Strategies for exercise assessment and training in patients with chronic obstructive pulmonary disease.

Tania Janaudis-Ferreira
To my family
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ABSTRACT

Rationale: Chronic obstructive pulmonary disease (COPD) is not only a common lung disease but is a major cause of morbidity and mortality worldwide. Pulmonary rehabilitation (PR) helps optimize function and independence by increasing exercise capacity, reducing symptoms and improving health related quality of life (HRQL). Exercise training is certainly a key component of the PR programs; however, many of its aspects still need to be better defined such as optimal exercise assessment and training modality for these patients. The general purpose of this thesis was to generate new knowledge that could contribute to new strategies for exercise assessment and training in patients with COPD.

Methods and results: This thesis is comprised of four independent studies. Thigh muscle strength, endurance and fatigue were compared between 42 patients with moderate to severe COPD and 53 healthy controls (Study I). Impaired thigh muscle strength and endurance in patients with COPD was found, except for muscle strength in knee extension in male patients. Female patients had higher fatigue index than female controls while no difference was found between male patients and controls. The six-minute walk test (6MWD) performed on a non-motorized treadmill (6MWD-T) was compared with the 6MWD performed in a corridor (6MWD-C) in 16 healthy elderly subjects (Study II). They performed twelve tests (six 6MWD-C and six 6MWD-T) on two different days in a randomized order. An average discrepancy was found between the two methods with the subjects walking a shorter distance on the non-motorized treadmill. However, the results showed good test-retest reliability between days and test repetitions. A systematic review (Study III) was done of studies that investigated the effects of an arm training program in patients with COPD. The findings of this review indicated that there is evidence that an arm training program improves arm exercise capacity, but its effects on dyspnea, arm fatigue and healthy-related quality of life is unclear. Finally, a two-armed randomized controlled trial examined the effects of an arm training program on arm function, arm exercise capacity, muscle strength, symptoms and HRQL in patients with COPD (Study IV). The groups were randomized to arm training or sham. Compared with the changes observed in the control group, the magnitude of change in the intervention group was greater for arm function, arm exercise capacity and muscle strength. There was no difference between groups in HRQL or symptoms.

Conclusions: Upper extremity resistance training improves arm exercise capacity, arm function and muscle strength in patients with COPD. Training and assessment of upper and lower limb muscles should be included into PR programs. The 6MWD performed on a non-motorized treadmill may offer an alternative option to the standard 6MWD when a 30-meter corridor is not available.

Key words: COPD, exercise assessment, physical training, muscle strength, arm function.
SVENSK SAMMANFATTNING

**Background:** Kroniskt obstruktiv lungsjukdom (KOL) är ett stort globalt problem. KOL kan inte botas men sjukdomen kan delvis behandlas. Lungrehabilitering för patienter med KOL syftar till att minska funktionsnedsättning och förbättra hälsorelaterad livskvalitet. Efter rökstopp är fysisk träning den viktigaste komponenten i lungrehabiliteringen. Former för fysisk träning, liksom utvärdering av fysisk förmåga hos patienter med KOL, bör dock definieras bättre. Syftet med denna avhandling var att generera ny kunskap som kan bidra till nya strategier för utvärdering och träning av fysisk förmåga hos patienter med KOL.

**Metoder och resultat:** Avhandlingen består av fyra enskilda studier. maximal styrka och uthållighet i lärets muskulatur jämfördes mellan 42 KOL-patienter med 53 åldersmatchade friska kontroller (Studie I). Den maximala muskelstyrkan och den muskulära uthålligheten i läret var lägre hos patienter med KOL jämfört med friska kontroller, med undantag av maximal styrka i knäextension hos män med KOL. Muskulär trötthet var högre hos kvinnor med KOL men ingen skillnad observerades hos män med KOL jämfört med friska kontroller. Sex minuters gångtest (6MWD) genomfört på en gångamatta (6MWD-T) jämfördes med 6MWD genomfört i en korridor (6MWD-C) hos 16 friska, äldre personer (Studie II). De genomförde tolv tester (sex 6MWD-C och sex 6MWD-T) på två olika dagar i en slumpmässig ordning. Det förelåg skillnad mellan de två metoderna (försökspersonerna gick en kortare sträcka på gångmattan). Resultaten visade dock god test-retest reliabilitet mellan dagar och testrepetitioner. Studie III var en systematisk litteraturgranskning av studier som har undersökt effekter av armträning hos patienter med KOL. Resultaten visar att armträning förbättrar förmåga att genomföra armaktiviteter men dess effekter på andfådhett, armtrötthet och hälsorelaterad livskvalitet är oklar. Slutligen undersöktes effekter av armträning på armarnas funktion, fysisk förmåga, muskelstyrka samt symptom och hälsorelaterad livskvalitet hos patienter med KOL. Två grupper var randomiserad till armträning eller "sham". Armfunktion, fysisk förmåga i armarna samt muskelstyrka förbättrades i träningsgruppen jämfört med kontrollgruppen. Det fanns ingen skillnad mellan grupperna på hälsorelaterad livskvalitet eller symptom.

**Konklusioner:** Styrketräning av övre extremiteter hos patienter med KOL förbättrar armfunktion och muskelstyrka. Utvärdering och träning av övre och nedre extremiteter hos patienter med KOL bör inkluderas i lungrehabiliteringsprogram. 6MWD genomfört på en gångmatta kan vara ett alternativ till det standardiserade 6MWD när en 30 meter lång korridor inte är tillgänglig.
# ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ADL</td>
<td>Activity of Daily Living</td>
</tr>
<tr>
<td>ANOVA</td>
<td>Analysis of Variance</td>
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<tr>
<td>ATP</td>
<td>Arm Training Program</td>
</tr>
<tr>
<td>ATS</td>
<td>American Thoracic Society</td>
</tr>
<tr>
<td>BTS</td>
<td>British Thoracic Society</td>
</tr>
<tr>
<td>BMI</td>
<td>Body Mass Index</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence Interval</td>
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<tr>
<td>COPD</td>
<td>Chronic Obstructive Pulmonary Disease</td>
</tr>
<tr>
<td>CRDQ</td>
<td>The Chronic Respiratory Disease Questionnaire</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 1 second</td>
</tr>
<tr>
<td>FEV1/VC</td>
<td>Forced Expiratory Volume (in 1 Second)/Vital Capacity</td>
</tr>
<tr>
<td>FI</td>
<td>Fatigue index</td>
</tr>
<tr>
<td>FRC</td>
<td>Functional Residual Capacity</td>
</tr>
<tr>
<td>GOLD</td>
<td>The Global Initiative for Chronic Obstructive Lung Disease</td>
</tr>
<tr>
<td>HRQL</td>
<td>Health-related Quality of Life</td>
</tr>
<tr>
<td>ISWT</td>
<td>Incremental Shuttle Walk Test</td>
</tr>
<tr>
<td>LoA</td>
<td>The limits of Agreement Method</td>
</tr>
<tr>
<td>LVRS</td>
<td>Lung Volume Reduction Surgery</td>
</tr>
<tr>
<td>MMRC</td>
<td>Modified Medical Research Council</td>
</tr>
<tr>
<td>PR</td>
<td>Pulmonary Rehabilitation</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomized Controlled Trial</td>
</tr>
<tr>
<td>RM</td>
<td>Repetition Maximum</td>
</tr>
<tr>
<td>6MWD</td>
<td>Six-minute walking distance test</td>
</tr>
<tr>
<td>6MWD-C</td>
<td>Six-minute walking distance test performed in a corridor</td>
</tr>
<tr>
<td>6MWD-T</td>
<td>Six-minute walking distance test performed on a non-motorized treadmill</td>
</tr>
<tr>
<td>6PBRT</td>
<td>6-minute Pegboard and Ring Test</td>
</tr>
<tr>
<td>UULEX</td>
<td>Unsupported Upper Limb Exercise Test</td>
</tr>
<tr>
<td>VA/Q</td>
<td>Ventilation-perfusion</td>
</tr>
</tbody>
</table>
ORIGINAL PAPERS

The present thesis is based on the following papers:


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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a major public health problem responsible for substantial morbidity, mortality and health care costs. According to the World Health Organization, approximately 210 million people throughout the world have COPD and it is likely to become the third leading cause of death globally by 2030. In Sweden, an estimated 500,000 - 700,000 people are diagnosed with COPD and die prematurely from it or its complication.

Definition

COPD is a preventable, treatable but not curable lung disease with important extra-pulmonary (systemic) effects that may contribute to serious complications in some patients. The impairment in the lungs is characterized by airflow limitation which can be slightly reversible by a bronchodilator. The airflow limitation in people with COPD is caused by a combination of two inflammatory conditions: small airway disease (chronic bronchiolitis) and parenchymal destructions (emphysema). The proportion of each specific condition varies from patient to patient. The chronic inflammation present in these patients causes structural changes remodelling and narrowing the small airways and leading to loss of alveolar attachments which in its turn decreases the lung elastic recoil. The airflow limitation may follow the presence of cough and sputum but the opposite could also occur; presence of airflow obstruction without cough or sputum.

COPD is mainly caused by long-term cigarette smoking; however, indoor and outdoor air pollution is also considered a COPD risk factor in many countries. The course of COPD varies for each patient and the impact of the disease depends on the severity of symptoms. Nevertheless, COPD is considered a progressive disease where the presence of airflow limitation, lung hyperinflation and systemic inflammation contribute to dyspnea and exercise tolerance debilitating patients and affecting their quality of life. Because COPD develops in long-time smokers in middle age, patients often possess other co-morbidities related to their age or smoking which intensify the severity of the disease.

Different classifications of the disease severity have been suggested by guidelines from national and regional organizations such as European Respiratory Society (ERS), American Thoracic Society (ATS) and British Thoracic Society (BTS). More recently, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) has created, for educational purposes, a spirometric classification of disease severity into four stages (Table 1). Spirometry is crucial for diagnosis and informs about the severity of the disease. However, the impact of COPD does not only
depend on the severity of the airflow limitation but also on the degree of symptoms such as dyspnea and exercise intolerance.\textsuperscript{1,5}

**Table 1. Spirometric classification of COPD severity (post-bronchodilator)**

<table>
<thead>
<tr>
<th>Stage</th>
<th>FEV\textsubscript{1}/FVC</th>
<th>FEV\textsubscript{1} (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I: Mild</td>
<td>&lt; 0.70</td>
<td>≥ 80% predicted</td>
</tr>
<tr>
<td>II: Moderate</td>
<td>&lt; 0.70</td>
<td>50% ≤ FEV\textsubscript{1} &lt; 80% predicted</td>
</tr>
<tr>
<td>III: Severe</td>
<td>&lt; 0.70</td>
<td>30% ≤ FEV\textsubscript{1} &lt; 50% predicted</td>
</tr>
<tr>
<td>IV: Very severe</td>
<td>&lt; 0.70</td>
<td>FEV\textsubscript{1} &lt; 30% predicted or FEV\textsubscript{1} &lt; 50% predicted plus chronic respiratory failure</td>
</tr>
</tbody>
</table>

FEV\textsubscript{1}- Forced expiratory volume in one second
FVC- Forced vital capacity

* Table extracted from GOLD guidelines\textsuperscript{5}

**Pathology, pathogenesis and pathophysiology**

The chronic and increased number of inflammatory cells such as T lymphocytes, neutrophils and macrophages present in COPD are responsible for pathological changes in peripheral and proximal airways, lung parenchyma and pulmonary vasculature.\textsuperscript{5}

Cigarette smoking and other deleterious particles (air pollution and occupational exposures to dusts and chemicals) are considered the main causes of lung inflammation present in COPD.\textsuperscript{5} The inflammatory response to the respiratory system seems to be augmented in patients with COPD compared to healthy individuals.\textsuperscript{5} The reason for that is unknown but oxidative stress and imbalance of proteinases and antiproteinases in the lungs have been suggested to be some of the causes for this amplified inflammatory response.\textsuperscript{5} Genetics may also play a role and one risk factor is a genetic deficiency of the protective protease inhibitor, Alpha-1 Antitrypsin.\textsuperscript{1,5} Although it is a rare hereditary deficiency, it can cause COPD. Low levels of Alpha-1 Antitrypsin might allow the uninhibited action of elastase on the lung parenchyma contributing to the destruction of the alveoli and to the development of emphysema.\textsuperscript{1,5}
**Manifestations and symptoms**

**Airflow limitation and hyperinflation**
Progressive airflow limitation leads to air trapping during the exhale phase causing hyperinflation (increased end expiratory lung volume) which in its turn reduces inspiratory capacity and increases functional residual capacity. This occurs particularly during exercise (dynamic hyperinflation) and results in dyspnea and exercise limitation.

**Gas exchange**
As the disease progresses, the gas exchange deteriorates in COPD, resulting in hypoxemia and hypercapnia. The airflow limitation combined with the mechanical disadvantage of the respiratory muscles due to the hyperinflation results in ventilation-perfusion (VA/Q) imbalance and retention of carbon dioxide. The pathologic alterations in alveolar ventilation and the reduction in pulmonary vascular bed further worsen the VA/Q.

**Mucus hypersecretion**
Chronic cough and mucus hypersecretion is generally associated with chronic bronchitis and is not necessarily related to the airflow limitation. In fact, not all patients with COPD are symptomatic for mucus hypersecretion. The presence of mucus hypersecretion is probable due to the enlarged submucosal glands and increased numbers of goblet cells in response to the chronic exposure to cigarette smoke and other deleterious agents.

**Pulmonary hypertension**
The hypoxic vasoconstriction of small pulmonary arteries and the loss of pulmonary capillary bed in emphysema contribute to an increased pressure in the pulmonary circulation causing what it is called as pulmonary hypertension. Pulmonary hypertension is progressive and may lead to right ventricular hypertrophy and possibly to right-side cardiac failure (cor pulmonale).

**Systemic effects**
It is well-known that COPD is a systemic disease that affects organs and systems other than the lungs. Cachexia, osteoporosis, depression and chronic anemia are often seen in patients with severe COPD. Skeletal muscle dysfunction, including muscle weakness and atrophy, is another common complication of COPD and will be discussed further in this thesis.
Gender-related differences

In 1990, the prevalence of COPD throughout the world was approximately 9.34/1,000 in men and 7.33/1,000 in women suggesting that COPD was predominantly a male condition. However, in the past 20 years, the prevalence of COPD in women has rapidly increased and, to date the mortality rates are greater in women than men. The occurrence of emphysema in women and men is equivalent, however, chronic bronchitis affects twice as many women as men in the USA. This raises a question of whether or not women and men have different susceptibility to tobacco smoke. In fact, studies suggest that women are more prone to have worse airway hyper-responsiveness than men. This is of clinical importance as airway hyper-responsiveness is a risk factor for the development of COPD.

Gender-related differences in patient with COPD are present not only in terms of prevalence and mortality but also in clinical manifestations. Studies have shown that women experience considerably higher degree of dyspnea (measured by the Modified Medical Research Council (MMRC)), cough and sputum production than men despite the similar forced expiratory volume in 1 second (FEV1). Moreover, it appears that more women with COPD suffer from depression and experience significantly worse health-related quality of life than male patients for similar degree of severity of the disease. In terms of exercise performance, two recent studies have shown that women with COPD had lower exercise capacity compared to male counterparts.

A study from 2000 suggested that women are more susceptible than men to risk factors other than smoking. Potential factors may be hormonal effects, genetics and biomass exposure. However, further research is required to investigate the role of these factors in the development and progression of COPD in men and women.

Besides the biological differences, evidence from two different studies suggest that there is a bias towards a COPD diagnosis in men, especially when spirometry is not part of the assessment. When the physicians that participated in these two studies were shown the results of the spirometry, the bias did not remain which highlights the value of performing spirometric tests. In addition Watson et al showed, in a multicenter study, that women are less likely to receive spirometric tests than men by the primary care physicians. These data indicate that women may be less likely to be diagnosed and treated for their COPD.

Skeletal muscle dysfunction

Skeletal muscle dysfunction, including muscle weakness and atrophy, is a common systemic co-morbidity of COPD and is a better predictor of
disease mortality than lung function. It contributes to exercise limitation leading to a poor quality of life and an increased need for medical assistance.

Muscle abnormalities observed in patients with COPD include muscle atrophy, reduced oxidative metabolism, reduced muscle capillarization and change in muscle fiber type (reduced proportion of type I fibers and increased proportion of type IIb) which contribute to leg and arm fatigue. Deconditioning has been traditionally suggested as the main reason for the presence of these peripheral muscle abnormalities in patients with COPD. Physical training has been shown to enhance muscle function in these patients, suggesting that inactivity is an important contributor to skeletal muscle dysfunction. However, other important factors have been identified as contributors to skeletal muscle changes. These factors include malnutrition, exposure to corticosteroids, tissue hypoxia, coexisting heart disease, systemic inflammation (elevated levels of cytokines), skeletal muscle apoptosis, oxidative stress, tobacco use, individual susceptibility and hormone alterations.

Both lower and upper limb muscle force are impaired in individuals with COPD. Nevertheless, it seems that this muscle weakness does not affect all muscles to a similar extent. Some authors have suggested that there might be a preferential involvement of lower limb muscle over upper limb muscle. Bernard et al have found that quadriceps strength in patients with COPD was more affected than pectoralis major and latissimus dorsi. The author explained that this may be because of lower limb muscles are generally underused in activities of daily living compared to upper limb muscles. Moreover, Gosselink et al have shown that inspiratory muscle strength was more affected than peripheral muscle strength and that proximal upper limb muscle strength was more impaired than distal upper limb muscle strength. This may indicate a systemic process that preferentially affects the proximal muscles. Therefore, assessment of muscle strength in patients with COPD should be specific to the muscle group of interest.

The strength of the diaphragm in COPD patients has been found to be normal. This preservation of the strength in the diaphragm might be due to a constant and involuntary training effect from the work of breathing against an increased load.

Limited evidence is available on reduced lower or upper extremity muscle endurance in patients with COPD. The results from the available studies differ in methodology and findings.
Management of COPD

Once the diagnosis of COPD is confirmed, the management of the disease should initiate shortly to optimize the treatment. The main goals of management of COPD are as follow 5, 53:

- Smoking cessation and elimination of other risk factors aiming prevention of disease progression
- Prevent and treat exacerbations and complications
- Alleviate symptoms of dyspnea and other respiratory symptoms
- Improve exercise tolerance and consequently daily activity
- Improve health status
- Reduce mortality

The selection of the treatment plan will depend on the benefits, risks and costs to each patient or family. Different strategies that could be used to achieve these goals are described below.

Pharmacologic treatment

Medications are administered basically to decrease symptoms and complications. Some medications may improve health status and exercise tolerance 5, 53 but the decline in lung function does not appear to be interrupted by any type of pharmacologic treatment 5. Bronchodilators are essential for the symptomatic patient with COPD. It is worthwhile adding corticosteroids to the therapy of patients with severe and very severe COPD if multiple exacerbations 53. Influenza vaccination is another important component of the pharmacologic therapy of patients with any degree of COPD as it is believed to prevent exacerbations 53.

Non-pharmacologic treatment

Besides the pharmacologic therapy, other important types of treatment should be considered for patients with COPD. These include: oxygen therapy, ventilatory support, lung surgery and pulmonary rehabilitation (PR).

Oxygen therapy is one of the most significant non-pharmacologic treatments for patients with very severe COPD (stage IV) 1, 5. For these patients oxygen is usually administered in three different ways: long-term continuous therapy, during exercise and/or to alleviate acute dyspnea. The objective of long-term oxygen therapy (> 15 h per day) is to increase
PaO₂ to at least 60 mm Hg (8.0 kPa) or to improve SaO₂ at least 90% ensuring an adequate oxygen delivery and thus preserving vital organ function. It extends survival in hypoxemic patients with COPD, prevents the progression of pulmonary hypertension and improves neuropsychological health. However, long-term ambulatory oxygen should be administered in selected patients who meet criteria for mortality reduction. Nonoyama et al. demonstrated that although ambulatory oxygen acutely improved exercise capacity in patients with COPD, no effect of oxygen use on health-related quality of life (HRQL) was observed.

Although non-invasive ventilation has been used during acute exacerbation in patients with COPD, there is no evidence for the positive effect of this treatment on dyspnea, exercise tolerance, respiratory muscle strength, arterial blood gases or HRQL in stable patients with respiratory failure. Nevertheless, the combination of non-invasive ventilation with long-term oxygen therapy appears to be an option for patients who experience daytime hypercapnia.

Bullectomy, lung volume reduction surgery (LVRS) and lung transplantation are treatment options for specific selected patients. Bullectomy can be performed thoracoscopically and is effective at improving lung function and reducing dyspnea. LVRS has been shown to improve exercise capacity, HRQL and to reduce frequency of exacerbations. In addition, patients who undergo LVRS have greater survival compared to those who receive conservative medical treatment. Lung transplantation improves HRQL and functional status but it is the most drastic treatment being recommended only for patients with very advanced COPD. A limitation of these surgical procedures is certainly their cost. The elevated economic cost is due to hospitalizations, complications and immunosuppressive regimens that are associated with the surgical act.

In the next section, pulmonary rehabilitation and specifically exercise training will be discussed.

Pulmonary rehabilitation

PR is defined as “an evidence-based, multidisciplinary, and comprehensive intervention for patients with chronic respiratory disease 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.”
As the definition suggests, the principal objectives of PR are to reduce symptoms, increase participation in physical and social daily activities and improve the quality of life of these patients. PR addresses pulmonary and non-pulmonary impairments associated with the respiratory disease and that may not be treated by traditional medical therapy. To accomplish its goals, PR includes different components such as patient assessment, exercise training, disease education, nutritional support, psychological and social support for the patients and their relatives.

**Exercise training**

As described earlier in this thesis, several physiologic factors contribute to exercise intolerance in patients with COPD. These include: ventilatory and gas exchange limitations, cardiac dysfunction and skeletal muscle abnormalities. Anxiety and motivation have also been shown to impact on symptom perception but its direct association with exercise tolerance has not been established yet. Exercise training has been identified to be the most important component of the PR and is undoubtedly the best strategy to revert the impairments associated with exercise limitation. It improves exercise performance, health-related quality of life, muscle and cardiovascular function and alleviates dyspnea. Exercise training may also have a positive impact on motivation for exercise and mood disturbances.

**Lower limb exercise training**

Although exercise training is a cornerstone of PR programs, the specific characteristics of the lower limb endurance programs (duration, frequency and intensity) for patients with COPD have not been broadly investigated. To date there is no consensus on the optimal duration of PR programs for patients with COPD. A program of just 10-days long has been shown to be effective at improving exercise capacity, dyspnea and HRQL of patients with COPD. However, the guidelines suggest longer programs (over 12 weeks) to obtain greater gains in exercise tolerance and maintain the benefits over time. Indeed, recent evidence suggests that long-term programs (6 months) translate into better daily functioning and increased activity levels for patients with COPD.

In terms of exercise intensity for patients with COPD, to date there is insufficient evidence to recommend high intensity training (about 60-80% of the peak work rate achieved in a incremental maximum exercise test) over low intensity training or vice versa. Only few randomized controlled trials (RCT) have investigated the optimal intensity for exercise training in patients with COPD. The results of these studies
suggest that training at higher percentages of peak exercise is well-tolerated and confers physiologic benefits such as increased aerobic capacity and reduced ventilatory demands. However, high-intensity training in the available studies was defined as 60%-80% of the maximum peak work rate achieved in an incremental exercise test which is not representative of a high absolute work level. Moreover, the impact of high-intensity training on other clinical outcomes such as dyspnea, HRQL and ability to perform ADL is still unknown. Exercises at lower intensity produce clinical benefits for patients with COPD and may be associated with better adherence to training in patients with severe symptoms. Lately, interval training has gained attention as an alternative option for achieving greater physiologic effects compared to continuous training in patients with COPD. In a recent systematic review, it was noted that interval training is equally effective as continuous training in terms of exercise capacity or HRQL in patients with COPD.

Lower limb resistance training has been in the recent years incorporated into the PR programs in order to address the musculoskeletal dysfunction present in patients with COPD. It has been shown to be a safe type of exercise for these patients except when serious contra-indications are present; i.e. severe osteoporosis.

A recent systematic review revealed that short-term resistant training results in increased muscle mass and strength in patients with COPD. Resistance training alone may improve HRQL but does not seem to have additional impact on this outcome when combined with endurance training. There is limited evidence on the effect of resistance training on the ability to perform ADL or on any other outcome on a long-term basis.

**Upper limb exercise training**

Patients with COPD often report dyspnea and arm fatigue during arm activities. The sensation of dyspnea during arm activities in these patients may be due to the irregular and superficial breathing pattern imposed by the mechanical effects of arm elevation. During exercises when the upper limbs are not supported by any device, some upper limb muscles such as the sternocleidomastoid and upper trapezius diminish their participation in ventilation as they are recruited to help with the postural support of the arms. As a consequence, the respiratory work is shifted to the diaphragm which is already at a mechanical disadvantage in patients with COPD.

In addition, elevating the arms above the shoulders increases functional residual capacity (FRC) in these patients. This may be explained by the fact that the thoracic muscles are passively stretched expanding the rib cage when the arms are being raised. This higher FRC increases lung hyperinflation resulting in a greater load that must be overcome by the diaphragm, decreasing its capacity for generating force and thus, increasing the sensation of dyspnea. As a result of these mechanical
changes, many patients with COPD struggle with or even avoid performing essential ADLs that involve upper extremities.

Arm fatigue is another common limiting symptom during arm activity in patients with COPD. Like the impairment observed in quadriceps of patients with COPD, strength of upper limb muscles such as pectoralis major, latissimus dorsi, biceps and middle deltoids is also impaired in these patients.

In contrast to studies that have investigated the effects of lower limb training, RCTs of arm training in patients with COPD are relatively sparse. Although previous work indicates that arm training increases arm exercise capacity and decreases metabolic load associated with arm activity, the effects on other outcome measures such as dyspnea, fatigue and HRQL following arm training are mixed. This inconsistency is likely to result, at least in part, from the differences in methodology and training programs described by the previous studies. To date, only one study has examined the long term effects of arm training. This study demonstrated that at 6-month follow-up, the increased arm exercise capacity and the improved ability to perform ADL were better maintained in the trained group compared to the control group.

The components of an optimal arm training program (ATP) for patients with COPD are not clear. Only one study has compared two different training exercises: supported arm training (arm cycling) and unsupported arm training (moving rings across a wire and hand weight lifts). This study demonstrated that unsupported arm training conferred greater benefits in arm exercise capacity and metabolic load during unsupported arm activity. In contrast with the training programs described for other chronic diseases, such as congestive cardiac failure, most ATP described in studies of patients with COPD do not use resistance training exercise. This is surprising as such training has been demonstrated to result in adaptations in muscle mass, morphology and histochemistry of the muscles and in peak oxygen consumption in both health and disease.

Few studies have examined the physiological mechanisms responsible for any improvements in arm exercise capacity demonstrated on completion of an ATP. Gigliotti et al. demonstrated a decrease in both ventilation and dynamic hyperinflation but no change in the rate of oxygen consumption or carbon dioxide production after an ATP. However, this study had methodological shortcomings, the most notable of which was the lack of a control group.

**Strategies to enhance exercise training**

Numerous strategies have been found to be valuable adjuncts to enhance the effects of exercise training (improvement in dyspnea and exercise tolerance) in patients with COPD. These strategies are mostly used in research settings and include: inspiratory muscle training, breathing retraining with or without visual biofeedback, neuromuscular electrical
stimulation, use of bronchodilator before exercise, non-invasive ventilation, one-legged exercise, heliox mixture (helium + oxygen) and supplemental oxygen alone. This thesis will not review these adjuncts in details.

Assessment

Lower limb exercise capacity

The purposes of exercise testing in PR are to objectively assess patients’ functional exercise capacity and to measure response to treatment. Exercise testing may also help determine the need for PR, surgery or supplemental oxygen, prescribe a walking program and/or identify patients likely to benefit from a rollator. Moreover, functional exercise capacity is a strong predictor of mortality and post-operative complications and weakly correlated with pulmonary function, which emphasizes the importance of assessing patients’ ability to function.

Different exercise tests have been used in patients with COPD. Treadmill testing has been found to be more sensitive to detect change in function than the 6-minute walk distance test (6MWD). Treadmill is also a good option in case of space restrictions or when a more advanced monitoring is required. However, it is usually expensive and may require expertise to deal with the equipment. Stationary cycle tests can precisely quantify external work and calculate specific parameters during a cardiopulmonary exercise test. Nevertheless, it has been shown to have significant different ventilatory and metabolic adaptations when compared with walking and is less representative of activities of daily living. In addition, similar to treadmill, stationary cycles are expensive and the test requires expertise.

The 6MWD test is technically simple to perform, inexpensive, safe and is more representative of activities of daily living than cycle tests or other walk tests such as the shuttle walk test. It requires an undisturbed corridor of approximately 30 m and it is well-standardized with normal reference equations.

The 6MWD is an adaptation of the original 12-minute walking test developed by Cooper et al. In 1976 McGavin et al. modified this test in order to use it for disabled population and finally, Guyatt et al. and Butland et al. adapted the 12-minute walk test to the 6MWD for patients with chronic heart failure and respiratory diseases. The 6MWD could be considered as submaximal test for healthy individuals; especially for the young ones as it is not allowed to run, however, patients with respiratory disease may experience this test as a maximal test. The main disadvantage of the 6MWD is that it only assesses general exercise capacity and does not specifically address the cause of the limitation. Furthermore, patients with mild disability may not be able to
demonstrate their impairment as walking on a level ground is the only activity allowed and the way to show an improvement is to walk faster. Some patients may have difficulty in walking faster but could demonstrate any improvement in exercise capacity by walking longer or on a steeper grade. Also, as the recommendation is to perform the 6MWD on an undisturbed corridor of 30 metres, lack of space may be a barrier for performing this test.

The incremental shuttle walk test (ISWT) \(^\text{107}\) is another test that assesses functional exercise capacity in patients with respiratory diseases. Unlike the 6MWD, the ISWT is externally paced; however, patients can only demonstrate improvement by walking faster as well. The endurance shuttle walk test (ESWT) \(^\text{108}\) is a complement to the ISWT and it allows the patients to demonstrate improvement in walking time (endurance). It requires the patients to do the ISWT first and then to walk at 85\% of their speed along the 10-metre course \(^\text{108}\). The ESWT may also be an alternative option to the constant work load on a treadmill; however, further studies are needed.

Although little used for patients with lung diseases, the step test is another option of field test that evaluates functional exercise capacity. It is tolerable and highly reproducible in patients with COPD \(^\text{109}\) and elicits maximal cardiopulmonary and metabolic responses comparable to those observed during a maximal cycle ergometry \(^\text{110}\) and walking test \(^\text{109}\).

**Upper limb exercise capacity**

It is recommended that upper limb exercises be part of the PR programs \(^\text{6, 7}\). Therefore, it is important to specifically assess arm exercise capacity in order to document progress and effectiveness of upper extremity training. However, in contrast to tests that measure lower limb exercise tests, there are few reliable and valid measures to assess arm exercise capacity in patients with COPD. Traditionally, arm exercise capacity has been assessed with arm cycle ergometry using different protocols \(^\text{84, 85}\). However, arm cycle ergometry evaluates supported arm exercise which is not relevant for activities of daily living where most of the activities are performed with no support. More recently, unsupported arm exercise tests have been created. Takahashi and colleagues \(^\text{111}\) developed a reliable incremental test (unsupported upper limb exercise test (UULEX)) to assess arm exercise endurance in patients with COPD. Zhan and colleagues \(^\text{112}\) developed a reliable test called six-minute pegboard and ring test which requires minimal equipment and no specific expertise to perform the test being a good option for a clinical setting. Finally Hill et al.\(^\text{113}\) developed the Grocery Shelving Task which is a standardized test to evaluate arm functional performance. Despite the good reproducibility of these tests, further research is required to determine their sensitivity to interventions.
Muscle function

Specific assessment of peripheral muscle function (muscle strength and endurance) is essential to identify muscle impairment, prescribe appropriate exercise training and evaluate treatment efficacy. Muscle function can be tested using different devices and approaches. Specifically, muscle strength can be evaluated using manual testing, weight machines, portable devices (e.g. hand held dynamometer, strain gauge) or stationary and more complex equipments (e.g. computerized dynamometers). Effort independent methods such as direct electrical or magnetic stimulation of the muscle nerve are also used to assess muscle strength in people with COPD.

Manual testing is undoubtedly the most simple and common test used in clinical settings. However, its reliability is unknown as it relies on the tester’s subjective rating. The hand held dynamometer is a more accurate and objective option to measure muscle strength. It is portable, easy to apply and reliable being a good option for either a clinical or research settings. Computerized dynamometers are also used to perform isometric and isokinetic tests in people with COPD. These systems are accurate, safe and have good test retest reliability being an excellent option for research studies. However, in clinical settings, there is limited access to these equipments due to high cost and time required for testing.

Rationale for this thesis

COPD is a major public health problem responsible for substantial morbidity, mortality and health care costs. Individuals with COPD are debilitated by the presence of irreversible airflow limitation, lung hyperinflation, systemic inflammation and peripheral muscle dysfunction all of which contribute to dyspnea and exercise intolerance.

Initially, these impairments are encountered during hurried walking or stair climbing but as the disease progresses, patients with COPD are limited during simple activities of daily living (ADL) that involve the arms, such as self grooming, showering, making the bed and carrying groceries. The presence of dyspnea and exercise limitation is of concern as they limit the patients’ independence during day-to-day life. PR helps optimize function and independence by increasing exercise capacity, reducing symptoms and improving HRQL. Exercise training is certainly a key component of PR programs; however, many of its aspects still need to be better defined such as optimal exercise assessment and training modality for these patients.

The majority of the studies on lower extremity muscle function in COPD are focused on muscle strength rather than muscle endurance. Moreover, the best training modality to improve muscle function in COPD is
unclear. Therefore, it is important to investigate whether patients with COPD possess reduced muscle strength or/and endurance compared to healthy controls in order to better define the exercise modality for these patients. In addition, it is of great interest to investigate whether there are gender-related differences in muscle function in patients with COPD in order to specifically design rehabilitation programs as preconceived notions of COPD may not hold true for both men and women.

The 6MWD is undoubtedly the gold standard test to assess functional exercise capacity in patients with COPD. Nevertheless, the recommendation is to perform the 6MWD test in an undisturbed corridor of approximately 30 m; this is rarely found in busy clinics and hospitals. Therefore, there is a need to search for alternative tests due to space restrictions.

Pulmonary rehabilitation guidelines recommend upper extremity training as part of PR programs as it increases upper limb exercise capacity and reduces ventilation and oxygen consumption during upper limb exercise. However, they do not provide clear instructions regarding the exact type of training that should be prescribed. Moreover, the effects of an arm training program on other clinical outcomes are unknown. The lack of guidelines reflects the paucity of rigorously performed studies on upper extremity training in this population.
AIMS OF THIS THESIS

The general purpose of this thesis was to generate new knowledge and strategies for exercise assessment and training in patients with COPD.

Specific research questions:

- Do patients with COPD have impaired thigh muscle function compared to age-matched healthy controls? (Study I)
- Are there gender-related differences in thigh muscle performance in patients with COPD? (Study I)
- Is the 6-minute walk test performed on a non-motorized treadmill comparable and interchangeable to the 6-minute walk test performed in a corridor? (Study II)
- What are the evidences for the impact of an arm training program on symptoms, exercise capacity and HRQL? (Study III)
- What are the effects of upper extremity resistance training for patients with COPD on dyspnea during ADL, arm function, arm exercise capacity, muscle strength and HRQL? (Study IV).
METHODS

Ethics

All studies included in this thesis were approved by either the Research Ethics Committee of the Faculty of Medicine, Umeå University, Sweden (Study I and II) or West Park Healthcare Centre, Toronto, Canada (Study IV). All subjects gave their informed consent before participating in the studies.

Design

Study I is a cross-sectional study where a group of patients with COPD and an age-matched healthy control group were evaluated for thigh muscle strength, endurance and fatigue. Study II is a method evaluation study where the 6MWD in a corridor (6MWD-C) was compared to the 6MWD performed on a non-motorized treadmill (6MWD-T). Healthy elderly subjects performed twelve tests in total (six 6MWD-C and six 6MWD-T) on two different days in a randomized order. Study III is a systematic review of studies that have investigated the effects of an ATP on symptoms, exercise capacity and health-related quality of life. Study IV involved a prospective, double-blind, randomized controlled trial in which patients were randomly assigned to an intervention or control group. The intervention group underwent upper extremity resistance training while the control group performed sham exercises. Both groups exercised for 6 weeks three times a week. The outcome measures were collected before and within 2 days of completing the 6-week exercise program.

Subjects

Forty-two outpatients (26 women and 16 men) diagnosed with COPD according to GOLD criteria were recruited from the Department of Respiratory Medicine and Allergy at the University Hospital in Umeå and from the Department of Medicine at the Regional Hospital in Skellefteå. Patients were aged 53 to 74 years. Inclusion criteria were forced expiratory volume (in one second)/vital capacity (FEV1/VC) < 0.7; FEV1 < 80% of predicted; stable medication and no infection during the last month before participating in the study; and absence of cardiac, orthopaedic, neurological or psychological disorders. None of the patients was engaged in any organised physical activity before the study. Fifty-three healthy controls (29 women and 24 men) were recruited from pensioner’s associations in Umeå, Sweden. The inclusion criteria were: age between 53 and 74 and no presence of pulmonary, cardiac, orthopaedic, neurological or psychological disorders. The controls should not have smoked in the last ten years and should not be participants in
any organised physical activity. Characteristics of the subjects included in this study are presented in Table 2 (Study I).

Table 2. Characteristics of the subjects (Study I)

<table>
<thead>
<tr>
<th></th>
<th>COPD Patients (n=41)</th>
<th>Healthy Controls (n=52)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men (n=15)</td>
<td>Women (n=26)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Women (n=28)</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>66±6</td>
<td>64±5</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>79±10</td>
<td>72±15</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26±3</td>
<td>28±5*</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>173±7</td>
<td>160±5</td>
</tr>
<tr>
<td>FEV₁ (L)</td>
<td>1.5 ± 0.4</td>
<td>1.2 ± 0.24</td>
</tr>
<tr>
<td>FEV₁ (%)</td>
<td>50 ± 11.5</td>
<td>56 ± 11</td>
</tr>
<tr>
<td>FEV₁/VC %</td>
<td>40 ± 12</td>
<td>45 ± 9.5</td>
</tr>
</tbody>
</table>

Data are presented as mean ± Sd

BMI=Body Mass Index; FEV₁ - Forced Expiratory Volume in one second
VC - Vital Capacity

* Significantly different from control (p<0.05)

Sixteen healthy elderly subjects (8 women and 8 men) were recruited from pensioner's associations in Umeå, Sweden. All subjects were healthy, aged 63-75 years without any history of chronic disease or musculoskeletal disorder that could adversely affect exercise capacity. Characteristics of the subjects are presented in Table 3 (Study II).

Table 3. Characteristics of the subjects (Study II)

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (f/m)</td>
<td>8/8</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>68 ± 3.4</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>71 ± 9</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>169 ± 8.6</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD

An electronic search was conducted of MEDLINE, CINAHL, EMBASE, PEDro and The Cochrane Library of clinical trials, using the following keywords; chronic obstructive pulmonary disease, arm and training. The review included only studies that were; (i) written in English, (ii) performed in subjects with a diagnosis of COPD and, (iii) randomized controlled trials (RCT) in which the difference between the two groups was the use of an ATP. Specifically, it was included studies that compared
ATP alone to a control group and those that compared ATP combined with lower extremity training to lower extremity training alone. In total, 157 patients with moderate to severe COPD were included in these studies (Study III).

Thirty-six patients (33 in-patients and 3 out-patients) with stable COPD were recruited from the pulmonary rehabilitation program at West Park Healthcare Centre (Toronto, Canada). Inclusion criteria comprised: (i) a diagnosis of COPD with FEV1 < 80% predicted as per GOLD guidelines [1]; (ii) dyspnea and/or arm fatigue during at least one activity of daily living that required arm exercise; and (iii) the ability to provide written informed consent. Exclusion criteria comprised; (i) an acute exacerbation of COPD that required a change in pharmacological management within the preceding two months, (ii) inability to communicate in English; (iii) taking oral corticosteroids; (iv) musculoskeletal or neurological conditions that might affect their exercise performance, symptomatic cardiac disease or previous lung surgery. Characteristics of the subjects are presented in Table 4 (Study IV).

<table>
<thead>
<tr>
<th>Table 4. Characteristics of the subjects (Study IV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group (n = 19)</td>
</tr>
<tr>
<td>Sex (f/m)</td>
</tr>
<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>Height (cm)</td>
</tr>
<tr>
<td>Weight (kg)</td>
</tr>
<tr>
<td>BMI (kg/m^2)</td>
</tr>
<tr>
<td>Supplemental oxygen (n, %)</td>
</tr>
<tr>
<td>MRC</td>
</tr>
<tr>
<td>FEV1 (L)</td>
</tr>
<tr>
<td>FEV1 (% pred)</td>
</tr>
<tr>
<td>FVC (L)</td>
</tr>
<tr>
<td>FVC (% pred)</td>
</tr>
</tbody>
</table>

BMI- body mass index; MRC- Medical Research Council
FEV1- forced expiratory volume in one second; FVC- forced vital capacity
IQR- Interquartile range
Values are mean ± SD unless otherwise stated.

Main outcome measures

Lower limb muscle function

Subjects were tested for thigh muscle strength and endurance on an isokinetic dynamometer (KinCom®, Chattanooga, Illinois) (Study I).

Maximal voluntary contractions (MVC)

Subjects performed four repetitions of maximal knee extension and four repetitions of maximal flexion at 90°/s. During the maximal knee
extensions, subjects were instructed to extend the dominant leg four times in a row with maximal effort and to rest on the way back (flexion phase). During the maximal knee flexions, the subjects were instructed to flex the dominant leg four times in a row with maximal effort and to rest on the way back (extension phase). At least a two-minute rest was given between the repetitions of maximal knee extension and flexion. The highest mean force value (Newton) of the four repetitions was chosen as the outcome measure.

Muscle endurance test

During this test, the subjects were instructed to extend the dominant leg as many times as possible. They continued until the test leader asked them to stop (when 100 repetitions were attained) or until exhaustion. No rest was allowed between the passive flexion phase and the active extension phase. The maximal force in the extension phase was obtained.

Muscle endurance was expressed as the number of attained repetitions of knee extension. Muscle fatigue was analysed using the first 30 contractions of the endurance test and expressed as a fatigue index (FI). This index was a slight modification of an index suggested by Merletti 116, 117. To form the FI, the intercept (m) from the regression analysis of the initial 30 contractions of the endurance test was calculated for each subject. The intercept represents the initial value of the endurance test. From m and the force values of each individual, the FI was calculated as,

\[ FI = \frac{1}{mN} \sum_{i=1}^{N} (m - X_i) \]

where X is mean force value, i is the contraction number, and N is the number of contractions. Higher values for FI indicate increased muscle fatigue. FI represents the relative loss in mean force throughout the 30 first contractions and is presented in percentage (%).

Six-minute walk tests

Subjects performed six 6-minute walk tests (6MWD) on two days, 48 hours apart (Study II). Specifically, subjects performed three 6MWD on a non-motorized treadmill (6MWD-T) and three in a corridor (6MWD-C) on each day. The first test was randomised, and thereafter, the order of the tests was alternated. On the second day, the tests were performed in the same order and at the same time as on the first day. The instructions were as described in the American Thoracic Society guidelines 118, and standardised encouragement 119 was given to the subjects during the tests in the corridor and on the treadmill. Subjects rested for at least 20 minutes between each test.
Methods

For the 6MWD-C test, a 30-m indoor hall was used. The 6MWD-T test was performed in a well-ventilated room on a non-motorised treadmill (Skip Sport Walker 2000; Tyresö; Sweden) which was driven by the subjects. The subjects could decide the speed and when they wanted to stop walking since their walk drove the treadmill. Immediately before and after each test, subjects were asked to score their perceived exertion and leg fatigue using the modified Borg scale (range 0 to 10) 120, 121. Distance walked was recorded after each test.

Systematic literature review

The results of the articles included in the review (study III) were extracted using a standardized form and were summarized according to the effect of the ATP on four outcome measures: (i) arm exercise capacity, (ii) dyspnea during activities of daily living, (iii) health-related quality of life, (iv) symptoms of dyspnea and arm fatigue during arm exercise tests.

HRQL and dyspnea during ADL

HRQL was measured using the Chronic Respiratory Disease Questionnaire (CRDQ) 122 (study IV). The CRDQ is a disease-specific instrument evaluating four domains (dyspnea, fatigue, mastery and emotional function) that are considered important to individuals with chronic airflow limitation. Subjects are required to quantify events and/or experiences that have taken place over the two-week period preceding the administration of the questionnaire. Higher scores indicate less impairment. This instrument has been extensively used in patients with COPD and has well-established validity, reliability and responsiveness 122, 123. The minimal clinically important difference is 0.5 on a 7-point scale 124.

Specifically, dyspnea during activities of daily living was measured using the dyspnea domain of the CRDQ. Patients were asked to self-select five arm activities during which they experienced dyspnea and then to rate the magnitude of this sensation on a 7-point scale.

Arm function

Direct measure of arm function was assessed using the six-minute pegboard and ring test (6PBRT) 112 (study IV). Subjects were asked to move as many rings as possible in 6 minutes and the final score was the number of moved rings during a 6-minute period. Scores for dyspnea and arm fatigue (Borg 0-10) 120 were collected before and immediately after the test. The 6PBRT has been previously used to evaluate the effect of an
ATP in patients with COPD \(^89\) and has been shown to be valid and reliable \(^112\).

**Arm exercise capacity**

Unsupported arm exercise capacity was measured using an incremental unsupported upper limb exercise test (UULEX) \(^111\) (study IV). The patients held a plastic bar (0.2 kg) with both hands and were instructed to lift it at a constant metronome cadence of 30 beats per minute. Once the patient reached his or her maximum height, the bar was replaced by a heavier one (0.5 kg). Thereafter, at every minute the weight of the bar was increased by 0.5 kg to a maximum weight of 2 kg. This is a symptom-limited test and the result was expressed in seconds. Scores for dyspnea and arm fatigue (Borg 0-10) \(^120\) were collected before, every minute during the test and immediately after the test. This test is valid, reproducible and has been used previously to evaluate the effect of an ATP in patients with COPD \(^86, 111, 125\).

**Upper limb muscle force**

An isometric hand-held dynamometer (MicroFET 2; 21-4002) was used to measure peripheral muscle force (Study IV). Measurements of elbow flexion and extension, shoulder flexion and extension and abduction/adduction were performed on the dominant side. During each test, the patients were asked to generate their maximal force against the device. The average of the highest three measures within 5% of each other were used for analysis. Good reproducibility of these tests has been previously shown in patients with COPD \(^126\).

**Intervention program**

Patients in the intervention group (study IV) underwent an individual, supervised, resistance ATP three times a week for 6 weeks, for a total of 18 sessions. The following muscle groups were targeted: biceps brachii, triceps brachii, pectoralis major and minor, latissimus dorsi, deltoids and rhomboids, using free weights and a multi-station gym (Eurosport; Model # 200i). Training was started using loads equivalent to the 10-12 repetition maximum (RM) \(^114\). For the first 4 sessions, one set of 12 repetitions of each exercise was performed. Thereafter, 2 sets of 12 repetitions were undertaken for all remaining training sessions. The loads were increased when the patients could manage more than 12 repetitions for both sets on two consecutive training sessions, provided they did not report any joint pain or muscle soreness. Exercises started on the multi-gym and progressed to free weights for the last four sessions \(^127\). Patients in the control group underwent sham training that consisted
Methods

of upper limb flexibility and stretching exercises 3 times a week for 6 weeks. The duration of their training sessions was the same as the sessions in the intervention group. The outcome assessor and the patients remained unaware of the group allocation. Each patient exercised individually at different times and locations and was fully supervised. Both groups were trained by the same physiotherapist, ensuring a consistent and uniform training among all individuals.

Statistical analysis

All data were analysed using SPSS version 12.0. P-values < 0.05 were considered significant. Distribution of data was evaluated using either the Kolmogorov-Smirnov test or the Shapiro-Wilk test. An overview of the statistical methods used in each study is presented in Table 5.

In study I, when data were normally distributed, independent t-test was undertaken to compare the two groups. The non parametric Mann–Whitney U-test was used to compare differences between groups when data were not normally distributed. In study II, the limits of agreement method (LoA) was used to assess the degree of agreement between the 6MWD-C and 6MWD-T tests. LoA was also used to examine test-retest reliability between days and between test repetitions. The limit of agreement was defined as the mean difference between the distances of the two tests being compared ± 1.96 SD of the difference. Wilcoxon signed ranks tests were undertaken to compare the changes in perceived exertion and leg fatigue on the Borg scale during walking between the tests on day 1. The average of the three tests was used for this analysis. As the methodology used in the studies included in study III (review) was heterogeneous with regard to exercise type, program duration and outcome measures, a meta-analysis of their results was not possible. In study IV, between-group comparisons of baseline data were undertaken using either an independent t-test or the Mann-Whitney U test depending on the distribution and type of data. Repeated measures analysis of variance (ANOVA) was used to evaluate main effects and group vs. time interaction. Analyses were undertaken according to the intention-to-treat principle.
Table 5. Statistical methods used in studies I-IV

<table>
<thead>
<tr>
<th>Statistical Methods</th>
<th>Study I</th>
<th>Study II</th>
<th>Study III*</th>
<th>Study IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kolmogorov-Smirnov test</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shapiro-Wilk test</td>
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<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Mann-Whitney U-test</td>
<td>✓</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Wilcoxon signed ranks test</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Independent t-test</td>
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<td>✓</td>
</tr>
<tr>
<td>Limits of agreement method</td>
<td>✓</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Repeated measures analysis of variance ANOVA</td>
<td></td>
<td></td>
<td>✓</td>
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<tr>
<td>Regression analysis</td>
<td></td>
<td>✓</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Meta-analysis was not possible as the methodology used in the studies included in the review was heterogeneous.

Sample size calculations

Sample size was not determined prior to the study I; however, power was calculated when non-significant differences were found. Although sample size was not calculated prior to this study II, the confidence interval of the limits of agreement was only ±6.78 metres, which indicates good reliability of this estimate. A larger sample size would not have changed the estimate of agreement, but would only have narrowed the confidence interval around the limits of agreement. This is because sample size calculations for studies of agreement between two methods of measurement are based on the confidence interval of the limits of agreement and on the standard deviation of the differences between measurements by the two methods.\(^{128}\)

Sample size of study IV was determined using data available from West Park Healthcare Centre’s rehabilitation program and following a review of the literature. A sample size of 34 (17 per group) was determined to yield 80% power (alpha = 0.05) and detect a between-group difference of 0.5 points per item (the minimal clinically important difference)\(^{124}\) in the domain of dyspnea during activities of daily living, from the CRDQ questionnaire\(^{122}\) using a two-tailed independent t-test.
MAIN RESULTS

Lower limb muscle function

MVC in knee extension was demonstrated to be 17% lower (p=0.017) in female patients but there was no difference in male patients (p=0.56) compared with controls. MVC in flexion was 51% lower in female (p<0.001) and 40% lower in male (p<0.001) patients compared with controls. (Table 6)

Muscle endurance was demonstrated to be lower in patients with COPD. All controls performed 100 repetitions in the endurance test while only 27% of the female patients and 53% of the male patients were able to attain this number. Fatigue index ($FI$) was found to be higher in female patients with COPD (22.5%) compared to female controls (10%) (p=0.001) (Fig 1). No significant difference was found in $FI$ between male patients (15%) and male controls (10%) (p=0.103) (Fig 1).

Table 6. Maximal strength of the thigh muscles and fatigue during the 30 first contractions of the endurance test

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
<th>COPD</th>
<th>Controls</th>
<th>COPD</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximal strength in extension (Newton)</td>
<td>274±83</td>
<td>289±70</td>
<td>225±61 $^*$</td>
<td>272±77</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximal strength in flexion (Newton)</td>
<td>121±51 $^*$</td>
<td>203±46</td>
<td>87±34 $^b$</td>
<td>179±47</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intercept (Newton)</td>
<td>243 (51-349)</td>
<td>271 (177-446)</td>
<td>198 (89-337)</td>
<td>230 (96-380)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue index ($FI%$)</td>
<td>15 (-222-27)</td>
<td>10 (-90-25)</td>
<td>22.5 (-39-33) $^b$</td>
<td>10 (-54-25)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Borg ratings at 30th contraction</td>
<td>4 (2-10)</td>
<td>4 (0-9)</td>
<td>6 (2-10) $^b$</td>
<td>3 (0-10)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data are presented as mean±SD for maximal strength and as median (minimum-maximum) for intercept, $FI$ and Borg

$^a$Significantly different from female controls (p<0.05)
$^b$Significantly different from female controls (p<0.001)
$^c$Significantly different from male controls (p<0.001)
Results

Figure 1. Pattern of force loss during the endurance test for men (a) and women (b) in controls and patients with COPD. All controls performed 100 repetitions and all patients performed 30 repetitions. Some patients dropped out successively during the test. The remaining number of patients is illustrated at every 10th contraction. The dashed line shows the area for calculation of the fatigue index (FI). * Significantly higher FI for women with COPD (p=0.01).

Six-minute walk tests

The mean distance walked during the 6MWD-C and 6MWD-T tests for each test repetition and each day is presented in figure 2 .

The mean difference in distance walked between the two methods was 153.3 m. The upper and lower limits of agreement were 278.4 and 28.2 m, respectively (Fig 3).

The mean difference in distance walked between the 6MWD-C tests on days 1 and 2 was -7.2 m. The lower and upper limits were -45.4 and 30.8 m, respectively. The mean difference in distance walked between the 6MWD-T test on days 1 and 2 was -1.6 m. The lower and upper limits of agreement were -64.0 and 60.7 m, respectively (Figs 4 and 5).
The mean difference and the lower and upper limits of agreement between test repetitions of the two different methods (6MWD-C and 6MWD-T) are presented in Table 7.

The changes in perceived exertion [2.1 (6MWD-C) vs. 5.1 (6MWD-T)] and leg fatigue [0.7 (6MWD-C) vs 1.9 (6MWD-T)] on the Borg scale were greater for the 6MWD-T test compared with the 6MWD-C test.
Results

Figure 2. Distance walked during 6MWD-C and 6MWD-T for each test and day (Mean ± SD).

Figure 3. Bland-Altman plot of the difference between the methods against the mean distance walked for both tests on day 1. SD, standard deviation; CI, confidence interval.
Results

Figure 4. Bland-Altman plot of the difference in distance walked between days 1 and 2 during the 6MWD-C against the average of the two days. SD, standard deviation.

Figure 5. Bland-Altman plot of the difference in distance walked between days 1 and 2 during the 6MWD-T against the average of the two days. SD, standard deviation.
Table 7. Mean difference, lower and upper limits of agreement between test repetitions (a, b and c) of the two different methods.

<table>
<thead>
<tr>
<th></th>
<th>6MWD-C</th>
<th></th>
<th>6MWD-T</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>a and b</td>
<td>a and c</td>
<td>b and c</td>
<td>a and b</td>
</tr>
<tr>
<td>Mean difference (meters)</td>
<td>-5</td>
<td>-11.25</td>
<td>-6.25</td>
<td>-16.88</td>
</tr>
<tr>
<td>Upper limit (meters)</td>
<td>30.78</td>
<td>35.06</td>
<td>22.27</td>
<td>51.29</td>
</tr>
<tr>
<td>Lower Limit (meters)</td>
<td>-40.78</td>
<td>-57.56</td>
<td>-34.77</td>
<td>-85.05</td>
</tr>
</tbody>
</table>

Systematic review of the effects of an arm training program

Following screening of study titles and abstracts, five articles were included in the systematic review. Training protocols prescribed in the studies varied considerably. Two studies used supported (arm cycle ergometer) as well as unsupported arm exercises 84, 85 and three studies used solely unsupported exercises such as dowel lifts, hand weights 86, 87, 89. There were also variations in number of repetitions and sets for each exercise and training frequency. Training duration among the studies were similar (6-8 weeks). Training progression was based on a predetermined period e.g. each 3 sessions or on symptom limitation.

Arm exercise capacity

Unsupported arm exercise capacity was assessed in four studies 84, 86, 87, 89, using different test protocols. Two studies 84, 86 reported between group difference when training and control groups were compared. Supported arm exercise capacity was assessed in two studies 84, 85; of which one study 85 reported that this increase was greater than in the control group.

Dyspnea during ADL

Two studies assessed dyspnea during ADL that involved arms using either the Breathlessness and Fatigue Scale (BFS) 89 or the dyspnea domain of the CRDQ 86. In these studies, post training changes in dyspnea during ADL did not differ from those observed in the control subjects.

Health-related quality of life and self efficacy

Two studies assessed HRQL 86 or self efficacy 85 using the CRDQ domains of dyspnea, fatigue, emotional function and mastery and a modified scale of Bandura and Adam 129 respectively. No between group differences were found.

Symptoms during arm exercise tests

Two studies 85, 86 assessed dyspnea scores at iso-work load or iso-time using a 1-4 scale or the Borg scale. Neither study demonstrated
Results

differences in the magnitude of change between the control and intervention groups. Arm fatigue before and after an unsupported exercise test was assessed in only one study\textsuperscript{86} with no difference between the intervention and control groups.

**Effects of a resistance arm training program (RCT)**

There was no statistical difference in dyspnea during ADL between the intervention and control groups after the training period (p = 0.08) (Table 8). Compared with the changes observed in the control group, the magnitude of change in the intervention group was greater for the 6PBRT (p = 0.03), arm exercise capacity (UULEX) (p = 0.01) and elbow flexion force (p = 0.01); elbow extension force (p = 0.02), shoulder flexion force (p = 0.03) and shoulder abduction force (p = 0.01) (Table 8). There was no difference between groups in HRQL (Table 8) or symptoms (dyspnea and arm fatigue) during the 6PBRT or UULEX (Table 9).

Attendance rate for the intervention and sham training were 77.8 % and 83.3 %, respectively. No differences were observed in number of training sessions attended by the intervention (14 ± 2) and control groups (15 ± 2) (p = 0.53).
Table 8. Outcome measures for control and intervention groups

<table>
<thead>
<tr>
<th>Measure</th>
<th>Control group</th>
<th>Intervention group</th>
<th>Between-group comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-training</td>
<td>Post-training</td>
<td>% difference</td>
</tr>
<tr>
<td>Dyspnea during ADL (CRDQ)</td>
<td>3.7 ± 0.9</td>
<td>5.0 ± 0.9</td>
<td>35.10%</td>
</tr>
<tr>
<td>6PBRT (moved rings)</td>
<td>306 ± 46</td>
<td>335 ± 66</td>
<td>9.50%</td>
</tr>
<tr>
<td>UULEX (seconds)</td>
<td>522 ± 90</td>
<td>566 ± 75</td>
<td>8.50%</td>
</tr>
<tr>
<td>Elbow flexion (pounds)</td>
<td>48.2 ± 9.5</td>
<td>47.8 ± 12.0</td>
<td>-0.80%</td>
</tr>
<tr>
<td>Elbow extension (pounds)</td>
<td>36.3 ± 8.4</td>
<td>37.8 ± 8.2</td>
<td>4.10%</td>
</tr>
<tr>
<td>Shoulder flexion ** (pounds)</td>
<td>47.2 ± 11.2</td>
<td>47.1 ± 12.6</td>
<td>-0.20%</td>
</tr>
<tr>
<td>Shoulder abduction (pounds)</td>
<td>35.2 ± 10.0</td>
<td>36.2 ± 10.4</td>
<td>2.80%</td>
</tr>
<tr>
<td>HRQL (CRDQ-total)</td>
<td>4.4 ± 0.8</td>
<td>5.3 ± 0.7</td>
<td>20.40%</td>
</tr>
</tbody>
</table>

**no difference between groups in baseline data- except for shoulder flexion force p = 0.04
6PBRT: Six-minute pegboard and ring test; UULEX: Unsupported upper limb exercise test
CRDQ: Chronic Respiratory Disease Questionnaire; HRQL: Health-related quality of life
CI: Confidence Interval
Data are presented as mean ± SD.
Table 9. Symptoms during arm exercise tests for control and intervention groups.

<table>
<thead>
<tr>
<th>Test Type</th>
<th>Control group</th>
<th>Intervention group</th>
<th>Between-group comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-training</td>
<td>Post-training</td>
<td>% difference</td>
</tr>
<tr>
<td>6PBRT Dyspnea</td>
<td>1.7 ± 1.1</td>
<td>1.1 ± 0.8</td>
<td>-35.30%</td>
</tr>
<tr>
<td>6PBRT Arm fatigue</td>
<td>3.2 ± 1.4</td>
<td>1.6 ± 1.1</td>
<td>-50.00%</td>
</tr>
<tr>
<td>UULEX Dyspnea</td>
<td>2.9 ± 2.3</td>
<td>2.5 ± 1.5</td>
<td>-13.80%</td>
</tr>
<tr>
<td>UULEX Arm fatigue</td>
<td>4.9 ± 1.8</td>
<td>3.5 ± 1.5</td>
<td>-28.60%</td>
</tr>
<tr>
<td>UULEX Dyspnea (iso-work level)</td>
<td>3.2 ± 1.9</td>
<td>2.2 ± 1.9</td>
<td>-31.20%</td>
</tr>
<tr>
<td>UULEX Arm fatigue (iso-work level)</td>
<td>4.1 ± 1.5</td>
<td>3.1 ± 1.8</td>
<td>-24.40%</td>
</tr>
</tbody>
</table>

6PBRT- Six-minute pegboard and ring test; UULEX - Unsupported upper limb exercise test
The symbol Δ represents the change in symptoms from before and after each test.
CI- Confidence Interval, iso-work level = identical work level.
DISCUSSION

Lower limb muscle function

Thigh muscle strength (except for extension in male patients) and endurance were demonstrated to be impaired in patients with COPD compared to age-matched healthy controls.

The impaired muscle strength may be related to the reduced muscle cross-sectional area (muscle atrophy) previously reported in patients with COPD. Interestingly, MVC in knee extension was not statistically significant different between male patients and controls. The reason for this relatively preserved maximal strength in knee extension of male patients compared to controls is not clear. The small sample of men with COPD might have contributed to this finding as the statistical power for this variable (calculated retrospectively) was only 9%.

It was also demonstrated that FI during the first 30 contractions was higher in female patients with COPD (22.5%) compared to female controls (10%) but did not differ between male patients and controls. This finding may be explained by the difference in fiber composition of the vastus lateralis in healthy men and women. The percentage area of the fast oxidative type IIa fibers is larger for men; whereas the percentage area of the slow oxidative type I fibers is larger for women. Male subjects might preferentially use a greater proportion of type IIa fibers and may, therefore, not be affected by a reduced proportion of type I fibers present in COPD. Another reason might be that the subjects worked at different intensities of their maximal force in extension during the endurance test. Male controls started the endurance test at their maximal force in extension while male patients began the test at approximately 80% of their maximal force in extension. Although this difference was not significant (p= 0.058), it might have contributed to a greater fatigue of the control subjects during the 30 first contractions. However, despite the fact that we did not find any difference in FI between male patients and male controls, the patients did not manage to attain 100 repetitions which indicates impaired endurance of the thigh muscles.

Six- minute walk tests

There was an average discrepancy between the two methods (the mean difference in distance walked between the tests was 153.3 m, with the subjects walking a shorter distance on the non-motorized treadmill). It was also demonstrated that the performance of the subjects during the 6MWD-C and 6MWD-T tests was consistent regardless of the day and
test repetition suggesting that the 6MWD-T test is reproducible and reliable.

There are numerous reasons for the difference in distance walked between the two tests. Familiarity with the treadmill may be one factor; walking in a corridor is certainly more familiar to the patients. In addition, the treadmill may have required greater effort from the subjects to walk compared with walking in a corridor. Also, the non-motorized treadmill used in study II had a slight inclination which may have imposed extra work for the subjects. These factors may also explain the greater ratings of perceived exertion and leg fatigue during walking on the non-motorized treadmill, and the differences in variability in distance walked between the two methods.

It was demonstrated that distance walked improved, to some extent, after each test repetition in both methods. Learning effect is a well-known phenomenon in the 6MWD test \(^1\), and the present data showed that the 6MWD-T test acted similarly. As a consequence to that, similar to the 6MWD-C test, the 6MWD-T test should be performed at least twice to account for practice effects. However, the mean differences between test repetitions in the 6MWD-T test were small, suggesting good test–retest reliability (Table 7). Furthermore, the results showed that both the 6MWD-C and 6MWD-T tests are reliable with mean differences between days of -7.2 m (6MWD-C) and -1.6 m (6MWD-T) (Figs 4 and 5, respectively).

Given that the 6MWD-T and 6MWD-C tests are not interchangeable, distance walked during a 6MWD-T test should not be predicted from a 6MWD-C test or vice versa. In addition, predicted values for the 6MWD-C test cannot be used for the 6MWD-T test, and data comparisons with studies that performed the 6MWD-C test should not be undertaken.

Even though the 6MWD-C is considered the gold standard test to measure functional exercise capacity in healthy older adults and people with heart and lung disease, there is a need to search for alternative tests due to space restrictions. The results of the 6MWD-T test showed good intrasubject reliability, suggesting that this method could be an alternative option to the 6MWD-C test when a long corridor is not available. Furthermore, a non-motorized treadmill is cheaper, smaller, lighter and easier to standardize than a motorized treadmill. Evidently, other alternatives such as the step test, cycle test and shuttle walk test have been used to assess exercise capacity in healthy elderly subjects and people with chronic lung disease. However, the 6MWD test is more representative of activities of daily living, allowing the patients to walk at their own pace.
Systematic review of the effects of an ATP

The main findings of the systematic review are that, although in patients with COPD there is evidence to support an ATP increasing supported or unsupported arm exercise capacity, its effects on other outcomes such as dyspnea, arm fatigue and quality of life, were uncertain. This is mainly because of methodological issues such as small sample sizes, inadequate blinding and inconsistent training protocols.

Potential mechanisms responsible for an improvement in arm exercise capacity with ATP may include; (i) improved aerobic capacity of the arm muscles, (ii) desensitization to symptoms during arm activity, (iii) increased muscle strength of the upper limb, and (iv) improved muscular coordination. A study by Martinez and colleagues demonstrated that a 6 week ATP decreased minute ventilation in patients with COPD at a standardized level of arm exercise. This change was attributed to a decrease in respiratory rate and suggests that ATPs may increase aerobic capacity of the arm muscles despite the small muscle mass. Alternatively, the increase in arm exercise capacity might be a result from the improved upper limb efficiency and coordination from practice of the activity. Also, a single-group study observed a post-training reduction in dyspnea at isoventilation during supported arm exercise; this observation was attributed to dyspnea desensitization from repeated exercise. Moreover, as performance during incremental exercise tests may be dependent on muscle strength, any increase in force-generating capacity of the upper limb muscles may contribute to an improved exercise performance.

To date there is no guidance on which modality of upper extremity training should be recommended. The training protocols of the studies included in the review varied considerably, providing little information regarding the optimal ATP for patients with COPD. Nevertheless, a previous uncontrolled study demonstrated that unsupported arm exercise training conferred greater benefits in arm exercise capacity and metabolic load during unsupported arm activity compared with a program of supported arm exercises. Furthermore, unsupported arm exercises appear to be of great functional relevance for patients with COPD as they closely imitate many activities of daily living.

The review concluded that although the impact of an ATP on arm exercise capacity seems to be well-defined, the benefits of such intervention in improving upper limb muscle strength, symptoms and health related quality of life need to be determined.

Effects of a resistance arm training (RCT)

A resistance arm training program improved objective measures of arm function, arm exercise capacity and arm muscle strength in patients with
COPD. No improvement in dyspnea during ADL, HRQL or symptoms was demonstrated.

Previous studies have also demonstrated an improvement in arm exercise capacity following an ATP. Study IV extends these observations by addressing the methodological shortcomings such as short duration studies, inadequate blinding and absence of a sham training group.

Possible mechanisms that explain the increased arm exercise capacity following an arm training program include: improved muscular coordination, improved aerobic capacity of upper limb muscles, desensitization to symptoms during arm exercise and increased force-generating capacity of the muscles. The findings of study IV attest to at least two of these mechanisms: 1) desensitization to symptoms as the patients who participated in the arm training program were able to perform better during the 6PBRT and UULEX with no increase in their symptoms (Table 9), and 2) increased force-generating capacity of the muscles of the upper limbs which likely allowed the improved arm exercise performance.

Previous randomized controlled trials that investigated the effect of an arm training program in patients with COPD did not include specific assessment of muscle strength. Assessing arm muscle strength is essential to determine the effect of resistance training particularly as it has been shown that patients with COPD present with a reduction in muscle strength of the upper limbs. In study IV, the greater improvement in muscle strength in the trained group confirms the positive effect of the resistance training.

The magnitude of change in dyspnea during ADL on the CRDQ between the intervention and control groups was not statistically significant. However, a clinically important difference of 0.7 units in this variable was demonstrated between groups (magnitude of improvement was higher in the intervention group (60%) compared to the control group (35%) (Table 8). The CRDQ may not have been the optimal instrument to measure dyspnea during ADL that involve arms or HRQL as the questions were not specifically designed for arm function. Also, it may lack sensitivity to detect changes in dyspnea during activities that occur in hospital rather than at home. Most patients in study IV were in-patients (83%) and may not have performed activities in the same way compared to at home (reported during the pre-assessment session). It is also probable that any impact of arm training on HRQL is overshadowed by the impact of the lower limb activities such as walking and stair climbing. The length of the pulmonary program may also have played a roll as the optimal length of PR in order to obtain the best clinical gains in HRQL and symptoms related to arm activity is still unknown. Previous studies had different program durations (range 3-8 weeks); none was able to demonstrate the benefits of an ATP on HRQL or symptoms during ADL.
Methodological considerations/Limitations of the studies

Several studies have used isokinetic tests to assess isotonic strength of lower extremity muscles of COPD patients. The isokinetic dynamometers have been found to be a valid and reliable method to measure strength and endurance of the thigh muscles. In contrast to isotonic measures such as 1RM and hydraulic resistance system, the isokinetic tests permit maximal muscle contraction throughout the full range of movement and a more reliable standardization. However, isokinetic equipments are expensive which limits its use in a clinical setting.

The treadmill used in study II might not be the ideal equipment to perform the 6MWD-T as it has a pre-determined and fixed angle. This slight angle is intended to assist the individuals to pull the tread but it imposes extra work for the subjects. This may have greater consequences for patient with chronic lung disease.

The main limitation of study III is the small number of articles included. Only 5 studies met the inclusion criteria. Besides the small number of available studies that investigated the effects of an ATP, these trials presented methodological shortcomings including the inconsistent reporting of between-group comparisons, absence of procedures to ensure appropriate blinding of the subjects, therapists or assessors and concealment of the randomization sequence.

In study IV, as dyspnea during ADL was the primary outcome, the main methodological limitation of the study pertains to the use of the CRDQ to assess changes in this variable and in HRQL after the arm training program. The CRDQ may not be a responsive measure to document the impact of an ATP on HRQL or dyspnea during ADL. It would have been useful to include a specific test to assess the ability to perform activities of daily living and related symptoms; however, to date a valid and reliable test of this nature has not been developed.

A number of studies in the healthy population have previously demonstrated that resistance training is highly specific to the muscle recruitment, motor patterns and contraction type. As the exercises included in study IV were of a dynamic nature, testing muscle strength using an isometric dynamometer may have reduced the potential benefit of the training program. Nevertheless, it was demonstrated that the intervention group achieved a significantly greater improvement in muscle strength of the upper limbs compared to the control group.
External Validity

The large number of patients with COPD (men and women) included in study I and the presence of a control group make the results generalizable for patients with moderate to severe COPD. Study II was performed on healthy elderly subjects therefore the findings pertain exclusively to this population. However, in a randomized controlled trial by Wadell and colleagues 137, patients with COPD walked between 210 and 400 m during the 6MWD-T before an exercise training period. These distances are slightly lower than that demonstrated in study II in which the distances walked by healthy elderly individuals ranged between 376 and 408 m. These similar distances walked by the healthy elderly subjects in study II and patients with COPD in the study by Wadell et al.137 suggest that the 6MWD-T may be an applicable test for patients with chronic lung disease.

Despite the small number of articles included in the systematic review, the results altogether were sufficient to suggest that there is evidence to support the use of ATP to improve arm exercise capacity in patients with moderate to severe COPD. The effect of an ATP on patients with mild COPD is unknown. More trials with larger number of patients and standardized training methodology are needed to better define the effects of an ATP on different stages of COPD.

The large number of excluded patients due to musculoskeletal problems in study IV limits the external validity of the findings to the COPD population. However, the exclusion of these patients was necessary to ensure that they would be able to complete the pre-tests and training program without pain. In clinical practice, it would be worthwhile to adapt the resistance training protocol for patients with musculoskeletal conditions. Study IV is a short term study; therefore, any conclusion pertaining to the longevity of the training benefits can not be drawn.

Clinical Implications

To date PR programs for patients with COPD are mainly focused on endurance based training such as walking and cycling with the aim at improving the cardiovascular system. Nevertheless, the findings of this thesis and previous studies 9, 36, 43-45, 138 demonstrated that patients with COPD present muscle impairment. Since muscle weakness has been shown to be associated with exercise intolerance, poor quality of life and an increased need for medical assistance 29-31, it is crucial to include assessment of muscle function and resistance based training in the PR programs. Specifically, both muscle strength and muscle endurance training should be included in the exercise training programs. Moreover, since it was demonstrated that there are gender-related differences in muscle performance in patients with COPD, this finding should also be considered when designing rehabilitation programs for these patients.
The findings of study II enable healthcare professionals and researchers to use the 6MWD-T test as an alternative to the 6MWD-C test when a 30-m corridor is not available. Although study II was performed on healthy elderly individuals, these findings may have implications for execution of the 6MWD-T test within cardiac and pulmonary rehabilitation.

The results of study IV highlight the benefits of arm exercise training as part of COPD rehabilitation, as it is effective, feasible and improves arm function without an increase in symptoms. Neither adverse effects nor issues with adherence to the ATP were reported in any of the studies reviewed in study III or during study IV suggesting that arm training is safe and well-tolerated by patients with COPD. The findings of study IV should guide clinical practice concerning to upper extremity training in individuals with COPD.

**Implications for future research**

Resistance training in patients with COPD is based largely on available evidence for older adults. However, people with COPD have lower exercise tolerance and impaired muscle function compared to age-matched healthy controls and are often limited by dyspnea during activities of daily living. For those reasons, the optimal resistance exercises for people with COPD may differ from those being used in healthy. Also, this thesis demonstrated that there is gender-related difference in muscle function in patients with COPD suggesting that specific training should be designed for men and women. Further research is required to better define the most appropriate training protocol for individuals with COPD.

The findings of study III and IV imply that there is evidence that an ATP increases arm exercise capacity, arm function and muscle strength in patients with COPD following a training period. However, long-term studies are needed to evaluate the longevity of these training benefits.
GENERAL CONCLUSIONS

This thesis generated new knowledge and strategies for exercise assessment and training in patients with COPD. The findings of this thesis are based on data from patients with moderate to severe COPD and healthy subjects and can be summarized as follows:

- Thigh muscle strength and endurance are impaired in patients with COPD.
- Female patients with COPD present higher index of fatigue in the thigh muscles compared with female controls.
- Female patients with COPD seem to be more prone to deteriorate in thigh muscle function compared to male patients.
- There is a divergence between the 6MWD performed in a corridor with the 6MWD performed on a non-motorized treadmill in terms of distance walked. Subjects walk farther in the corridor.
- The 6MWD performed in a corridor and on a non-motorized treadmill are reproducible and reliable between test repetitions and days.
- An arm training program consisted of resistance exercises improves arm function, arm exercise capacity and muscle strength of the upper limbs in patients with COPD.
- It appears that resistance arm training has no effect on health-related quality of life or dyspnea during activities of daily living in patients with COPD.
- Resistance arm training is feasible, safe and well-tolerated by patients with COPD.
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