatine accumulation, with evidence of non-responders [Greenhaff PL, 1994]. Enhanced PCr resynthesis following intense exercise is seen in individuals who increase muscle TCr > 20 mmol/kg/d after loading. The most pronounced effects on exercise performance are usually seen in individuals who increase muscle TCr >25% [Maughan R, 1997].

The mean increase in TCr after creatine loading shown in this chapter was 45.1 mmol/kg dmm. Over 60% of subjects achieved an increase >20 mmol/kg/d (responders). Despite sufficient uptake, no relationship between the degree of creatine uptake and subsequent physiological improvements were seen. Small subject numbers may make it difficult to identify a subgroup of respondents to creatine loading. The definition for responders in healthy subjects may not apply to COPD populations, especially as they have a lower initial TCr concentration. The large standard deviation may suggest that there is a subset of respondents to creatine loading not identified in this work. There is a suggestion that the response
to CrS loading is poorer in older women which was not detected in this work [Lemon PW, 2002].

**Conclusion**

Significant increases in peripheral skeletal muscle TCr and Cr content confirm sufficient muscle uptake following 5-days creatine loading in subjects with COPD, against placebo. Maintenance supplementation during PR preserved muscle creatine metabolite content for 4-weeks, but retention then declined, almost reaching baseline levels post-PR. Despite sufficient uptake post-loading, there were no correlations between uptake and exercise performance. Subsets of responders to CrS were not identified.
Chapter 7. Discussion and conclusions

7.1. Discussion

The main aim of this thesis was to investigate the use of creatine monohydrate as an ergogenic aid to enhance physical performance in patients with COPD. Exercise intolerance is a major cause of disability in patients with COPD leading to social isolation, depression and dependence (1.1.1). Leg fatigue more than breathlessness is often the most prominent symptom limiting cycling exercise [Killian KJ et al, 1992b]. Improving physical performance is therefore an important therapeutic goal.

Chapter 1 explored how loss of muscle strength accompanies ageing (1.1.2) but also how peripheral skeletal muscle dysfunction (PMD) in chronic lung disease contributes to reduced muscle bulk and strength, with evidence of reduced type I (fatigue resistant) muscle fibres and a shift towards glycolytic metabolism (1.1.3) [ATS, 1999]. Phosphocreatine (PCr) breakdown is the principal source of energy during early muscular exercise and greater PCr breakdown and slower resynthesis are evident in COPD [Maughan R, 1997; Sala E, 1999]. Although the cause of PMD is multifactorial, deconditioning plays a major role as patients reduce activity to avoid dyspnoea. Exercise training, the logical step to improving physical performance, is successfully achieved through well-established pulmonary rehabilitation (PR) programmes (1.3.1), which improve quality of life, dyspnoea and functional exercise capacity [Ries AL, 2007].

Pharmaceutical manipulation is popular amongst athletes to augment their performance. Creatine supplementation (CrS) enhances training, increasing muscle bulk and improves high-intensity short-duration exercise in healthy subjects (1.3.3) [Casey A, 1996; Greenhaff PL, 1995]. It would not be unreasonable to
consider this in patients with COPD. Small improvements in short-burst exercise, such as getting to the toilet, may have a considerable impact on quality of life.

The hypothesis that CrS, combined with aerobic and resistance exercise training, will augment the physical benefits of PR in subjects with COPD was tested by conducting a large, randomised, double blind, placebo-controlled, parallel group trial (RCT). In addition, preliminary work examined the use and reliability of isokinetic dynamometry as a measure of peripheral muscle performance, while developing a protocol for isokinetic testing in this population. Functional performance measures (Chapter 4) showed that as an adjunct therapy to well-conducted multidisciplinary PR, enhanced with resistance training (RT), CrS did not significantly augment the training effect.

**Performance measures**

Muscular strength is an important measurement of disability and restoring muscle strength is the foundation to rehabilitation therefore, tests of muscular function are an essential assessment tool (1.2.2). Isokinetic dynamometry is a reliable and objective measure of dynamic muscle function used to measure strength in healthy individuals and also in some patient groups [Frontera WR, 1993; Karatas GK et al, 2002; Tredinnick TJ, 1988]. Dynamic muscle force, measured against a controlled resistance at a constant angular velocity, is thought to be more representative of everyday activities [Dvir Z, 1995c; Isokinetics Explained, 2008]. Dynamic muscle testing is often reported following trials involving subjects with COPD but there is no standard protocol.

Chapter 3 examined the use of isokinetic dynamometry and its reliability in a group of subjects with moderate-severe COPD. In contrast to isometric measurements of quadricep muscle strength, isokinetic dynamometry testing showed moderate short-term reliability, probably representing a learning phase (over 1-week), followed by longitudinal drift despite high within-session reliability. A protocol for future isokinetic testing was recommended, incorporating a same-session
submaximal "learning phase", minimising testing time and fatigue. Chapter 3 concluded that if isokinetic measurements were used as an outcome measure for an uncontrolled clinical trial, a familiarisation visit on a separate day to formal testing would be recommended.

Isometric and isokinetic dynamometry measurements, following the RCT of CrS, were presented in Chapter 4. Quadriceps isokinetic peak torque (PT) and isometric force improved significantly in both groups following supplement loading and combined with PR. A learning/placebo effect may have occurred but this should be the same for both groups and hopefully, any effects of CrS would be evident in measurements within this group. This trial however was not powered for isokinetic dynamometry but for ISWT. Muscle strength is related to incremental but not endurance shuttle walking performance and increases in strength would hopefully be translated into improvements in ISWT [Steiner MC, 2005]. Although non-volitional measurements may have identified improved strength in the CrS group, this RCT was a pragmatic study, focusing on the functional benefits in a disabled population, which were not identified.

Relatively poor relationships between tests of muscular function and dynamic functional performance have been shown [Augustsson J et al, 2000]. Isometric, isokinetic and isotonic dynamometry assessments each has its own limitations. Isometric assessment bears little resemblance to the dynamic nature of most physical activities. Isokinetic assessments occur in the absence of acceleration and stretch-shortening cycles, and isolated single-joint assessment is often used, bearing little resemblance to functional performance. Isotonic assessments are argued to show poor reliability and objectivity due to inter-subject, inter-trial and inter-laboratory variations [Abernethy P, 1995; Augustsson J, 2000].

The type of exercise studied is crucial in accessing the effects of CrS loading [Lemon PW, 2002]. Increased availability of PCr theoretically enhances cellular bioenergetics of the phosphagen system involved in high-intensity exercise
performance, enhancing ATP production during recovery, leading to a greater training potential over time (1.1.2). Evidence suggests that creatine loading in athletes and healthy individuals can improve high-intensity, short burst, intermittent exercise (1.3.3) [Kreider RB, 2003]. Many studies report improvements in maximal power and work performed during short-duration cycle sprints and also improvements in maximal voluntary contractions and isometric knee extensor (KE) strength have been shown.

There is less evidence that CrS enhances moderate to high-intensity prolonged exercise. This may explain why additional improvements were not identified using ISWT or ESWT, as these measures may not be sensitive to the intervention. The ESWT is considerably more responsive to endurance training and has been shown to be sensitive to change after PR but it shows greater biological variability than ISWT [Revill SM, 1999]. Home activity monitors may have identified improvements in daily activities.

It is unclear why CrS subjects did not show an improvement in muscle performance; particularly dynamic measures and it may be related to the multifactorial nature of PMD seen in COPD or the age of this population. The PR programme, well established and effective in improving functional performance in patients with COPD, was enhanced with individually prescribed optimal RT, in order to potentiate any effects of creatine during training. Mean improvement in ISWT after PR was better than expected in both groups and probably attributed to supervised RT. Any potential benefits of creatine were most likely submerged by the large training effect of physical training alone.

**Previous creatine studies**

Nearly 70% of studies focusing on the effects of CrS have reported significant improvements in exercise capacity [Buford TW et al, 2007; Kreider RB, 2003]. Gains of 10-15% in strength and functional performance are common. CrS combined with RT has been shown by two meta-analyses (1.3.3) to have positive
effects on body composition and muscular strength in young healthy subjects, along with increasing PCr muscle content [Branch JD, 2003; Nissen SL, 2003; Vandenberghe K, 1997]. CrS in the elderly, with or without exercise training, has produced inconsistent results, possibly explained by low statistical power due to small subject numbers [Gotshalk LA, 2002; Lemon PW, 2002; Rawson ES, 2000]. Conflicting results have been produced following CrS combined with RT in healthy elderly men. CrS combined with 7-weeks RT showed no benefits, compared to 12-14 weeks RT, which demonstrated ergogenic effects. FFM, isometric KE strength and power of the lower body (isokinetic dynamometry) increased, but no improvements in dynamic muscle strength (1-RM) or functional capacity were seen against placebo, despite evidence of increased muscle TCr [Bermon S, 1998; Brose A, 2003; Chrusch MJ, 2001]. Short-term CrS (10 days) however significantly increased quadriceps muscle strength (5%) and endurance (10-20%) in patients with chronic heart failure [Gordon A, 1995].

Two RCT of CrS during PR programmes in subjects with COPD have been published [Faager G, 2006; Fuld JP, 2005]. The first suggested creatine might constitute a new ergogenic treatment in COPD, while the second was a negative study. Both studies were small (creatine groups n=14 and 13 respectively). Fuld et al had difficulties with recruitment and statistical power [Griffiths TL, 2005]. Faager et al underpowered their study (based on ESWT), did not report post-loading measurements and their effects of PR alone were negligible.

Fuld et al and the RCT described in this thesis were powered to detect improvements in ISWT, which significantly improved in both studies following PR. CrS produced no statistically significant improvements in whole body functional performance (ISWT, ESWT and cycle ergometry) after initial loading or after training in either study.

While subjects described in this thesis (Chapter 4) appear fairly well matched in age and disease severity to COPD subjects in previous studies, they showed
higher baseline body composition variables and overall poorer baseline functional performance (measured using shuttle walking tests). Baseline muscle strength is difficult to compare between studies as different methods of measurement were used although subjects appeared to be well matched in muscle strength with those in the Fuld study.

Supplementation was given differently in each study. Subjects in the Faager study loaded over 7-days once PR had commenced (~20g·d⁻¹, followed by maintenance 5g·d⁻¹), while in the other two studies subjects loaded before physical training commenced. Subjects in this thesis loaded with creatine monohydrate powder alone (22.3g·d⁻¹) for 5-days (maintenance 3.76g·d⁻¹), while Fuld et al loaded with creatine combined with a glucose polymer over 2-weeks (15g·d⁻¹, maintenance 5·d⁻¹). Carbohydrate may increase gastrointestinal absorption of creatine, increasing the effects of supplementation and therefore post-loading measurements. However, Chapter 6 provides muscle biopsy evidence suggesting adequate muscle creatine uptake after CrS loading without carbohydrate. Fuld and Faager both used glucose-based placebos whereas this RCT used lactose.

Exercise programmes, as well as outcome measures, differed between studies. Faager et al showed no significant improvements against placebo in physical performance, using the ESWT, after 8-weeks training (16 sessions) predominantly cycle ergometry, combined with free weight or theraband RT. Fuld et al showed significant increases against placebo in muscle performance (lower limb strength), after 2-weeks loading with CrS without training and further significant improvements following maintenance supplementation combined with 8-weeks training (16 sessions). Training utilized cycle ergometry, combined with circuit based dynamic RT. Isokinetic lower limb strength improvements described in Chapter 4 were of similar magnitude to those in the Fuld study following PR, (19.2 Nm or 30% vs. 19.5 Nm or 22.8% [Fuld JP, 2005]) but this thesis found no additional improvement over placebo.
Health status

Chapter 5 presented health status (generic and disease specific) and functional status questionnaire results following the RCT of CrS. Improvements were not significantly different between treatment groups and some domains showed no improvement after PR. All domains in the CRQ-SR, dyspnoea (PFSDQ-M) and change in health and social functioning (SF-36) improved in both groups. If creatine were to improve muscle performance, significant improvements in activity or fatigue domains of the PFSDQ-M might be expected but this was not seen. The creatine group nevertheless, did show a significant improvement in "change in activities performed" mean score that was not seen in the placebo group.

Other studies have used the St George's Respiratory questionnaire (SGRQ). Faager et al showed no improvements while Fuld et al showed enhanced total and activity domain scores in the CrS group following PR. The time course of changes in performance and adaptations to lifestyle following rehabilitation may be different though [Green RH, 2001].

Body composition

Gains in body mass (BW), following acute creatine loading, are thought to be a result of intramuscular water retention due to the osmotic action of creatine in the muscle compartment and the influence of increased water content on protein synthesis [Branch JD, 2003; Hultman E, 1996]. Gains of BW 1-2kg during the first week of CrS suggest adequate loading [Buford TW, 2007]. Chapter 4 showed significant change in mean (SD) BW 0.41 (0.7) kg after creatine loading and 0.76 (1.6) kg after PR from baseline, predominantly FFM. Baseline BMI (but not FFM) was slightly higher in the creatine group but this did not affect performance. Fuld et al showed a significant increase in BW after CrS loading (1.1 kg), while Faager et al showed no change.
The increase in BW may be disadvantageous in mass-dependent activities such as running or walking. The ergogenic effects of CrS may be reduced due to the additional work required to move a larger body mass [Lemon PW, 2002]. It is suggested however that the effects of CrS can overcome body mass effects in brief repeated mass-dependent activities. The use of body mass-supported activities such as cycling could minimise any possible adverse performance effects due to gains in body mass. No significant improvements were seen in incremental cycle ergometry, which is not surprising as training effects are task specific and the main training mode during PR was walking.

**Gender effects**

Men are reported to produce significantly higher muscle torque than women at all ages [Borges O, 1989]. Isokinetic and isometric torque decrease with age, with significant decreases between 60-70 years. The placebo group (Chapter 4) consisted of more men than women, which may have "swamped" any effects of CrS, although covariate analysis did not alter the final outcome. Baseline muscle TCr may be greater in women and there is evidence suggesting women respond to a lesser extent to CrS, with respect to changes in BW and FFM. [Harris RC, 1992; Lemon PW, 2002]. It is unclear as to whether these gender differences contribute to inconsistent results. Effects of CrS may generally be reduced with age [Bermon S, 1998; Rawson ES et al, 1999]. The mechanism(s) responsible for any ageing-gender interactions have not been investigated but insulin insensitivity may play a role.

**Cellular adaptations**

Understand the impact of CrS on cellular adaptations within skeletal muscle was an important component in this thesis. The main findings (Chapter 5) showed that CrS increased intramuscular metabolite content significantly after loading and levels were retained for at least 4-weeks during maintenance CrS combined with PR. Increased TCr did not correlate with performance. Although this was a negative trial, there are a number of factors that should be considered, providing
ideas for future work. The main questions are: was this failure of creatine muscle retention or failure of the intervention.

The beneficial effects of CrS appear to be related to the extent of muscle creatine accumulation, with evidence of non-responders [Greenhaff PL, 1994]. Subjects with COPD have low initial PCr levels (~30%), usually maintained through diet and endogenous synthesis, stored in inflamed dysfunctional muscle (1.1.3). Muscle uptake occurs by a specific sodium-dependent Cr transporter [Brault JJ, 2003]. Intramuscular TCr increased after loading suggesting that the muscle transport system was functioning but uptake varied considerably between individuals. The mean increase in TCr with CrS was 45.1 mmol/kg dmm, with wide 95% confidence intervals, suggesting that their may be a subset of subjects who are responders to creatine loading that cannot be identified.

TCr did not remain elevated during the 7-week maintenance period. The simple answer would be that subjects did not take their supplement. Muscle creatine returns to baseline without maintenance CrS 4-weeks after 5-days loading (20g·d⁻¹) [Febbraio MA et al, 1995]. Alternatively, it may be that the maintenance dose used for healthy elderly subjects was not sufficient in this disabled population to maintain muscle stores or the muscle is just unable to retain stores. Increased maintenance dosage may be all that is required to achieve an ergogenic effect. Evidence (in rodents) indicates that transporter activity may be down-regulated by high intracellular creatine concentrations therefore, athletes often use a "cycling strategy" (varying high to low dosage) [Brault JJ, 2003].

Insulin facilitates Cr muscle uptake, carbohydrate is therefore often taken together with CrS. Very large intakes of high glycaemic index carbohydrate (~100 g) or carbohydrate combined with protein (50 g of each) are required [Lemon PW, 2002]. Creatine uptake without carbohydrate was efficient during loading but adding carbohydrate to the maintenance dose may have benefited retention of TCr in this population of COPD subjects. The insulin effect however, appears to be short lived
in vivo (1 day) and increasing insulin concentration over prolonged periods of time may produce little advantage over CrS alone [Steenge GR et al, 2000].

The hypothesis for this thesis was based on the fact that increased type II fibres in subjects with COPD (which contain 12% more PCr than type I fibres) results in lower oxidative metabolism, but potentially higher anaerobic metabolism. The elderly however have been noted to have fewer type II fibres and therefore would be expected to have lower PCr levels. Fibre typing would have been helpful but was not done due to insufficient biopsy samples.

Exercise itself may increase the efficiency of dysfunctional muscle to uptake creatine in both groups, improving muscle performance. This may explain the slightly elevated levels of PCr in the placebo group muscle biopsy samples. Diet was not controlled and information sheets informed subjects of how creatine was obtained naturally. Some subjects may have increased their meat intake resulting in creatine loading over time and this may bias placebo results [Lemon PW, 2002]. Submaximal exercise during CrS can enhance uptake but CrS was not always taken 30-minutes before exercise and was difficult to control. High-intensity aerobic and RT were employed during this trial but the anabolic stimulus may not have been sufficient to enhance muscle uptake. A 60-120 second recovery period is suggested to maximise the ergogenic effect of Cr on repetitive exercise bouts [Lemon PW, 2002]. Again, this disabled population may require longer recovery time. It may be that a longer treatment and training period is required [Chrusch MJ, 2001].
7.2. Conclusions

The results presented in this thesis strongly support the extensive benefits of pulmonary rehabilitation in subjects with COPD. Exercise training alone significantly improved a range of outcome measures including strength, functional performance and health status, measured using well-established, reproducible measurements. Supplements and the addition of RT to standard aerobic training were well tolerated. The training response following PR was better than expected in both groups and probably attributed to closely supervised training.

A placebo or learning effect following supplement loading is suggested by small but significant improvements in strength and functional performance prior to physical training. A familiarisation test incorporated into the warm-up prior to isokinetic testing was felt to be adequate to minimise learning effects. The ISWT is reproducible after a single practice walk, which all subjects had before baseline measurements. CrS produced no additional effects on functional performance after training despite evidence of creatine uptake into peripheral muscles. Creatine concentrations however, were not maintained throughout PR. These results suggests that a good quality training stimulus has more impact than the anabolic effect of CrS and any ergogenic effects of creatine have been submerged by the large training effects of physical exercise alone.

This thesis presents a large, randomised, double blind, placebo-controlled trial, powered to detect clinically important differences in functional performance. In conclusion, creatine supplementation does not significantly augment the substantial training effect of multidisciplinary pulmonary rehabilitation for patients with COPD.
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Appendix I: Estimating VO₂peak from shuttle performance

The shuttle walking test, an incremental maximal field exercise test of disability, provides an objective measure of a patient's cardiorespiratory capacity. Performance on the shuttle walking test can be used to predict a patient's VO₂peak (ml/kg/min) using a regression equation: 4.19 + (0.025 x ISWT distance), derived from treadmill walking tests [Singh SJ, 1994]. A walking speed can then be selected which relates to a specific percentage of the predicted VO₂peak, for example, 85% predicted VO₂peak. This value can then be used to determine the appropriate walking speed (or level) from the graph above (i.e. locate the value you have calculated on the y-axis, read across to the graph and at the point of intersection locate the speed from the x-axis).

Abbreviations: VO₂peak, peak oxygen uptake, ISWT, incremental shuttle walking test.
Appendix II: MRC dyspnoea scale

Degree of breathlessness graded in relation to activities:

1. Not troubled by breathlessness except on strenuous exercise.
2. Short of breath when hurrying 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 100 m or after a few minutes on level ground.
5. Too breathless to leave the house, or breathless when dressing or undressing.


Appendix III: ERS regression equations for FEV\textsubscript{1}

**Males:** \[ \text{FEV}_1 \text{ (L)} = [4.30 \times \text{height (metres)} - 0.029 \times \text{age (years)}] - 2.49 \]

**Females:** \[ \text{FEV}_1 \text{ (L)} = [3.95 \times \text{height (metres)} - 0.025 \times \text{age (years)}] 2.60 \]

FEV\textsubscript{1} values are expressed as a percentage of predicted values calculated from ERS regression equations [Quanjer PH, 1993].
Appendix IV: BIA equations

Bioelectrical impedance analysis (BIA) is based upon the principle that the impedance to an electrical flow of current is related to the volume of the conductor (the human body) and the square of the conductors' length (or height) [Lukaski HC, 1985; Segal KR et al, 1985].

\[ V = L^2 / R \]

\( V \) = conductive volume, assumed to represent fat-free mass (FFM)

\( L \) = length/height of conductor, cm

\( R \) = whole body resistance or impedance, ohms

Body composition measurements subdivide the human body into different compartments. FFM, or lean body mass (LBM), contains virtually all the water, electrolytes and functional muscle mass. FFM therefore has a lower resistance than FM, resulting in lower impedance.

FFM was estimated from impedance measurements using the following sex-specific equations [Steiner MC, 2002]:

**Males:**

\[ \text{FFM} = 8.383 + 0.465ht^2 / R + 0.213wt \]

**Females:**

\[ \text{FFM} = 7.610 + 0.474ht^2 / R + 0.184wt \]

Where;

- \( ht \) is height (cm);
- \( R \) is resistance (ohms);
- \( wt \) is weight (kg).
Appendix V: CRQ-SR questionnaire

CHRONIC RESPIRATORY QUESTIONNAIRE (Self Reported)

This questionnaire is designed to find out how you have been feeling during the last two weeks. You will be asked how short of breath you have been, how tired you have been feeling and how your mood has been.

NAME..............................................................................

DATE..............................................................................

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[Williams JE, 2001]
**ACTIVITIES**

We would like you to think of ways in which your shortness of breath limits your life. We are particularly interested in activities, which you still do, but which are limited by your shortness of breath.

Listed below are some activities, which can make people with lung problems feel short of breath.

If you have felt short of breath doing any of the activities listed below during the last two weeks then please circle each relevant activity. If you have not done the activity during the last two weeks or it does not make you short of breath then leave it blank.

THE ACTIVITIES ARE:

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<td>1. BEING ANGRY OR UPSET</td>
<td>14. PLAYING SPORTS</td>
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<tr>
<td>2. HAVING A BATH OR SHOWER</td>
<td>15. REACHING OVER YOUR HEAD</td>
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<td>3. BENDING</td>
<td>16. RUNNING - SUCH AS FOR A BUS</td>
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<td>4. CARRYING - SUCH AS GROCERIES</td>
<td>17. SHOPPING</td>
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<td>5. DRESSING</td>
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<td>6. EATING</td>
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<td>7. GOING FOR A WALK</td>
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<td>10. MAKING YOUR BED</td>
<td>23. WALKING UPSTAIRS</td>
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<td>11. MOPPING OR SCRUBBING A FLOOR</td>
<td>24. WALKING WITH OTHERS ON LEVEL GROUND</td>
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<td>12. MOVING FURNITURE</td>
<td>25. PREPARING MEALS</td>
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<td>13. PLAYING WITH CHILDREN/GRANDCHILDREN</td>
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Please list any other activities you have done during the last two weeks that have made you feel short of breath. These should be activities which you do frequently and which are important in your day-to-day life.
We would now like you to identify the **five most important activities** in which you have been limited by your shortness of breath.

Please write your **five most important activities** on the lines below and then tell us how short of breath you have been while performing each activity by ticking the box which best describes how you feel.

**HOW SHORT OF BREATH HAVE YOU BEEN DURING THE LAST 2 WEEKS WHILE PERFORMING THESE ACTIVITIES?**

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<tr>
<th></th>
<th>Extremely short of breath</th>
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<th>Quite short of breath</th>
<th>Moderate shortness of breath</th>
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*PLEASE MAKE SURE YOU HAVE COMPLETED THE ABOVE TABLE BEFORE TURNING THE PAGE*

Thank you
5. In general, how much of the time during the last two weeks have you felt frustrated or impatient? Please indicate how often during the last two weeks you have felt frustrated or impatient by ticking one of the following options from the list below.

1. ALL OF THE TIME
2. MOST OF THE TIME
3. A GOOD BIT OF THE TIME
4. SOME OF THE TIME
5. A LITTLE OF THE TIME
6. HARDLY ANY OF THE TIME
7. NONE OF THE TIME

6. How often during the past 2 weeks did you have a feeling of fear or panic when you had difficulty getting your breath? Please indicate how often you had a feeling of fear or panic when you had difficulty getting your breath by ticking one of the following options from the list below.

1. ALL OF THE TIME
2. MOST OF THE TIME
3. A GOOD BIT OF THE TIME
4. SOME OF THE TIME
5. A LITTLE OF THE TIME
6. HARDLY ANY OF THE TIME
7. NONE OF THE TIME

7. What about fatigue? How tired have you felt over the last 2 weeks? Please indicate how tired you have felt over the last 2 weeks by ticking one of the following options from the list below.

1. EXTREMELY TIRED
2. VERY TIRED
3. QUITE A BIT OF TIREDNESS
4. MODERATELY TIRED
5. SOMEWHAT TIRED
6. A LITTLE TIRED
7. NOT AT ALL TIRED
Appendix V: CRQ-SR

8. How often during the last 2 weeks have you felt embarrassed by your coughing or heavy breathing? Please indicate how much of the time you felt embarrassed by your coughing or heavy breathing by ticking one of the following options from the list below.

1. ALL OF THE TIME
2. MOST OF THE TIME
3. A GOOD BIT OF THE TIME
4. SOME OF THE TIME
5. A LITTLE OF THE TIME
6. HARDLY ANY OF THE TIME
7. NONE OF THE TIME

9. In the last 2 weeks, how much of the time did you feel very confident and sure that you could deal with your illness? Please indicate how much of the time you felt very confident and sure that you could deal with your illness by ticking one of the following options from the list below.

1. NONE OF THE TIME
2. A LITTLE OF THE TIME
3. SOME OF THE TIME
4. A GOOD BIT OF THE TIME
5. MOST OF THE TIME
6. ALMOST ALL OF THE TIME
7. ALL OF THE TIME

10. How much energy have you had in the last 2 weeks? Please indicate how much energy you have had by ticking one of the following options from the list below.

1. NO ENERGY AT ALL
2. A LITTLE ENERGY
3. SOME ENERGY
4. MODERATELY ENERGETIC
5. QUITE A BIT OF ENERGY
6. VERY ENERGETIC
7. FULL OF ENERGY
11. In general, how much of the time did you feel upset, worried or depressed during the past 2 weeks? Please indicate how much of the time you felt upset, worried or depressed during the past 2 weeks by ticking one of the following options from the list below.

1. ALL OF THE TIME
2. MOST OF THE TIME
3. A GOOD BIT OF THE TIME
4. SOME OF THE TIME
5. A LITTLE OF THE TIME
6. HARDLY ANY OF THE TIME
7. NONE OF THE TIME

12. How often during the last 2 weeks did you feel you had complete control of your breathing problems? Please indicate how often you felt you had complete control of your breathing problems by ticking one of the following options from the list below.

1. NONE OF THE TIME
2. A LITTLE OF THE TIME
3. SOME OF THE TIME
4. A GOOD BIT OF THE TIME
5. MOST OF THE TIME
6. ALMOST ALL OF THE TIME
7. ALL OF THE TIME

13. How much of the time during the last 2 weeks did you feel relaxed and free of tension? Please indicate how much of the time you felt relaxed and free of tension by ticking one of the following options from the list below.

1. NONE OF THE TIME
2. A LITTLE OF THE TIME
3. SOME OF THE TIME
4. A GOOD BIT OF THE TIME
5. MOST OF THE TIME
6. ALMOST ALL OF THE TIME
7. ALL OF THE TIME
14. How often during the last 2 weeks have you felt low in energy?
Please indicate how often during the last 2 weeks you have felt low in energy by ticking one of the following options from the list below.

1. ALL OF THE TIME
2. MOST OF THE TIME
3. A GOOD BIT OF THE TIME
4. SOME OF THE TIME
5. A LITTLE OF THE TIME
6. HARDLY ANY OF THE TIME
7. NONE OF THE TIME

15. In general, how often during the last 2 weeks have you felt discouraged or down in the dumps?
Please indicate how often during the last 2 weeks you felt discouraged or down in the dumps by ticking one of the following options from the list below.

1. ALL OF THE TIME
2. MOST OF THE TIME
3. A GOOD BIT OF THE TIME
4. SOME OF THE TIME
5. A LITTLE OF THE TIME
6. HARDLY ANY OF THE TIME
7. NONE OF THE TIME

16. How often during the last 2 weeks have you felt worn out or sluggish?
Please indicate how much of the time you felt worn out or sluggish by ticking one of the following options from the list below.

1. ALL OF THE TIME
2. MOST OF THE TIME
3. A GOOD BIT OF THE TIME
4. SOME OF THE TIME
5. A LITTLE OF THE TIME
6. HARDLY ANY OF THE TIME
7. NONE OF THE TIME
17. How happy, satisfied or pleased have you been with your personal life during the last 2 weeks? Please indicate how happy, satisfied or pleased you have been by ticking one of the following options from the list below.

1. VERY DISSATISFIED, UNHAPPY MOST OF THE TIME
2. GENERALLY DISSATISFIED, UNHAPPY
3. SOMEWHAT DISSATISFIED, UNHAPPY
4. GENERALLY SATISFIED, PLEASED
5. HAPPY MOST OF THE TIME
6. VERY HAPPY MOST OF THE TIME
7. EXTREMELY HAPPY, COULD NOT HAVE BEEN MORE SATISFIED OR PLEASED

18. How often during the last two weeks did you feel upset or scared when you had difficulty getting your breath? Please indicate how often during the past 2 weeks you felt upset or scared when you had difficulty getting your breath by ticking one of the following options from the list below.

1. ALL OF THE TIME
2. MOST OF THE TIME
3. A GOOD BIT OF THE TIME
4. SOME OF THE TIME
5. A LITTLE OF THE TIME
6. HARDLY ANY OF THE TIME
7. NONE OF THE TIME

19. In general how often during the last 2 weeks have you felt restless, tense or uptight? Please indicate how often you have felt restless, tense or uptight by ticking one of the following options from the list below.

1. ALL OF THE TIME
2. MOST OF THE TIME
3. A GOOD BIT OF THE TIME
4. SOME OF THE TIME
5. A LITTLE OF THE TIME
6. HARDLY ANY OF THE TIME
7. NONE OF THE TIME
Appendix VI: PFSDQ-M questionnaire

Scoring PFSDQ-M

An example of the PFSDQ-M questionnaire is given below. Scores include a frequency score (how many times a month for dyspnoea and fatigue), general scores (how you feel Most Days during the past year, Today, and with Most Day to Day Activities for dyspnoea and fatigue), Total, Mean and Individual Activity Scores for all three components.

The Activity Component evaluates the degree to which each of the ten specific activities has changed since the development of pulmonary problems or as a result of COPD. Change is based on the patients' perception of how an activity is performed now compared to before breathing difficulties (CA, change in activities score).

The dyspnoea component measures general rating of the patient's dyspnoea experienced with five general questions (see below), designed to be descriptive (frequency and general dyspnoea (GD) scores) and the level of dyspnoea encountered with the ten specific activities, using a numerical 11-point scale from 0 (none) to 10 (very severe). A rating of 7 or greater is considered significant dyspnoea. Total dyspnoea score (DA, dyspnoea with activities score) is obtained by summing the dyspnoea rating for each activity and a mean score by dividing DA by the number of activities rated.

The fatigue component rates the patients level of tiredness, generally (frequency and general fatigue (GF) scores) and during the same ten activities (FA, fatigue with activities score), in a manner similar to the dyspnoea component.

[Lareau SC, 1998]
Appendix VI: PFSDQ-M

Patient's Name: ____________________________

Date: ____________________________

PULMONARY FUNCTIONAL STATUS & DYSPNEA
QUESTIONNAIRE-MODIFIED

PFSDQ-M

Developed by:
Suzanne C Lareau RN, MS
Paula M Meek RN, PhD

For information:
Suzanne C Lareau RN, MS
Jerry I. Pettis VAMC
11201 Benton Street
Loma Linda, CA 92357
(909) 422-3095
DYSPNEA ASSESSMENT

INSTRUCTIONS: The following questions relate to your discomfort in breathing. Please check the most accurate answer.

1. Do you ever experience shortness of breath? Yes____ No____

2. How many times a month do you experience severe to very severe shortness of breath? ______

Using the following scale, place a mark on the line between 0 (no shortness of breath) to 10 (very severe shortness of breath) in response to the following questions.

3. Indicate how you've felt on most days during the past year.

<table>
<thead>
<tr>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Very severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>No shortness of breath</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

4. Indicate how you feel today.

<table>
<thead>
<tr>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Very severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>No shortness of breath</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

5. Indicate how you feel with most day-to-day activities.

<table>
<thead>
<tr>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Very severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>No shortness of breath</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Appendix VI: PFSDQ-M

FATIGUE ASSESSMENT

INSTRUCTIONS: The following questions relate to how \textit{tired} or \textit{worn out} you feel. Please check the most accurate answer.

1. Do you ever experience tiredness/feeling worn out? \textit{Yes}______
\textit{No}______

2. How many times a month do you experience severe to very severe tiredness? \hfill \hfill 
Using the following scale, place a mark on the line between 0 (no tiredness) to 10 (very severe tiredness) in response to the following questions.

3. Indicate how you've felt on \textit{most days} during the past year.

\begin{tabular}{cccccccccccc}
Mild & Moderate & Severe \\
\hline
No Tiredness & | | | | | | | | | Very Severe \\
\hline
0 & 1 & 2 & 3 & 4 & 5 & 6 & 7 & 8 & 9 & 10 & Tiredness \\
\end{tabular}

4. Indicate how you feel \textit{today}.

\begin{tabular}{cccccccccccc}
Mild & Moderate & Severe \\
\hline
No Tiredness & | | | | | | | | | Very Severe \\
\hline
0 & 1 & 2 & 3 & 4 & 5 & 6 & 7 & 8 & 9 & 10 & Tiredness \\
\end{tabular}

5. Indicate how you feel with most \textit{day-to-day} activities.

\begin{tabular}{cccccccccccc}
Mild & Moderate & Severe \\
\hline
No Tiredness & | | | | | | | | | Very Severe \\
\hline
0 & 1 & 2 & 3 & 4 & 5 & 6 & 7 & 8 & 9 & 10 & Tiredness \\
\end{tabular}
**ACTIVITY ASSESSMENT**

**INSTRUCTIONS:** The following is a list of activities commonly performed by adults. For each activity listed, please place an X in the appropriate box, indicating your involvement with the activity now as compared to before you developed breathing problems. Please respond to every activity listed. Complete the form as follows:

1. **"Has never been an Activity"**: Check this box near each activity in which you have never participated.
2. Columns numbered 0 through 10 represent a range of activities from "As Active As I've Ever Been" to "Have Omitted Entirely". Indicate by placing an X in the area which best reflects your current involvement in the activity.

<table>
<thead>
<tr>
<th>ACTIVITY</th>
<th>Has Never Been An Activity</th>
<th>As Active As I've Ever Been</th>
<th>Minor Change</th>
<th>Moderate Change</th>
<th>Extreme Change</th>
<th>Have Omitted Entirely</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Brushing/combing hair</td>
<td></td>
<td></td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>2. Putting on shirt</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Washing hair</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Showering</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Raising arms overhead</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. Preparing a snack</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. Walking</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8. Walking on inclines</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9. Walking on bumpy terrain</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10. Climbing 3 stairs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

![Image of the table with the activities listed]
**DYSPNEA ASSESSMENT**

**INSTRUCTIONS:** Rate the following activities on a scale of 0 to 10 according to the degree of shortness of breath each activity generally causes you.

Complete the form as follows: Place an "X" in the column under "0" if the activity generally causes you no shortness of breath.

**Leave blank** those activities you rated as "Has never been an activity" on the Activity Assessment.

**DEGREE OF SHORTNESS OF BREATH**

<table>
<thead>
<tr>
<th>ACTIVITY</th>
<th>None</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Very Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Brushing/combing</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Putting on shirt</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Washing hair</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Showering</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Raising arms</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. Preparing a snack</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. Walking ten feet (3½ meters)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8. Walking on inclines</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9. Walking on bumpy terrain</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10. Climbing 3 stairs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**FATIGUE ASSESSMENT**

**INSTRUCTIONS:** Rate the following activities on a scale of 0 to 10 according to the degree of tiredness each activity generally causes you.

Complete the form as follows: Place an “X” in the column under “0” if the activity generally causes you no tiredness. **Leave blank** those activities you rated as “Has never been an activity” on the Activity Assessment.

**DEGREE OF TIREDNESS**

<table>
<thead>
<tr>
<th>ACTIVITY</th>
<th>None</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Very Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Brushing/combs hair</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. Putting on shirt</td>
<td>5</td>
<td>6</td>
<td>7</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>3. Washing hair</td>
<td>10</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Showering</td>
<td></td>
<td>7</td>
<td></td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>5. Raising arms overhead</td>
<td></td>
<td>5</td>
<td></td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>6. Preparing a snack</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. Walking ten feet (3½ meters)</td>
<td></td>
<td>5</td>
<td></td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>8. Walking on inclines</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9. Walking on bumpy terrain</td>
<td></td>
<td>5</td>
<td></td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>10. Climbing 3 stairs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Appendix VII: Isokinetic Dynamometry Outcome Parameters

The conduct of isokinetic testing is described in the methods, Chapter 2. A set number of muscular contractions or repetitions are involved, which provide a broad range of output parameters and curves allowing examination of muscular contractions along an entire range of motion (ROM). These parameters are automatically computed by the computer software and presented as a report [figure A.3]. In this appendix, the “output” or performance parameters derived from strength testing are defined and described.

Maximal moment or torque

The rotational effect of a force about a joint, generated by a single or group of muscles, is termed maximal moment. Force is essentially a linear entity; therefore the appropriate term for this measurement of muscle force is strength.

\[
\text{Moment} = \text{leverage length} \times \text{force}
\]

The term torque, a force acting at a distance from an axis, rather than moment, originated in the early days of isokinetic testing [Dvir Z, 1995b]. The unit of measurement of moment is the Newton-meter (Nm). Providing gravity is accounted for, the value of the moment at any point on the moment-angular position (MAP) curve represents the strength of the tested muscle(s) at that point (figure A.4) [Dvir Z, 1995b].

Types of muscular contraction were described in Chapter 1 (1.2.2). Tension generated within muscle fibres results in a concentric (muscle shortening), eccentric (muscle lengthening) or isometric (no change in muscle length) contraction.
Appendix VII: Isokinetic dynamometry parameters

Force-velocity relationship
Different physical activities require different amounts of force and power. The peak force generated in a movement depends on the speed of muscle lengthening and shortening, which is dependent on the load placed on the muscle. As load increases, maximum shortening velocity decreases. During concentric contractions, a muscle's force generating capacity decreases as shortening velocity increases [Dvir Z, 1995c], as a result of neuromuscular recruitment patterns and the types of muscle fibres activated. Type I (slow-twitch) and II (fast-twitch) fibres can be maximally activated at slower speeds, while at faster movement speeds, type II fibres produce greater muscle force than type I fibres.

A concentric action becomes an eccentric action when the external load exceeds a muscle's maximum isometric force capacity. For eccentric contractions, higher velocities generate the greatest force. This may explain the greater muscle damage and delayed muscle soreness following eccentric exercise. Theoretically the eccentric strength could exceed the isometric and concentric strength by about 100% [Isokinetics Explained, 2008]. In reality this never happens because negative feedback loops, prevent excessive stresses on the muscle [Stauber WT, 1989].

Eccentric-concentric coupling
Following eccentric contractions, mechanical and chemical energy accumulates in the muscle. This pre-stretching of the muscle leads to concentric contraction potentiation. This phenomenon, termed the "stretch-shortening cycle" or "plyometric" contraction, is based on the mechanical behaviour of the elastic element found in the contractile elements and tendons [Dvir Z, 1995c].
Appendix VII: Isokinetic dynamometry parameters

Order of Strength

Highest
Isokinetic eccentric
Isotonic eccentric
Isometric
Isokinetic concentric
Isotonic concentric

Lowest

Figure A.2: Order of strength according to contraction and exercise mode.
Based on the principles that; i) at the same velocity eccentric strength is greater than
concentric strength, ii) that the order of strength is dependent on contraction mode i.e.
eccentric > isometric > concentric, and iii) the order of strength is also dependent on the
type of exercise performed i.e. isokinetic > isometric> isotonic. Adapted from [Isokinetics
Explained, 2008].
SPECIAL NOTE

This item is tightly bound and while every effort has been made to reproduce the centres force would result in damage.
**Patient ID:** cr035  
**Report Date:** July 3, 2008  
**Body Weight (Kg):** 64.60

### CYBEX Evaluation

**Muscle Group:** CON/ECC EXTS  
**Test Type:** Isokinetic Short Status  
**Test Action:** 0101 Knee Extension/Flexion CON/ECC EXTS

---

**CONCENTRIC EXTENSORS**

<table>
<thead>
<tr>
<th>Description</th>
<th>Left</th>
<th>9/17/04</th>
</tr>
</thead>
<tbody>
<tr>
<td>Torque (Nm)</td>
<td>60</td>
<td>60</td>
</tr>
<tr>
<td>Torque % BW</td>
<td>50</td>
<td>47</td>
</tr>
<tr>
<td>Torque % BW</td>
<td>78.1%</td>
<td>73.4%</td>
</tr>
<tr>
<td>Torque % BW</td>
<td>72.6%</td>
<td>59.8%</td>
</tr>
<tr>
<td>Power (BWR) (Watts)</td>
<td>37.8</td>
<td>30.8</td>
</tr>
<tr>
<td>Power (BWR) % BW</td>
<td>59.0%</td>
<td>48.1%</td>
</tr>
<tr>
<td>Total Work</td>
<td>197</td>
<td>180</td>
</tr>
</tbody>
</table>

---

**ECCENTRIC EXTENSORS**

<table>
<thead>
<tr>
<th>Description</th>
<th>Left</th>
<th>9/17/04</th>
</tr>
</thead>
<tbody>
<tr>
<td>Torque (Nm)</td>
<td>-97</td>
<td>-95</td>
</tr>
<tr>
<td>Torque % BW</td>
<td>-151.6%</td>
<td>-148.4%</td>
</tr>
<tr>
<td>Torque % BW</td>
<td>-125.6%</td>
<td>-122.8%</td>
</tr>
<tr>
<td>Power (BWR) (Watts)</td>
<td>-61.1</td>
<td>-60.2</td>
</tr>
<tr>
<td>Power (BWR) % BW</td>
<td>-95.5%</td>
<td>-94.1%</td>
</tr>
<tr>
<td>Total Work</td>
<td>-337</td>
<td>-342</td>
</tr>
</tbody>
</table>

---

**CONCENTRIC EXTENSORS / ECCENTRIC EXTENSORS**

<table>
<thead>
<tr>
<th>Description</th>
<th>Left</th>
<th>9/17/04</th>
</tr>
</thead>
<tbody>
<tr>
<td>Torque</td>
<td>-51.5%</td>
<td>-49.5%</td>
</tr>
<tr>
<td>Power (BWR)</td>
<td>-57.8%</td>
<td>-48.7%</td>
</tr>
<tr>
<td>Power (BWR)</td>
<td>-61.8%</td>
<td>-51.0%</td>
</tr>
<tr>
<td>Total Work</td>
<td>-58.6%</td>
<td>-52.7%</td>
</tr>
<tr>
<td>Age ROM (°)</td>
<td>68°</td>
<td>67°</td>
</tr>
</tbody>
</table>

---

*Figure A.3: Example of report produced by the Cybex II isokinetic dynamometer*

*Appendix VII: Isokinetic dynamometry parameters*
Appendix VII: Isokinetic dynamometry parameters

Parameters definitions

Peak torque (PT)
Peak torque, the most frequently used isokinetic measurement in clinical and scientific work (Newton-meters; Nm), refers to the highest or maximum single force (torque output) achieved by a muscular contraction, causing the limb to move through a ROM [Hsu AL, 2002; Kannus P, 1994]. The maximal value on the MAP curve (figure A.4) is termed the peak moment and often synonymous to maximal strength [Dvir Z, 1995b]. Measurements can be normalised for body weight (percentage body weight; Nm/kg), useful if comparing individuals but otherwise, of little functional value. PT has been shown to be an accurate and highly reproducible variable, accepted in critical reviews and has become a gold standard and reference point in isokinetic measurements [Hsu AL, 2002; Kannus P, 1994]. PT can be used to calculate;

\[ \text{Power} = \text{force (PT)} \times \text{speed} \]

\[ \text{Work} = \text{force (PT)} \times \text{shift (ROM)} \]

Angular velocity
Angular velocity is one of the primary factors effecting muscle strength. PT remains fairly unchanged between angular velocities of 0-60°/sec but thereafter, shows a linear decline with increasing velocity due to different recruitment of muscle fibres (the force-velocity relationship described earlier). Measurements at faster velocities are deemed to be more reliable than slower speeds. PT achieved at different angular velocities cannot be compared.

Angle of peak torque (APT)
Angle of PT is the joint angle at which maximum PT occurs. It is specific to individual muscle groups. Angle-specific torques (AST) can be quantified but this offers little additional information about muscle function.
Appendix VII: Isokinetic dynamometry parameters

Figure A.4: A characteristic isokinetic moment-angular position (MAP) curve. Adapted from [Kannus P, 1994]. x-axis shows joint position (angle), y-axis shows force exerted on lever arm at each point along range of moment. Abbreviations: PT, peak torque; TW, total work; AST; angle-specific torque (at 50°); Nm, Newton-meters.

**Total work (TW)**

Muscular work (joules; J) is the output of mechanical energy. The accumulated torque output produced (or energy expended) as the muscle/s being tested move through a specified ROM, defined as the area under the MAP curve (figure A.4) [Dvir Z, 1995b].

\[ TW = \text{torque} \times \text{angular displacement} \]
Appendix VII: Isokinetic dynamometry parameters

Set TW is the sum of work performed in all test repetitions (for example, five contractions), TW (BWR) is the total work done during the best work repetition (BWR).

**Average power (AP)**

Muscular power (Watts) is the rate of muscular work output. Average power is the "average work done per unit time", taking into account the velocity of muscle contraction [Dvir Z, 1995b]. This is predictable from PT but the clinical value is limited [Kannus P, 1994].

\[
AP = \frac{\text{total work done}}{\text{time taken}}
\]

PT and TW are theoretical the most reliable measurement parameters but it has been suggested that TW & AP are more representative of functional measures of muscle strength than PT [Hsu AL, 2002].

**Endurance indexes**

Muscular endurance is defined as "the ability of the contracting muscle to perform repeated contractions against load" and indicates the rate at which a muscle fatigues during muscular work [Kannus P, 1994]. There is no universally accepted or standardised testing protocol for assessing muscular endurance. Typically, isokinetic endurance tests measure the number of repetitions of maximum effort necessary to reach a 50% reduction in torque output. Alternatively, the percent decline in work, torque or power after a specified exercise or number of contractions can be measured [Kannus P, 1992; Kannus P, 1994].
Appendix VIII: Reproducibility of isokinetic measurements

Reproducibility of isokinetic dynamometry in COPD was explored in Chapter 3. Some of the potential sources of error during isokinetic dynamometry testing are discussed in further detail in this appendix.

Calibration
Calibration is related to the machines own stability (or drift) of the measurement between tests and is essential for reproducibility. Accurate calibration is essentially the responsibility of operator and system-measured quantities should be compared with a standard, in static and dynamic conditions at least once a week, and corrected if necessary [Dvir Z, 1995a].

Inter-model reproducibility
Data collected is dynamometer-specific due to different manufacturing components, data manipulation, positioning, stabilisation and attachments, therefore measurements from one system cannot serve as a population baseline or be compared with those obtained from another system. These problems with interpretation do not exist however, when examining repeat test results for an individual using the same dynamometer.

Intra-model reproducibility
Intra-model reproducibility refers to the difference between different machines of the same model, operated by different examiners. The Cybex II has shown good intra-model reliability (0.86-0.95, knee flexors; 0.69-0.95, KEs) suggesting comparable measurements could be obtained with different testers using this particular dynamometer. PT achieved at different angular velocities however, cannot be compared [Kannus P, 1994].
Appendix IX: Isokinetic protocols

Testing procedure errors

These factors need to be kept the same on retesting to achieve reproducibility [Dvir Z, 1995a]:

1. ROM
2. positioning
3. stabilisation
4. biological-mechanical axes alignment
5. test angular velocity

Earlier strength was defined as the moment, which is equal to lever-arm length × force. A deviation of only 1 cm from the original placement of the sensor may introduce errors of 2.5-5% on the reproducibility of the measurement.

Appendix IX: Isokinetic testing protocols

The test protocol is the most complex and least understood of the issues concerning reproducibility. Selecting the optimal protocol from an infinite number of potential protocols is difficult.

Factors associated with acceptable reproducibility [Dvir Z, 1995a]

1. 3-6 submaximal practice repetitions followed by 1-2 maximal repetitions,
2. 4-6 test repetitions are sufficient to yield a representative performance parameter,
3. continuous reciprocal protocol is appropriate for concentric and eccentric performance,
4. reproducibility may be higher for lower velocities; i.e. 30-120 °/sec,

The knee is the most studied joint, followed by the ankle and shoulder. Isokinetic knee extension and flexion have been shown to be reliable in healthy young adults and moderate test-retest correlations are reported for older adults [Frontera WR,
1993; Gleeson NP et al, 1992]. ICCs tend to be higher for PT than for average PT, for knee extension and older women [Pohl PS, 2000].

**Time span**

The time span is highly relevant to reproducibility, defined as the level of agreement between measured individual contractions within the same test session (intra-session) or between sessions (inter-session). The time span may be days, weeks or even years. Sequential contractions usually produce close scores and it is inter-session reproducibility that requires attention [Dvir Z, 1995a].

One of the first reproducibility studies looked at KE strength, three-submaximal, followed by six-maximal unidirectional contractions at 180°/sec (Cybex II), in 40 healthy women over six consecutive days. ICCs showed good reproducibility ranging from 0.93 to 0.99 (day 1-5) [Johnson J et al, 1978].

Reproducibility over three tests, each 2-weeks apart, consisting six maximal KE contractions at 30°/sec, showed stable measurements with no significant differences in PT across testing sessions [Mawdsley RH, 1982].

**Reciprocal protocols**

Reciprocal protocols, involving alternating extension and flexion movements (i.e. concentric-concentric and eccentric-eccentric), are good for research due to high correlation of power and work [Kannus P, 1994]. Concentric-eccentric contraction protocols are useful for measuring average strength. The reproducibility of intermittent reciprocal and continuous-reciprocal protocols has been widely studied (table A.1).
Table A.1: Summary of isokinetic measurement reproducibility studies.

Several dynamometers and muscular variables have been studied as shown in the table below [Li RC, 1996]. Abbreviations: CON, concentric; ECC, eccentric; KE, knee extensors; KF, knee flexors; Sub-max, submaximal (practice) contractions; max, maximal (test) contractions; °/sec, degrees per second testing velocity; ICC, intra-class correlation coefficient.

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Protocol</th>
<th>Muscle group</th>
<th>Machine</th>
<th>Repetitions</th>
<th>Speed °/sec</th>
<th>Sessions</th>
<th>ICC</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perrin (1986)</td>
<td>concentric</td>
<td>KF, KE</td>
<td></td>
<td>60, 180</td>
<td>2</td>
<td>7 days</td>
<td>KE 0.84-0.93</td>
<td>reliability coefficient Rt KE (60) 0.85 (180) 0.87</td>
</tr>
<tr>
<td>Tredinnick (1988)</td>
<td>eccentric</td>
<td>KE Kin Com</td>
<td></td>
<td>60, 120, 180</td>
<td></td>
<td></td>
<td>0.47-0.86</td>
<td></td>
</tr>
<tr>
<td>Snow (1988)</td>
<td>eccentric</td>
<td>KE Kin Com</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.94</td>
<td></td>
</tr>
<tr>
<td>Fering (1989)</td>
<td>concentric</td>
<td>KF, KE Biodex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.952</td>
<td></td>
</tr>
<tr>
<td>Harding (1989)</td>
<td>intermittent reciprocal CON-CON</td>
<td>KF, KE Kin Com</td>
<td></td>
<td>6</td>
<td>60</td>
<td>2</td>
<td>different days</td>
<td>0.936-0.952</td>
</tr>
<tr>
<td>Wessel (1989)</td>
<td>intermittent reciprocal CON-ECC</td>
<td>KE</td>
<td></td>
<td>3, 6</td>
<td>60, 180</td>
<td>2</td>
<td>1 week</td>
<td>&gt;0.85</td>
</tr>
<tr>
<td>Montgomery (1989)</td>
<td>continuous reciprocal CON-CON</td>
<td>KF, KE</td>
<td></td>
<td>5</td>
<td>90, 150, 210, 270, 330</td>
<td>3</td>
<td>2-4 days</td>
<td>KE 0.88</td>
</tr>
<tr>
<td>Kramer (1990)</td>
<td>continuous reciprocal CON-ECC</td>
<td>KF, KE</td>
<td></td>
<td>3, 1</td>
<td>45, 90</td>
<td>3</td>
<td>within 10 days</td>
<td>con. 0.82-0.91 ecc. 0.79-0.88</td>
</tr>
<tr>
<td>Steiner (1993)</td>
<td>eccentric (average PT)</td>
<td>KE LIDO Active</td>
<td>3sub/3max</td>
<td>6</td>
<td>60, 180</td>
<td>3</td>
<td>1 week</td>
<td>0.58-0.88</td>
</tr>
<tr>
<td>Li (1996)</td>
<td>continuous CON-ECC</td>
<td>KF, KE Cybex 6000</td>
<td>5</td>
<td>60, 120</td>
<td>2</td>
<td>4-10 days</td>
<td>0.82-0.91</td>
<td>ICCs greater for 120 &amp; KE</td>
</tr>
<tr>
<td>Hsu (2002)</td>
<td>eccentric</td>
<td>KE Cybex 6000</td>
<td>2</td>
<td>1</td>
<td>30, 90</td>
<td>2</td>
<td>1 week</td>
<td>between sessions &gt; 0.75</td>
</tr>
</tbody>
</table>
Intermittent reciprocal protocols

Harding et al (1988) looked at the reproducibility of intermittent reciprocal KE and flexion contractions at 60°/sec during two testing sessions on different days (KinCom) [Dvir Z, 1995a]. Six cycles of maximal reciprocal extension and flexion movements, with a 5 second pause between contractions and a 30 second pause between cycles, were performed. Both muscle groups showed good reproducibility, with high ICCs for PT 0.94-0.95, and low repetition and session variance.

Continuous-reciprocal protocols

The continuous-reciprocal protocol, developed by eliminating the long pause between cycles, resulted in higher ICCs but also significant linear decline in strength, probably due to fatigue [Stratford PW, 1990].

Montgomery et al assessed KE and flexor concentric muscle strength in healthy young subjects over three testing sessions, 2-4 days apart, at different test velocities [Montgomery LC, 1989]. No significant differences were seen in mean strength across 10 days at any velocity. ICCs relating to strength across all velocities were 0.88 (extension) and 0.79 (flexion). Lower velocities showed higher ICCs and lower coefficients of variation. This carefully designed study showed "minimal within-subject and inherent variation due to repeated testing" and therefore, suggested their protocol was appropriate for intervention studies [Dvir Z, 1995a; Montgomery LC, 1989]. A conflicting study strongly suggested multiple day-to-day trial protocols for isokinetic testing to adequately describe performance capacity. This would be time consuming both for the researcher and subjects for an interventional study.

Test-retest reliability of isokinetic KE and flexor concentric muscle strength, at 60°/sec (Cybex II) over 7-10 days, concluded that two tests may be necessary to determine isokinetic average PT, in 45-78 year old men and women [Frontera WR, 1993]. They found small but significantly higher PT (mean 3 Nm) on the second
Appendix IX: Isokinetic protocols

test. Such improvements may interfere with results when determining the effect of an intervention.

Eccentric contractions

Eccentric muscle actions are part of everyday activities; descending stairs, running, sitting down. Isokinetic testing of eccentric contractions however is different from the functional use of the muscle. The subject is required to resist the lever arm in a lengthening contraction that is often unfamiliar. Several studies suggest a "practice session", prior to the date of true testing, enhances reliability. Unfortunately, this is not always practical and protocols incorporating same session "learning phase" have been explored, reporting good reliability for quadriceps eccentric average PT (ICC > 0.80) [Steiner LA, 1993].

There are inconsistencies in the reported reliability of eccentric measurements. Quadriceps eccentric PT reliability has been reported as excellent (ICC 0.94), compared to moderate to good reliability (ICC 0.47-0.86) [Tredinnick TJ, 1988; Trudelle-Jackson E et al, 1989].

Wessel et al [Wessel J et al, 1988] examined the reproducibility of isokinetic KE work over 1-week. Four trials of three-submaximal, followed by six-maximal, intermittent reciprocal concentric-eccentric (CON-ECC) cycles were performed, separated by 1-minute pauses, at 60 and 180°/sec. ICCs for each contraction mode, test session and angular velocity were greater than 0.85, but were generally higher for the second session suggesting a learning effect.

Kramer et al [Kramer JF, 1990] developed a protocol, involving continuous reciprocal CON-ECC flexion and extension cycles at 45 and 90°/sec. They tested normal subjects, three times over 10 days, using three-submaximal and one-maximal CON-ECC practice cycles followed by three test cycles after a 2-minute pause. PT single-session ICCs ranged 0.82-0.91 (concentric) and 0.79-0.88 (eccentric), with higher ICCs with extension and if results from more than one
testing session were used. No differences in reproducibility were seen between angular velocities, both in the lower end of the spectrum [Dvir Z, 1995a; Kramer JF, 1990].

A further study examined the reliability of two tests, 4-10 days apart, of continuous CON-ECC KE testing (Cybex 6000) at 60°/sec, in young healthy subjects. Two-submaximal and one-maximal cycles were performed prior to the test phase of 5 cycles [Li RC, 1996]. Measurements for KE PT were seen to be highly reliable with ICCs 0.82-0.90. Differences in PT between sessions were 6.6-7% for concentric and 10.6-11.9% for eccentric modes.
Appendix X: Isokinetic reference equation

Few references exist for knee isokinetic strength in non-athletic subjects, especially the elderly. Predictive equation were presented by Neder et al following a prospective, randomised, controlled study of concentric knee isokinetic strength at 60°/sec (Cybex 6000) in healthy males and females, 20-80 years of age [Neder JA, 1999]. Prediction equations were mainly influenced by sex and age. Their final model using total body fat-free mass (FFM) was used to assess concentric peak torque at baseline and following PR.

\[ KE\ PT\ (Nm) = 23.36(sex) + 1.63(FFM) + 1.0(height) - 1.36(age) - 41.86 \]

Where;

<table>
<thead>
<tr>
<th>KE</th>
<th>Knee extensor</th>
</tr>
</thead>
<tbody>
<tr>
<td>PT</td>
<td>peak torque</td>
</tr>
<tr>
<td>sex</td>
<td>male = 1, female = 0</td>
</tr>
<tr>
<td>FFM</td>
<td>total body FFM</td>
</tr>
<tr>
<td>Height</td>
<td>cm</td>
</tr>
<tr>
<td>age</td>
<td>years</td>
</tr>
</tbody>
</table>

\( R^2 = 0.819,\ SEE = 21.11 \)

\( R^2 = \) coefficient of determination; \( \) SEE = standard error of the estimate
Appendix XI: Calculation of ICC

Using values obtained from 2-way ANOVA, the following ICC (2,1) equation was used [Shrout PE, 1979]:

\[
 r_t = \frac{M_s - M_r}{M_s + (m - 1)M_r + \frac{m}{n}(M_m - M_r)}
\]

Where;  
- **M**: mean square;  
- **M_s**: between subjects (people) mean square (BMS);  
- **M_m**: between methods (items) mean square (JMS);  
- **M_r**: residual mean square (EMS);  
- **m**: number of methods used in assessment i.e. 2 sessions;  
- **n**: number of subjects assessed i.e. 7 subjects.

<table>
<thead>
<tr>
<th>ANOVA</th>
<th>Sum of Squares</th>
<th>df</th>
<th>Mean Square</th>
<th>F</th>
<th>Sig</th>
</tr>
</thead>
<tbody>
<tr>
<td>Between People</td>
<td>3381.857</td>
<td>6</td>
<td>563.643</td>
<td>M_s</td>
<td></td>
</tr>
<tr>
<td>Within People</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Between Items</td>
<td>604.571</td>
<td>1</td>
<td>604.571</td>
<td>M_m</td>
<td>.163</td>
</tr>
<tr>
<td>Residual</td>
<td>1434.429</td>
<td>6</td>
<td>239.071</td>
<td>M_r</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>2039.000</td>
<td>7</td>
<td>291.286</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>5420.857</td>
<td>13</td>
<td>416.989</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Grand Mean = 89.2857

Table A.2: Example of output from SPSS for calculation of ICC.
Appendix XII: Patient information sheet

Appendix XII: Patient information and consent forms.

PATIENT INFORMATION SHEET (Version 7 – created on 01/01/05)

Enhancement of Cellular Adaptation to Physical Training in Chronic Obstructive Pulmonary Disease.
A Randomised Placebo Controlled Trial of Creatine Supplementation.

Principal Investigator: Dr. S. J. Deacon
Investigators: Dr. S. Singh
Emma Vincent
Dr. M.D.L. Morgan
Dr. Sarah Deacon - Direct Line: 0116 256 3652
Dr. Sally Singh
Dr. M. Morgan

Department of Respiratory Medicine
Glenfield Hospital
Groby Road
Leicester

Tel No: 0116 256 3663
0116 287 1471

We would like to invite you to participate in the above study.

What is the purpose of the study?

Patients who suffer with COPD usually complain of being unable to carry out some activities because of breathlessness and muscle fatigue. We know that exercise training as part of a pulmonary rehabilitation programme can improve this but we don't fully understand how. In addition many patients have reduced muscle bulk because of the restrictions in activity caused by the disease.

We wish to find out if giving patients dietary supplements whilst they are on the rehabilitation programme is beneficial. We also wish to study the impact of exercise training and dietary supplementation on muscle performance in patients with COPD.

Dr Sarah Deacon, Creatine Study, Glenfield Hospital, 0116 2563652
Appendix XII: Patient information sheet

The results will allow us to provide a more effective rehabilitation programme and increase the benefits of rehabilitation to patients.

What will be involved if I take part in the study?

**Dietary Supplementation and the Rehabilitation Programme**

The study aims to compare the effect of taking creatine supplements during the rehabilitation programme against rehabilitation with no supplements. Creatine is a natural substance found in the human body and in foods such as meat and fish. Athletes have been known to take creatine supplementation to improve their training and performance.

At the start of your rehabilitation course you will be randomly allocated into one of two groups. This means that it is complete chance as to which group you will be in. One group will take creatine and the other group will be given a placebo supplement. Placebo means that you will take a supplement that is an inactive substance and not creatine. It will not necessarily be beneficial to you and it will cause you no harm. The creatine and placebo will be packaged in the same way (both are a powder taken dissolved in water) and neither you nor we will know which group you are in until after the study is finished.

We know that creatine is beneficial when combined with training and we have introduced individually prescribed strength training to the rehabilitation classes. We also know that to get a good training effect, strength training should be done at least 3 times a week. You will therefore be asked to attend classes 3 times a week (Mondays, Wednesdays and Thursdays) for the duration of your pulmonary rehabilitation course.

This will not interfere with when you start your rehabilitation course and you should continue on your normal medications.

**Tests to be Carried Out**

You will be asked to attend 2 extra visits, 1 week apart, to undergo a number of tests before entering the programme and 1 visit after you have completed pulmonary rehabilitation. These tests are in addition to those that all patients have.

1. **Walking Tests**
   We will ask you to do walking tests to assess your exercising ability both before and after pulmonary rehabilitation. These tests form part of the standard pulmonary rehabilitation assessment. You will be asked to walk between 2 cones, 10 metres apart, aiming to turn around the cones in time with a pre-recorded “beep”. We will ask you to do this for as long as you can and you will be able to stop when you have had enough.

2. **Breathing Test**
Appendix XII: Patient information sheet

We will do a simple breathing test, called spirometry, which involves you blowing down a tube, for as long as you can, after taking a large breathe in.

3. Muscle Strength
i) We will measure the strength of your leg muscles, in particular the thigh (quadriceps) muscle, using a piece of equipment called a dynamometer. This consists of a large seat, which you will sit in, and a lever in front of you, which your leg will be attached to. We will ask you to push and pull this lever with your leg, as hard as you can, at a speed set by the dynamometer. We will also ask you to straighten your leg, as hard as you can against the lever, which will be fixed.

ii) We will then measure the strength of your arm muscles, in particular the upper arm (biceps) muscle, while seated on the same chair. This time you will be asked to hold a handle, which will be attached to the dynamometer, and asked to pull this up and down as hard as you can, at a speed set by the dynamometer.

4. Cycle Test
We will ask you to exercise on a static exercise bicycle for as long as you can both before and after the pulmonary rehabilitation course. The effort you will need to put in to cycling gradually increases during the test, which ends when you are too tired to continue. During this test we will ask you to wear a facemask or mouthpiece so that we can monitor your breathing. We will monitor your oxygen levels, with a probe placed on your finger, blood pressure and heart rate (ECG).

5. Fat Free Mass
We will measure the ratio of fat and muscle in your body by taking a special recording from your skin. Leads will be placed on your left hand and foot (like an ECG of the heart) and a recording of the electrical resistance of your body will be taken. This is completely harmless and painless.

6. Questionnaires
We will ask you to fill out questionnaires on how your breathing problems affect your daily life. We can help you with these if you have any problems.

7. Muscle Biopsy
This is optional and you can take part in the study without having a muscle biopsy taken.

We will take small muscle samples from your thigh (a muscle biopsy, the details of this are described below) before, during and after your course of pulmonary rehabilitation.

Dr Sarah Deacon, Creatine Study, Glenfield Hospital, 0116 2563652
Appendix XII: Patient information sheet

**Muscle Biopsies**
A biopsy (a small sample of muscle) is taken from the thigh muscle. The area is numbed with a small injection of local anaesthetic. A small cut or incision (approximately 1cm in length) is made in the skin and a biopsy is taken through this incision with a special needle. Afterwards the incision is closed using adhesive strips and a compression bandage is placed around the thigh. This can be removed after 24 hours.

You may experience a small amount of discomfort when the skin incision is made and when the biopsy is taken. You should not experience any pain. There is a small risk of bleeding from the incision but this should stop once pressure is applied to the leg. Your thigh may ache for a day or two after the biopsy (similar to as if you had banged it against a piece of furniture). You will be left with a very small scar on the skin that should fade with time.

There will be a total of 4 muscle biopsies taken, at rest, at the following times during the study:

i) Before pulmonary rehabilitation and supplements are started  
ii) After the first 5 days of the supplement (the loading phase)  
iii) 4-5 weeks after starting pulmonary rehabilitation  
iv) After you have completed pulmonary rehabilitation

**Visits to Hospital**
If you agree to have muscle biopsies, the study will involve seven extra visits to hospital. Four before, one during and two after the pulmonary rehabilitation programme.

If you do not have any muscle biopsies, the study will involve three extra visits to hospital. Two before and one after the pulmonary rehabilitation programme.

We can provide transport or travelling expenses for these extra visits.

You will be invited to attend hospital 6 months after you have finished this study for a follow-up visit. This visit is optional. The tests carried out during this visit include:

Walking tests  
Muscle strength  
Questionnaires

**Benefits and risks**
Currently, dietary supplementation is not provided for patients during the rehabilitation programme because we don't know if it helps or not. You may therefore gain a benefit from this new treatment by entering the study. You will be helping future patients by helping us understand how to maximise the benefits of pulmonary rehabilitation.

Dr Sarah Deacon, Creatine Study, Glenfield Hospital, 0116 2563652
Appendix XII: Patient information sheet

There is a small risk of bleeding from the site of the muscle biopsy and this is why a compression bandage is applied for 24 hours. The muscle biopsy involves a small amount of discomfort but the risks are small.

Will information obtained in the study be confidential?

The treatment you receive in the study will be recorded in your medical records and is confidential under the data protection act. You will not be identified in any documents relating to the study.

Your GP will be notified of your participation in the study.

What if I am harmed by the study?

Medical research is covered for mishaps in the same way as for patients undergoing medical treatment in the NHS i.e. compensation is only available if negligence occurs.

What happens if I do not wish to participate in this study or wish to withdraw from the study?

We are extremely grateful for your help with this research. If you would like to help but feel unhappy about having the muscle biopsy it will still be possible for you to take part in the rest of the study. If you do not wish to participate at all in the study or if you wish to withdraw from the study at any time you may do so without justifying your decision and your future treatment will not be affected.

Dr Sarah Deacon, Creatine Study, Glenfield Hospital, 0116 2563652
PATIENT CONSENT FORM

Enhancement of Cellular Adaptation to Physical Training in Chronic Obstructive Pulmonary Disease.
A Randomised Placebo Controlled Trial of Creatine Supplementation.

Principal Investigator: Dr. S. J. Deacon
Investigator: Dr. S. Singh
Supervisor: Dr. M. D. L. Morgan

This form should be read in conjunction with the Patient Information Leaflet Version 7 – created on 01/01/05.

I agree to take part in the above study as described in the Patient Information Sheet.

I understand that I may withdraw from the study at any time without justifying my decision and without affecting my normal care and medical management.

I understand that members of the research team may wish to view relevant sections of my medical records, but that all the information will be treated as confidential.

Medical research is covered for mishaps in the same way as for patients undergoing medical treatment in the NHS i.e. compensation is only available if negligence occurs.

I have read the patient information leaflet on the above study and have had the opportunity to discuss the details with .........................................................and ask any questions. The nature and the purpose of the tests to be undertaken have been explained to me and I understand what will be required if I take part in the study.

Dr Sarah Deacon, Creatine Study, Glenfield Hospital, 0116 2563652
Appendix XII: Patient consent form

Enhancement of Cellular Adaptation to Physical Training in Chronic Obstructive Pulmonary Disease.
A Randomised Placebo Controlled Trial of Creatine Supplementation.

I agree to participate in*: The main study plus the muscle biopsy study
The main study only

* please delete as applicable

Signature of patient ......................................................

Date.........................................................................................................

(Name in BLOCK LETTERS) ......................................................

I confirm I have explained the nature of the Trial, as detailed in the Patient Information Sheet, in terms which in my judgement are suited to the understanding of the patient.

Signature of Investigator ......................................................

Date.........................................................................................................

(Name in BLOCK LETTERS) ......................................................

Dr Sarah Deacon, Creatine Study, Glenfield Hospital, 0116 2563652
Appendix XIII: Supplementation instruction and compliance sheets

**LOADING PHASE**

❖ 5 days before starting pulmonary rehabilitation

Name: ............................................................

Starting on................................., please take your supplement as follows:

- dissolve 3 level scoops of powder (3 x 2.5ml) in warm (not boiling) flavoured water & drink within 10 minutes
- take 4 times a day, at equally spaced times, FOR 5 DAYS
- for example, 3-4 hrs apart: 8am, 12 noon, 4pm, 8pm
- avoid food and caffeine, e.g. tea & coffee, 30 minutes before and after taking the powder (you may drink alcohol in moderation)!
- if you forget to take a dose, take it as soon as you remember

Please return all pots, scoops and any contents remaining to myself or Emma

Please record the date and time each dose is taken in the table below

<table>
<thead>
<tr>
<th>Date</th>
<th>Time dose taken</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dose 1</td>
</tr>
<tr>
<td>Day 1</td>
<td></td>
</tr>
<tr>
<td>Day 2</td>
<td></td>
</tr>
<tr>
<td>Day 3</td>
<td></td>
</tr>
<tr>
<td>Day 4</td>
<td></td>
</tr>
<tr>
<td>Day 5</td>
<td></td>
</tr>
</tbody>
</table>

Comments/problems:

Dr Sarah Deacon, Creatine Study, Glenfield Hospital, 0116 2563652
Appendix XIII: Maintenance phase

**MAINTENANCE PHASE**

- Daily supplement during 7 weeks of pulmonary rehabilitation

Name:........................................................................................................

Starting on...........................please take your supplement every day as follows,

- dissolve 1 level scoop (1 X 5ml) of powder in warm (not boiling) flavoured water & drink within 10 minutes
- take EVERY DAY at roughly the same time of day, atleast 30 minutes before exercising (i.e. pulmonary rehab class/walking)
- avoid food and caffeine, e.g. tea & coffee, 30 minutes before and after taking the powder (you may drink alcohol in moderation)!

Please indicate when each dose is taken on the chart provided. If you forget to take a dose, take it as soon as you remember that day. If you realise the next day, record “missed dose” on the chart

What if I am ill or am on holiday?

Please continue taking your supplement as normal if possible. If this is not possible, please let us know. If you have to stop pulmonary rehabilitation classes for longer than a week, we may ask you to stop taking your supplement. We will then instruct you to restart the supplement when you return to class.

Comments/problems:

Dr Sarah Deacon, Creatine Study, Glenfield Hospital, 0116 2563652
SUPPLEMENT DIARY CARD (Maintenance Phase)

Please record the times you take your supplement each day on the chart below.

If you forget to take a dose, take it as soon as you remember. If you realise the following day that you missed a dose, write "missed dose" (or "MD") in the appropriate box and continue to take your supplement as normal.

<table>
<thead>
<tr>
<th>Week</th>
<th>Monday</th>
<th>Tuesday</th>
<th>Wednesday</th>
<th>Thursday</th>
<th>Friday</th>
<th>Saturday</th>
<th>Sunday</th>
</tr>
</thead>
<tbody>
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<td>2</td>
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<td></td>
<td></td>
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<tr>
<td>3</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
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<td></td>
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<tr>
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<td>10</td>
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</tbody>
</table>

Dr Sarah Deacon, Creatine Study, Glenfield Hospital, 0116 2563652
## Appendix XIV: Pulmonary Rehabilitation Training Timetable

<table>
<thead>
<tr>
<th>Anaerobic Training</th>
<th>Monday</th>
<th>Tuesday</th>
<th>Wednesday</th>
<th>Thursday</th>
<th>Friday</th>
<th>Saturday</th>
<th>Sunday</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supervised</td>
<td></td>
<td></td>
<td></td>
<td>□</td>
<td>□</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Walks</td>
<td></td>
<td></td>
<td></td>
<td>□</td>
<td>□</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cycle</td>
<td>□</td>
<td></td>
<td></td>
<td>□</td>
<td>□</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unsupervised</td>
<td></td>
<td></td>
<td></td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Home walks</td>
<td>□</td>
<td>□</td>
<td></td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Strength Training</th>
<th>Monday</th>
<th>Tuesday</th>
<th>Wednesday</th>
<th>Thursday</th>
<th>Friday</th>
<th>Saturday</th>
<th>Sunday</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supervised</td>
<td></td>
<td>□</td>
<td>□</td>
<td>□</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Free Weights</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leg Flexion &amp; Extension</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unsupervised</td>
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<td>□</td>
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<tr>
<td>Home Free Weights</td>
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<td></td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
</tbody>
</table>

### Notes:

1. No supervised walks during first 3-4 weeks – due to longer recovery time after leg exercises & learning phase
2. Fully supervised to reassess walking speed
3. Only performed towards end of programme as subjects become more confident & efficient in using equipment
4. Ideally one session over weekend, leaving approx. 48h before Monday pm class
### Appendix XV: Pulmonary Rehabilitation Strength Training Log

<table>
<thead>
<tr>
<th>SESSION</th>
<th>Number of reps</th>
<th>Perceived Exertion</th>
<th>BORG Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date</td>
<td>Weight</td>
<td>Set 1</td>
<td>Set 2</td>
</tr>
<tr>
<td>Bicep Curl</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sitting to Standing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pull Ups</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Step Ups</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leg Curl</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leg Extension</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Please tick box below each day you took your supplement:**

<table>
<thead>
<tr>
<th></th>
<th>MON</th>
<th>TUE</th>
<th>WED</th>
<th>THUR</th>
<th>FRI</th>
<th>SAT</th>
<th>SUN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Please</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tick</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Please indicate if you take/need any of the following over this coming week. If “yes”, please give details:**

**Antibiotics?**

- Yes/No

**Steroids?**

- Yes/No

**Changes in any treatment?**

- Yes/No

**GP visit?**

- Yes/No

**Hospital admission (other than clinic)?**

- Yes/No
## Appendix XV: Pulmonary Rehabilitation Strength Training Log

### Session Log

<table>
<thead>
<tr>
<th>SESSION</th>
<th>Number of reps</th>
<th>Perceived Exertion</th>
<th>BORG Score</th>
<th>Date</th>
<th>Weight</th>
<th>Set 1</th>
<th>Set 2</th>
<th>Set 3</th>
<th>After 3 sets</th>
<th>After 3 sets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bicep Curl</td>
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<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Sitting to Standing</td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>Pull Ups</td>
<td></td>
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<tr>
<td>Step Ups</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Leg Curl</td>
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<td></td>
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<td></td>
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</tr>
<tr>
<td>Leg Extension</td>
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</table>

### Perceived Exertion

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>Nothing at all</td>
</tr>
<tr>
<td>7</td>
<td>Very, Very Light</td>
</tr>
<tr>
<td>8</td>
<td>Very Light</td>
</tr>
<tr>
<td>9</td>
<td>Fairly Light</td>
</tr>
<tr>
<td>10</td>
<td>Somewhat Hard</td>
</tr>
<tr>
<td>11</td>
<td>Hard</td>
</tr>
<tr>
<td>12</td>
<td>Very Hard</td>
</tr>
<tr>
<td>13</td>
<td>Very Very Hard</td>
</tr>
</tbody>
</table>

### BORG Score

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Maximal</td>
</tr>
<tr>
<td>0.5</td>
<td>Very, very slight</td>
</tr>
<tr>
<td>1</td>
<td>Very slight</td>
</tr>
<tr>
<td>2</td>
<td>Slight</td>
</tr>
<tr>
<td>3</td>
<td>Moderate</td>
</tr>
<tr>
<td>4</td>
<td>Somewhat Severe</td>
</tr>
<tr>
<td>5</td>
<td>Severe</td>
</tr>
<tr>
<td>6</td>
<td>Very Severe</td>
</tr>
<tr>
<td>7</td>
<td>Very, Very Severe</td>
</tr>
<tr>
<td>8</td>
<td>Maximal</td>
</tr>
</tbody>
</table>

### Any problems?

Any problems?
Hand Held Weight System Using Plastic Milk Containers

Fill up the milk container with water to the pint marking that is closest to the weight you have been using at the hospital.

1 pint = 0.6 kg (or 1 lb 5 oz)

2 pints = 1.2 kg (or 2 lb 10 oz) (Pink dumbbell = 1.1 kg or 2.5 lbs)

3 pints = 1.8 kg (or 3 lb 13 oz)

4 pints = 2.4 kg (or 5 lb 4 oz) (Green dumbbell = 2.2 kg or 5 lbs)

5 pints = 3 kg (or 6 lb 9 oz)

6 pints = 3.6 kg (or 7 lb 14 oz) (Blue dumbbell = 4.5 kg or 10 lbs)
Reference List


References


References


References


References


Chan KM & Maffulli N. (1996). *Principles and practice of isokinetics in sports medicine and rehabilitation*. Williams & Wilkins, Hong Kong.


References


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265


References


References


References


References


References


References


References


References


References


References


References


References


280
References


References


References


References


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References


References


References


References


References

