

# Single limb exercises in patients with chronic obstructive pulmonary disease

Feasibility, methodology, effects and evidence

Andre Nyberg



**Department of Community Medicine and Rehabilitation,  
Physiotherapy**

Umeå University, Sweden  
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To my family

Emilia, Edvin, Katrin

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## **Abstract**

Chronic obstructive pulmonary disease (COPD) is a major cause of morbidity and mortality worldwide. COPD is a slowly progressive, inflammatory disease in the airways and lungs, caused mainly by smoking. The inflammation leads to a narrowing of the small airways (airway obstruction) and a destruction of tissue in the lungs. This gives a decreased expiratory airflow which leads to dyspnea, the primary symptom of the disease. The chronic airflow limitation also is associated with the development of limb muscle dysfunction. Decreases in both limb muscle strength and endurance have been shown which, in turn, is associated with exercise intolerance, one of the key disabling factors of the disease. Pulmonary rehabilitation including exercise training is the cornerstone of treatment and is strongly recommended. However, it is still unclear how to optimize exercise training for this group of patients. Also how to address the increase in dyspnea which limits the exercise stimulus, and how to assess muscular strength, need further study. Partitioning the exercising muscle mass, known as single limb exercises, is a novel exercise strategy aimed at reducing the negative consequences of chronic airflow limitation in patients with COPD.

The aim of this thesis was to study the current evidence of single limb approaches in patients with COPD, to examine the feasibility and effects of a high-repetitive single limb exercise (HRSLE) regimen in patients with COPD and to examine whether elastic resistance could be used to evaluate muscular strength.

This thesis is based on five papers. In order to study the evidence on single limb exercises, a systematic review of randomized controlled trials was performed. The review showed that single limb exercises, performed as one-legged cycling appeared to be more effective than two-legged cycling with regard to exercise capacity but not dyspnea, and might be included in exercise programs for patients with COPD (Paper I). Thirty healthy older women and men participated in a validation study comparing elastic resistance maximal strength with isokinetic dynamometry measurements. Excellent levels of agreement and no differences between the two pieces of equipment were found which indicates that elastic resistance could be used to evaluate muscular strength (Paper II). A study protocol was created for a randomized controlled trial designed to identify the effects of HRSLE in combination with COPD-specific patient training (experimental group) in comparison to patient information alone (control group) (Paper III). HRSLE was performed as resistance training, using a single limb at a time, elastic bands as resistance and a high number of repetitions (25 repetitions in 2 sets) with the aim of increasing limb muscle endurance. After eight weeks of exercise, the differences between the groups were in favor of the experimental group on lower- and upper-extremity functional capacity, upper-extremity endurance capacity and muscular function. No differences were seen between the groups on endurance-cycle capacity or

health-related quality of life (Paper IV). In patients with COPD, the HRSLE regimen was considered feasible with a high attendance rate, excellent compliance and high relative exercise intensity. No severe adverse events occurred. The physiotherapists conducting the HRSLE in the clinical setting also found it to be feasible (Paper V).

This thesis shows that single limb exercises performed as one-legged cycling may be useful and effective for patients with COPD. Eight weeks of HRSLE was feasible and effective with regard to exercise capacity but without effect with regard to health-related quality of life. Elastic resistance could be used as exercise equipment to improve limb muscle function in patients with COPD and to evaluate muscular strength in healthy older adults.

## Svensk sammanfattning

Kroniskt obstruktiv lungsjukdom (KOL) är idag ett stort globalt problem. KOL är en långsamt fortskridande inflammatorisk sjukdom i luftvägar och lungor, i huvudsak orsakad av cigarrettrökning. Inflammationen leder till en förträngning i de små luftvägarna och förstör vävnaden i lungorna. Detta medför en luftvägsobstruktion där flödet av luft vid utandning är minskat, vilket bidrar till varierande grad av andnöd hos patienten. Luftvägsobstruktionen är relaterad till försämrad muskelfunktion hos patientgruppen. Både nedsatt muskulär styrka och uthållighet har påvisats vilket är relaterat till ett av huvudproblemen vid KOL; nedsatt förmåga till fysisk aktivitet och träning. Lungrehabilitering inklusive fysisk träning är centralt i behandlingen och starkt rekommenderat. Det är dock inte fastställt hur patientgruppen skall träna för att optimera effekterna av träningen eller hur träningen bäst kan utvärderas. Det är också oklart hur man skall hantera den successivt ökande andfåddheten vid träning. Träning med en arm eller ett ben i taget, så kallad lokal muskelträning är en strategi som syftar till att minska andnöd under träning hos patienter med KOL.

Syftet med denna avhandling var att undersöka vilken evidens det finns för lokal muskelträning hos patienter med KOL, utvärdera genomförbarhet och effekter av lokal högrepitiv muskelträning utförd med elastiska träningsband hos patienter med KOL samt att undersöka ifall elastiska träningsband kan användas för att utvärdera muskelstyrka.

Avhandlingen består av fem delstudier. För att undersöka evidens för lokal muskelträning genomfördes en systematisk litteraturgranskning av randomiserade kontrollerade studier. Granskningen visade att lokal muskelträning, i form av cykling med ett ben i taget kan vara effektivt, avseende fysisk förmåga, men utan effekt avseende andfåddhet för patienter med KOL (delstudie 1). Trettio friska kvinnor och män, deltog i en valideringsstudie där jämförelser gjordes mellan maximal kraftutveckling utförd med elastiska träningsband och en isokinetisk dynamometer. Ett högt samband mellan de två metoderna och ingen skillnad i maximal kraft, indikerade att elastiska band kan användas för att utvärdera muskelstyrka (delstudie 2). Ett studieprotokoll skapades för en randomiserad kontrollerad studie, som syftade till att undersöka effekterna av lokal högrepitiv muskelträning i kombination med KOL-specifik patientutbildning (interventionsgrupp) jämfört med enbart KOL-specifik patientutbildning (kontrollgrupp) (delstudie 3). Lokal högrepitiv muskelträning utfördes i grupp med elastiska träningsband som redskap. Övningarna genomfördes med en arm eller ett ben i taget med 25 repetitioner i 2 set med syfte att påverka muskulaturens uthållighet. Efter åtta veckors träning hade interventionsgruppen bättre muskelfunktion i både övre och nedre extremitet samt en bättre funktionell förmåga jämfört med kontrollgruppen. Inga skillnader i effekt sågs mellan grupperna avseende uthållighet vid test på ergometercykel eller avseende

hälsorelaterade utfallsmått, såsom livskvalitet och tilltro till sin egen förmåga (delstudie 4). För patienter med KOL, visade sig lokal högrepetitiv muskelträning vara en genomförbar metod avseende följsamhet och närvaro i träningen. De fysioterapeuter som ledde träningen i klinisk verksamhet ansåg att den var möjlig att genomföra med hög relativ intensitet och utan allvarliga biverkningar (delstudie 5).

Sammanfattningsvis visar denna avhandling att lokal muskelträning kan vara en användbar och effektiv metod för patienter med KOL. Åtta veckor med lokal högrepetitiv muskelträning är genomförbart och effektivt avseende fysisk förmåga hos dessa patienter. Elastiska träningsband kan användas som träningsredskap för att förbättra muskelfunktion hos patienter med KOL samt för att utvärdera muskelstyrka hos friska vuxna.

## Abbreviations

6MWT	6 Minute Walk Test
6PBRT	6 Minute Pegboard and Ring Test
ACSM	American College of Sport Medicine
CHF	Chronic Heart Failure
CI	Confidence Interval
CONSORT	Consolidate Standards Of Reporting Trials
COPD	Chronic Obstructive Pulmonary Disease
CR <sub>10</sub>	Category Ratio scale (Borg)
CRQ	The Chronic Respiratory Disease Questionnaire
FEV <sub>1</sub>	Forced Expiratory Volume during one second
FVC	Forced Vital Capacity
GOLD	The Global Initiative for Chronic Obstructive Lung Disease
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HADs	Hospital Anxiety and Depression scale
HRSLE	High Repetitive Single Limb Elastic Band Resistance Training
mMRC	modified Medical Research Council scale
MPF	Maximum Peak Force
PE	COPD-specific Patient Education
PEDro	Physiotherapy Evidence Database
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analyses
QoL	Quality of Life
RCT	Randomized Controlled Trial
RM	Repetition Maximum
SD	Standard Deviation
STROBE	Strengthening The Reporting of Observational studies in Epidemiology
UULEX	Unsupported Upper Limb Exercise Test

Abbreviations that are only included in tables/figures are explained in the description of that table/figure.

## Original papers

This thesis is based on the following papers, referred to in the text by their Roman numerals I – V.

- I. **Nyberg A**, Lindström B, Wadell K. Evidence for single limb exercises on exercise capacity, quality of life and dyspnea in patients with chronic obstructive pulmonary disease or chronic heart failure. *Physical Therapy Reviews*. 2013;18(3);157-172
- II. **Nyberg A**, Hedlund M, Kolberg A, Alm L, Lindström B, Wadell K. The accuracy of using elastic resistance bands to evaluate muscular strength. *European Journal of Physiotherapy*. 2014; Early online: 1-9, doi: 10.3109/21679169.2014.889746
- III. **Nyberg A**, Lindstrom B, Wadell K. Assessing the effect of high-repetitive single limb exercises (HRSLE) on exercise capacity and quality of life in patients with chronic obstructive pulmonary disease (COPD): study protocol for randomized controlled trial. *Trials*. 2012;13:114
- IV. **Nyberg A**, Rickenlund A, Lindström B, Wadell K. Low Load / High Repetition Elastic Band Resistance Training in patients with COPD – a Randomized Controlled Multicenter Trial. *Clinical Respiratory Journal*. (In press)
- V. **Nyberg A**, Lindström B, Wadell K. A cohort study to evaluate the feasibility of a high-repetitive single limb exercise regimen for patients with chronic obstructive pulmonary disease. *J Nov Physiother* 4:1. doi: 10.4172/2165-7025.1000190

Figures/tables/boxes in the papers will in the thesis be referred to with the number of the figure/table/box followed by the Roman numeral of the paper (e.g., Figure 2:II = Figure 2 in Paper II).

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# 1. Introduction

Chronic obstructive pulmonary disease (COPD) is a major cause of morbidity and mortality worldwide (1). It is one of our most common chronic diseases, and as many as 700,000 people are estimated to suffer from COPD in Sweden (2). The number of patients is steadily increasing and COPD is projected to become the third leading cause of death worldwide in 2030 (3). The increasing prevalence of COPD can be explained to some extent by continued exposure to COPD risk factors in combination with the aging of the world's population (4). COPD was once a disease more commonly seen in men, but now it affects men and women almost equally (3, 5, 6).

## 1.1 Definition of COPD

COPD is today considered as a systemic and multicomponent disease with cough, sputum production and chronic, progressive dyspnea as typical symptoms (4). COPD is characterized by a progressive chronic airflow limitation associated with the development of respiratory and peripheral muscle dysfunctions (7). The Global Initiative for Chronic Obstructive Lung Disease (GOLD) defines COPD as:

“COPD, a common preventable and treatable disease, is characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases. Exacerbations and comorbidities contribute to the overall severity in individual patients” (4).

## 1.2 Pathology, pathogenesis, and pathophysiology

COPD is characterized by chronic inflammation that appears to be the amplification of normal inflammatory response to chronic irritants in the respiratory tract. Chronic airflow limitation is caused by a combination of chronic bronchitis (central airways), chronic bronchiolitis (small airways disease) and emphysema (parenchymal destruction). Nowadays, the main focus is on the small airways rather the central airways. Chronic inflammation is caused by inhaled noxious particles and gases such as cigarette smoke. This inflammation causes structural changes and the narrowing of the walls within the peripheral airways. Emphysema results in a loss of alveolar attachments to the peripheral airways and decreases the elastic recoil of the lungs. This results in the reduced ability of the airways to remain open during expiration (4). More specifically, the inflammation in COPD results in an increased number of inflammatory cell types such as neutrophils, macrophages and T lymphocytes (predominantly CD8+) and structural changes in the lungs. The inflammation may also induce lung tissue destruction (emphysema) and disrupt normal repair and defense mechanisms (small airway fibrosis) and

is further increased by oxidative stress and an excess of enzymes (proteinases) in the lung which are present particularly during exacerbations (1, 4, 8, 9).

Chronic inflammation in combination with the narrowing of the peripheral airways and a dynamic airway collapse (in more severe emphysema) are the primary reasons for the decreased forced expiratory volume during one second (FEV<sub>1</sub>) in COPD. In other words the decreased elastic recoil of the lungs reduces the force that drives air out of the lungs, as a consequence patients with emphysema have a high lung compliance with no problem in inflating the lungs but severe difficulties exhaling. The destruction of parenchymal is the main reason for decreased gas exchange which results in both hypoxemia and hypercapnia (1, 8).

The pathological changes caused by COPD include enlarged mucus-secreting glands and an increase in the number of goblet cells in the central airways, structural remodeling of the peripheral airways and the destruction of the lung parenchyma (8, 10). In addition to changes in central and peripheral airways and in the lung parenchyma, pulmonary vascular changes occur as a consequence of COPD which involves thickening of vessel walls, increase in smooth muscle cells and inflammatory cell infiltration in the vessel walls (8, 11). In the late course of COPD, pulmonary hypertension (increase of blood pressure in the pulmonary artery, pulmonary vein or pulmonary capillaries) develops which is considered the major cardiovascular complication of COPD and is associated with both cor pulmonale (pulmonary heart disease) and a poor prognosis for the patient (8, 12). In summary, these pathological changes in COPD lead to, but are not limited to, mucus hypersecretion, ciliary dysfunction, airflow limitation, pulmonary hyperinflation, gas exchange abnormalities and pulmonary hypertension (4, 8). Structural changes in the airways are in general increased with disease severity (1).

### 1.3 Diagnostic and disease severity

The persistent airflow limitation seen in patients with COPD is best measured by spirometry. Spirometric classification is essential for diagnosis and provides a description of the severity of the pathological changes in COPD (1, 4, 8, 13-15).

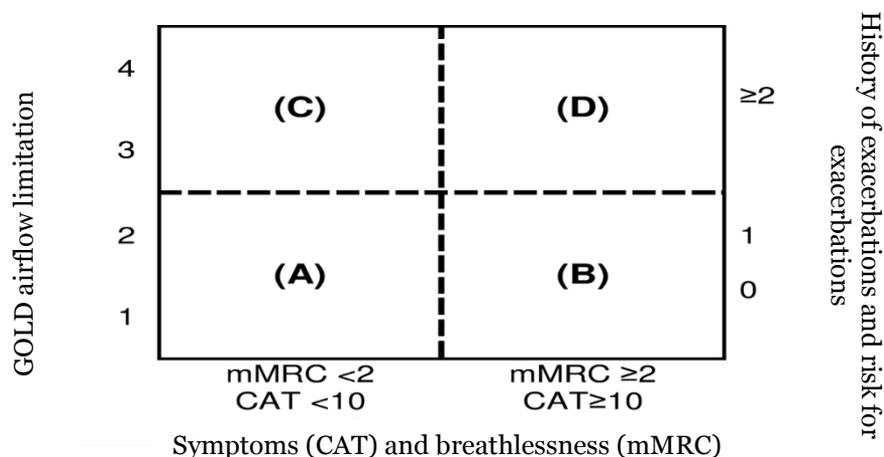
The diagnosis of COPD and the criteria used to classify the stages of COPD have been changed over time. In 1995 people were classified with the diagnosis of COPD if the FEV<sub>1</sub>/FVC (forced vital capacity) ratio was below 88% of the predicted value in men and below 89% of the predicted value in women (15). Since 1997, when the British Thoracic Society published their guidelines, people have been classified with COPD if the airway obstruction results in a FEV<sub>1</sub>/FVC ratio below 0.70 for both men and women and since 2004 the cut-off points for airflow obstruction (e.g. FEV<sub>1</sub> % of predicted) have been the same for the different stages of the disease (1, 4, 8, 13, 14) (**Table 1**).

**Table 1.** Grading of severity of airflow limitation in patients with COPD

<b>Diagnosis of COPD</b> $FEV_1/FVC < 0.70$ and $FEV_1 \leq 80\%$ predicted					
	BTS 1997(14)	GOLD 2001(8)	ATS/ERS 2004(13)	GOLD 2006 (1)	GOLD 2011 (4)
<b>Disease severity</b> $FEV_1$ % of predicted					
GOLD 1: Mild	60 - 80	$\geq 80$	$\geq 80$	$\geq 80$	$\geq 80$
GOLD 2: Moderate	40 - 59	30 - 80	50 - 80	50 - 80	50 - 80
GOLD 3: Severe	< 40	< 30	30 - 50	30 - 50	30 - 50
GOLD 4: Very severe			< 30	< 30	< 30

ATS = American Thoracic Society, BTS = British Thoracic Society, ERS = European Respiratory Society, GOLD = The Global Initiative for Chronic Obstructive Lung Disease,  $FEV_1$  = Forced Expiratory Volume during one second, FVC = Forced Vital Capacity.   = criteria used in **Paper IV** and **Paper V**.

A clinical diagnosis and assessment of COPD severity includes, or at least should include, an assessment of the patient's symptoms, medical history and exacerbation history/risk. Patients with COPD are now classified in a combined assessment into category A, B, C, or D depending on the severity of the airflow obstruction in combination with assessment of symptoms and history of exacerbations (4). In brief, in the classification (**Figure 1**) the traditional assessment of airflow limitation is illustrated on the left side on the y-axis and is one part of the classification. It is combined either with history of exacerbations (y-axis on the right) or presence of symptoms on the x-axis. For example, a patient with an  $FEV_1$  of 40% (GOLD 3) who on level ground walks more slowly than a person of the same age because of breathlessness or has to stop for breath when walking at his or her own pace (modified Medical Research Council Scale [mMRC] score of 2) or has a score on the COPD assessment test of 10 or higher would be categorized in group D which means a high risk of exacerbations and more severe symptoms. The mMRC is a scale measuring the experience of breathlessness in daily life activities (16, 17) and the COPD assessment test is a test measuring the effect of COPD on the individual patient's daily life and how it changes over time (18). Vestbo and colleagues (4) explain that the cut-off points (mMRC and COPD assessment test) used should be considered as indicators and the primary aim is to separate patients with severe symptomatic burden from those with a lesser number symptoms. In other words a patients in group D has a higher risk, and a greater history, of exacerbations and more severe airflow obstruction in comparison to a patient in group C, who has fewer symptoms and less breathlessness, even with the same airway obstruction and/or history of exacerbations.



**Figure 1.** COPD severity according to new GOLD guidelines. Modified from (4)

CAT = COPD Assessment Test; GOLD = Global Initiative for Chronic Obstructive Lung Disease; mMRC = modified Medical Research Council.

### 1.3.1 Comorbidities

The fact that many patients with COPD also suffer from comorbidities is increasingly recognized. Comorbidities include, but are not limited to, cardiovascular disease (ischemic heart disease, cardiovascular disease, heart failure, pulmonary hypertension etc.), osteoporosis, lung cancer, metabolic syndrome, type II diabetes mellitus, obstructive sleep apnea, lung fibrosis, depression and skeletal muscle dysfunctions. (4, 19). More specifically, coexisting COPD and chronic heart failure (CHF) are common and approximately 20-30% of patients with COPD also have CHF (20). This can be explained somewhat by both diseases sharing risk factors such as smoking and physical inactivity (21). Patients with CHF is a group of patients with many similarities to patients with COPD such as reduced exercise capacity and exertional dyspnea. Reduced exercise capacity can, to some extent, be explained by muscle wasting and weakness, determinants seen in both disorders (22, 23). Both diseases are characterized by a central limitation, ventilatory in COPD and circulatory in CHF (1, 24, 25) reducing the amount of oxygen to working muscles during exercise and physical activity. A recent systematic review also has demonstrated similar skeletal muscle alterations in patients with COPD and CHF including loss of muscle mass, decrease in cross-sectional area, reduced capillary-fiber ratio, impaired energy metabolism etc. (23). The loss of skeletal muscle mass and the resulting muscle atrophy have major clinical and therapeutic implications in patients with both CHF and COPD (26) and the skeletal muscle atrophy has been shown to contribute to muscle fatigue during exercise for both groups of patients (27, 28).

## 1.4 Burden of COPD

### 1.4.1 Prevalence

The international prevalence of stage II and higher COPD has been reported as 10.1%. However variation is large and an accurate estimate of the prevalence and incidence of COPD may be difficult to make due to differences in diagnostic criteria used, for example, different survey methods, diagnostic criteria and analytic approaches (29, 30). For example, in the northernmost province of Sweden, the region of Norrbotten, the prevalence of COPD in people older than 45 is estimated at 17% (31) in accordance with the GOLD criteria (8), 9.7% according to the British Thoracic Society criteria (32), and 15.4% according to the European Respiratory Society criteria (15). In east middle Sweden, in Stockholm, the total prevalence of diagnosed COPD was 1.8%, however as in northern Sweden, it is more prevalent among people aged 45 and older with the highest prevalence (10.1%) reported among older adults aged 75-84 years (6) (criteria used not specified).

### 1.4.2 Morbidity and mortality

Morbidity due to COPD increases with age and may be affected by other chronic comorbidities (4, 33). The mortality rate associated with COPD is affected by the underestimation and underdiagnosis of COPD which is associated with disease severity (34, 35). Nevertheless, COPD is projected to become the third leading cause of death by 2030 (3).

### 1.4.3 Risk factors

The most important single-cause risk factor for COPD is cigarette smoking; thus, cigarette smoking cessation programs are a key element in COPD prevention and treatment (1). However, among younger people, women and residents of developing countries a substantial burden of disease occurs not related to smoking. A population-attributable fraction for smoking as the cause of COPD is less than 80% and has ranged from approximately 9% to 98% (33). Non-smoking risk factors for COPD include specific genetic syndromes and occupational exposures. In addition, passive exposure to noxious particles such as traffic and other outdoor pollution, secondhand smoke and biomass smoke are also associated, together with dietary factors, with COPD (1, 33).

### 1.4.4 Exercise intolerance, dyspnea and quality of life

Exercise intolerance is the key disabling factor in COPD; decreased exercise capacity, dyspnea and leg fatigue are among the most frequently-reported symptoms (7, 36, 37). Increased dyspnea during physical activity is also the major reason for patients seeking medical care and is associated with a definitely lower quality of life (QoL) (1). The ventilatory limitation,

gas exchange abnormalities, cardiac dysfunctions and limb muscle dysfunctions, either alone or in combination, have been considered as explanations for exercise limitation in COPD (38). The presence of an impaired skeletal muscle function and its association to exercise intolerance in patients with COPD is well known. Both a decrease in peripheral muscle strength and limb muscle endurance have been demonstrated as contributing to muscle dysfunction seen in this group of patients (39, 40). However, the reduction in limb muscle endurance has been shown to be greater than the reduction in muscular strength (41). In addition, Serres and colleagues, (39) argued that decreased peripheral muscle endurance in patients with COPD should also be considered, as well as decreased muscle weakness, to explain the decreased peripheral muscle performance seen in patients with COPD. In comparison to healthy individuals, impaired limb muscle endurance has been found in both upper- and lower-limbs (42), with a higher fatigability for upper-extremity muscles (43). The prevention of muscle dysfunction in patients with COPD is considered of utmost importance (7).

A progressive increase in dyspnea during exercise training and physical activities is common in COPD (38). The origin of exertional dyspnea has been considered multifactorial (38), a consequence of the limb muscle dysfunction, hyperinflation and inadequate energy supply to respiratory and peripheral muscles (44-46).

### 1.4.5 Gender-related differences

Dyspnea is common in both male and female patients with COPD but some studies demonstrate even more severe dyspnea and more sensitive airways for women than men with the same degree of airway obstruction (47). Also health-related QoL has been shown to be decreased in patients with COPD in comparison to healthy control groups, with a more prominent decrease in women (47, 48). QoL also deteriorates with increased disease severity (49). In patients with COPD, the prevalence and mortality of the disease during the two last decades have increased more rapidly among women than men which could be attributed, in large part, to changes in smoking trends (50). COPD is now a disease that affects men and women almost equally both internationally as well as in Sweden (3, 5, 6). Aryal and colleagues (50) reported in a review of gender-related differences published in 2013 that the disparity observed between men and women could be explained by both behavioral and environmental factors, as well as biological factors. Some evidence indicates gender-related differences in susceptibility to the effects on the lungs, and that women develop more severe COPD at younger ages with lower smoking exposure than men (51, 52). However, the results in general seems to be mixed (50). Also gender-related differences in biomarkers have been demonstrated (53), which may be important because it could help us understand some of the different aspects of the clinical presentation of the disease. For example, women have reported higher degrees of dyspnea, poorer functional and

psychological status, lower QoL and poorer exercise performance for the same degree of airflow obstruction (54-57). In addition to clinical presentation, there also appears to be gender-related differences in comorbidities, including higher degrees of anxiety and depression, more frequent CHF, osteoporosis and diabetes mellitus, but lower prevalence of ischemic heart disease and alcoholism among women with the disease (58). With regard to physical capacity, the results of a study by our research group (59) indicate that female patients with COPD seems to be more prone to decrease in muscle function. It was stated that more focus should be placed on improving muscle strength and endurance in patients with COPD, and that these gender-related differences should be taken in account. It is therefore important to determine whether the treatment effects differ between men and women in order so that we are able to optimize treatment for all patients suffering from this troublesome disease. Thus, in a recent review studying the evidence for gender-related differences after pulmonary rehabilitation with regard to dyspnea, health-related quality of life, physical capacity, physiological and functional status and coping strategies, the authors concluded that there was insufficient evidence to support or refute gender-related differences in pulmonary rehabilitation outcomes (54). More research is necessary to study potential gender-related differences.

## 1.5 Management of COPD – Smoking cessation and pharmacological treatment

The primary aim in the management of COPD is to relieve symptoms, to improve exercise tolerance and health status, to prevent disease progression and exacerbations and to reduce mortality (4).

### 1.5.1 Smoking cessation

Because the reduction of exposure to chronic irritants such as tobacco smoke, occupational exposures, and indoor and outdoor air pollution are of utmost importance in preventing progression and disease onset, smoking cessation is the first priority in the management of COPD. All patients should be encouraged to quit smoking (1, 4).

### 1.5.2 Pharmacological treatment

Patient-specific pharmacological treatment is often the next step in the symptomatic management of COPD. Pharmacological treatment includes, but is not limited to, bronchodilators ( $\beta_2$ -agonists and anticholinergics) and corticosteroids which have been shown to reduce symptoms, frequency and severity of exacerbations, improve health status and improve exercise tolerance (1, 4). With regard to bronchodilators, long-acting bronchodilators are preferred over short-acting; a combination of long- and short-acting may be considered if symptoms are not improved by single agents; inhaled bronchodilators are recommended over oral.

However, the effect of modern bronchodilator medications on dyspnea is relatively small, and no existing medication for COPD has been shown to affect the long-term decline in lung function (4, 60). With regard to corticosteroids inhalation is recommended for patients with frequent exacerbations and/or an FEV<sub>1</sub> less than 50% of predicted, long-term monotherapy with oral corticosteroids is not recommended and short-term use of oral corticosteroids cannot be used to determine who will respond to long-term use. Vaccination should be offered to every patient with COPD. Other treatment options include long-term oxygen therapy, ventilatory support, and surgical treatments such as lung volume reduction surgery or lung transplantation (1, 4).

### 1.6 Management of COPD - Pulmonary rehabilitation

“a comprehensive intervention based on a thorough patient assessment followed by patient-tailored therapies, which include, but are not limited to, exercise training, education, and behavior change, designed to improve the physical and psychological condition of people with chronic respiratory disease and to promote the long-term adherence of health enhancing behaviors” (38).

In addition to pulmonary rehabilitation, physical activity is recommended to all patients with COPD (4). The goals of pulmonary rehabilitation include diminishing symptoms, increasing exercise performance, enhancing QoL, promoting independence and increasing participation in the activities of daily living (38).

Exercise training is a cornerstone of pulmonary rehabilitation. Numerous randomized controlled studies (RCTs) examining the effects of exercise training on patients with COPD have shown considerable improvements on dyspnea (61), exercise capacity (62), and QoL (63). Furthermore, it has been established that pulmonary rehabilitation, including exercise training, leads to greater improvements in QoL compared to pharmacological treatment (64) and has shown to be cost-effective in reducing the number of hospital admissions and days in hospital (65, 66).

The purpose of exercise training is to improve cardio respiratory endurance, strength and/or flexibility, and a large number of exercise modalities have been studied in order to optimize the effects of exercise training in patients with COPD. These include endurance (continuous and interval), resistance training, neuromuscular stimulation, and inspiratory muscle training (38).

#### 1.6.1 Endurance training

Cycling (stationary cycle ergometer) and walking (ground-based or treadmill) are the most commonly-applied modalities in pulmonary rehabilitation (38, 61, 67). Walking is given the advantage of being a

functional exercise and is, in line with the principle of specificity, the choice of exercise if walking endurance is the primary goal of treatment (38). The efficacy of leisure walking has been paid increased attention and Nordic walking has been considered as an effective alternative (68). As concerns continuous endurance training for patients with COPD, it is recommended to follow the American College of Sport Medicine (ACSM) recommendations, that is, > 60% of maximal work rate for 20 to 60 minutes per session (69). Higher-intensity continuous endurance training is recommended, however these high intensities may be difficult to achieve for many patients with COPD (67). For those having difficulties reaching targeted intensities and durations, interval training is considered an effective alternative (67). No important differences in effect have been shown between interval and continuous endurance training which could be explained by matched workloads in research studies on the topic (38, 70). In theory, higher workloads could be achieved with interval training giving greater effects, however at this moment this has not been studied (38).

### 1.6.2 Resistance training

Resistance training is considered an effective and feasible intervention for patients with COPD, especially with regard to increasing muscular strength (37, 71). Positive effects on cycle endurance capacity and upper-extremity functional capacity have also been demonstrated (40, 71, 72). In accordance with the latest guidelines in pulmonary rehabilitation (38), resistance training studies are encouraged to follow ACSM recommendations (73), that is, exercising on initial loads equal to 60-70% of 1 repetition maximum (RM), in 1 to 3 sets of 8 to 12 repetitions in 2 to 3 days, every week. The increase in muscle force is the most evident effect of resistance training. It seems that translation of a muscle force increase into maximal or submaximal exercise capacity is dependent, to some extent, on the magnitude of the exercise load, recommending exercises loads > 80% of 1 RM (38). Lower loads are considered ineffective (38, 74). Resistance training is recommended to include both lower- and upper-extremity exercises, focusing on the upper-extremities on both endurance and arm strength training (75). The effects of resistance training on other outcomes, such as QoL, dyspnea and functional lower-extremity capacity, are limited (37, 71, 76).

#### 1.6.2.1 Elastic resistance

The vast majority of resistance training studies have used weight machines as primary resistance. The need to examine the effects and safety of alternate exercise equipment has been highlighted as patients with COPD have limited access to weight machines after they complete a pulmonary rehabilitation program (71). Elastic equipment such as elastic bands and tubing could be an exercise alternative. Elastic bands has been found effective in increasing muscle strength in older adults (77-79) and has also been used with beneficial results in home exercise programs (80). Training

with dumbbells/weight machines and training with elastic resistance has been shown to produce comparable results in both lower- and upper-extremity muscles (81, 82). Elastic resistance equipment is proposed as an inexpensive alternative that is easy to use and more accessible than free weights or weight-machines (78, 83). The use of elastic bands as resistance in resistance training studies about people with COPD has been limited. Elastic bands as resistance have been used as an exercise alternative in a few studies (74, 83-86). The study by O'Shea and colleagues (74) is, to our knowledge, the only study that has used elastic bands as primary resistance.

### 1.6.3 Flexibility training, transitional neuromuscular electric stimulation and inspiratory muscle training

Flexibility training is incorporated into many exercise regimens involving patients with COPD. Nevertheless, there are no clinical trials that have proven its effectiveness (38). Transitional neuromuscular electric stimulation seems to be effective and a promising training modality for patients with more severe limitations, improving limb muscle strength and exercise capacity and reducing dyspnea in patient with severe COPD and poor exercise tolerance (38, 87, 88). In a study published in 2014, Sillen and colleagues demonstrated that high-frequency transitional neuromuscular electric stimulation is more effective than low-frequency transitional neuromuscular electric stimulation and as effective as strength training in severely dyspnoeic patients with COPD (89). However the effects on patients with a higher baseline exercise tolerance and less severe COPD remains unclear (38). Inspiratory muscle training seems to be beneficial for patients with COPD, showing increased inspiratory muscle strength and endurance, increased exercise capacity, decreased dyspnea and improved QoL (90).

### 1.6.4 Optimizing exercise training

In order to optimize the effects of exercise training, several strategies could be used, including the addition of pharmacotherapy such as bronchodilators and anabolic hormonal supplementation, training with supplemental oxygen and helium-hyperoxic gas mixtures, breathing strategies, walking aids, and the like (38, 91). In addition, single limb exercises have received increased attention as an opportunity to maximize the effects of exercise training (91).

#### 1.6.4.1 Single limb exercises and limb muscle endurance

As previously mentioned, the primary methods of exercise training within pulmonary rehabilitation traditionally have been different types of exercises incorporating a large amount of muscle mass, that is, cycling or walking (38). However, a progressive increase in dyspnea, a result of the ventilatory limitation characterizing the disease, during activities such as walking and cycling is common for the majority of patients with COPD. A

consequence of this progressive increase in exertional dyspnea is that it limits patients' ability to achieve optimal exercise stimulus because it causes them to stop exercise before their skeletal muscles are maximally stressed (91, 92). Furthermore, an important determinant of the physiological response to exercise training is exercise intensity, and moderate scientific evidence indicates that training at a higher exercise intensity produces greater physiological benefits compared to lower-intensity exercises in patients with COPD (93). Hence, with higher intensities comes a greater demand for oxygen by working muscles, which further increases the load on the ventilatory system resulting in a further increase in dyspnea. As a consequence, many patients are limited to lower-intensity activities when performing interventions with the involvement of a large amount of muscle mass.

Partitioning the exercising muscle mass during training, that is, exercising using a single limb at a time, is one way of dealing with this issue. Single limb exercises reduce the load on the ventilatory system by reducing the amount of simultaneously-involved muscle mass. This diminishes the extent to which the ventilatory limitation hinders the exercise stimulus and thereby optimizes the effects of exercise training. This concept of exercise has been found to give a higher metabolic rate (94), and more recent exercise training studies have examined the promising results of single limb exercises (95-97). Two studies (95, 96) focusing on one-legged cycling concluded that it was superior to two-legged cycling regarding aerobic capacity for patients with COPD. In the study by Bjørgen and colleagues (95), the total amount of work was larger in the group working with one leg at a time compared to the group working simultaneously with both legs. This is important because the effects of any exercise training are influenced by the amount of work performed. The higher amount of work performed in the one-legged group could be explained to some extent by increased limb muscle endurance, due to increased oxygen uptake and increased maximal mitochondrial respiration in working muscles, as demonstrated in the one-legged knee extensor training study by Brønstad and colleagues (97). However, since the local effects of exercise training only occur in the muscles involved, one drawback of these studies are that they only incorporate the leg muscles and the quadriceps muscle in particular (42, 95-97). As both upper- and lower-limb muscles are impaired, and because higher dyspnea scores and higher fatigability during upper- compared to lower-extremity activities have been demonstrated in COPD (22, 42, 98, 99), an exercise regimen incorporating both upper- and lower-limbs would be beneficial.

One way to incorporate both upper- and lower-extremity muscles within the same exercise regimen is with resistance training (71, 72). Resistance training studies in patients with COPD have focused primarily on increasing muscular strength which has been warranted because of the relationship to the muscular dysfunction in COPD (40, 71). The evidence for the effects of resistance training of this design on functional outcomes

such as walking is limited, however (71). Since quadriceps muscular endurance has been demonstrated to be reduced to a greater extent, in comparison to quadriceps muscular strength, and to be associated with physical activity level (39, 41), the potential effect of a resistance training regimen on limb muscle endurance is of interest. Even though limb muscle endurance has been shown to be improved by low load/high repetition resistance training in healthy adults (73), the research is sparse on the effects of resistance training with this design on patients with COPD. It is also not clear whether changes in functional exercise capacity could be achieved by single limb exercises if they are performed as resistance training with a focus on increasing limb muscle endurance in this group of patients (100).

Single limb resistance training, incorporating both upper- and lower-extremity muscles, and focusing on increasing limb muscle endurance (low load/high repetition) has been used previously with success in patients with CHF. These exercises demonstrated increased maximal oxygen uptake, walking ability and health-related QoL. The high-repetitive single limb exercise (HRSLE) regimen was performed with elastic bands as resistance, using group training and was considered both effective and feasible with an excellent attendance rate and no reporting of adverse events other than an increase in edema in one of the patients (101). As previously explained, patients with CHF show many similarities to patients with COPD such as reduced exercise capacity and exertional dyspnea (22, 23). The similarities in exercise limitations, the positive effects one-legged approaches in COPD (95-97) and the effectiveness of the HRSLE approach used in patients with CHF (101) generate an interest in investigating the potential use of a similar exercise regimen in patients with COPD. The use of low load/high repetition exercises recently has been recommended when training the upper-limbs in patients with COPD (99).

### 1.6.3 Assessment

Below is a brief summary of common valid and reliable tests used in the assessment of outcomes after completing pulmonary rehabilitation in patients with COPD. The description is focused on outcomes and tests relevant to the aim of this thesis.

In the assessment of functional capacity, the 6-minute walk test (6MWT) is the most established and most commonly used test (102, 103). Other tests include the incremental shuttle walk test (104) and the endurance shuttle walk test (105). Upper-extremity tests are not as established; nevertheless both the 6-minute pegboard and ring test (6PBRT) (72, 106, 107) and the unsupported upper limb exercise test (UULEX) have been used in patients with COPD (72, 108).

In the assessment of muscle function in patients with COPD a variety of methods have been used, including hand-held dynamometers, strain gauge systems, computerized dynamometers and dynamic 1 RM tests using

mainly weight-lifting machines. Isometric evaluations have been the most common method to assess muscular function in COPD. In dynamic evaluations, computerized dynamometers and 1 RM testing have been the most commonly used approaches and 1 RM tests were also the main field test used in the assessment of muscle performance (109). In order to obtain an accurate evaluation of an exercise intervention it seems that the same approach should be used in both training and assessment (i.e. if the exercises are performed with a weight-machine, a weight-machine should be used in the assessment because it may be more sensitive to gains) (110).

In the assessment of QoL and symptoms, the St. George's Respiratory Questionnaire (111), the Chronic Respiratory Disease Questionnaire (CRQ); and its self-administered version and the Medical Research Council Dyspnea Scale are the most common (16, 17, 112-114). More recently the COPD assessment test has been developed, and is considered a short and easily-understood questionnaire (18). Anxiety and depression could be evaluated with the Hospital Anxiety and Depression Scale (HADs) (115). The questionnaire is widely used in association with COPD (116).

## 1.7 Evaluation of methodological quality in clinical trials

“The whole of medicine depends on the transparent reporting of clinical trials” (117).

Increased attention has been paid to patient-centered outcomes in studies of patients with COPD (118). Also the design of trials and of interventions for patients with COPD and their clinical applicability are beginning to attract more attention within the field (119). The most reliable evidence of health-care interventions is provided by well-designed and accurately executed RCTs, however the reporting of RCTs is unfortunately not optimal. A lack of reporting and inadequate methods are associated with biased results which may lead to incorrect conclusions (120). The lack of reporting in trials is often a problem caused by poor methodology. Regarding parallel group RCTs, the lack of reporting is fundamental, for example, only 58% defined their primary outcome, 49% stated that a sample size calculation was made, 63% did not report method of random sequence generation, 70% did not report method of allocation concealment, 89% had not made a trial registration and 99% had not reported any trial protocols (121, 122). Lack of reporting and methodological shortcomings were also demonstrated in COPD trial. In a large systematic review incorporating a total of 103 studies, of which 84 were RCTs focusing on the evidence of physiotherapy interventions, the average Physiotherapy Evidence Database (PEDro) score (123) was 5.1/10 (124). Their conclusions regarding resistance training in particular was supported by an average PEDro score (123) of 4.8/10. No specification of reasons for the PEDro score was expressed within the systematic review (124). The lack of reporting and methodological shortcomings in trials have led to the development of specific guidelines for different study designs. When constructing a systematic review, following the Preferred Reporting

Items for Systematic reviews and Meta-Analyses (PRISMA) statement is recommended (125), and when constructing RCTs the Consolidated Standards of Reporting Trials (CONSORT) (120, 126) guidelines are recommended. Furthermore, there is a lack of description of the interventions used within an exercise regimen, with a specific lack in standardization of interventions (120, 126). The recommendation is that the description should be thorough, including the description of the control intervention, so that clinicians wanting to use the intervention will know exactly how to administer the interventions used within a trial and to enhance the ability of researchers to reproduce the trial (120).

### 1.8 Key messages - Introduction

- COPD is a major cause of morbidity and mortality and projected to become the third leading cause of death worldwide by 2030.
- COPD is characterized by chronic airflow limitation and is diagnosed by a  $FEV_1/FVC < 0.70$  and  $FEV_1 < 80\%$  predicted.
- Smoking cessation is the first priority in the management of COPD, and optimal pharmacological treatment is vital.
- Exercise training is a cornerstone of pulmonary rehabilitation.
- Ventilatory limitation results in increased dyspnea during traditional exercise training for patients with COPD involving a large amount of simultaneously involved muscle mass which limits exercise stimulus and reduces potential effects
- Single limb exercises is a novel strategy used to optimize the effects of exercise training.
- Single limb exercises reduces the load on the ventilatory system by reducing the amount of muscle mass simultaneously involved, allowing higher intensity training.
- Lack of reporting and methodological shortcomings have been demonstrated in resistance training studies in patients with COPD.

## **2. Rationale for this thesis**

Single limb exercises is a novel strategy used to optimize the effects of exercise training in patients with COPD. However, the evidence to support the use of single limb exercise interventions have not been evaluated systematically and remains unclear. Because we adapted and modified our HRSLE regimen (used in Papers IV and V) from a regimen used in patients with CHF, the similarities between the diseases and the fact that no systematic evaluation had been made on single limb exercises in patients with CHF either, we also included studies with patients with CHF in the systematic review.

Weight-machines are both the most commonly used dynamic tool for assessment of muscle strength, and the predominant choice of exercise equipment in resistance training for patients with COPD. One drawback of weight-machines is the lack of access to this exercise equipment after completing a pulmonary rehabilitation program. This has highlighted the need to examine the effects and safety of alternative exercise equipment (71). Elastic resistance equipment such as elastic bands and tubing offer an alternative that has shown comparable results with weight-machines regarding both upper- and lower-extremity exercises in healthy adults (81, 82). Because it seems that the same approach should be used in both training and assessment in order to gain an accurate evaluation of an exercise regimen, (110) the validity of elastic resistance as a tool for evaluating muscular strength would be of interest.

Little is known with regard to feasibility of single limb exercises in patients with COPD. One previous study reported that all patients completed the training and achieved the desired training intensity with no adverse events. However, it was not clear how the information was collected (95). In other studies, sparse or no information on the feasibility of the programs were presented (96, 97). Even though HRSLE has shown beneficial results and appears to be feasible in patients with CHF (101), the concept of incorporating HRSLE performed as resistance training using elastic bands in patients with COPD has not been studied and its feasibility and effects are still unknown. A detailed account of the rationale and methodology of HRSLE in patients with COPD also would be beneficial to increase reproducibility and implementation in clinical settings.

### **3. Aims of the thesis**

The general aim of this thesis was to generate knowledge regarding the feasibility, methodology, effects and evidence of single limb exercises that could contribute to optimize treatment for patients with COPD.

#### **3.1 Specific aims of this thesis were to:**

- Investigate the evidence for single limb exercise regimens compared to any comparator, on any relevant outcome measurement for exercise capacity, QoL or dyspnea in patients with COPD or in patients with CHF (Paper I).
- Investigate if elastic resistance bands could be used to accurately evaluate muscular strength during shoulder flexion in healthy older men and women (Paper II).
- Develop a trial protocol with detailed description of HRSLE for patients with COPD (Paper III).
- Investigate if eight weeks of HRSLE in addition to COPD-specific patient education (PE) improve walking capacity, upper extremity functional capacity or quality of life in patients with COPD compared to PE alone (Paper IV).
- Investigate if HRSLE in addition to PE could improve upper and lower extremity muscular strength / limb muscle endurance, endurance cycle capacity or health related outcomes compared to PE alone in patients with COPD (Paper IV).
- Investigate if the eight week HRSLE regimen could be feasible in patients with COPD (Paper V).
- Investigate if the HRSLE regimen could be consider feasible for the physiotherapists supervising and conducting the intervention in clinical settings (Paper V).

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## 4. Methods

### 4.1 Study designs

Several different study designs were used in the present thesis. A *systematic review* was used to determine the current evidence for single limb exercises (Paper I). A *validation study* was constructed to investigate if elastic resistance could be used to accurately evaluate muscular strength (Paper II). A *trial protocol* (Paper III) was constructed to provide rationale and detailed description of the methodology of a *multicenter RCT* investigating effects (Paper IV) and feasibility (Paper V) of HRSLE in patients with COPD.

#### 4.1.1 Methodological quality, registration and study protocol

To increase methodological quality, the systematic review was designed in accordance with the PRISMA statement (125) and the CONSORT guidelines (120, 126) were followed in the design of the multicenter study. Investigation of the feasibility of the HRSLE (Paper V) was considered a sub-study of the multicenter trial and was reported in line with strengthening the reporting of observational studies in epidemiology (STROBE) guidelines (127). The multicenter study was registered at ClinicalTrials.gov (NCT01354067), and the study protocol was published in the TRIALS journal (128) (Paper III). The systematic review was registered in PROSPERO (2011:CRD42011001050) with the review protocol available at [http://www.crd.york.ac.uk/PROSPEROFILES/1050\\_PROTOCOL.pdf](http://www.crd.york.ac.uk/PROSPEROFILES/1050_PROTOCOL.pdf)

#### 4.1.2 Ethics

Both the validation study (Paper II) and the multicenter study (Paper IV and V) were approved by the Regional Ethical Board, Umeå University, Umeå, Sweden (Dnr: 2010-344-31 M). No ethical approval was necessary for the systematic review (Paper I). Written informed consent was received from all participants (Papers II, IV and V).

### 4.2 Participants

An overview of baseline characteristics of participants is presented in **Table 2**, in which the subjects in the experimental group in Papers IV and Paper V were the same. There were no differences between the experimental group and the control group on any of the baseline characteristics (Paper IV).

**Table 2.** Characteristic of participants

Characteristic	Paper II	Paper IV		Paper V
	n = 30	n = 44		n = 27
		Con (n = 22)	Exp (n = 22)	PT (n = 5)
<b>Participants</b>				
Age (years)	60 (7)	68 (6)	69 (5)	45 (37-49)
Female, n (%)	15 (50)	11 (50)	12 (55)	5 (100)
Body Mass Index (Kg/m <sup>2</sup> )	24 (3)	25 (5)	26 (4)	NA
<b>Disease severity</b>				
GOLD A, n (%)	NA	10 (45)	8 (36)	NA
GOLD B, n (%)	NA	5 (23)	10 (45)	NA
GOLD C, n (%)	NA	1 (5)	1 (5)	NA
GOLD D, n (%)	NA	6 (27)	3 (14)	NA
VC (% of predicted)	NA	101 (21)	98 (18)	NA
FEV <sub>1</sub> (L)	NA	1.5 (0.5)	1.6 (0.5)	NA
FEV <sub>1</sub> (% of predicted)	NA	55 (15)	59 (11)	NA
FEV <sub>1</sub> /VC	NA	42 (10)	47 (9)	NA
mMRC	NA	1.9 (1.1)	2.0 (1.1)	NA
<b>Smoking history</b>				
Pack years	NA	28 (7)	30 (7)	NA
<b>Muscle Function</b>				
SF-MPF (Nm)	52 (18)	34 (16)	34 (16)	NA
<b>Work experience (years)</b>				
working as PT	NA	NA	NA	15 (9-19)
with Patients*	NA	NA	NA	7 (4-10)
with Exercise training	NA	NA	NA	12 (10-19)
with Elastic bands	NA	NA	NA	3 (3-3)

Data is presented as mean (SD) or median (interquartile range, 25-75). Con = control group, Exp = experimental group, FEV<sub>1</sub> = forced expiratory volume during the first second, GOLD = The Global Initiative for Chronic Obstructive Lung Disease, mMRC = modified Medical Research Council scale NA = Not applicable, Nm = newton meter, pred = predicted, PT = physiotherapist, SF-MPF = shoulder flexion maximum peak force value, VC = vital capacity.  = participants included in Paper IV, grey = participants included in Paper V. \* patients with COPD or patients with CHF.

#### 4.2.1 Patients with COPD or CHF included in the systematic review (Paper I)

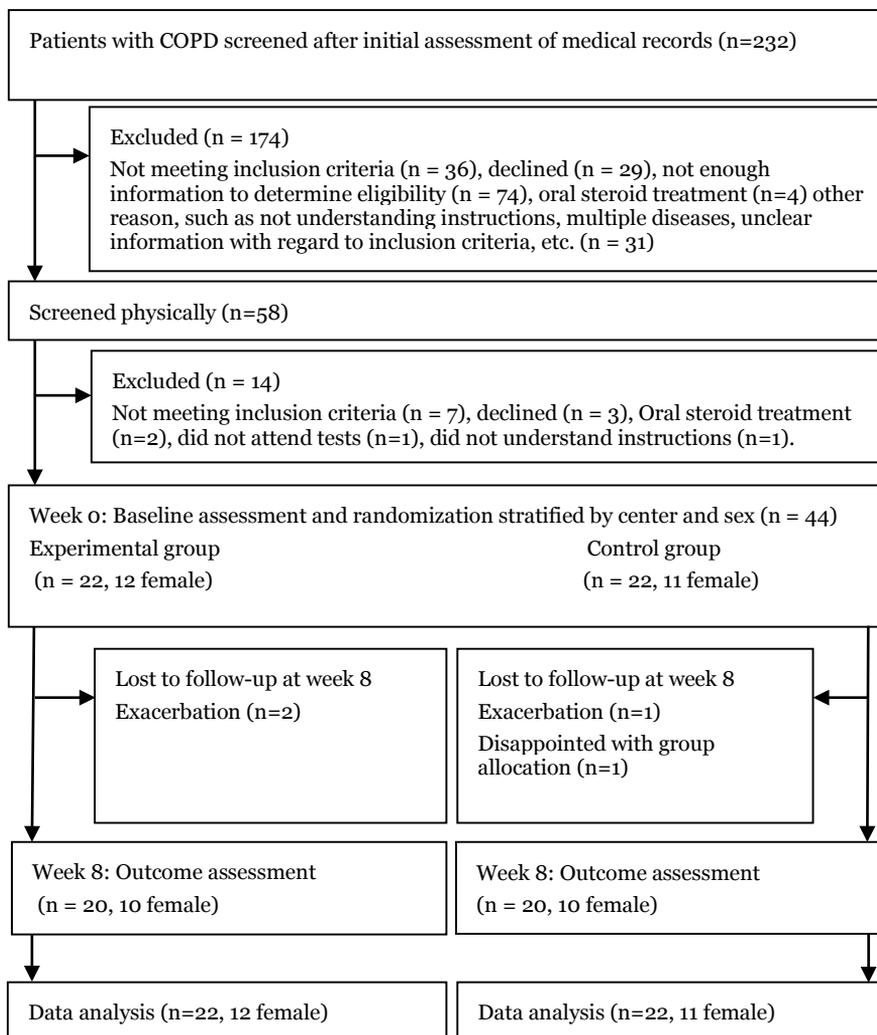
The included studies ( $n = 6$ ) in the systematic review incorporated a total of 41 (15 male) patients with COPD and 89 (63 male) patients with CHF. Eligible studies were studies with adult participants with a clinical diagnosis of stable COPD according to GOLD criteria (1) or studies of participants with CHF according to New York Health Association criteria (129, 130), where COPD or CHF was the primary diagnosis (at least 90% of study population within inclusion criteria).

#### 4.2.2 Healthy individuals included in the validation study (Paper II)

A total of 30 healthy individuals, 15 men and 15 women, were included (mean 60 years; 174 cm, and 73 Kg) and recruited using a convenience sample. Inclusion criteria for participants in Paper II included being 50 years of age or older and able to perform a maximal concentric contraction during shoulder flexion using their dominant (preferred) arm.

#### 4.2.3 Patients with COPD included in the multicenter RCT (Papers IV and V)

All inclusion criteria were pre-specified before enrollment of the first patient in the trial protocol (Paper III). Potentially eligible patients were recruited who fulfilled inclusion criteria after initial screening of medical records from the Norrlands University Hospital, Umeå, Karolinska University Hospital, Huddinge, Örnköldsvik Hospital, Örnköldsvik, as well as from primary care centers in the vicinity of each hospital. The hospitals that were included volunteered to participate. After a baseline assessment, a total of 44 patients with COPD, 23 women and 21 men, met all inclusion criteria and were included. For a flowchart of included patients with COPD, see **Figure 2**. Inclusion criteria included adults > 40 years with stable (no exacerbations within 4 weeks before start of baseline testing) moderate to very severe COPD, stages II–IV, according to GOLD criteria (1): that is,  $FEV_1/FVC < 0.70$ ,  $FEV_1 < 80\%$  predicted; ex-smoker with stable medical treatment (no changes < 4 weeks before start of baseline testing); living fewer than 60 km from the training facility. Exclusion criteria were musculoskeletal, rheumatic, cardiac, or neurological disorders that might affect the exercise performance in training and tests, previous lung surgery, and acute exacerbations of COPD that required a change in pharmacological management within four weeks preceding the start of the intervention. Patients were also excluded if they were on long-term oxygen treatment, participated in organized exercise training > 2 times a week within 6 months before the start of the intervention, and/or had a body mass index < 18 Kg/m<sup>2</sup> (Papers IV and V). In addition, participants were included for Paper V only if randomized to the experimental group.



**Figure 2.** Flowchart of included patients in Paper IV.  
COPD = chronic obstructive pulmonary disease

#### 4.2.4 Physiotherapists included in the multicenter RCT (Paper V)

A total of five physiotherapists—two from the Norrlands University Hospital, Umeå, two from Karolinska University Hospital, Huddinge, and one from Örnsköldsvik Hospital, Örnsköldsvik—met inclusion criteria and were included (**Table 2**). Inclusion criteria for physiotherapists conducting the HRSLE regimen was at least two years’ experience of working as a physiotherapist, at least one year’s experience working with patients with COPD or one year with heart failure patients, and at least one year’s experience of leading training groups. In addition, three

physiotherapists, one at each center (hospital) performed the COPD-specific patient education given to both the experimental and the control group (Paper IV). Inclusion criteria for those leading the patient education were at least two years' experience working as a physiotherapist, at least one year's experience working with patients with COPD, and previous experience leading patient education or pulmonary rehabilitation for patients with COPD.

### 4.3 Interventions

#### 4.3.1 Single limb exercise regimens

Studies examining single limb exercise regimens, that is, at least 50% of intervention performed with one arm or one leg at a time, supervised or unsupervised in in- and out-patient populations were included (Paper I).

HRSLE was the single limb exercise regimen used in the multicenter study (Papers IV and V). A comprehensive description of the exercise regimen is presented in the study protocol (Paper III). In brief, the HRSLE regimen was performed by the experimental group for three sessions per week for eight weeks (24 sessions in total) in groups of three to seven patients. Each session was supervised by physiotherapists fulfilling inclusion criteria and lasted approximately 60 minutes (6 minutes warm-up, 44 minutes exercises, and 10 minutes cool-down). Warm-up and cool-down were standardized in accordance to ACSM recommendations. Warm-up focused on dynamic flexibility exercises, familiarization with exercise movements, and execution of motions at optimal velocity to rehearse desired motion patterns (131). Cool-down consisted of stretching the targeted muscles: holding each stretch 30 seconds to mild discomfort, two repetitions for each limb (i.e., two minutes active stretching for each muscle) targeting pectoralis major, biceps brachii, hamstrings, quadriceps, and triceps surae (132).

The HRSLE regimen consisted of eight upper- and lower-extremity exercises, and each exercise was performed with a single limb at a time, alternating left to right side. Six exercises were performed with elastic resistance bands, Thera-Bands (The Hygenic Corporation 1245 Home Ave. Akron, OH 44310). The elastic exercises were (targeted muscle): latissimus row (m. latissimus dorsi), chest press (m. pectoralis major, m. deltoid anterior), leg extension (mm. quadriceps), straight-arm shoulder flex (m. deltoid anterior), leg curl (mm. hamstrings), and elbow flexion (m. biceps brachii). The two other exercises, single-leg heel-raise (mm. triceps surae) and single-leg step-up (mm. quadriceps, mm. iliopsoas), were performed with body weight as the primary resistance; elastic resistance was incorporated when progression occurred (**Figure 3**). Pictures from one of the exercise sessions are presented in **Figure 4**.

The exercises were selected based on an *a priori* literature search identifying important upper- and lower-extremity muscle groups for

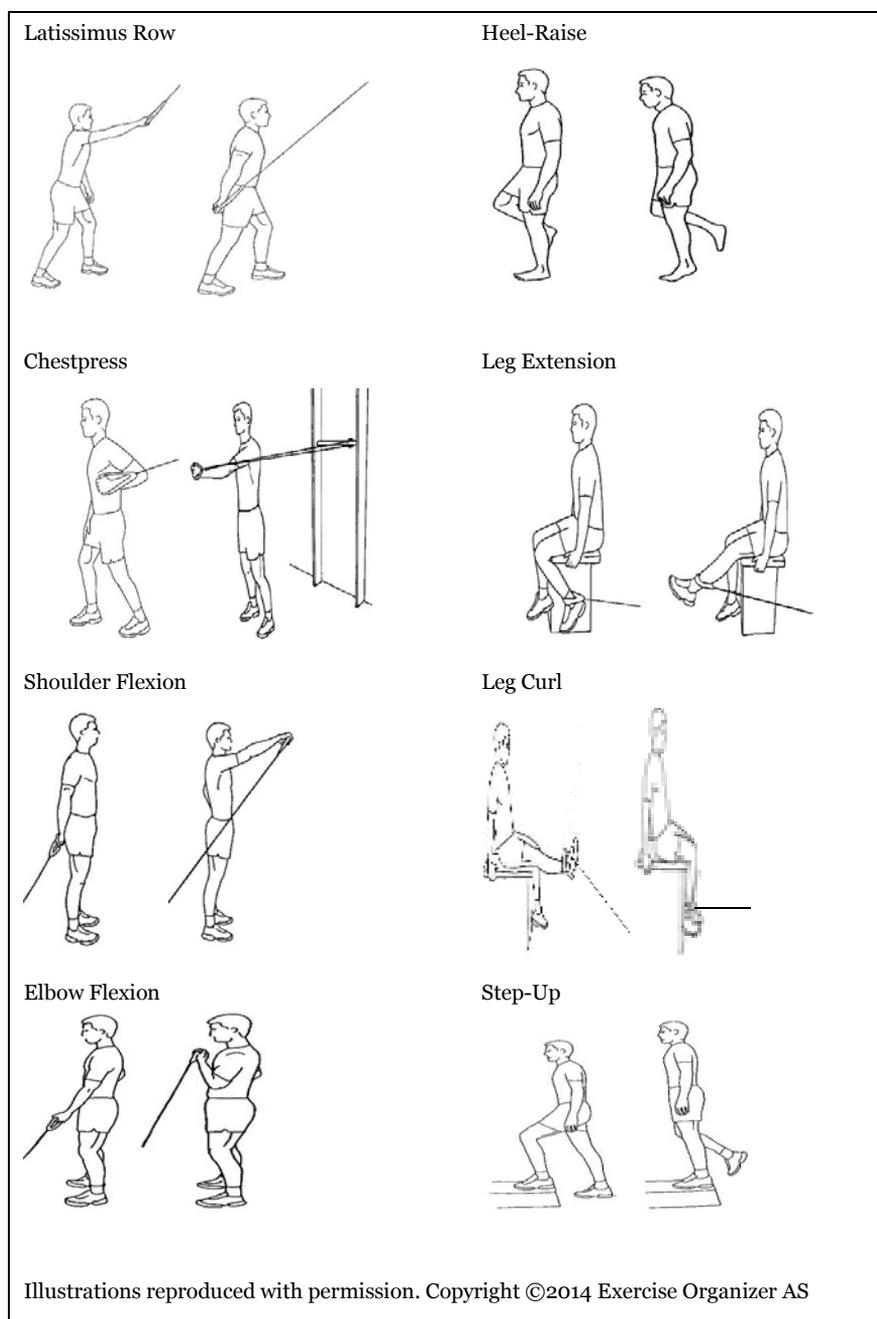
patients with COPD; the exercises focused on important muscles for walking and muscles with decreased strength or endurance compared to healthy individuals and important for upper-extremity activities of daily living (22, 133-135). Each exercise was performed for 25 repetitions in two sets (alternating left to right side), with a rest period of one minute and a repetition velocity of one second in both concentric and eccentric phases of the movements in all exercises except for the step-up exercise. This design was used to facilitate an effect on limb muscle endurance in line with ACSM recommendations (73). An overview of measurements of standardization taken in order to enhance implementation of the HRSLE regimen in clinical settings and to enhance the reproducibility is presented in **Box 1**, modified from Table 1:IV. Determination of resistance (color of elastic band) and progression were individually adjusted. Starting resistance was set from a baseline 25 RM shoulder flexion test and then altered for other exercises based on an identified strength relationship between exercises: (in percent, described as weight at end position if knee extension is seen as maximal: knee extension [100%], chest press [85%], leg curl [65%], elbow flexion [50%], latissimus row [35%], and shoulder flexion [30%]). For example, if 10 Kg was considered 25 RM for leg extension, 3 Kg would be considered 25 RM for shoulder flexion etc. The Borg category-ratio (Cr10) scale (136) was used for progression: if a patient rated < 4 and performed  $\geq 20$  repetitions in at least three of six elastic band exercises, in two out of three following sessions, the resistance was increased by changing the color of the elastic band (i.e., increasing the tension of the elastic band). Irrespective of muscle fatigue, a rating of at least three of six exercises > 5 on dyspnea (137), resulted in a decrease in resistance. The muscle fatigue and dyspnea ratings were done after each exercise for each patient and noted by the physiotherapists. The exercises where body weight was the primary resistance, that is, heel-raise and step-up were progressed individually following the same approach, in five levels, respectively (128).

### 4.3.2 Control groups

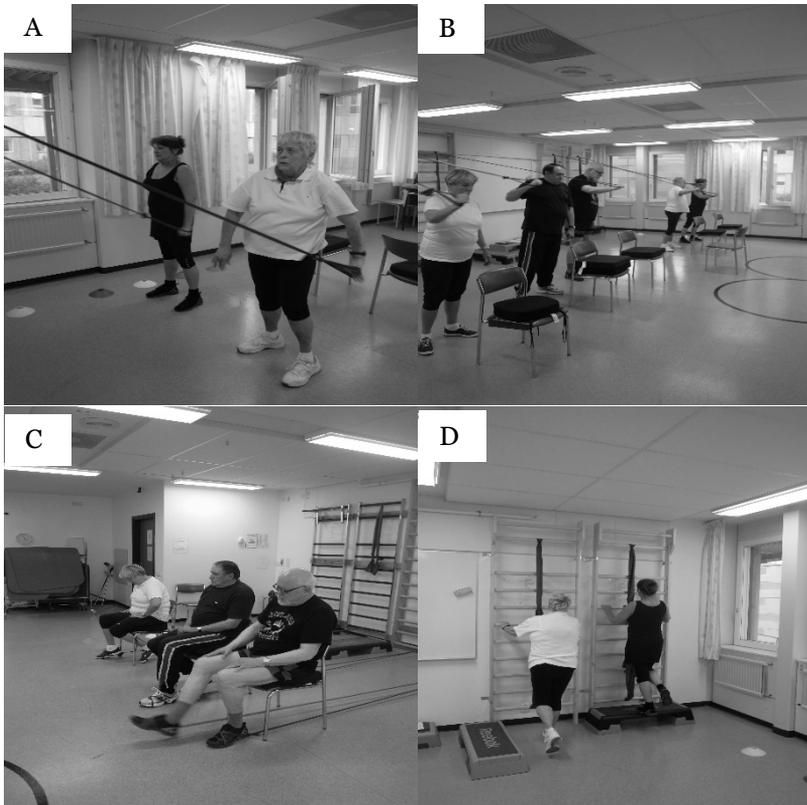
All studies included in Paper I compared the single-limb exercise regimens with any kind of intervention, no intervention, or placebo interventions. COPD-specific patient education (PE) was the control group in Paper IV. The PE was given to both the experimental group and the control group, but was the only treatment in the control group. The PE was given four times during the intervention period. Each session lasted 60 minutes and consisted of information regarding: anatomy, physiology, COPD (causes and mechanisms), nutrition, aids/tools, and energy-saving procedures. The PE material was standardized and the same for all groups at all locations, and informed consent was given from each physiotherapists to follow the standardized material. The PE was the same for both the experimental and the control groups but was given at separate occasions. The patients randomized to the control group, receiving PE alone, were offered participation in exercise training after the end of outcome assessments.

**Box 1. Standardization of HRSLE treatment**

<b>Standardization</b>	<b>Reason for standardization</b>
Two elastic resistance band were used with standardization of the elastic band length to one meter and stretched in different lengths depending on exercise	to facilitate implementation in clinical settings by reducing the amount of equipment needed by stretching the resistance band instead of adding bands to increase the resistance
Each elastic resistance band was pre-stretched 20 times to stabilize the material.	to ensure equal resistance in every repetition
Individual starting resistance (color of elastic resistance band) were standardized using 55% of baseline isokinetic peak value in shoulder flexion and then altered for other exercises according to a identified strength relationship between involved muscles. Verified by a 25 repetition maximum test.	to enhance the accuracy of each patient receiving an accurate starting load in each elastic exercise and thereby optimizing the effects of the exercise regimen. Fifty-five percent of peak value is also recommended for 25 repetitions maximum.
The length of the resistance band at end of movements was standardized by the strength relationships between involved muscles and information obtained from the manufacturer regarding the properties of elastic bands	to ensure optimal resistance in every exercise for each patient
Different colored cones were used to position all patients in the different exercises	to ensure that the end of movement would be accurate
The elastic resistance bands were changed every eight session and exercises were executed within the most clinically effective portion of elastic resistance	to ensure less than 1.1 Newton change in force generating potential
Instructions on execution of the elastic exercises were standardized	to ensure optimized activation of targeted muscles for each exercise separately.
Individual progression were performed with use of the Borg category-ratio 10 scale according to a standardized protocol	to ensure individual tailoring and accurate resistance
Physiotherapists visually and orally instructs the exercises in the targeted repetition velocity	to enhance the ability of patients performing the exercises in targeted repetition velocity
A standardized exercise protocol including illustrations, targeted muscles, description of execution were given to both patients and physiotherapists	to enhance adherence and familiarization to the exercise regimen.
All physiotherapists conducting the resistance training were given one hour of written, oral and visual education on how to perform and instruct each exercise within the resistance training regimen.	to enhance the accuracy of the resistance training regimen being performed per protocol and to simplify conduction of the regimen.



**Figure 3.** Illustrations of exercises



**Figure 4.** Exercise pictures. A: Latissimus Row, B: Chestpress, C: Leg Extension, D: Heel-Raise

#### 4.4 Outcomes and data collection

An overview of outcome measures and methods used for data collection in Papers I-V can be seen in **Table 3**. Outcome measures for the RCT presented for each study (Papers IV and V) are shown in the text below; all of these are also shown in the trial protocol for the RCT (Paper III).

In Paper I, a ranking based on the importance of the outcomes used for both patients with COPD and CHF was constructed in accordance with Grading of Recommendations Assessment, Development and Evaluation (GRADE) guidelines (138-142) in collaboration with experts in COPD and CHF rehabilitation. Database searches started 1 April 2011. PubMed, PEDro, the Cochrane Airways Group, and the Cochrane Heart Group Specialized Register of trials in the Cochrane Central Register of Controlled Trials Databases were searched from inception until 31 May 2011. We identified additional studies by using the related articles function in PubMed, contacting authors of the included trials, and performing a manual search of reference lists from both reviews and primary studies.

**Table 3.** Overview of outcome measures and data collection methods

Outcome measures	Paper I	Paper II	Paper III	Paper IV	Paper V
<b>Exercise capacity</b>					
Cycle ergometer test	•		•	•	
6MWT	•		•	•	
6PBRT			•	•	
UULEX			•	•	
<b>Limb muscle strength and endurance</b>					
Isokinetic measurements		•	•	•	
Elastic measurements		•	•		
<b>Quality of life</b>					
SGRQ	•				
CRQ-SA	•		•	•	
SF-36	•		•	•	
CCQ	•		•	•	
ESES			•	•	
Self-Eff Walking			•	•	
SIP*	•				
SOC*	•				
Lhfe*	•				
HADs			•	•	
<b>Dyspnea</b>					
Borg CR10	•		•	•	
<b>Feasibility</b>					
Attendance			•		•
Exercise intensity			•		•
Compliance			•		•
Adverse events			•		•

6MWT = 6 Minute Walk Test, 6PBRT = 6 Minute Pegboard and Ring Test, Borg CR10 = Borg Category Ratio scale, CCQ = Clinical COPD Questionnaire, CRQ-SA = Chronic Respiratory Disease Questionnaire – self-administrated, ESES = Exercise Self-Efficacy Scale, HADs = Hospital Anxiety and Depression scale, Lhfe = Minnesota living with heart failure questionnaire, SIP = Sickness of Impact Profile, SF-36 = Medical Outcome Short Form-36, SGRQ = St George’s Respiratory Questionnaire, SOC = Sense Of Coherence, \* = Heart failure outcomes.

Data were collected in Paper II in one occasion lasting approximately 90 minutes for each participant. Recruitment and collection of data were performed in March 2011 at the Department of Community Medicine and Rehabilitation, Physiotherapy, Umeå University, Umeå, Sweden.

In Papers IV and V data were collected during four visits before and during three visits after the intervention period with each visit lasting 60-120 minutes. Data were collected at each included center (Umeå, Huddinge, and Örnsköldsvik), respectively. Data collection of primary outcomes for each of the included centers was performed by the same test leader who was blinded to group allocation. Recruitment and data collection were performed between August 15, 2011 and May 3, 2012. A detailed description of the outcomes used in Paper IV is available in the study protocol (Paper III).

Below is a description of the outcome measures/tests used in Papers II-V. Because a wide range of outcome measures was considered eligible in the systematic review (Paper I), these are mentioned only in the description in the adequate category.

#### 4.4.1 Pulmonary function

In Paper IV pulmonary function tests—spirometry, body plethysmography, and single-breath diffusing capacity maneuvers—were performed in accordance with recommended techniques (143, 144).

#### 4.4.2 Exercise capacity

During all exercise and muscle function tests in Paper IV, dyspnea and muscle fatigue in the legs and arms, depending on the test, were measured with the Borg CR10 (136), and oxygen saturation and pulse were measured with pulseoximetry (Nellcore NPB-40, Pleasanton, USA). Dyspnea, breathlessness, and leg discomfort in patients with COPD had been measured previously with the Borg CR10 scale (136) and the scale was found to be reliable (145). A symptom-limited incremental cardiopulmonary exercise test (146) was carried out to assess cycle exercise capacity and provide data for the constant work rate test used as an outcome measure. Cycle exercise capacity—that is, Watts maximum—was defined as the greatest work rate that the subject was able to maintain for at least 30 seconds.

A constant work rate exercise test was performed at 75% Watts maximum (obtained from an incremental test). Endurance time—recorded as the time from the increase in work rate to 75% W<sub>max</sub> to the point of symptom limitation and peak VO<sub>2</sub> measured with ergospirometry (VMAX Encore 229, CareFusion, Palm Springs, CA, USA in Huddinge and Jaeger Oxycon, CareFusion, GmbH, Hoechberg, Germany in Umeå)—was performed.

Patients in Örnsköldsvik traveled to Umeå because the equipment was not available in Örnsköldsvik.

The *primary lower-extremity outcome* in Paper IV was functional lower-extremity, endurance capacity, measured with the 6MWT (102, 103). The walking course was 30 meters in length, and the patients were instructed in accordance with standardized guidelines (147) to walk as far as possible in 6 minutes.

In Paper IV the participants performed a 6PBRT (106) to assess functional upper-extremity, exercise capacity (*primary upper-extremity outcome*). The pegboard and ring board test consists of a peg and ring board with the pegs set at the subject's shoulder height and 10 cm above shoulder height. The test is performed by repeatedly moving 10 rings simultaneously (one ring in the left and right hands, respectively) from the bottom pegs to the upper pegs. The final score is the total number of rings moved in the given amount of time. The test has been used previously in patients with COPD (106).

To measure unsupported, upper-extremity, endurance capacity, the UULEX was used (108). The UULEX test is performed by moving a plastic bar, held with both hands, from the hip to fully extended arms, repeatedly, at different levels. The UULEX consists of eight levels. Level one is performed for two minutes, and the remaining levels for one minute. Each level is performed lifting the plastic bar at a cadence of 30 beats per minute, controlled with a metronome, from the hip to the UULEX eight-level chart. If a participant reaches his/her maximum height, the bar will be replaced with a heavier one (0.2, < 0.5, < 1, < 1.5, < 2 Kg), and the test is performed until symptom limitation.

### 4.4.3 Limb muscle strength and endurance

In Paper II an isokinetic test of maximal concentric shoulder flexion was performed in an isokinetic dynamometer (Kin-Com®, Chattanooga Group Inc.). The test consisted of five maximal concentric repetitions performed consecutively (148, 149). The maximum peak force (the maximum value of the five contractions [Kg]), the mean peak force (the mean value of the peak torque [maximum] contraction [Kg]), and the maximum mean force (the highest mean value of the five contractions [Kg]) were collected from the isokinetic test.

In Paper IV, both a maximal (five maximal concentric contractions) and an endurance (30 maximal concentric contractions) test were performed during shoulder flexion and knee extension with the Biodex Multi-Joint System 3 (Biodex Corp., Shirley, New York) at the Department of Community Medicine and Rehabilitation, Physiotherapy, Umeå University and The Biodex Multi-Joint System 4 (Biodex Corp., Shirley, New York) at Karolinska University Hospital, Huddinge. Patients in Örnsköldsvik traveled to Umeå because the equipment was not available in Örnsköldsvik. As in Paper I, maximum peak force—the maximum value of

the five contractions—was collected to determine maximal strength. Endurance was assessed as the total work (Joules) during 30 consecutive repetitions.

The isokinetic tests in both Papers II and IV were performed unilateral on the self-reported, dominant side. The participants were seated in accordance to manufacturer recommendations and the tests was performed in an angular velocity of  $60^\circ \cdot s^{-1}$ . The angular velocity of  $60^\circ \cdot s^{-1}$  is considered ideal for evaluating muscle strength in patients with COPD (150) and is found reliable in endurance tests (151). In both studies the participants were instructed to exert themselves maximally during the concentric contraction and relax during the passive movement to the starting position, and the arm was to be held with the elbow extended and the forearm semi-pronated (152). The rest period between tests was at least one minute in Paper II (148, 153, 154) and five minutes in Paper IV (59, 155). The shoulder flexion test was performed between  $0^\circ$  and  $110^\circ$  in Paper II and  $0^\circ$  and  $100^\circ$  in Paper IV. The test of knee extension (Paper IV) was performed between  $90^\circ$  flexion to a maximal knee extension of  $-5^\circ$ .

An elastic band test of maximal concentric shoulder flexion using Thera-Band elastic bands (Thera-Band, The Hygenic Corporation, 1245 Home Ave., Akron, OH 44310) was performed in Paper II. Elastic resistance 1 RM, the highest load that could be lifted successfully throughout the whole range of motion in a single bout, was collected. The test followed the same procedures and was performed in the same position as the isokinetic shoulder flexion test to mirror the tests. After each successful repetition, the load was increased by 0.4-0.5 kg by combining the elastic bands in line with instructions from a pre-specified manual. The manual consisted of information on color(s) and number of elastic bands equivalent to a specific load at 100% elongation, measuring four meters at the end position of the elastic bands' relaxed length. Adequate recovery was provided between attempts, and when the participant failed an attempt at a certain load, he/she was given a second try at that load. If the second attempt failed, the participant's 1 RM was determined to be the last load that was successfully performed (156). Verbal encouragement and instructions were standardized and were given during both elastic and isokinetic tests to facilitate maximal effort (152, 157); no visual feedback was provided.

#### 4.4.4 Quality of Life

QoL was a *primary outcome* in Paper I. the following questionnaires were considered eligible to assess QoL: the St. Georges Respiratory Questionnaire (111), the CRQ (113, 114), the Medical Outcomes Study Short Form-36, or the Clinical COPD Questionnaire used in patients with COPD. The Sickness of Impact Profile (158), Sense Of Coherence scale (159) and the Minnesota Living with Heart Failure questionnaire (160, 161) were used in patients with CHF.

The following questionnaires were used in the assessment of health-related QoL in Paper IV: The Swedish version of the CRQ self-administrated version of the Chronic Respiratory Disease Questionnaire (CRQ) (113, 114) determined the *primary outcome* for QoL. The CRQ is a widely used disease-specific questionnaire to assess patients with COPD's symptoms (162). The Swedish CRQ - self administrated version consists of 20 health-related questions. The Swedish CCQ (163) consists of 10 questions and is valid and reliable in Swedish patients with COPD (164). The Medical Outcomes Study Short Form-36 is a 36-item questionnaire used to evaluate generic QoL through eight subscales: physical functioning, role-physical, role-emotional, social functioning, general health, mental health, bodily pain and vitality (165). It is considered the gold standard generic health assessment tool (166) being valid, reliable and vigorously tested (165) and has been used in patients with COPD (38, 167) (Paper IV). Anxiety and depression were assessed with the HADs. HADs consist of 14 items, producing separate scores for anxiety and depression (115) and is used widely in association with COPD (116). Self-efficacy of patients in Paper IV was evaluated with the 10-question Swedish version of the Exercise self-efficacy scale (168) and with the self-efficacy for walking questionnaire used on patients with COPD (169).

### 4.4.5 Dyspnea

Dyspnea was a secondary outcome measured in Paper I by the Borg Cr10 scale (136) in the study by Dolmage and colleagues (96). The Borg Cr10 scale (136) also was used to assess dyspnea before, during and after each exercise in the HRSLE regimen performed by the experimental group in Paper IV. In the same paper dyspnea was also assessed before and after baseline and follow-up exercise tests.

### 4.4.6 Feasibility of the HRSLE regimen

An attendance rate was calculated for each patient as the number of attended sessions divided by total number of sessions.

Exercise intensity was measured by dividing mean muscle fatigue rating on the Borg CR10 (136) with the mean muscle fatigue rating on a baseline 25 RM test. The mean ratings on the 25 RM test as baseline were considered the predicted maximum intensity.

Severity of adverse events was assessed and rated into four different categories as previously used (170): (1) minor and temporary, (2) serious symptoms (potential risk of severe injury or life-threatening), (3) manifest injury or disease, or (4) death. The adverse events were evaluated by two independent pulmonologists and one physiotherapist who were not involved in the study. An adverse event rate was calculated for each patient as the total number of sessions in which any adverse events occurred divided by the total number of attended sessions. The adverse events were

collected from exercise diaries and post-intervention interviews with the physiotherapists conducting the intervention.

A standardized questionnaire of seven questions was used to evaluate compliance with the exercise regimen for both patients and physiotherapists. Each question was rated 1-5. A rating of 1-3 was defined as a small extent and a 4-5 large extent. For example:

To what extent could **you** follow the instructions regarding: the whole exercise regimen/the warm-up/the eight exercises/the number of repetitions/speed of movement/the cool-down or the ratings of exertion?

- |   |                          |                               |   |              |
|---|--------------------------|-------------------------------|---|--------------|
| 5 | <input type="checkbox"/> | Very large extent             | } | Large extent |
| 4 | <input type="checkbox"/> | Large extent                  |   |              |
| 3 | <input type="checkbox"/> | Neither large or small extent | } | Small extent |
| 2 | <input type="checkbox"/> | Small extent                  |   |              |
| 1 | <input type="checkbox"/> | Very small extent             |   |              |

The questions were asked of both the patients and the physiotherapists. In addition, the physiotherapists were asked: To what extent could the **patients** follow the instructions regarding the whole exercise regimen?

#### 4.5 Randomization, blinding and allocation concealment

No randomization of exercise order was possible in Paper II because the isokinetic maximum peak force value was used to determine the initial load in the elastic resistance band 1 RM test. In the multicenter study, Papers IV and V, participants were allocated randomly into either the experimental or a control group by the use of a randomly permuted blocks design with a computer random number generator ([www.randomization.com](http://www.randomization.com)) using random block sizes. The randomization procedure was stratified for *center* and *sex* with a 1:1 allocation. Group allocation was performed by a third party, independent of the recruitment and randomization process. The allocation sequence was kept in an opaque sealed and stapled envelope locked away. The envelope was made impermeable to intense light by using aluminum foil inside and sealed using tamper-proof labels. In addition, the participants were requested especially not to reveal any aspects of their intervention to the blinded outcome assessors at any stage of the post-intervention assessment. A second trained assessor was available during outcome assessment to step in if a patient revealed his/her group allocation at any process during the intervention period. Allocation of physiotherapists was not randomized (Paper III).

### 4.6 Sample size and power calculations

A total of 15 participants were needed in order to have the power to detect an intraclass correlation coefficient  $> 0.40$  between isokinetic measures and elastic resistance band 1 RM during shoulder forward flexion with a 5% precision and a power of 80%. This was based on a previous study on elastic resistance and maximal-effort isokinetic torque (110). A total of 30 individuals, 15 men and 15 women, were included so that we would be able to draw conclusions for both sexes (Paper II).

The sample size calculations for the multicenter RCT were pre-specified in the trial protocol (Paper III). A relevant difference in means of 50 meters with a standard deviation (SD) of 52 meters on the 6MWT with a 5% precision, a power of 80% and a two-tailed test of significance were the assumptions used in the sample size calculation based on a study by Costi and colleagues (171). In addition, a calculation was also made for QoL where the difference in means of 1 unit (SD: 1.07) (172) on the Swedish version of the CRQ self-administered version was considered relevant. Based on these calculations a sample size of 22 in each group (experimental, control) was required to obtain the power to detect a significance difference allowing for a 20% loss to follow-up and considering the design effect (37, 173, 174). Because participants in a multicenter study from the same center are likely to be more similar than participants from other centers, a correlation in data is expected. As such, a correlation potentially affects the power of the data within the trial; the sample size needs to be adjusted, often increased, to account for the design of the study—that is, the design effect (173, 174). No sample size calculation was made for Paper V; the sample size was a result of the sample size calculation in Paper IV.

### 4.7 Data analyses

No statistical analyses were used in the systematic review (Paper I); data were presented as narrative because a majority of interventions were heterogeneous, there were a low number of studies for the separate outcomes, and necessary data (for a meta-analysis) were not provided by included studies. Data and evidence for single limb exercise regimens were summarized in accordance to GRADE guidelines (138-142). The evidence was considered to be very low, low, moderate, or high quality (**Box 2**). The PEDro scale (123) and the Cochrane risk of bias tool (175) were used for risk of bias assessment and contributed to the GRADE rating. Authors of included studies were contacted for missing data. Results were presented for COPD and CHF separately.

**Box 2** Levels of quality of evidence and rating in accordance to GRADE**Quality**

High quality (++++) – Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality (+++) – Further research is likely to have an important impact in our confidence in the estimate of effect and may change the estimate

Low quality (++) – Further research is very likely to have an important impact in our confidence in the estimate of effect and is likely change the estimate

Very low quality (+) – Any estimate of effect is very uncertain

**Rating**

No serious (o), some limitations but not enough for rating down (?), serious (-1 level) or very serious (-2 levels) limitations to study quality

No serious (o), some inconsistency but not enough for rating down (?), or important inconsistency (-1)

No serious (o), some uncertainty but not enough for rating down (?), some (-1) or major (-2) uncertainty about directness

No serious (o), some imprecise or sparse data but not enough for rating down (?) or imprecise or sparse data (-1)

No serious (o), some probabilities of reporting bias but not enough for rating down (?) High probability of reporting bias (-1)

NA – Not applicable due to insufficient information for rating

In Paper II, evaluation of differences between elastic resistance band 1 RM and isokinetic values paired t-tests were used and for difference between men and women, an independent t-test was used. From the mean difference (d), individual variation, that is, 95% limits of agreement (limits of agreement =  $d + 2 \text{SD}_{\text{diff}}$ ) were calculated (176). The intraclass correlation coefficient (3.1) absolute agreement was used to interpret the correlation between the tests. Intraclass correlation coefficient magnitudes (1) smaller than 0.40 indicate poor to fair agreement; (2) from 0.41 to 0.60 indicate moderate agreement; (3) from 0.61 to 0.80 good agreement; and (4) from 0.81 to 1.00 indicate excellent agreement (177). The Shapiro-Wilk test measured the distribution of the dependent variables in the assessment of normality of the distribution. All dependent variables of this study were transformed logarithmically to stabilize the variance.

Linear mixed models were used for analysis of data in Paper IV. *Center*, *sex*, *group*, *time*, and *group x time* interaction were fixed effects. *Participant* was included in the model as a random effect and mean difference; 95% confidence interval (95% CI) was used to estimate the difference in change from the model. F-values, degrees of freedom, and p-values from the model were presented, and estimates of effect sizes were computed using Cohen's d ( $d = \text{difference in group means/error SD within}$ ). The difference between predicted means from the final mixed-effects model for a given pair of groups divided by the estimated within-

group error standard deviation in the model with the estimated value of  $2\sigma_e^2$ , where  $\sigma_e^2$  is the residual variance were used to calculate Cohen's d. In contrast to the trial protocol (Paper III), between group differences were presented with 95% CI instead of SD (Paper IV). For this thesis a sub-analysis of responders and non-responders was made on outcomes with a known minimal important difference or a minimal detectable change. The sub-analysis was done separately for each outcome. This means that there could be different responders and non-responders on the different outcomes. Results were described descriptive. A difference between baseline values on a specific outcome between responders and non-responders were presented (in percentages).

In Paper V, a sample t-test and Wilcoxon signed rank test used for exercise intensity and complete-case comparisons were paired when appropriate, and the Chi-square test was used in the comparison between participants and physiotherapists regarding compliance to the exercise regimen. Data were presented as means (95% CI or SD) or medians (interquartile range) depending on the distribution of data unless otherwise stated. An on-treatment analysis was planned, including on those who completed at least 20 out of 24 exercise sessions. An additional week was offered to all patients to reach at least 20 exercise sessions. We had decided to use this additional week when we designed the study missed to put the information in the trial protocol (Paper III). For some patients the intervention period was nine weeks, to reach the intended number of exercise sessions.

### 4.7.1 Software and significance levels

Data were analyzed using SPSS version 20 (SPSS Inc., Chicago, IL, USA) and a significance level of .05 was used.

### 4.7.2 Missing data and intention-to-treat

Intention-to-treat analysis was used—that is, data analysis involved all patients, analyzed by original assigned group (Papers II-V). Missing data were used in the assessment of study quality of included trials in Paper I. No data were missing in Paper II. In Paper IV, linear mixed models were used to handle missing data. Because the linear mixed model does not require a balanced data set, it is possible to analyze datasets with non-completers. In Paper V, data were available for almost all outcomes with the exception of the questionnaire used to assess compliance with the exercise regimen and some ratings (0.7%) of muscle fatigue and dyspnea during HRSLE, which may lead to potential bias. Data were missing on the compliance questionnaire from one participant with COPD due to an exacerbation after the end-of-intervention period. This missing data were not considered missing not at random. Missing ratings were due to the physiotherapists' forgetting to note the rating, which was considered missing at random (178). The overall mean (i.e., the mean value of the question/test) was used to impute both data considered missing not at random and missing at random (179). A sensitivity analysis was performed

comparing the results with imputed data to a complete case analysis (127). In brief, the data with missing values (the complete case) were compared with the data with imputed values to see if it differ.

#### 4.8 Key messages – Methods

- The different study designs were a systematic review, an experimental study, and a randomized controlled multicenter trial.
- PRISMA, CONSORT, and STROBE guidelines were followed to increase methodological quality.
- Participants included healthy older adults, patients with stages II-IV COPD, patients with stages I-III CHF, and physiotherapists.
- Different single limb interventions included single limb strength training using weights or elastic resistance, one-legged cycling, one-legged knee-extensor training, and HRSLE.
- The HRSLE regimen was designed to increase limb muscle endurance, was executed with a single limb at a time, included eight exercises (upper- and lower-extremity), used elastic resistance and body weight as resistance, and had a comprehensive standardization to facilitate implementation in the clinical setting and to increase reproducibility.
- Outcome measures were for functional capacity, muscle function, QoL, dyspnea, and feasibility.
- Power calculations were used to achieve adequate sample sizes.
- Data analyses included narrative (GRADE), linear mixed models, t-test, Wilcoxon signed rank test, and Chi-square test

## 5.0 Results

### 5.1 Is there evidence for single limb exercises in patients with COPD or CHF? (Paper I)

In the assessment of evidence for single-limb exercises, a total of 5,257 papers were identified as possible eligible studies through a high sensitivity search strategy. The majority of papers were excluded after screening title and removing duplicates (5,199). Six articles met inclusion criteria, enrolling 41 patients with COPD, mean (SD) FEV<sub>1</sub> % predicted ranged from 37 (8) to 45 (8), FEV<sub>1</sub>/FVC ratio ranged from 35 (9) to 54 (10) and disease severity was at least stage II (95, 96). Disease severity ranged from I to III in CHF studies (101, 180-182), including a total of 89 participants.

Different single limb exercise regimens were identified. In COPD studies one-legged cycling on a cycle ergometer was used (95, 96). In CHF studies single limb strength training using weights (182) or elastic resistance (101) and one-legged knee-extensor training on a modified cycle ergometer (180, 181) were used.

The *frequency* of exercise sessions was three times a week for 7-8 weeks in COPD trials (95, 96), and three times a week for 8-12 weeks in CHF trials (101, 180-182). *Exercise intensity* was determined by the percentage of peak heart rate (95) and the percentage of peak power (96) in the COPD trials. The Percentage of the peak workload (180-182) and perceived exertion (according to Borg ratings of perceived exertion scale (101)) were used in the CHF trials. The *duration* of the exercises varied: from COPD one-legged cycling (16-30 min work) (95, 96), to CHF single limb strength training (20-60 min) and one-legged knee-extensor training (39-45 min) (180, 181).

Control groups in the included COPD studies used two-legged cycling (95, 96). In CHF studies the comparators were no intervention (101, 181), two-legged knee-extensor training on a modified cycle ergometer (181), and two-legged cycle ergometer training (180, 182).

Methodological quality was in mean (range) 4.5 (4-5) out of 10 in accordance to the PEDro (97) scale in COPD studies and 5 (5) out of 10 in CHF studies. Absolute differences between groups is presented. If the outcome was assessed by two or more studies, a mean absolute difference of these studies is presented.

#### 5.1.1 Is there evidence for single limb exercises in patients with COPD?

Studies by Dolmage and colleagues (96) and Bjørgen and colleagues (95) investigated the effects of single limb exercises in patients with COPD. Both these studies compared one-legged cycling to two-legged cycling.

#### Low-quality evidence indicates

- that one-legged cycling is superior to two-legged cycling with regard to peak Watts, peak oxygen consumption ( $\text{L}/\text{minute}^{-1}$ ) and ( $\text{mL}/\text{kg}^{-1}/\text{minute}^{-1}$ ) and submaximal oxygen consumption ( $\text{mL}/\text{Kg}^{-0.67}/\text{minute}^{-1}$ ) during cycle ergometer testing. Between-group differences were 12.3 W, 0.152 L, 1.3  $\text{mL}/\text{Kg}^{-1}/\text{minute}^{-1}$  and 5.3  $\text{mL}/\text{Kg}^{-0.67}/\text{minute}^{-1}$  respectively ( $p < .05$ ) in patients with COPD (95, 96).
- that there are no differences between one- and two-legged cycling regarding dyspnea measured with the modified Borg ratings of perceived exertion scale in patients with COPD (95, 96).

#### Very low-quality evidence indicates

- that there are no between-group differences regarding peak minute ventilation ( $\text{L}/\text{minute}^{-1}$ ). Contradictory results: one study did demonstrate a significant difference of 4.3  $\text{L}/\text{min}$  ( $p < .05$ ) (96) and one did not (difference between groups, 1.9  $\text{L}/\text{min}$  ( $p > .05$ ) (95).

### 5.1.2 Is there evidence for single limb exercises in patients with CHF?

Single limb resistance training in combination with two-legged cycling was compared to two-legged cycling alone (182). Low-quality evidence indicates

- that single limb resistance training in combination with two-legged cycling is superior to two-legged cycling alone on maximal strength (2 RM). A between-group difference of 10 Kg ( $p < .05$ ) in favor of one-legged cycling is seen.
- that there are no between-group differences regarding peak Watts, Peak oxygen consumption ( $\text{mL}/\text{Kg}^{-1}/\text{minute}^{-1}$ ), or submaximal oxygen consumption ( $\text{mL}/\text{Kg}^{-0.67}/\text{minute}^{-1}$ ) during cycle ergometer testing.

Single limb training with elastic bands has been compared to a passive control receiving no intervention (101). Low-quality evidence indicates

- that single limb resistance training with elastic bands is superior to a passive control receiving no intervention with regard to peak Watts, peak oxygen consumption ( $\text{mL}/\text{Kg}^{-1}/\text{minute}^{-1}$ ) during cycle ergometer, meters walked during the 6MWT and QoL measured with the Minnesota Living with Heart Failure questionnaire. Between-group differences of 16W, 2.7  $\text{mL}/\text{Kg}^{-1}/\text{minute}^{-1}$  and, 55 meters ( $p < .05$ ), respectively were demonstrated. An absolute difference on the Minnesota Living with Heart Failure questionnaire could not be presented due to insufficient information.

One-legged knee-extensor training was compared to cycle ergometer training (180), to two-legged knee extensor training, and to a passive control group receiving no intervention (181). Low quality evidence indicates

- that one-legged knee extensor training is superior to two-legged cycle ergometer training with regard to peak Watts, peak oxygen consumption ( $\text{mL/Kg}^{-1}/\text{minute}^{-1}$ ) and ( $\text{L}/\text{minute}^{-1}$ ). The between-group differences were 15 W, 2.5  $\text{mL/Kg}^{-1}/\text{minute}^{-1}$  and, 0.24  $\text{L}/\text{minute}^{-1}$  ( $p < .05$ ).
- that there are no between-group difference between one-legged knee extensor training and two-legged cycle ergometer training regarding peak Watts, peak oxygen consumption ( $\text{L}/\text{minute}^{-1}$ ), and ( $\text{mL/Kg}^{-1}/\text{minute}^{-1}$ ) during knee extensor testing, and walking measured with the 6MWT self-paced and high-speed test.
- that no differences were seen with regard to QoL measured with Minnesota Living with Heart Failure questionnaire (total, physical, emotional), Sickness of Impact Profile subscales ambulation, social interaction, sleep & rest, home management or on the Sense Of Coherence scale.
- that two-legged knee extensor training is superior to one-legged knee extensor training with regard to meters walked during the 6MWT and QoL measured with Sickness of Impact Profile scale on its subscales sleep & rest and home management. The between-group between values 35 meters, -6 points and, -10 points ( $p < .05$ ), respectively. A lower score indicates a better QoL on the Sickness of Impact Profile scale.
- that there are no between-group difference between two-legged knee extensor training and one-legged knee extension regarding QoL on Sickness of Impact Profile overall and the subscales physical and psychosocial.
- that one-legged knee extensor training is superior to a passive control with regard to meters walked during the 6MWT, +28 meters ( $p < .001$ ), and QoL measured with the Sickness of Impact Profile: overall -4 points ( $p < .05$ ) and subscales physical -5 points ( $p < .05$ ), psychosocial -4 points ( $p < .05$ ) and sleep & rest -2 points ( $p < .05$ ).
- that there are no between-group difference regarding QoL in comparison to a passive control on the Sickness of Impact Profile subscale home management.

## 5.2 Can elastic resistance bands accurately evaluate muscular strength in healthy older adults? (Paper II)

A total of 30 healthy older men and women were included. Anthropometrics, elastic 1 RM, isokinetic values of muscular strength including mean differences, and ICC are seen in **Table 4**. No differences and an excellent agreement was seen between elastic 1 RM and isokinetic MPF values. If analyzed separately, the agreement was excellent among men and moderate among women. Individual variations, that is, 95% LOA, between elastic 1 RM and isokinetic maximum peak force was + 3.3 Kg if all participants were analyzed together, + 2.8 Kg among women, and + 3.2 among men if analyzed separately. Elastic band 1 RM was reached in a mean (SD) number of 7.7 (4.5) attempts.

**Table 4.** Anthropometrics, elastic 1 RM and isokinetic values including mean differences and intraclass correlation coefficient.

	All (n = 30)	Women (n = 15)	Men (n = 15)
<b>Anthropometrics</b>			
Age	60 (7)	59 (7)	61 (7)
Height (cm)	174 (7)	167 (6) **	180 (7)
Weight (Kg)	73 (13)	64 (7) **	82 (12)
<b>Shoulder flexion: Elastic bands</b>			
1 RM (Kg)	9.4 (3.8)	6.7 (1.8) **	12.0 (3.3)
<b>Shoulder flexion: Isokinetic values</b>			
MPF (Kg)	9.2 (3.0)	7.2 (1.4) **	11.2 (2.8)
MMF (Kg)	5.2 (2.0) *	3.7 (0.9) *,**	6.7 (1.6) *
PMF (Kg)	5.5 (2.1) *	3.7 (0.9) *,**	6.7 (1.6) *
<b>Mean difference (Kg) and ICC between elastic 1 RM and isokinetic values</b>			
1 RM / MPF	0.15 (-0.5 to 0.8)	-0.49 (-1.3 to 0.3)	0.80 (-0.1 to 1.7)
ICC	0.85	0.54	0.81
1 RM / MMF	4.2 (3.4 to 4.9) *	3.0 (2.3 to 3.7)*	5.4 (4.3 to 6.4) *
ICC	0.43	0.18	0.24
1 RM / PMF	3.9 (3.2 to 4.6) *	2.8 (4.0 to 5.9) *	5.0 (2.1 to 3.4) *
ICC	0.48	0.24	0.29

Data is presented as mean and standard deviation (SD) or 95% confidence intervals (95% CI). Log transformed ICC values are presented for all variables. \* p <.05, compared with elastic resistance band 1 RM \*\* p <.001, women compared to men. ICC; intraclass correlation coefficient, MMF = maximum mean force, MPF = maximum peak force, PMF = peak mean force, RM; repetition maximum.

### 5.3 Effects of HRSLE in patients with COPD (Paper IV)

A total of 44 patients with COPD met inclusion criteria and were randomized to either eight weeks of HRSLE+PE (experimental group) or to PE alone (control group). The sample size was based on a power calculation for the primary lower-extremity outcome (6MWT) and the primary QoL outcome (CRQ self-administered version). Both the HRSLE and the PE were implemented and administered in accordance with the trial protocol (Paper III). The mean attendance rate in the PE for both groups was 3.9 out of 4 sessions. No difference between groups in attendance was seen (mean difference 0.2, 95% confidence interval (95% CI) (-0.1 to 0.5),  $F(1,5) = 39$ ,  $p = .225$ ). No difference between groups in any of the tests performed was seen after test oxygen saturation regarding heart rate, dyspnea, and muscle fatigue ( $p = .051$  to  $.985$ ). All analyses were pre-specified in the trial protocol, with no additional analyses performed (Paper III).

Baseline values for exercise capacity and health-related outcomes are presented in **Table 5**. There was no difference in any of these variables or other characteristics between the experimental and the control group at baseline (see **Table 2**). Four (9%) patients used short-acting beta-2 agonists, five (11%) used inhaled long-acting beta-2 agonists, 31 (70%) used inhaled corticosteroids and, 34 (77%) used anti-muscarinic agents.

In **Table 6**, there are between-groups differences in effects presented. HRSLE+PE was more effective than PE alone with regard to most exercise capacity outcomes but without an effect on health-related outcomes.

**Table 7** provides descriptive data on responders and non-responders to the different outcomes. A responder was considered a patient experiencing a change equal to or larger than the known minimal important difference or the minimal detectable change for the specific outcome. For example, all individuals with a change of 10 or more on the CRQ were considered responders. The difference in baseline values (in percentages) for the specific outcomes between responders and non-responders is also presented. The responders had more than 20% better baseline values on the majority of outcomes (range 17-58%). Responders' baseline values had a mean 57% of the best possible score in contrast to non-responders, who had a mean baseline score of 78% of a possible optimal score.

**Table 5.** Baseline values for exercise capacity and health-related outcomes using linear mixed models.

Outcome	Randomized (n = 44)		
	Exp (n = 22)	Con (n = 22)	P
<b>Exercise capacity</b>			
6MWT (meters)	515 (473 to 557)	496 (454 to 538)	NS
6PBRT (rings)	260 (238 to 282)	267 (247 to 291)	NS
UULEX (seconds)	542 (486 to 599)	593 (536 to 649)	NS
SF-Strength (Nm)	34 (28 to 40)	34 (28 to 40)	NS
SF-Endurance (Joules)	474 (367 to 581)	476 (369 to 594)	NS
KE-Strength (Nm)	100 (87 to 113)	102 (88 to 115)	NS
KE-Endurance (Joules)	1936 (1667 to 2205)	1942 (1673 to 2211)	NS
CWR (Seconds)	321 (231 to 407)	311 (225 to 397)	NS
CWR (peak VO <sub>2</sub> )	17.5 (16 to 19)	16.6 (15 to 18)	NS
<b>Health-related QoL</b>			
CRQ-SA total (20-140) <sup>†</sup>	106 (99 to 114)	104 (96 to 112)	NS
CCQ total (0-60) <sup>‡</sup>	20 (16 to 24)	15(11 to 18)	NS
SF36 (PCS) <sup>†</sup>	43 (39 to 46)	43 (39 to 46)	NS
SF36 (MCS) <sup>†</sup>	52 (48 to 56)	53 (49 to 57)	NS
HADs (Anxiety) (0-21) <sup>‡</sup>	4.5 (3.1 to 6.0)	4.2 (2.8 to 5.6)	NS
HADs (Depression) (0-21) <sup>‡</sup>	3.5 (2.5 to 4.6)	3.2 (2.1 to 2.8)	NS
ESES (10-40) <sup>‡</sup>	24 (21 to 27)	25 (21 to 28)	NS
Self-efficacy walking (0-100) <sup>†</sup>	61 (50 to 72)	57 (46 to 68)	NS

6BRPT = 6 minute ring and pegboard Test, 6MWT = 6 minute walk test, CCQ = Clinical COPD Questionnaire, Con = Control group, CRQ-SA = Chronic Respiratory Questionnaire – Self-Administered, CWR = constant work rate cycle endurance test, ESES = Exercise Self-Efficacy Scale, Exp = experimental group, HADs = Hospital Anxiety and Depression scale, KE = knee extension, Nm = Newton meter, NS = Non significant, P = P-value, SF = shoulder flexion, SF36 = Medical Outcome Short Form-36, SF36 (MCS) = Mental Component Summary, SF36 (PCS) Physical Component Summary, UULEX = Unsupported upper extremity exercise test, VO<sub>2</sub> = maximal oxygen consumption (mL . Kg<sup>-1</sup> . min<sup>-1</sup>). Data is mean and 95% confidence interval. Grey = primary outcome for lower-extremity, upper-extremity and QoL respectively. <sup>†</sup> higher score is better, <sup>‡</sup> lower score is better. No differences were seen at baseline on any of these variables (p>.05)

**Table 6.** Between-group differences for exercise capacity and health-related outcomes using linear mixed models.

Outcome	Difference between groups*		
	Exp minus Con	F-value df	p-value ES
<b>Exercise capacity</b>			
6MWT (meters)	34 (14 to 54)	F(8.7) =39, p=.005	0.95
6PBRT (rings)	20 (3 to 37)	F(5.3) =39, p=.026	0.73
UULEX (seconds)	127 (78 to 176)	F(21.3) =39, p<.0001	1.46
SF-Strength (Nm)	4 (-0.2 to 8)	F(3.7) =36, p=.061	0.62
SF-Endurance (Joules)	60 (19 to 102)	F(8.7) = 36, p=.005	0.96
KE-Strength (Nm)	9 (3 to 16)	F(10.0) =38, p=.003	1.00
KE-Endurance (Joules)	184 (24 to 343)	F(6.1) =38, p=.018	0.79
CWR (Seconds)	38 (-79 to 155)	F(0.2) =35, p=.690	0.13
CWR (peak VO <sub>2</sub> )	0.2 (-1.5 to 1.9)	F(0.1) =35, p=.786	0.09
<b>Health-related QoL</b>			
CRQ-SA total (20-140) <sup>†</sup>	-0.9 (-9 to 7)	F(0.1) =39, p=.815	0.08
CCQ total (0-60) <sup>‡</sup>	-3 (-8 to 0.9)	F(2.6) =38, p=.117	0.51
SF36 (PCS) <sup>†</sup>	-1.2 (-5 to 3)	F(0.4) =39, p=.557	0.18
SF36 (MCS) <sup>†</sup>	2.5 (-2 to 7)	F(2.1) =39, p=.152	0.46
HADs (Anxiety) (0-21) <sup>‡</sup>	-1,2 (-3 to 0.7)	F(1.6) =39, p=.207	0.40
HADs (Depression) (0-21) <sup>‡</sup>	-1 (-2 to -0.1)	F(1.8) =39, p=.035	0.69
ESES (10-40) <sup>‡</sup>	-2 (-5 to 1)	F(1.7) =39, p=.202	0.41
Self-efficacy walking (0-100) <sup>†</sup>	7 (-7 to 21)	F(1.0) =40, p=.325)	0.31

6BRPT = 6 minute ring and pegboard Test, 6MWT = 6 minute walk test, CCQ = Clinical COPD Questionnaire, Con = Control group, CRQ-SA = Chronic Respiratory Questionnaire – Self-Administered, CWR = constant work rate cycle endurance test, ES = Effect Size (ES > 0.2 small effect size; ES > 0.5 medium effect size; ES > 0.8 large effect size), ESES = Exercise Self-Efficacy Scale, Exp = experimental group, HADs = Hospital Anxiety and Depression scale, KE = knee extension, Nm = Newton meter, SF = shoulder flexion, SF36 = Medical Outcome Short Form-36, SF36 (MCS) = Mental Component Summary, SF36 (PCS) Physical Component Summary, UULEX = Unsupported upper extremity exercise test, VO<sub>2</sub> = maximal oxygen consumption (mL . Kg<sup>-1</sup> . min<sup>-1</sup>). Log transformed F-values, df, p-values and ES are presented for variables with residuals not normally distributed. Data is mean and 95% confidence interval \* group x time interaction adjusted for center and sex set as fixed factors. Grey = primary outcome for lower-extremity, upper-extremity and QoL respectively. † higher score is better, ‡ lower score is better

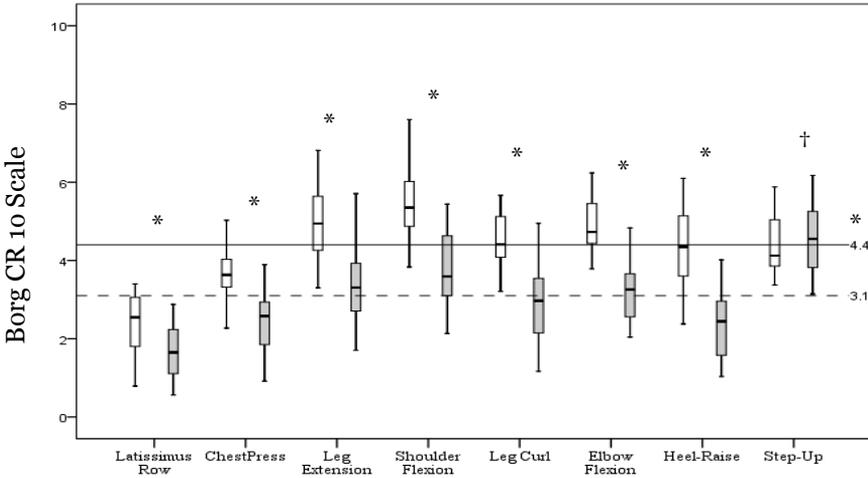
**Table 7.** Responders and non-responders in the experimental group including percentage difference in mean baseline values

Outcome	Experimental group (n = 22)			
	Responders	Non-responders	% Diff	MDC/MID
<b>Exercise capacity</b>				
6MWT (meters)	518 (463 to 573)	514 (437 to 590)	1 %	24
6PBRT (rings)	NA	NA	NA	NA
UULEX (seconds)	NA	NA	NA	NA
SF/KE-Strength (Nm)	NA	NA	NA	NA
SF/KE-Endurance (Joules)	NA	NA	NA	NA
CWR (Seconds)	284 (138 to 430)	321 (236 to 407)	12%	100
CWR (peak VO <sub>2</sub> )	NA	NA	NA	NA
<b>Health-related QoL</b>				
CRQ-SA total (20-140) <sup>†</sup>	84 (72 to 97)	114 (107 to 121)	26%	10
CCQ total (0-60) <sup>‡</sup>	26 (21 to 31)	17 (13 to 21)	35%	4
SF36 PCS <sup>†</sup>	NA	NA	NA	NA
SF36 MCS <sup>†</sup>	NA	NA	NA	NA
SF36 Physical Functioning <sup>†</sup>	55 (47 to 63)	67 (60 to 74)	18%	10
SF36 Role-Physical <sup>†</sup>	64 (46 to 82)	77 (68 to 86)	17%	12.5
SF36 Bodily Pain <sup>†</sup>	64 (49 to 80)	89 (74 to 105)	28%	10
SF36 General Health <sup>†</sup>	41 (36 to 47)	53 (44 to 63)	23%	10
SF36 Vitality <sup>†</sup>	54 (42 to 67)	66 (57 to 75)	18%	12.5
SF36 Social Functioning <sup>†</sup>	71 (57 to 85)	88 (79 to 98)	19%	12.5
SF36 Role-emotional <sup>†</sup>	68 (48 to 88)	94 (88 to 100)	28%	8.3
SF36 Mental health <sup>†</sup>	66 (55 to 77)	87 (80 to 93)	24%	10
HADs (Anxiety) (0-21) <sup>‡</sup>	7.4 (6.1 to 8.7)	4.2 (2.5 to 5.9)	43%	3.8
HADs (Depression) (0-21) <sup>‡</sup>	7.7 (5.3 to 10.0)	3.2 (2.5 to 3.8)	58%	3.99
ESES (10-40) <sup>‡</sup>	NA	NA	NA	NA
Self-efficacy walking (0-100) <sup>†</sup>	NA	NA	NA	NA

6BRPT = 6 minute ring and pegboard Test, 6MWT = 6 minute walk test, CCQ = Clinical COPD Questionnaire, CRQ-SA = Chronic Respiratory Questionnaire – Self-Administered, CWR = constant work rate cycle endurance test, Diff = Difference, ESES = Exercise Self-Efficacy Scale, HADs = Hospital Anxiety and Depression scale, KE = knee extension, MID = minimal important difference, MDC = minimal detectable change, NA = not available, Nm = Newton meter, SF = shoulder flexion, SF36 = Medical Outcome Short Form-36, SF36 (MCS) = Mental Component Summary, SF36 (PCS) Physical Component Summary, UULEX = Unsupported upper extremity exercise test, VO<sub>2</sub> = maximal oxygen consumption (mL . Kg<sup>-1</sup> . min<sup>-1</sup>). Box around outcomes = primary outcome for lower-extremity, upper-extremity and QoL respectively. † higher score is better, ‡ lower score is better

## Results

The HRSLE consisted of eight exercise; if muscle fatigue ratings (Borg CR10) from all exercises were combined and analyzed together, these ratings were higher than the combination of dyspnea ratings (mean difference 1.3 (1.1 to 1.5), ( $p < .001$ ). If each exercise was analyzed separately, the muscle fatigue rating was higher than the dyspnea rating in all of the eight exercises ( $p < .001$ ) except for the single-leg step-up ( $p = .349$ ) (Figure 5, modified from Figure 2:IV).



**Figure 5.** Muscle fatigue and dyspnea ratings

Borg CR10 rating on the elastic band exercises. Data is in mean (SD). Muscle fatigue (white boxes) and dyspnea (grey boxes) ratings on the different exercises in the high-repetitive single limb exercise regimen. Horizontal lines illustrate mean muscle fatigue (complete line) and dyspnea (scattered line) rating. \*  $p < .001$ , †  $p = .396$

### 5.3.1 Gender-related differences in training effects

Men in the experimental group showed larger improvements on walking ability measured with the 6MWT than women did (mean difference (95% CI), (19.3 meters [8.1 to 30.5], [ $p = .004$ ]). No differences in training effects were seen between men and women on any of the other outcomes: 6PBRT (mean difference [95% CI], (-3.2 rings [-28.7 to 22.3], [ $p = .783$ ]); UULEX (mean difference (95% CI), (14.4 seconds [80.12 to 109.0], [ $p = .738$ ]); maximal strength (mean difference [95% CI], [-2 Nm (-13.2 to 9.1)], [ $p = .691$ ]); limb muscle endurance (mean difference [95% CI], [103.8 Joules (-136.2 to 343.8)], [ $p = .353$ ]), during knee-extension or on maximal strength (mean difference [95% CI], [-2.3 Nm (-8.7 to 4.0), [ $p = .422$ ]); and limb-muscle endurance (mean difference [95% CI], [14.7 Joules (-40.5 to 70.0), [ $p = .555$ ]) during shoulder flexion. Paper IV was not properly powered to make clear conclusions regarding gender-related differences in effects of HRSLE, so the results should be interpreted as trends.

#### 5.4 Feasibility of HRSLE in patients with COPD and physiotherapists conducting the intervention (Paper V)

A total of 22 patients (12 female) with COPD and 5 physiotherapists (all female) conducting the HRSLE regimen were included. Data were used from all patients in accordance with intention-to-treat.

Participants randomized to the experimental group attended a mean (95% CI) 94% (91 to 97) of exercise sessions. These data include an additional week that was offered to all patients to reach the goal of a minimum of 20 out of 24 attended sessions. The additional week was not mentioned in the trial protocol (Paper III). Without the additional week, the attendance rate was 91% (87 to 94).

The mean exercise intensity measured as rated muscle fatigue during the intervention was 4.4 out of 5.6 obtained from the baseline 25 RM test, that is, 79% (74 to 83) of the predicted maximal intensity. An increase in resistance, exemplified for the knee-extension exercise, of mean 1.7 Kg (0.9 to 2.6) ( $p < .001$ ), that is, a 28% increase in resistance, was seen between the first and last exercise session for all elastic exercises. All patients started at level one in the heel-raise and the step-up exercise. At week eight the median (interquartile range) level was 2 (1-2.25) ( $p < .001$ ) and 1 (1-2) ( $p = .003$ ) for single-leg heel raise and single-leg step-up, respectively.

A total number of 26 adverse events were reported among 8 of the 22 patients and were distributed over 3.6% out of the total attended session.

- All adverse events were judged to be minor and temporary by one pulmonologist as well as by two physiotherapists. None of those who judged the severity of adverse events was involved in the study.
- The adverse events were musculoskeletal (such as pain or soreness: 64%), related to the elastic resistance bands (such as bruising, pain, laceration, swelling: 32%), and dizziness (4%).
- A total of 78% (7 out of 9) of adverse events related to the elastic bands were reported during the first seven sessions.

Compliance was assessed by rating of the ability to follow the instructions of the HRSLE regimen to a large extent. A rating of  $\geq 4$  was considered a large extent. Patient and physiotherapist ratings on the individual components of the HRSLE regimen are seen in **Table 8**. When looking at components together:

- In median (95%CI), 96% (94 to 96) of **patients** thought that they could follow the instructions to a large extent.
- In median (95%CI), 100% (94 to 100) of **physiotherapists** thought that they could follow the instructions to a large extent.

## Results

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**Table 8.** Percentages of patients and physiotherapists who could follow the instructions on the different parts of the HRSLE regimen to a large extent.

Outcome	Included (n = 27)	
Component	Patients ability to follow the instructions to a large extent (n = 22)	Physiotherapists ability to follow the instructions to a large extent (n = 5)
The whole HRSLE regimen	100%	100%
The warm-up	96%	100%
The eight exercises*	96%	100%
The cool-down	82%	50%
The speed of movement**†	96%	88%
The no. of repetitions*	96%	100%
The ratings of exertion*‡	91%	100%

\*Questions related to the elastic bands, †one second in each direction for all but the step-up exercise, ‡ muscle fatigue and dyspnea. Data is presented in percent. HRSLE = high-repetitive single limb exercise

The physiotherapists were also asked: To what extent could the **patients** follow the instructions regarding the whole exercise regimen?

- There was no difference between the patients' and the physiotherapists' ratings on any of the different components of the HRSLE regimen regarding the patients' ability to follow the instructions to a large extent ( $p=.261$  to  $733$ ).

The physiotherapists were also asked about the progression, and 71% thought that they could follow the instructions to a large extent.

## 5.7 Key messages - Results

### **Paper I:** Evidence for single limb exercises

- In patients with COPD, a low quality of evidence indicates that one-legged cycling seems to be more effective than two-legged cycling regarding cycle endurance capacity but not dyspnea.
- In patients with CHF, a low quality of evidence indicates that a single-limb exercise regimen seems to be more effective than two-legged cycling and a passive control regarding exercise capacity outcomes and QoL. Two-legged knee-extensor training seems to be more effective than one-legged knee-extensor training regarding walking ability and some QoL outcomes

### **Paper II:** Elastic bands to evaluate muscle strength

- No significant difference between values were seen between elastic 1 RM and isokinetic MPF. Agreement was excellent among men and if both men and women were analyzed together. Agreement was moderate among women if analyzed separately.

### **Paper IV:** Effects of HRSLE in patients with COPD

- Between groups differences in favor of HRSLE + PE in comparison to PE alone were found regarding primary (6MWT and 6PBRT) and a majority of secondary exercise capacity outcome measures and on the HADs depression scale.
- No differences were found between groups on a majority of health-related QoL outcome measures including the primary QoL outcome (CRQ self-administrated) and no gender-related differences in training effects other than a larger effect regarding meters walked among men on the 6MWT.

### **Paper V:** Feasibility of HRSLE in patients with COPD

- HRSLE seems to be feasible for patients with COPD and physiotherapists conducting the intervention with excellent attendance and compliance to the HRSLE. A high exercise intensity was achieved, and no serious adverse events occurred.

## 6. Discussion

The aim of the present thesis was to examine the feasibility, methodology effects and evidence of single limb exercises in patients with COPD. A systematic review was conducted as a first step to study the current evidence for single limb exercises in patients with COPD and in patients with CHF (Paper I). The low quality of the current evidence, mainly due to the poor methodological quality of the studies included, indicates that further research is very likely to have an important impact on our confidence in the estimates of the effects reported in the review.

Results from the validation study (Paper II) indicate that elastic resistance bands could be used to evaluate muscular strength in healthy older adults. The agreement between the measurements was moderate (women) to excellent (men and men and women analyzed together). Nevertheless these results are of importance since isokinetic dynamometry is thought to provide the most accurate evaluation of muscular strength.

With regard to the HRSLE regimen evaluated in the multicenter RCT, a trial protocol including a comprehensive description and standardization was developed (Paper III). The eight-week HRSLE regimen was found to be effective regarding most exercise capacity outcomes but showed no change in health-related QoL in patients with moderate to severe COPD (Paper IV). The HRSLE regimen was performed as resistance training with elastic resistance bands as exercise equipment and was considered feasible in patients with COPD with a high attendance rate, high relative exercise intensity, no severe adverse events and excellent compliance. Compliance was also excellent among the physiotherapists conducting the HRSLE in a clinical setting (Paper V).

### 6.1 Effects, mechanisms and explanations

#### 6.1.1 Low quality evidence for single limb exercises (Paper I)

The quality of evidence for single limb exercises in both patients with COPD and patients with CHF, is explained mainly due to the low methodological quality, small sample sizes, and poor reporting in included studies. These shortcomings, were the main reasons for the low quality of available evidence in accordance to GRADE guidelines (138-142), which limits the strength of the conclusions that could be drawn at that time. Specifically, only two studies for patients with COPD met inclusion criteria at the time for the review. Since then two studies, one by Brønstad and colleagues (97) and one presented in this thesis (Papers IV and V) have been performed on single limb exercises in this group of patients. The single limb strategies (one-legged knee extension and HRSLE) differ in comparison to the studies included in the review, however, and would most likely be analyzed separately if a new systematic review were to be performed.

#### 6.1.1.1 Effects on exercise capacity

Because the effects of exercise training are determined by the intensity and duration of the exercise performed, the larger-scale effects in the single limb exercise groups in COPD studies included could be somewhat explained by the larger amount of muscle-specific work obtained in these groups (95, 96). Positive effects of single limb exercise regimens on exercise capacity were also seen for the patients with CHF when compared to a two-legged cycling group and a passive control group receiving no intervention. A maintained peripheral blood flow and muscle perfusion have been demonstrated when involving only one limb at a time, (i.e. a reduced simultaneous muscle mass involved), but not seen when involving a major muscle mass (180). This could be a reason for the advantage of single limb approaches. Interestingly, in patients with CHF two-legged knee extensor training was superior to one-legged knee extension training with regard to exercise capacity. Although the relative training load was similar in the two training groups, the training intensity determined in the percentage of peak oxygen uptake was higher in the two-legged group which could be an explanation for the larger-scale effects in that group (181). The idea of single limb exercises is that involvement of a smaller amount of muscle mass would allow higher muscle-specific training loads than if a larger amount of muscle mass were involved since the central limitation would not be a limiting factor. In the study by Tyni-Lenné and colleagues (181) the relative training loads were matched and the potential benefit of single limb exercises (allowing higher muscle specific training loads) was not assessed. Moreover, the intensity of the activity performed (70% of peak performance) could perhaps been low enough for the circulatory system to provide sufficient oxygen to working muscles even when the patients with CHF performed the two-legged knee extension exercise. It would have been interesting to see what would have happened with no match of exercises intensities and if the patients had carried out exercises at higher intensities.

#### 6.1.1.2 Effects on QoL and dyspnea

None of the COPD studies included in the systematic review covered the effects of one-legged cycling on QoL. In patients with CHF, the results from the systematic review indicate that single limb exercise regimens seems to be more effective than no intervention in a control group. These differences between groups in favor of the single limb regimens no longer appeared if compared to a control group performing an activity such as two-legged knee extensions and cycle training. It has been argued that the positive effects seen on QoL in comparison to control groups receiving no intervention may not be the result of the physical training itself, but of other placebo effects such as the training situation, attention, supervision and peer support (181). The results regarding dyspnea, indicate no difference between one-legged cycling and two-legged cycling in patients with COPD (96).

### 6.1.2 Evaluating muscular strength with elastic bands (Paper II)

Elastic resistance bands previously have been found to be valid and reliable in measuring muscle performance with a focus on muscle endurance in older adults performing elbow flexion (110). Our results indicate that elastic resistance bands could also be used to evaluate maximal effort, that is, 1 RM during shoulder flexion in healthy older adults. These results are important for patients with COPD because 1 RM testing is the main field test used in the assessment of muscle performance in this group of patients (109). Since the limited availability of weight-machines after completing a pulmonary rehabilitation program can be a barrier to maintenance of exercise capacity (71), the potential use of elastic resistance bands both as an exercise and an assessment tool is of interest. Especially because using the same approach in both training and assessment appears more sensitive to gains. Thus, these data were collected among healthy individuals, and not patients with COPD. The transferability of the results directly to patients with COPD could be questioned and specific studies in this group of patients are necessary to explore whether the results could be reproduced in COPD.

The increase in the length of an elastic band, which occurs in any dynamic movement, will result in a progressive increase in resistance (80, 183). It could therefore be argued that the properties of the elastic equipment make accurate evaluations of 1 RM difficult. However, most interestingly, our observed difference between the elastic resistance 1 RM / the isokinetic MPF, and the individual variation was even lower than in a test-retest study of isokinetic shoulder flexion previously performed by our group (22). The individual variation among both women and men and the moderate agreement among women are also important to consider when deciding to use elastic resistance to evaluate muscular strength.

### 6.1.3 Effects of HRSLE on patients with COPD (Paper IV)

#### 6.1.3.1 Effects on exercise capacity

The effects of HRSLE on upper-extremity capacity were similar or greater in comparison to other resistance training studies on patients with COPD using the 6PBRT (72, 171) or the UULEX (72, 184, 185). Comparable increases in isokinetic knee-extension strength and endurance was also shown (186, 187). Since no minimal detectable change or minimal important difference values, to our knowledge, are available for these outcomes measurements in patients with COPD the clinical relevance of these differences are difficult to determine. Thus, we found a significant effect on walking ability in contrast to the previous resistance training studies (71). The change from baseline in the experimental group is in line with the minimal important difference for the 6MWT reported in 2010 (188). This even though, 95% of the patients in the experimental group had a baseline walking distance of more than 350 meters and 64% were older than 65, which have indicated a smaller change in walking distance (188).

The musculoskeletal response to exercise training is greater in individuals with lower initial values (as expected with larger-scale dysfunctions) compared to those with higher values (189). The high baseline values in the present study could therefore even indicate a possible underestimation of the treatment results of the group compared to the populations in other studies or when generalized to the COPD population in total. However, the results from our study are valid only in patients with moderate to severe COPD performing the HRSLE regimen in a supervised hospital outpatient setting. This is unfortunate, as we also aimed to incorporate patients with very severe COPD to increase the external validity of the results.

In comparison to previous single limb exercise strategies in COPD, one advantage of HRSLE is that both upper- and lower-limb muscles were incorporated. This is important because both upper- and lower-limb muscles are impaired in this group of patient (42, 95-97), especially when considering that the local effects of exercise training occur only in the muscles involved. Another advantage is the use of elastic bands and body weight as resistance. Elastic bands offer portable and inexpensive exercise equipment that is easy to use and that has shown comparable results to weight machines in both upper- and lower-extremity exercises in healthy adults (78, 81-83). The portability of elastic bands and the standardization of the HRSLE regimen offer the opportunity of performing the HRSLE at home and thereby offers an alternate approach to accessing pulmonary rehabilitation for patients with COPD (71, 74, 91). Although this could increase the availability of exercise training for this group of patients, especially for those with more severe disease, we do need to examine the possible effects and feasibility of HRSLE in this setting before any assumptions can be made. No within- or between-group differences were found on the constant work cycle endurance test regarding maximal oxygen uptake and peak endurance time. This was not surprising since we used a single limb approach, which minimize the load on the ventilatory and circulatory system. These results are in line with the study by Brønstad and colleagues (97) showing no change in maximal oxygen uptake following single leg knee-extension.

#### 6.1.3.2 Possible explanations for effects on exercise capacity

As previously mentioned, intensity and duration of the activity performed are key factors determining the response to exercise training. In Paper IV, higher fatigue than dyspnea ratings were achieved in seven out of eight exercises in the HRSLE. This indicates that this single limb strategy was successful as the ventilatory limitation was not the main limiting factor. As for the positive effects of single limb exercise regimens on exercise capacity outcomes in patients with COPD reported in the systematic review, the effects in the multicenter RCT could therefore be explained, to some extent, by the large workloads and thus the high exercise intensities achieved for muscles involved.

The differences between groups in favor of the HRSLE on functional upper- and lower-limb capacity in Paper IV were achieved without an increase in maximal oxygen uptake which supports a peripheral rather than a central adaptation. The results of the isokinetic tests also supports a peripheral adaptation after the HRSLE since an increased force-generating capacity in both upper- and lower-extremity muscles in favor of the HRSLE were demonstrated. The results were obtained without any increase in symptoms, which is important, because an increased force-generating capacity together with desensitization to symptoms are considered potential mechanisms that explain improved functional capacity in patients with COPD (71, 76).

Furthermore, in COPD, unpublished data suggest that a single-leg low-load high-repetition exercise induced muscle fatigue in the absence of muscle deoxygenation despite low cardiorespiratory demand and exercise load (190). This is important since greater training effects in terms of functional exercise capacity have been shown in patients with COPD who develop quadriceps contractile fatigue during exercise training (191). Perhaps this could explain to some extent the positive effects of the HRSLE on exercise outcome measures.

Because none of the patients had exercised within the preceding six months before the start of the study, and the intervention lasted for only eight weeks, we acknowledge that the increase in muscle strength and limb muscle endurance in part could be explained by neuronal adaptations (192). On the other hand, an increased percentage of type IIAX muscle fibers, myosin heavy chain isoform and cross-sectional area have been demonstrated in healthy untrained men following eight weeks of high-repetitive (20-28 repetitions maximum) resistance training (193). In COPD, increased oxygen uptake and increased maximal mitochondrial respiration in working muscles have been reported after six weeks of one-legged knee extensor training (194). These data imply that changes, other than neuronal adaptations, in muscle characteristics are possible even in a short intervention period.

### 6.1.3.3 Effects on health-related QoL

With regard to health-related QoL, no differences between groups were observed between the single limb approach (HRSLE) and the passive control other than a significant difference in favor of the HRSLE group on the depression component of the HAD scale. The passive control in our study received educational sessions (PE) in order to minimize potential placebo effects.

### 6.1.3.4 Possible explanations for lack of effect on health-related QoL

The possible low responsiveness of the primary outcome (CRQ self-administrated) (72) and the high baseline values on this outcome, which may have reduced the possible room for improvement (195), could to some

extent explain the results. A sub-analysis of responders and non-responders to health-related outcomes with known minimal important differences or minimal detectable changes was made. This analysis demonstrated differences in baseline values between responders and non-responders between 17% and 58%. Also of interest, responders' baseline values were a mean of 57% of the best possible score in contrast to non-responders having a mean baseline score of 78% of a possible optimal score. These differences do not tell us whether we would have found an effect if patients with lower health-related QoL had been incorporated. Thus, the results indicate that we need to include patients with lower health-related QoL before we can conclude the potential effect, or lack of effect, of HRSLE on these outcomes in this group of patients.

#### 6.1.4 Feasibility of the HRSLE regimen (Paper V)

The HRSLE used demonstrated excellent attendance, high relative exercise intensity, excellent compliance and only minor and temporary adverse events. A possible explanation for the feasibility of the HRSLE regimen might be the design of the intervention, that is, the single limb approach. The perception of dyspnea in patients with COPD is a major obstacle to exercise training and physical activity. Since single limb exercises are design to lower the load on the ventilatory system patients will be less dyspnoeic during single limb exercises in comparison to traditional exercises. As seen during the HRSLE regimen that was not used, the limiting factor during exercises was muscle fatigue and not dyspnea (Borg ratings). The knowledge that they were performing an intervention in which they did not feel ventilatory limited may have contributed to the high attendance rates and the high exercise intensity. The lack of dyspnea may also work as a motivational tool for the patients, knowing that they can exert themselves without worrying that they are not getting air or are having difficulties breathing. The low number of temporary and minor adverse events indicate that the exercise regimen and the use of elastic bands as resistance could be as feasible alternative to established exercise modalities in patients with COPD.

#### 6.1.5 Gender-related differences

We only found few gender-related differences in our studies. The lack of differences between women and men indicate, in similarity with a systematic review on the topic, that women and men can benefit from the same exercise regimen (54). It is important that the results with regard to gender-related differences in patients with COPD should be seen only as trends because we did not have an adequate sample size. The evidence today for potential gender-related differences is inconsistent, it seems to be insufficient evidence to support or refute gender-related differences in pulmonary rehabilitation outcomes (54).

## 6.2 Methodological considerations

One overall aim of this thesis was that reporting of results should be based on studies of high methodological quality. In an attempt to improve the quality of the methodology used in the different study designs, specific guidelines were followed. The systematic review (Paper I) was designed in accordance with the PRISMA statement (125), the multicenter RCT (Paper IV) in accordance with the CONSORT guidelines (120, 126) with a development of a trial protocol (Paper III) and the sub analysis of the feasibility of the HRSLE used in the multicenter RCT (Paper V) reported in line with STROBE guidelines (127). This is important because biased results that could lead to incorrect conclusions may be a consequence of a poor reporting and inadequate methods, a problem often arising from poor methodology (121, 122, 196). The use of these guidelines is not a guarantee of high methodological quality, but they could assist with the design of the studies. In our studies the guidelines have definitely contributed to the methodology. However, even though following these guidelines we do need to acknowledge that if our studies would be examined we would not be able to receive the highest ratings. In methodological quality ratings there are some aspects that are more difficult to fulfill depending on the design of the study performed. In our studies on the HRSLE regimen it is difficult to blind patients and personnel (the physiotherapists). The lack of blinding will result in a lower methodological quality in comparison to a study able to blind both patients and personnel. However, this is not an issue of the guidelines but rather of the scales used to grade study quality.

In addition to following the PRISMA statement (125) in the design of the systematic review (Paper I), it was decided to use a high-sensitivity search strategy in order to minimize the risk of missing potentially eligible studies. Thus, the decision to include only English-language RCTs may have resulted in potentially relevant studies being omitted. There could have been studies in other languages or studies with other study designs that might have provided additional information but these were not investigated. Another limitation is that a meta-analysis was considered impossible mainly due to lack of homogeneity in the majority of single limb exercise regimens and outcome measures used. Although, in COPD, both studies included used similar interventions, control groups and outcome measures. It would therefore have been possible to perform a meta-analysis in COPD. However, it is argued that such a low number of studies is not suitable for conducting a meta-analysis (197). Consequently it was decided to summarize the evidence with accordance to GRADE (138-142), one advantage of GRADE, in comparison to other similar tools, is that it takes into account more than the internal validity (study quality) in the assessment. GRADE also looks at directness, precision, consistency and publication bias (138-142). Although it is important to look not only at study quality, the ratings in these other categories are not always straightforward. For example, publication bias (i.e., missing studies) was difficult to investigate as well as assessment of precision and directness.

This was mainly due to lack of information provided in the articles included. The use of guidelines such as the CONSORT statement (120, 126) and the STROBE guidelines (127), together with trial registrations and the publication of trial protocols, hopefully will make this easier in the future.

In the validation study (Paper II), the use of comprehensive standardization, including mirroring of tests, standardization of rest periods, execution in accordance with recommended guidelines and standardized instructions and encouragement are considered as strengths of the study. Other strengths included the use of an isokinetic dynamometer as a “gold standard” in the assessment of validity of elastic bands to evaluate 1 RM since isokinetic dynamometers are considered to provide the most accurate assessment of muscular strength (148). Isokinetic dynamometers are found to be valid and reliable across a wide range of velocities and in different exercises (198-201). As the capacity of muscles has proved to differ depending on how far from the body the movement is performed (202) one limitation is that even though the execution of the movements were standardized in the same way for both tests' equipment, some differences were observed. Specifically, the degree of abduction during shoulder flexion could not be controlled with elastic bands. Since the joint loading on the muscle will be affected by the angle of insertion of the elastic resistance band, we cannot say if a similar relationship and minor differences would be obtained by sitting in a different position (203). This is important because the dynamometer involves a sitting position that is different from sitting in an ordinary chair or standing, positions that are used in clinical settings, which may affect the feasibility of the results. The lack of randomization (starting order) is also a limitation that has to be considered. Even though we aimed to include participants in the validation study of similar age as potential eligible patients with COPD for the multicenter RCT, these data pertain exclusively to healthy older individuals. Because there are differences in muscular strength between patients with COPD and healthy individual(40, 59, 133, 204), we also need to perform similar studies in patients with COPD in order to determine the feasibility of using elastic resistance to evaluate muscular strength in these patients.

A systematic review of peripheral resistance training for patients with COPD has suggested increased attention on minimizing the risk of bias in studies (71). In a review of parallel group RCTs, published between 2000 and 2006 only 1% reported a trial protocol (124). A comprehensive description and standardization of the HRSLE and PE used, the design in line with the CONSORT guidelines (120, 126), and the construction and publication of a trial protocol (Paper III) represented the main methodological strengths of the multicentre RCT (Papers IV and V). This was performed in order to facilitate implementation and increase the reproducibility of the trial. Other strengths were that outcome assessors were blinded to treatment allocation, and that data analyzed using intention-to-treat and primary outcome data were controlled and verified

by a third independent party also blinded to treatment allocation. The decision to design the HRSLE in accordance to ACSM recommendations (73) for increasing limb muscle endurance also gives strength to the design of the intervention. It could be argued that these guidelines are for healthy individuals and not patients with COPD. Although, the latest guidelines in pulmonary rehabilitation now also encouraged resistance training studies to follow ACSM recommendations (4).

The use of a passive control is a limitation of the study; the decision was made because of to the lack of research on both low load /high repetition resistance training and the use of elastic equipment in this group of patients. Other limitations included lack of inclusion criteria for centers included in this multicenter RCT that was based solely on interest in participating and that the majority of patients included were only moderate in the stage of their disease. However, the healthcare system was the same for all centers, several considerations were made to minimize the effect of using different centers (128) and patients with moderate disease are one of the larger groups in the COPD population (205). Another limitation is that no long-term follow-up was performed. With specific regard to the feasibility of the HRSLE, strengths included the rating of severity of adverse events, the use of raters not involved in the study and the assessment of compliance to the different parts of the HRSLE regimen in both participants and physiotherapists. Limitations included that no particular instructions were given to the physiotherapists at baseline to note adverse events which may imply a possible underestimation of the occurrence of adverse events and that no participants with very severe COPD were included, as originally intended.

### 6.3 Clinical implications

The main clinical implication of this thesis is that a high-repetitive single limb exercise regimen performed as resistance training using elastic bands as primary resistance (the HRSLE regimen) is effective with regard to upper-extremity functional capacity and endurance and lower-extremity functional capacity strength and endurance in patients with moderate to severe COPD. This is of importance since it offers an exercise alternative that incorporates both upper- and lower-extremity muscles that could be performed with a high load on the muscles involved without a high-level perception of dyspnea.

The HRSLE regimen was tested in a clinical setting and is considered feasible for patients demonstrating excellent attendance and compliance, high relative exercise intensity and no severe adverse events. Of importance, is that the HRSLE regimen is also feasible for the physiotherapists who are to perform the intervention in their clinical setting. The HRSLE regimen is highly standardized with well-described exercises and individualized resistance and progression. This training regimen could, consequently, easily be implemented in clinical settings. The use of elastic bands as resistance, in combination with the design of

the study (group training, use of inexpensive elastic bands as equipment, stretching of elastic band instead of adding bands to increase resistance and low number of bands needed to exercise the entire body) indicate that the HRSLE regimen may be cost-effective. It also seems possible, in healthy older individuals, to use elastic bands to evaluate the effects of resistance training on muscular strength. This is of importance since elastic resistance bands offer an inexpensive alternative for the assessment of muscular performance, which also may be more sensitive to change.

#### 6.4 Implications for future research

It is of importance to see if the feasibility and effects of a high-repetition single limb exercise regimen could be reproduced in this group of patients with COPD. Future studies should also involve patients with more severe disease, patients with larger muscular dysfunctions and with lower health-related QoL. Specific study of resistance training involving patients with low QoL, self-efficacy and the presence of anxiety or depression would be of interest in order to be able to determine the effect of resistance training alone on health-related QoL in COPD. Since there is a lack of well-described, high-quality studies especially comparing the effects of one single limb exercise regimen over another, such studies are necessary. They should preferably involve both upper- and lower-extremity muscles and incorporate both subjective and objective outcome measures for both exercise capacity and health-related QoL with long-term follow-up. It is also important to investigate if single limb exercises such as one-legged exercises are better than two-legged exercises with regard to functional outcome measures. If single limb exercises are better than functional exercises with regard to functional outcomes and if single limb exercises have an effect on daily physical activity and/ or activities in daily life.

Of personal interest is that potential structural and muscular adaptations could not be confirmed since the mechanisms underlying the improvements were not assessed in the RCT performed in this thesis. Also, as no comparisons were made with an active control, we could not conclude if the patients would have been able to perform the HRSLE regimen with the same response involving a larger amount of muscle mass (e.g. exercising with both legs or both arms simultaneously compared to one leg or one arm at a time as used in the HRSLE regimen). I hypothesize that an increase in muscle mass involved during training would lead to larger restraints on the ventilatory system and, as a consequence, to reduced exercise stimulus for the muscles involved and lesser treatment effects in comparison to single limb high-repetitive exercise. Conversely, single limb interventions should produce less dyspnea and more muscle deoxygenation and fatigue than arms/legs simultaneous training. Single limb training should therefore be associated with greater physiological adaptation to training in comparison to arm/leg simultaneous training. However, this needs further study, especially considering that in patients with CHF, two-legged knee extension seemed not to result in circulatory

limitation. Furthermore, it has been suggested that a single-leg low load/high repetition exercise can induced muscle fatigue in patients with COPD. This is of importance since greater training effects in terms of functional exercise capacity have been shown in patients with COPD who develop quadriceps contractile fatigue during exercise training. Whether muscle fatigue can be induced by HRSLE resistance training remains to be investigated.

Future research is also recommended to study the reliability of elastic resistance bands for maximal effort and the relationship between elastic resistance and isokinetic measures. It is also of interest to investigate the relationship using different numbers of repetitions, assessing different aspects of muscular performance preferably involving also other upper and also lower limb movements in both healthy individuals and in patients.

## 7. General conclusions

From the results of the studies in this thesis the following conclusions are made:

- Very low to low quality evidence indicate that one-legged cycling may be effective, with regard to exercise capacity outcomes but not dyspnea in patients with COPD.
- Low quality of evidence indicate that single limb exercise regimens may be effective, with regard to exercise capacity outcomes and QoL in patients with CHF if compared to two-legged cycling or a passive control. Two-legged knee extensor training seems to be more effective than one-legged knee extensor training regarding walking ability and some QoL outcomes.
- Elastic resistance bands could be used to evaluate shoulder flexion muscular strength in healthy older men since an excellent agreement and no difference between elastic resistance band 1 RM and isokinetic MPF was found.
- Elastic resistance bands may be used to evaluate shoulder flexion muscular strength in healthy older women even though only a moderate agreement was found between elastic resistance band 1 RM and isokinetic MPF since no significant difference between values were seen.
- HRSLE appears to improve walking capacity, upper-extremity functional capacity, upper-extremity endurance, and upper- and lower-extremity muscular function but not cycle endurance capacity in patients with moderate to severe COPD.
- HRSLE appears to have no effect on health-related QoL outcomes in patients with moderate to severe COPD.
- HRSLE is feasible for both patients with moderate to severe COPD and physiotherapists conducting the intervention.

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