Physical training in patients with chronic obstructive pulmonary disease – COPD

Karin Wadell

Umeå 2004
To my family
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ABSTRACT

Physical training in patients with chronic obstructive pulmonary disease – COPD

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Chronic obstructive pulmonary disease, COPD, places a substantial burden of disability on the growing number of patients and causes large costs for the society. Tobacco smoke is the most important risk factor. Progressive exertional dyspnea is the major symptom which leads to diminished physical and social activities, reduced physical capacity and decreased health related quality of life, HRQoL.

The aim of this thesis was to evaluate different physical training modalities in patients with COPD with regard to physical capacity and HRQoL. Patients with moderate to severe COPD were included in the studies. In the first intervention, 20 patients trained on a treadmill with or without supplemental oxygen, three times per week, during eight weeks. In the second intervention, 30 patients were randomised to high-intensity group training either in water or on land, and 13 patients were included in a control group. The patients in the water and land groups trained three times per week during three months and once a week during the following six months.

Oxygen supplementation during physical training did not enlarge the positive effects of the same training with air in patients with exercise-induced hypoxaemia. Both groups improved the distance walked after training. High-intensity group training in water and on land was found to be effective with regard to walking distance and HRQoL compared to the control group. Training in water seemed to be of greater benefit compared to training on land concerning walking distance and experienced physical health when the training was accomplished three times per week. The thigh muscle strength increased after training in both the water and the land group. The muscle endurance in knee extension was low in the majority of the patients and was not improved after the training intervention. An evaluation of the long-term effects of physical group training and the effects of decreased training frequency showed that training with low frequency (once a week) during six months did not seem to be sufficient to maintain the level achieved after a three months period.
of higher frequency training (three times per week). However, the two periods combined seemed to prevent decline in physical capacity and HRQoL compared to baseline.

The conclusion is that physical training is of benefit for patients with COPD with regard to physical capacity and HRQoL. Training can be performed individually or in groups, with high intensity, in water and on land. It is also concluded that the training can, under controlled conditions, be performed without supplemental oxygen even in patients with exercise-induced hypoxaemia.

Keywords: Chronic obstructive pulmonary disease; Physical training; Oxygen; Water training; Group training; Physical capacity; Health related quality of life; Long-term effect
SVENSK SAMMANFATTNING

Fysisk träning vid kroniskt obstruktiv lungsjukdom – KOL

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Kroniskt obstruktiv lungsjukdom (KOL) är idag den fjärde vanligaste dödsorsaken i världen och sjukdomen ökar i förekomst. Tobaksrökning är den största riskfaktorn för sjukdomen som orsakar ett avsevärt lidande för både patienter och anhöriga. Hosta och en alltmer ökande ansträngningsutlöst andfåddhet är de vanligaste symtomen vid KOL. Den ökande andfåddheten leder till att patienter med KOL minskar sina fysiska och sociala aktiviteter, får sänkt fysisk förmåga och försämrad livskvalitet. De mediciner som används idag har begränsade möjligheter att minska symtomen. Fysisk träning har visat sig ha bra effekt på symtom och är numera en av hörnstenarna vid rehabilitering av KOL patienter. Det finns dock ännu ingen konsensus om hur man bäst förbättrar patienternas fysiska förmåga och hälsorelaterade livskvalitet.

Syftet med denna avhandling var att utvärdera effekterna av olika typer av fysisk träning med avseende på fysisk förmåga och livskvalitet. Patienter med måttlig till grav KOL inkluderades. I första interventionen tränade 20 patienter på gångmatta, med eller utan syrgas, tre gånger/vecka under åtta veckor. I andra interventionen randomiserades 30 patienter till gruppiträning antingen i bassäng eller på land, tre gånger/vecka under tre månader, därefter en gång/vecka under sex månader. Tretton patienter inkluderades i en kontrollgrupp. Syrgas under träning gav inga ytterligare positiva effekter jämfört med samma träning med luft hos patienter med ansträngningsutlöst hypoxemi. Högintensiv gruppträning i bassäng och på land ledde till ökad gångsträcka jämfört med kontrollgruppen. Patienterna i bassänggruppen ökade även sin utåthållighet i gång och förbättrade sin upplevda fysiska hälsa mer än de i landgruppen. Den maximala lårmuskelstyrkan förbättrades i båda träningsgrupperna. Den muskulära utåthålligheten i knäextension låg hos majoriteten av patienterna och den förbättrades inte efter träning. Vid utvärdering av långtids effekter av högintensiv träning och effekt av reducerad träningsfrekvens påvisades att lågfrekvent träning (en gång per vecka) under sex månader inte var tillräckligt för att bibehålla de positiva
effekterna på gångsträcka och livskvalitet som uppmätts efter en tremånadersperiod med högfrekvent träning (tre gånger per vecka). Däremot förhindrade dessa två träningsperioder tillsammans en försämring jämfört med utgångsvärdena före studiestart.

ABBREVIATIONS

6MWD = 6 minute walking distance test
ACCP/AACVPR = American College of Chest Physicians/American Association of Cardiovascular and Pulmonary Rehabilitation
ACSM = American College of Sports Medicine
ANOVA = Analysis of variance
ATS = American Thoracic Society
BMD = Bone mineral density
BTS = British Thoracic Society
COPD = Chronic obstructive pulmonary disease
CR10 = Category ratio scale (Borg)
CRDQ = Chronic Respiratory Disease Questionnaire
ECG = Electrocardiography
ERS = European Respiratory Society
ES = Effect-size
ESWT = Endurance shuttle walking test
FEV1 = Forced expiratory volume during one second
FRC = Functional residual capacity
FVC = Forced vital capacity
GOLD = Global initiative for chronic obstructive lung disease
HRQoL = Health related quality of life
ISWT = Incremental shuttle walking test
ITT = Intention to treat
MCID = Minimum clinically important difference
MCS = Mental component score
OT = On treatment
PCS = Physical component score
RPE = Ratings of perceived exertion (Borg)
RPM = Rates per minute
RV = Residual volume
SaO2 = Arterial oxygen saturation (measured in arterial blood)
SpO2 = Oxygen saturation (measured with pulse oximeter)
SF-36 = Short form-36 health survey
SGRQ = St George’s Respiratory Questionnaire
VC = Vital capacity
VE = Minute ventilation
VCO2 = Carbon dioxide production
VO2 = Oxygen uptake
The present thesis is based on the following papers, which will be referred to by their Roman numerals:


IV Wadell K, Henriksson-Larsén K, Lundgren R, Sundelin G. Group training in patients with COPD - Long-term effects of decreased training frequency. Accepted for publication in Disability and Rehabilitation.

The original papers have been reprinted with kind permission of the publishers.
INTRODUCTION

Chronic obstructive pulmonary disease (COPD), mainly caused by tobacco smoking, is a major cause of chronic morbidity and mortality throughout the world. It is now the fourth leading cause of death in the world (WHO 2002) and further increase in the prevalence and mortality of the disease is predicted in the coming decades. COPD is one of few major causes of death with increased prevalence worldwide (ERS 2004).

Definition

COPD is a chronic, progressive disorder characterised by reduced maximum expiratory flow and slow forced emptying of the lungs (reduced FEV₁/VC ratio and FEV₁) which is not fully reversible and does not change markedly over several months (Siafakas, Vermeire et al. 1995). There are different classifications of COPD; BTS and GOLD have the criteria of FEV₁/VC ratio < 0.7 (BTS 1997; Pauwels, Buist et al. 2001), ERS has differed between men and women (Siafakas, Vermeire et al. 1995) whereas ATS defined the obstruction as “airflow obstruction due to chronic bronchitis or emphysema” (ATS 1995). ATS/ERS have recently agreed on common guidelines in which the criterion of FEV₁/VC ratio is < 0.7 (Celli and MacNee 2004). Various definitions of COPD do also have different classifications of disease severity. Table 1 presents the different definitions and disease severity classifications. Most of the airflow obstruction is slowly progressive and irreversible. The airflow obstruction is due to varying combinations of airway disease (chronic bronchitis, chronic bronchiolitis or small airway disease) and emphysema. Emphysema is defined anatomically as permanent, destructive enlargement of airspaces distal to the terminal bronchioles without obvious fibrosis (Siafakas, Vermeire et al. 1995).
Table 1. Definitions and classifications of disease severity in COPD.

<table>
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<tbody>
<tr>
<td>Definition of obstruction</td>
<td>FEV1/VC &lt; 0.88 % pred. in men</td>
<td>FEV1/FVC &lt; 0.7</td>
<td>FEV1/VC ≤ 0.7</td>
<td>FEV1/VC &lt; 0.7 and FEV1&lt;80 % pred.</td>
</tr>
<tr>
<td>Disease severity</td>
<td>FEV1 % of predicted</td>
<td>Mild: ≥ 70</td>
<td>Moderate: 50-69</td>
<td>Severe: &lt; 50</td>
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Pathology

Pathologic changes in COPD is characterised by chronic inflammation throughout the central and peripheral airways, lung parenchyma and pulmonary vasculature. It is currently accepted that an excessive/inadequate inflammatory response of the lungs to a variety of noxious inhaled gases or particles (i.e. cigarette smoke) is a key pathogenic mechanism in COPD (Pauwels, Buist et al. 2001). A systemic oxidative stress and an imbalance of proteinases and antiproteinases in the lung is demonstrated in these patients, particularly during exacerbations (Rahman, Morrison et al. 1996; Repine, Bast et al. 1997; Pauwels, Buist et al. 2001). The term oxidative stress includes all functional and structural alterations caused by reactive oxygen species (Repine, Bast et al. 1997). Also alterations in various circulating inflammatory cells, including neutrophils and lymphocytes as well as increased plasma levels of cytokines and acute phase proteins, are shown in patients with COPD (Agusti, Noguera et al. 2003). The pathologic changes mentioned lead to corresponding physiologic changes characteristic of the disease, including mucus hypersecretion, ciliary dysfunction, airflow limitation, pulmonary hyperinflation, gas exchange abnormalities, pulmonary hypertension and cor pulmonale. They usually develop in this order.
over the course of the disease. Mucus hypersecretion and ciliary dysfunction lead to chronic bronchitis with cough and sputum production. These symptoms can be present for many years before other symptoms or physiologic abnormalities develop (Pauwels, Buist et al. 2001).

**Prevalence and incidence**

In Sweden COPD caused 1.3% of all hospitalisations 1998 and approximately 2500 people die every year from this disease (Jansson 2002). Accurate epidemiologic data are difficult to collect but prevalence and morbidity data greatly underestimate the total burden of COPD because the disease is usually not diagnosed until it is clinically apparent and moderately advanced (Pauwels, Buist et al. 2001). The prevalence of COPD is largely dependent on the criteria used (Viegi, Pedreschi et al. 2000). The overall prevalence of COPD in ages > 45 years was 8% according to the BTS criteria and 14% according to the GOLD criteria (Lundback, Lindberg et al. 2003). In the past, most studies showed that COPD prevalence and mortality were greater in men than in women but more recent studies show that the prevalence is almost equal (Pauwels, Buist et al. 2001). It is difficult to find accurate incidence rates because of the different criteria. The figures vary from 1-2% per year among smokers over 40 years (Lundback 2002).

**Risk factors**

Tobacco smoke is by far the most important risk factor for developing COPD (Celli and MacNee 2004) and there is a clear dose response relationship with increased risk the higher number of pack-years (one pack-year = 20 cigarettes per day in one year) (Pauwels, Buist et al. 2001; Lundback 2002). Some studies have suggested that women are more susceptible to the effects of tobacco smoke than men (Carter, Nicotra et al. 1994; Pauwels, Buist et al. 2001). Other risk factors are increasing age, heavy exposure to occupational dusts and chemicals, and indoor/outdoor air pollution. There is a rare hereditary deficiency of alfa-1-antitrypsin which can cause COPD.
with no additional environmental factor (Pauwels, Buist et al. 2001; Lundback 2002).

**Consequences of COPD**

*Health related quality of life*

Decreased health related quality of life (HRQoL), compared to healthy, age-matched controls is common in patients with COPD (Williams and Bury 1989; Engstrom, Persson et al. 1996). A 50 % prevalence of depression and anxiety has been described among these patients (Mikkelsen, Middelboe et al. 2004). Disturbance of physical activity in patients with early COPD is restricted largely to leisure and recreation. These are areas of life over which individuals may exert a wide range of choices, so these restrictions could be termed “life style limitation”. When the FEV₁ falls below 50 % of predicted normal, essential activities of daily living becomes disturbed. At this level the patients are clearly handicapped, but also patients with mild COPD are handicapped since their impairment constrains the activities that they wish to perform (Jones 1995).

*Exercise limitation*

COPD is characterised by decreased airflow, which is more prominent on maximal efforts. Dyspnea and exercise intolerance are frequent symptoms and are the most common reasons for the patient to first consult the clinician. To avoid dyspnea the patients often limit their activity, which causes deconditioning and leads to a cycle of progressively decreased exercise tolerance (ATS 1999; O'Donnell 2001). Although the dyspnea is partly a result of impaired pulmonary mechanics, exercise performance remains substantially reduced even if both lungs are replaced (Williams, Patterson et al. 1992). Exercise limitation is multifactorial in COPD and several contributing factors are recognised including ventilatory limitation due to impaired respiratory mechanics and ventilatory muscle dysfunction, metabolic and gas exchange abnormalities, peripheral muscle dysfunction, cardiac impairment, exertional symptoms, and any combinations of these independent factors. The contributory factors to exercise limitation vary among patients and also in a given patient over time. The more advanced the disease, the more of these factors come into
play in a complex integrative manner (O'Donnell 2001). There are several studies in later years that have pointed out that COPD not only is a disease that affects the lungs. There is also an increasing realisation that these “systemic effects of COPD” are clinically relevant and may contribute to better understanding and management of the disease (Agusti, Noguera et al. 2003).

**Nutritional abnormalities and weight loss**

The presence of nutritional abnormalities, including alterations in caloric intake, basal metabolic rate, intermediate metabolism and body composition, has been described. The causes are unclear since a decreased caloric intake does not appear to be prominent, however most patients exhibit an increased basal metabolic rate (increased resting energy expenditure). Also the total daily energy expenditure (TDE) is found to be increased in COPD patients compared to healthy subjects (Baarends, Schols et al. 1997). Several mechanisms could conceivably contribute to the increased metabolic rate. Drugs commonly used in the treatment of COPD (e.g. β2-agonists), systemic inflammation and tissue hypoxia, are mechanisms mentioned (Agusti, Noguera et al. 2003). Malnutrition is found to significantly affect muscle aerobic capacity and exercise tolerance (Palange, Forte et al. 1995). Reduced body mass seem to have an independent negative effect on the muscle aerobic capacity, which may explain the variability in exercise tolerance among patients with comparable ventilatory limitation (Palange, Forte et al. 1998). Weight loss is also an important prognostic factor, independent of other prognostic indicators, such as FEV1 or PaO2, which assess the degree of pulmonary dysfunction (Landbo, Prescott et al. 1999). Low body weight and malnutrition are strong predictors for increased mortality risk (Gray-Donald, Gibbons et al. 1996).

**Skeletal muscle dysfunction**

Exercise limitation is a common complaint in COPD (Siafakas, Vermeire et al. 1995; Pauwels, Buist et al. 2001) and a significant contributor to the poor HRQoL in these patients (Jones 1995; Jones and Bosh 1997). The exercise limitation has traditionally been explained by the increased work of breathing and dynamic hyperinflation that is a result of the flow limitation characteristic of
Introduction

COPD. However, several recent studies have clearly shown that skeletal muscle dysfunction is often a very significant contributor to exercise limitation in these patients (ATS/ERS 1999).

After the first studies indicating that many patients with COPD stop exercise because of leg fatigue rather than dyspnea (Killian, Leblanc et al. 1992; Killian, Summers et al. 1992) several publications now confirm that skeletal muscle dysfunction is common in patients with COPD. The respiratory muscles, particularly the diaphragm, appear to behave quite differently from skeletal muscles in these patients, both from structural and functional points of view (ATS/ERS 1999). This is probably due to the different conditions under which both work, the skeletal muscles being generally underused whereas the diaphragm is constantly working against an increased load (Levine, Kaiser et al. 1997; Sauleda, Gea et al. 1998). Several studies have found decreased peripheral (skeletal) muscle performance in COPD patients (Gosselink, Troosters et al. 1996; Gosselink and Decramer 1998; Debigare, Cote et al. 2001). Decreases in both maximal and endurance strength have been shown (Bernard, LeBlanc et al. 1998; Van't Hul, Harlaar et al. 2004). Recent studies have concluded that the muscle strength in upper extremities is less affected than in the lower extremities (Clark, Cochrane et al. 2000; Gosselink, Troosters et al. 2000; Franssen, Wouters et al. 2002; Heijdra, Pinto-Plata et al. 2003; Man, Soliman et al. 2003). Potential mechanisms of skeletal muscle dysfunction found in the literature are sedentarism, nutritional abnormalities/cachexia, tissue hypoxia, systemic inflammation, skeletal muscle apoptosis, oxidative stress, abnormal nitric oxide regulation, tobacco smoke, individual susceptibility, hormone alterations, electrolyte alterations and medications (ATS/ERS 1999; Gosker, Wouters et al. 2000; Mador and Bozkana 2001; Agusti, Noguera et al. 2003). Since the muscle strength in upper and lower extremities has been found to be affected to a various degree there is no clear consensus about the underlying mechanisms.

Abnormal structure and function of skeletal muscles

A reduced proportion of type I fibres and an increased proportion of type II fibres in skeletal muscles are found in patients with COPD (Jakobsson, Jorfeldt et al. 1990; Malais, Sullivan et al. 1999). Biopsies of the quadriceps muscle have also shown a reduction in oxidative
enzyme capacity (Jakobsson, Jorfeldt et al. 1995; Maltais, Simard et al. 1996) and an increase in glycolytic enzyme capacity (Jakobsson, Jorfeldt et al. 1995). One study found a transition from type I fibres to hybrid fibres and that the oxidative capacity of the type II fibres was lower in patients with COPD, compared to controls (Gosker, van Mameren et al. 2002). Catabolic/anabolic disturbances have also been found, leading to a shift toward catabolism and possibly to the development of peripheral muscle wasting (Debigare, Marquis et al. 2003). The identification of skeletal muscle dysfunction as a major systemic effect of the disease has increased the interest in skeletal muscle physiology in COPD and has clearly contributed to a better definition of the role of exercise training (Sala, Roca et al. 1999) and rehabilitation programmes in the clinical management of these patients (Ries, Kaplan et al. 1995; Lacasse, Wong et al. 1996; Griffiths, Burr et al. 2000).

**Osteoporosis**

Osteoporosis, with resulting fractures, is found to be a significant problem in patients with advanced COPD. The etiology of bone loss in COPD is diverse and includes smoking, vitamin D deficiency, low body mass index, hypogonadism, sedentary lifestyle and use of glucocorticoids (Goldstein, Fallon et al. 1999; Biskobing 2002; Sin, Man et al. 2003; Melton, Patel et al. 2004).

**Sedentarism**

Due to shortness of breath during exercise and since anxiety appears while participating in activities, patients with COPD often adopt a sedentary lifestyle (ATS 1999; Agusti, Noguera et al. 2003). It is well documented that physical inactivity causes net loss of muscle mass, muscle strength, muscle endurance and also a decreased cardio-respiratory endurance (Wilmore and Costill 2004).
Treatment

Medications

The most important effort for patients with COPD is to quit smoking. As long as they continue to smoke tobacco their pulmonary function will decline more rapidly than if they manage to quit (Fletcher and Peto 1977). There is also strong evidence that smoke cessation increases survival and decreases symptoms (SBU 2000).

Since the definition of COPD includes irreversible obstruction and progressively decreased pulmonary function, there are not many pharmaceuticals available that have a substantial effect on the disease. Long-term acting β2-agonists and anticholinergic bronchodilator (ipratropium) are found to have small positive effects on symptoms and HRQoL (SBU 2000). Just recently a new long-acting anticholinergic bronchodilator (tiotropium) was found to reduce lung hyperinflation, increase inspiratory capacity and contribute to improvements in both exertional dyspnea and exercise endurance (O'Donnell, Fluge et al. 2004). Corticosteroids have small positive effects on patients’ wellbeing and number and length of hospital stays (SBU 2000). Long term oxygen treatment has been found to improve survival in COPD patients with severe hypoxia, however no effect is seen in HRQoL (SBU 2000).

Pulmonary rehabilitation

Rehabilitation for patients with chronic lung disease is well established and widely accepted as a means of enhancing standard therapy in order to alleviate symptoms and optimise function (ACCP/AACVPR 1997; SBU 2000). The primary goal of rehabilitation is to restore the patient to the highest possible level of independent function. This goal is to be accomplished by helping patients to increase their activity through exercise training and to reduce and gain control of their symptoms. Patients and relatives are supposed to learn more about the disease, treatment options, and coping strategies. Patients are to be encouraged to become actively involved in providing their own health care, more independent in
Introduction

daily activities, and less dependent on health professionals and expensive medical resources. Rather than focusing solely on reversing the disease process, rehabilitation attempts to improve disability from disease (ACCP/AACVPR 1997). Pulmonary rehabilitation is supposed to integrate expertise from various health-care disciplines integrated into a comprehensive, cohesive program tailored to the needs of each patient (ACCP/AACVPR 1997). The rehabilitation process should incorporate a programme of nutritional intervention, physical training, education about the disease, nutritional, psychological, social and behavioural intervention.

The American College of Chest Physicians (ACCP) and the American Association of Cardiovascular and Pulmonary Rehabilitation (AACVPR) have presented evidence grades for different interventions in pulmonary rehabilitation. The group concluded that pulmonary rehabilitation improves the symptoms of dyspnea, evidence grade A (scientific evidence provided by well-designed, well conducted, controlled trials with statistically significant results that consistently support the guideline recommendation). It was also found to improve health related quality of life (HRQoL) and to reduce the number and lengths of hospitalisations, evidence grade B (scientific evidence provided by observational studies or by controlled trials with less consistent results to support the guideline recommendation), (ACCP/AACVPR 1997). There are other systematic overviews which have come to the same conclusions, that pulmonary rehabilitation, assumed that physical training is included, is likely to improve exercise tolerance and HRQoL (Lacasse, Guyatt et al. 1997; Salman, Mosier et al. 2003). Improved HRQoL after pulmonary rehabilitation including physical training has also been shown in other studies (Wijkstra, Van Altena et al. 1994; Engstrom, Persson et al. 1999).

Health economic benefits of rehabilitation including physical training are only just beginning to be explored but reductions in hospital admission frequency, durations of stay, exacerbation rate, general practitioner home visits, and bronchodilator usage have been reported (Gallefoss and Bakke 1999; Guell, Casan et al. 2000; 2001; Griffiths, Phillips et al. 2001).
Nutrition

Several studies have evaluated the effect of nutritional support in COPD patients and different conclusions are drawn. Small gains have been observed with increased dietary intake (Saudny-Unterberger, Martin et al. 1997; Creutzberg, Wouters et al. 2003), however concurrent treatment with corticosteroids seems to have an adverse effect on the muscles and to limit the effect of nutritional support (Saudny-Unterberger, Martin et al. 1997; Creutzberg, Wouters et al. 2003). Different characteristics have been found in patients who respond to oral nutritional therapy and those who don’t (Creutzberg, Schols et al. 2000). Similarly different kinds of nutritional supplements seem to give different responses. A fat-rich supplement promoted more shortness of breath than a carbohydrate-rich supplement (Vermeeren, Wouters et al. 2001). Indications of positive effects of dietary intervention during multidisciplinary intervention considering walking distance and ability to keep a stable weight have been found (Slindé, Gronberg et al. 2002). One study concluded that nutritional supplementation could improve the outcome of physical training in selected patients (Steiner, Barton et al. 2003).

Physical training

A large number of studies have in recent years reported positive effects in patients after participation in pulmonary rehabilitation including physical training (Lake, Henderson et al. 1990; Goldstein, Gort et al. 1994; Reardon, Awad et al. 1994; Wijkstra, Van Altena et al. 1994; Ries, Kaplan et al. 1995; Berry, Adair et al. 1996; Strijbos, Postma et al. 1996; O'Donnell, McGuire et al. 1998; Wedzicha, Bestall et al. 1998; Behnke, Taube et al. 2000; Finnerty, Keeping et al. 2001). Table 2 presents randomised controlled trials of different exercise programs. In the review by ACCP/AACVPR, lower extremity training was found improve exercise tolerance (evidence grade A) and upper extremity training was found to improve arm function (evidence grade B) (ACCP/AACVPR 1997).
Table 2. Randomised, controlled trials of physical exercise programs in patients with COPD.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Participants</th>
<th>Intervention</th>
<th>Outcomes and results</th>
</tr>
</thead>
</table>
| Lake et al (1990)      | N=26 (19 I; 7 C) 15 % | Outpatient exercise program (upper-limb, lower-limb or combined training; walking, arm-ergometer cycling) 8-wk, 3 times/wk, 40 min/session | I: Lower limb and combined increased 6MWD, upper-limb and combined increased WRpeak in arm-ergometer cycle  
C: No changes |
|                        | Mean age: 67 yr FEV₁: 0.88 L (32 % pred) | Intensity: unspecified Follow up: 8 wk | | |
|                        |              |                                                                                               | C: No changes                                               |
| Reardon et al (1994)   | N=20 (10 I, 10 C) 50 % | Outpatient rehabilitation program (lower/upper extremity and inspiratory resistive exercise; stair climbing, treadmill, cycle exercise, education) 6 wk, 2 times/wk, 3 h sessions | I: Increase of 40 % in duration incremental treadmill test, dyspnea ratings decreased  
C: No changes |
|                        | Mean age: 66 yr | Intensity: moderate dyspnea or HR 70-85 %max Follow up: 6 wk | | |
|                        | FEV₁: 0.87 L (34 % pred) | | | |
| Goldstein et al (1994) | N=89 (45 I, 44 C) 51 % | Inpatient rehabilitation program (upper and lower extremity exercise, education) + supervised outpatient program 8 wk inpt. + 16 wk outpt., 3 times/week, 40 min/session, diminishing to once/mo the last month | I: Improvement in 6 MWD and submaximal cycle time, improved HRQoL  
C: No changes |
|                        | Mean age: 66 yr | Intensity: increased as tolerated Follow up: 24 wk | | |
|                        | FEV₁: 0.45 L (44 % pred) | | | |
| Wijkstra et al (1994)  | N=43 (28 L, 15 C) 14 % | Outpatient rehabilitation program (cycle, upper extremity and inspiratory muscle exercise), monthly nurse and physician visits, daily home training program, education 12 wk, 2 times/wk, 30 min/session | I: Increase of 10 % in WRpeak, sign increase in VO₂peak  
C: 9 % decrease in WRpeak, decrease in VO₂peak. |
|                        | Mean age: 63 yr | Intensity: up to 76 % of Wmax Follow up: 12 wk | | |
|                        | FEV₁: 1.33 L (44 % pred) | | | |
| Ries et al (1995)      | N=119 (57 I, 62 C) 27 % | Outpatient rehabilitation program (treadmill/walking exercise, education and psychosocial support) 8-wk, 12 4 h sessions + monthly visits for 1 yr | I: At 8 wk; increase of 9 % in VO₂peak and of 33 % in max workload in incremental test, increase of 85 % in duration in endurance test, decreased dyspnea ratings. Benefits maintained up to one year.  
C: No changes |
|                        | Mean age: 63 yr | Intensity: highest tolerated symptom-limited level Follow up: 6 yr | | |
|                        | FEV₁: 1.23 L | | | |
| Strijbos et al (1996)  | N=45 (30 L, 15 rehab, 15 homecare, 15 C) 30 % | Outpatient and homecare rehabilitation program (walking, stair climbing, cycle ergometer (hospital based), individual exercise program (home care), education. Both groups in addition instructed to exercise 15 minutes daily) 12 wk, 2 sessions/wk, 60 min/session | I: Hospital based: Improvements in WR, 4MWD, HRQoL, reduced dyspnea and leg fatigue, remained for 6 months.  
Home-care: Improvements in WR, 4MWD, HRQoL, reduced dyspnea and leg fatigue, remained for 18 months.  
C: No changes |
|                        | Mean age: 61 yr | Intensity: 70 % of WRpeak (hospital based) Follow up: 18 months | | |
|                        | FEV₁: 1.2 L (43 % pred) | | | |
### Table 2. continued

<table>
<thead>
<tr>
<th>Trial</th>
<th>Selection</th>
<th>Intervention</th>
<th>Outcomes and results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Berry et al (1996) USA</td>
<td>N=25 (17 I, 8 C)</td>
<td>Outpatient rehabilitation program (walking, upper extremity strength training, inspiratory muscle training) 12-wk, 3 times/wk, 20 min + strength exercises</td>
<td>Increased 12MWD and treadmill time. Inspiratory muscle training did not add to the effect. C: Smaller increases in 12MWD and treadmill time.</td>
</tr>
<tr>
<td></td>
<td>Mean age: 69 yr.</td>
<td>12-wk, 3 times/wk, 20 min + strength exercises</td>
<td></td>
</tr>
<tr>
<td></td>
<td>FEV1: 1.44 L (47 % pred)</td>
<td>Intensity: 50-75 % of HR reserve</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Follow-up: 12-wk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wadzicha et al (1998) England</td>
<td>N=120 (63 I, 63 C; 66 moderate dyspnea, 60 severe dyspnea)</td>
<td>Outpatient rehabilitation program (moderate at hospital and severe at home. Upper and lower limb training, low intensity repetitions of isolated muscles, unloaded cycling, walking, education) 8-wk, 60 min</td>
<td>Moderately dyspnoeic; increase in exercise tolerance, improvement in HRQoL. Severely dyspnoeic; small improvement in HRQoL C: No changes</td>
</tr>
<tr>
<td></td>
<td>Mean age: 70 yr.</td>
<td>Intensity: Borg 3-4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>FEV1: 0.9 L (37 % pred)</td>
<td>Follow up: 8 wk</td>
<td></td>
</tr>
<tr>
<td>O'Donnell et al (1998) Canada</td>
<td>N=20 (20 I, 20 C)</td>
<td>Outpatient exercise program (stairs climbing, arm ergometry, treadmill, breathing exercises) 6-wk, 3 sessions/wk, 2.5 h/session</td>
<td>Improvements in endurance; walking, cycling, arm ergometry, respiratory muscles and in muscle strength, respiratory muscles, quadriceps, handgrps. Reduced ventilatory requirements, dyspnea and muscle discomfort. C: No changes</td>
</tr>
<tr>
<td></td>
<td>Two periods</td>
<td>Intensity: at or just below Borg max, the highest attainable work rate for the longest tolerable duration</td>
<td></td>
</tr>
<tr>
<td></td>
<td>40 %</td>
<td>Follow up: 6 wk</td>
<td></td>
</tr>
<tr>
<td>Behnke et al (2000) Germany</td>
<td>N=30 (15 I, 15 C)</td>
<td>Inpatient and home-based exercise program (10 days after exacerbation 5-6 walking sessions/day, thereafter instruction to walk at home 3 times/day, 15 min). Visits every 2 wk the first 3 months, thereafter once per mo. Diary cards</td>
<td>Increased 6MWD after 10 days, 3 and 6 months. Improved HRQoL at 3 and 6 mo. C: No changes</td>
</tr>
<tr>
<td></td>
<td>25 %</td>
<td>Intensity: unspecified</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mean age: 66 yr.</td>
<td>Follow up: 6 months</td>
<td></td>
</tr>
<tr>
<td></td>
<td>FEV1: 56 L (41 % pred)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Finnerty et al (2001) England</td>
<td>N=65 (36 I, 29 C)</td>
<td>Outpatient rehabilitation program (aerobic activities for arms and legs + home training walking program 1-2 times/day, 5 days/week, education) 6-wk, once/wk, 45 min/session</td>
<td>Increase in 6MWD at 3 mo. Improvements in HRQoL at 3 and 6 months. C: No changes</td>
</tr>
<tr>
<td></td>
<td>32 %</td>
<td>Intensity: unspecified</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mean age: 69 yr.</td>
<td>Follow up: 4 months</td>
<td></td>
</tr>
<tr>
<td></td>
<td>FEV1: 1.0 L (41 % pred)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

N: number of participants, I: intervention group, C: control group, wk: week, yr: year, FEV1: forced expiratory volume in one second, Pred: predicted value, VO2: oxygen uptake, LT: lactate threshold, VE: tidal volume, WR: work rate, HR: heart rate, VE: ventilation, HRQoL: health related quality of life, 6MWD: 6 minute walking distance test, 12MWD: 12 minute walking distance test
The length of training intervention varies in different studies. From 10-12 days of inpatient pulmonary rehabilitation program (Carter, Nicotra et al. 1988; Votto, Bowen et al. 1996) up to six months (Goldstein, Gort et al. 1994; Troosters, Gosselink et al. 2000). Most interventions, however, last for at least 6 weeks (see Table 2), which is the minimum length according to a statement from the BTS (BTS 2001). In studies comparing length of intervention periods, a longer period seems to provide greater benefits in terms of improvements of health status and physical capacity (Troosters, Gosselink et al. 2000; Green, Singh et al. 2001; Berry, Rejeski et al. 2003). Different conclusions have come from studies evaluating various settings for the training program. Inpatient, and outpatient programs, supervised and self-monitored programs have been studied (Wijkstra, Ten Vergert et al. 1995; Hernandez, Rubio et al. 2000; Puente-Maestu, Sanz et al. 2000; Finnerty, Keeping et al. 2001; Puente-Maestu, Luisa Sanz et al. 2003).

**Different training modalities**

Many studies have been performed to evaluate the effect of different physical training programs in patients with COPD. Endurance training has been compared to strength training (Ortega, Toral et al. 2002; Spruit, Gosselink et al. 2002) and both modalities were found to have positive effects. Interval training has been compared to continuous training (Vogiatzis, Nanas et al. 2002), and high intensity training has been compared to low intensity training (Casaburi, Patessio et al. 1991; Maltais, LeBlanc et al. 1997; Puente-Maestu, Sanz et al. 2000; Normandin, McCusker et al. 2002) and different conclusions were drawn. COPD patients are heterogeneous regarding underlying disease, disease severity, age and personal interests. Consequently, there is a need for evaluating the effect of different training modalities. It is also important to find methods that are cost effective since the number of patients are increasing. In most previous studies evaluating exercise in COPD, the patients have trained endurance individually on a treadmill or on a bicycle (Spruit, Gosselink et al. 2002; Vogiatzis, Nanas et al. 2002). The weight training has also been performed individually with weights, expanders or apparatus (Ortega, Toral et al. 2002; Spruit, Gosselink et al. 2002). Group training in gymnasium has been used for a long time in health promotion and has been found to be effective in patients with asthma.
(Emtner, Finne et al. 1998), cardiac disease (Stahle, Mattsson et al. 1999) and different musculoskeletal disorders (Ahlgren, Waling et al. 2001; Storheim, Brox et al. 2003). There are, so far, not many studies that have evaluated group training in patients with COPD. Training together in a group has been described as beneficial since the patients get encouragement and feel confidence in meeting other persons in the same situation (Stahle, Lindquist et al. 2000). Besides the psychological and psychosocial benefits of getting patients together in a group, the training form is also cost effective for the health care system. There is no need for specific equipment and up to twenty patients can train together under supervision from one leader. Another aspect is that this kind of training is available in the society, and can be adjusted to fit patients with specific needs. There are today many patient organisations arranging group training under supervision from experienced leaders.

Training with oxygen

Oxygen administered during physical exercise has been shown to improve exercise performance in patients with COPD both in those who are hypoxaemic at rest (Stein, Bradley et al. 1982; Davidson, Leach et al. 1988; Dewan and Bell 1994) and in those who get hypoxaemic during exercise (Bradley, Garner et al. 1978; Woodcock, Gross et al. 1981; Criner and Celli 1987; Light, Mahutte et al. 1989; Dean, Brown et al. 1992; Mitlehner and Kerb 1994).

Studies that examined the long-term effect of oxygen used during longer training periods have come to different conclusions. One study found that training with oxygen in COPD patients who desaturate during exercise had positive effects on exercise capacity after the training period (Ries, Kaplan et al. 1995). However, the effect of oxygen supplementation versus no supplementation was not evaluated in that study. As compared to breathing room air, supplemental oxygen used during daily activities at home by patients with COPD and mild hypoxaemia was found to be of limited benefit regarding exercise performance (McDonald, Blyth et al. 1995). A controlled study on 10-weeks pulmonary rehabilitation for inpatients showed that supplementation of oxygen during the training did not add to the effects of training on room air (Rooyackers, Dekhuijzen et al. 1997) and another study suggested that supplemental oxygen did
little to enhance exercise tolerance although there was a small benefit in terms of dyspnea (Garrod, Paul et al. 2000). In contrast, two studies showed that oxygen-supplemented exercise training yielded higher training intensity and gains in exercise tolerance (Zack and Palange 1985) (Emtner, Porszasz et al. 2003). Due to the varying results and designs in previous studies there are no obvious conclusions regarding the benefit of oxygen supplementation during exercise training in patients with COPD who do not have chronic respiratory insufficiency.

**Training in water**

Water exercise is a form of training which has been used for decades in the areas of physiotherapy and rehabilitation. The buoyancy of the water is of relevance for individuals seeking ways to improve fitness without the inherent risk of musculoskeletal injuries accrued with continuous impact on the skeletal system (Chu and Rhodes 2001). Training in water has been shown effective in healthy persons (Taunton, Rhodes et al. 1996; Chu and Rhodes 2001) and in different patient categories such as asthmatics (Emtner, Finne et al. 1998), patients with cardiac disease (Cider, Schaufelberger et al. 2003), poliomyelitis (Willen, Sunnerhagen et al. 2001), fibromyalgia syndrome (Mannerkorpi, Nyberg et al. 2000) and rheumatoid arthritis (Stenstrom, Lindell et al. 1991). Perk et al concluded that training in water was safe and applicable in patients with COPD (Perk, Perk et al. 1996) although no evaluation of the training on physical performance or HRQoL was performed. Training in water could be an attractive alternative as it combines strength, endurance and mobility training, as well as the psychosocial aspects and low-cost benefits of group training.

**Long term effects of training**

There is still no consensus, despite a large number of studies, on how to achieve the best long-term effects of training (Gosselink 2002). There are different conclusions drawn about how to maintain long-term positive effects on exercise tolerance, dyspnea and HRQoL achieved after an intensive training program in patients with COPD. Lasting effects in physical fitness was found in some studies (Cambach, Wagenaar et al. 1999; Engstrom, Persson et al. 1999;
Bestall, Paul et al. 2003) while other reported maintained improvements in HRQoL (Ries, Kaplan et al. 1995; Wijkstra, Ten Vergert et al. 1995; Foglio, Bianchi et al. 1999). Persisting benefits both in exercise capacity and HRQoL have also been shown (Guell, Casan et al. 2000; Troosters, Gosselink et al. 2000; Berry, Rejeski et al. 2003), while one recent study found no effect on these parameters in patients with COPD after two different follow-up programmes (Brooks, Krip et al. 2002).

**Rationale for this thesis**

The number of patients with COPD is high and continues to increase. The disease is now the fourth leading cause of death in the world.

Physical training solely, or as a part of pulmonary rehabilitation, has been found to be effective regarding physical capacity and health related quality of life in patients with COPD. In this thesis the term physical capacity comprises of distance walked, performance in cycle ergometer tests and muscle strength. A variety of training programs have been evaluated in COPD patients; endurance, strength, high-and low- intensity and different durations of intervention. Despite the number of studies performed, there is still no consensus about which training modality or which design of training program that is the most effective.

Since COPD causes a lot of suffering for the patients and large costs for the society, it is of great importance to find effective treatment modalities to improve health related quality of life and physical performance in this increasing and resource demanding group of patients.
AIMS OF THE THESIS

The general purpose of this thesis was to investigate the short and long term effects of different training modalities for patients with COPD compared to a control group, with regard to physical capacity and health related quality of life (HRQoL).

Specific research questions:

- Is supplemental oxygen during physical training of benefit compared to the same training with air regarding walking distance and perceived dyspnea and exertion? (Study I)
- What is the short term effect of high-intensity group training with regard to physical capacity and HRQoL? (Study II-III)
- Is there any difference regarding influence on physical capacity and HRQoL between high-intensity group training in water and on land? (Study II-IV)
- What is the long term effect of physical training with regard to physical capacity and HRQoL? (Study IV)
- Can the gained benefits after a high frequency physical training program be preserved with decreased training frequency? (Study II and IV)
METHODS

Subjects

The subjects were recruited from previously diagnosed outpatients under treatment at the Department of Respiratory Medicine and Allergy at the University Hospital in Umeå (study I-IV) and at the Department of Medicine at the Regional Hospital in Skellefteå (study II-IV). The patients had COPD according to the criteria from ERS (study I) (Siafakas, Vermeire et al. 1995), or GOLD (study II-IV) (Pauwels, Buist et al. 2001). Before entering the studies the patients performed a dynamic spirometry test (Spirolab, Medical International Research, Roma, Italy), to verify the diagnosis. FEV$_1$, VC and FVC were evaluated. They also performed a symptom limited exercise test with ECG registration on a cycle ergometer (Rodby™, RE 829, Enhörna, Sweden) to exclude cardiac disorders. Flow-charts of the patients in study II-IV are presented in Figure 1.

Inclusion criteria for the patients in study I were the following; under the age of 75, stopped smoking at least six months before entering the study, exercise-induced hypoxaemia (SpO$_2$ ≤ 92 % in 6MWD, performed in a corridor), FEV$_1$ < 70 % of predicted value, PaO$_2$ ≥ 8 kPa at rest, no infection during the last three weeks and no change in medical treatment the last month before entering the study. Inclusion criteria for patients in study II-IV were FEV$_1$/VC < 0.70, FEV$_1$ < 80 % of predicted, stable medication and no infection during the last month before entering the study. Patients were, in all studies, excluded if they had any past or present major illness, such as cardiac, orthopaedic, neurological, or psychological disease that might have interfered with exercise performance.

Baseline characteristics for the patients included in the studies are presented in Table 3. In study I, one patient in each group were excluded due to exacerbations and are not included in the table.
Figure 1. Recruitment procedure of patients to study II-IV, intervention and control group.
Table 3. Baseline characteristics of the patients included in study I (air and oxygen group) and in study II-IV (control, water and land group). Values presented as median (min-max).

<table>
<thead>
<tr>
<th></th>
<th>Study I</th>
<th>Study II-IV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Air (n=10)</td>
<td>Oxygen (n=10)</td>
</tr>
<tr>
<td>Sex (f/m)</td>
<td>5/5</td>
<td>5/5</td>
</tr>
<tr>
<td>Age</td>
<td>69 (60-72)</td>
<td>65 (52-73)</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.70 (1.56-1.80)</td>
<td>1.67 (1.57-1.83)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>75 (52-109)</td>
<td>66 (57-101)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.1 (19.9-38.9)</td>
<td>24.3 (18.4-30.2)</td>
</tr>
<tr>
<td>FEV₁ (l)</td>
<td>1.28 (0.74-1.76)</td>
<td>0.97 (0.76-1.92)</td>
</tr>
<tr>
<td>FEV₁ % pred.</td>
<td>52 (24-66)</td>
<td>39 (23-59)</td>
</tr>
<tr>
<td>VC (l)</td>
<td>3.31 (2.09-4.15)</td>
<td>2.84 (2.32-5.82)</td>
</tr>
<tr>
<td>VC % pred.</td>
<td>92 (82-139)</td>
<td>93 (73-131)</td>
</tr>
<tr>
<td>FEV₁/VC</td>
<td>0.37 (0.23-0.56)</td>
<td>0.35 (0.16-0.46)</td>
</tr>
</tbody>
</table>

* Significant difference in BMI between control, water and land group.
The medications used by the patients during the intervention in study II-IV are presented in Table 4.

Table 4. Medications used by the patients during the intervention in study II-IV.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Control (n=13)</th>
<th>Water (n=15)</th>
<th>Land (n=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long acting β₂-agonist</td>
<td>5</td>
<td>10</td>
<td>6</td>
</tr>
<tr>
<td>Ipratropium-bromide</td>
<td>8</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>Theofyllamine</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Inhaled</td>
<td>12</td>
<td>13</td>
<td>11</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Daily oral</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corticosteroids</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acetylcystein</td>
<td>3</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>Exacerbation treatment*</td>
<td>12 treatments in 6 patients</td>
<td>17 treatments in 10 patients</td>
<td>25 treatments in 11 patients</td>
</tr>
</tbody>
</table>

* Oral Corticosteroids and/or Antibiotics
¤ Two patients had 4 exacerbations
# One patient had 9 exacerbations, one patient had 6 exacerbations

Ethics

The studies were approved by the Ethical Committee, Faculty of Medicine, Umeå University. All patients gave their informed consent prior to the studies.

Design

The first intervention (study I) was designed as a randomised, single-blind study. The patients in this study were randomised to either training with air or with oxygen. They were blinded to which treatment they received. The second intervention (study II-IV) was controlled and semi-randomised, presented in Figure 2. The patients living more than 60 km away from the study hospital (n=13) were included in the control group. Thirty patients, living within 60 km from the study hospital were included in the intervention group and randomised to training either in water or on land. In randomisation the patients were stratified for sex, FEV₁ and working capacity. In study II and III the patients are separated in three groups in the data.
analyses (control, water and land). In study IV the patients in the intervention group is analysed as one group (control and training).

![Figure 2. Design of the second intervention (study II-IV).](image)

**Power**

No power analysis was performed to decide the sample size in study I. Sample size in study II-IV was determined by power analysis (nQuery Advisor® 3.0) based on the minimum clinically important difference (MCID) in the ISWT (Singh, Jones et al. 2002). A sample size of 30 subjects (10 subjects per group) was recommended to attain a power > 80% with a $\alpha$-level of 0.05. To adjust for potential dropout 30 subjects in the intervention group and 13 patients in the control group (i.e. a total of 43 patients) were enrolled.
Methods

Intervention programmes

Walking on treadmill

(Study I)
The patients were randomised to training with either air or oxygen at a flow rate of 5 l/min through a nasal cannula. The training programme consisted of walking on a motorised treadmill (Rodby RL 1500 E, Enhörna, Sweden) for 30 minutes, 3 times per week for 8 weeks. The programme was designed as interval training, comprised of 5 minutes warming up, 2-3 minutes higher speed, alternated with 2-3 minutes lower speed, ending with 2-5 minutes cooling down. Normally one session consisted of 5 intervals with higher speed. A physiotherapist adjusted the speed, and slowed down or stopped the treadmill on request from the patients. SpO₂ and heart rate were continuously monitored with a pulse oximeter using a finger or a forehead probe (“Omeda Biox 3700e”, Louisville, USA). The patients rated their perceived exertion (RPE) and dyspnea (CR10) according to Borg (Borg 1982) every 5th minute and after every speed interval. The intensity of the sessions was individualised with respect to the patients’ saturation and their subjective ratings of dyspnea and perceived exertion. Target dyspnea was set to 7 (out of 10) and target perceived exertion was set to 17 (out of 20). The treadmill was stopped if the patients rated 7/17 (respectively) or more on the Borg scales and/or if the patients’ SpO₂ dropped below 90 %. The patients were allowed to walk again when the ratings lowered and/or when the SpO₂ rose above 90 %. When the patients exceeded a walking speed above 6.0 km/hour, an inclination of the treadmill, instead of further increased speed, was used as an increased intensity. The inclination varied between 1.0 and 5.0 degrees.

Training in water and on land

(Study II-IV)
The patients were randomised to either training in water or on land. The training program for both groups consisted of, aerobic group training for 45 minutes (including warm-up and cool-down) 3 times per week for 12 weeks. Physiotherapists directed the training. The programs in water and on land were designed to have the same
Methods

intensity profile, presented in Figure 3. The sessions started with warm-up and flexibility exercises for 9 min. The session was then performed in the following order: 4 min endurance exercises, 3 min strength exercises for the legs, 4 min endurance exercises, 3 min strength exercises for the arms, 4 min endurance exercises, 3 min strength exercises for the torso, 3 min flexibility exercises and finally cool-down and stretching exercises for 12 minutes. The intensity increased for each successive endurance exercise portion. The endurance parts of the session consisted of varied repetitive large-muscle exercises intending to increase the load on the cardiovascular system and increase heart rate. The complete program was supported by music, which guided the intensity of the performance during the session. The water temperature was 33-34 degrees Celsius. The land training was performed in a gymnasium. The intensity during the training sessions was monitored using heart rate registration (Polar Accurex Plus™, Polar Elektro Oy, Kempele, Finland) once weekly and the patients rated their dyspnea (CR10) and perceived exertion (RPE) according to Borg score (Borg 1982) after each training session. The intensity goal during training was to achieve a mean heart rate on 80-100% of peak heart rate according to maximal test on cycle ergometer and the patients were encouraged to reach Borg score 5 for dyspnea and 15 for rated perceived exertion. The strength exercises in the land training program were, for the arms, performed with expanders and for the legs with the patients' bodyweight. In the water program the resistance for the strength exercises was achieved using the inherent resistance in the water, the faster the movement, the higher the resistance. Figure 3 presents the profile of the training program illustrated by the heart rate in two patients.
Methods

![Heart rate for one patient during a water training session](image1)

![Heart rate for one patient during a land training session](image2)

Figure 3. The intensity profile during the training sessions in water and on land, demonstrated with the heart rate of one patient from each training group. 1) Warm-up 2) Endurance exercises 3) Leg strength exercises 4) Endurance exercises 5) Arm strength exercises 6) Endurance exercises 7) Exercises for strength in torso 8) Cool-down.

Tests

Table 5 presents the different methods used for data collection in the studies. In study I the tests were performed before and after the training period. In study II-IV all tests were performed at all three test occasions (baseline, 3 and 9 months). In study I the same person (a physiotherapist) performed the training and the tests. In study II-IV there were different persons who performed the training and the tests.
Table 5. Overview of methods used for data collection in studies I-IV.

<table>
<thead>
<tr>
<th>Tests performed</th>
<th>Study I</th>
<th>Study II</th>
<th>Study III</th>
<th>Study IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary function test *</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Cycle ergometer test (inclusion)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>6 minute walking distance test (6MWD)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transcutaneous carbon dioxide measurement</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Arterial oxygen saturation (SaO2)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxygen saturation (SpO2)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Heart rate registration</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Subjective ratings of perceived exertion and dyspnea</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Incremental shuttle walking test (ISWT)</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Endurance shuttle walking test (ESWT)</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Cycle ergometer test</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Metabolic stress test</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Blood lactate measurement</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Body composition</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Thigh muscle strength and endurance</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Subjective ratings of leg fatigue</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>St George’s Respiratory Questionnaire (SGRQ)</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>SF-36</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Activity level questionnaire</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

* Static and dynamic pulmonary function tests were performed in study I while dynamic pulmonary function tests were performed in study II-IV.

The inclusion tests (pulmonary function tests and cycle ergometer tests) in all studies were performed 4-8 weeks before the tests at baseline. In the first intervention (study I) the walking tests were performed on the same day with one hour rest in between. In the second intervention (study II-IV) the tests were performed in two days with 1-2 weeks in between. The tests the first day were performed in the following order; ISWT, measurement of body composition, completion of SGRQ and activity level questionnaire,
Methods

and finally ESWT. The tests the second day were performed in the following order; tests of thigh muscle strength and endurance, completion of SF-36, and thereafter cycle ergometer test with metabolic stress test.

Walking tests

*Six minute walking distance test - 6MWD*

(Study I)
The 6-minute walking distance test (6 MWD) has been developed for use in patients with cardiorespiratory disease (Butland, Pang et al. 1982). It is based on a 12-minute walking test (McGavin, Gupta et al. 1976) which in turn is developed from Coopers 12-minute runners test (Cooper 1968) and the 6MWD is now common in the assessment of patients with COPD.

In study I, the patients performed two 6 MWD tests on a non-motorised treadmill (Skip Sport Walker 2000, Tyresö, Sweden) before and after training. They were tested breathing air or oxygen (the patients were blinded to which) through a nasal cannula (5 L/min), in a randomised order, with the instruction to walk as far as possible. The test leader was not supposed to intervene with the patient during the test. The time during which the patients’ oxygen saturation was below 90 % was recorded. Before, at 3 minutes, directly after the test and 2 minutes after the test the patients rated their dyspnea and perceived exertion according to Borg score (Borg 1982).

*Incremental shuttle walking test – ISWT*

(Study II-IV)
The ISWT was developed from a progressive, externally paced 20 meter shuttle running test, widely used as a field test of functional capacity in athletes (Léger and Lambert 1982). The protocol was modified for patients with COPD and it requires the patient to walk up and down a 10 m course, with the walking speed dictated by a pre-recorded audio signal played on a cassette recorder (Singh, Morgan et al. 1992). The speed at which the patient walks is dictated by an audio signal played on a tape cassette. The explanation to the patient is standardised and played from the tape before the start of the test. The speed is very slow the first minute, to get progressively faster every
Methods

minute. The patient should continue until he/she is unable to maintain the required speed without becoming unduly breathless. ISWT is used as a standardised, incremental field walking test that provokes a symptom limited maximal performance. In addition to patients with COPD, the test is also found to be valid in patients with heart failure (Morales, Montemayor et al. 2000; Green, Watts et al. 2001) and in patients with advanced cancer (Booth and Adams 2001). Before and after the test the patients rated their dyspnea and perceived exertion according to Borg scale (Borg 1982).

Endurance shuttle walking test – ESWT

(Study II-IV)  
To be able to evaluate the patients endurance capacity an endurance shuttle walk test was developed (Revill, Morgan et al. 1999). In ESWT the patients walk in the same course as in ISWT but with a constant, not incremental, speed. The speed is calculated from the result in ISWT, and is set at 85 % of the ISWT performance. Before and after the test the patients rated their dyspnea and perceived exertion according to Borg scale (Borg 1982).

Cycle ergometer tests

(Study II-IV)  
A symptom-limited incremental test on cycle ergometer (Rodby™, RE 829, Enhörna, Sweden) with ECG-registration was performed with measurement of lactate from a venous cannula in the arm. The patients cycled according to a ramp protocol, i.e. they started at 20 W and the load was increased by 20 W every 3rd minute until exhaustion. At the end of every load SpO₂ and Borg ratings for dyspnea (CR10) and for rated perceived exertion (RPE) (Borg 1982) were monitored. Instructions during the tests were standardised.

Metabolic stress test

(Study II-IV)  
During the cycle ergometer test a metabolic stress test system (MetaMax II, Cortex, Biophysik GmbH, Leipzig, Germany) was used to measure the patient’s oxygen uptake (VO₂), carbon dioxide
production ($VCO_2$) and ventilation ($VE$). The patients breathed through a breathing mask placed over the mouth and nose, and held in place with a head cap. In the mask a turbine flow meter is placed for $VE$ measurements. For each breath a small sample of expired air is drawn into a mixing chamber from which $O_2\%$ and $CO_2\%$ are measured twice each second. The MetaMax II was found to be valid for metabolic gas measurements in healthy subjects (Larsson, Wadell et al. 2004). We performed a study on COPD patients where we validated the MetaMax II against the Douglas bag method (regarded as the criterion method for validating metabolic measurements). The values of $VO_2$ and $VCO_2$ were significantly higher (0.31 l/min and 0.25 l/min respectively) in MetaMax II than in the Douglas bag. The ventilation was the same in both systems. Intra class correlation for $VO_2$, $VCO_2$ and $VE$ was 0.87, 0.88 and 0.94 respectively ($p<0.001$). The MetaMax II was considered to be valid for use in patients with COPD.

**Knee muscle strength and endurance**

*(Study III)*

The dominant leg of the patients was evaluated with an isokinetic dynamometer (KinCom®, Chattanooga, Illinois). Maximal dynamic strength and endurance of the thigh was measured. An isokinetic movement means that the muscle contracts and lengthens at a constant velocity. All isokinetic systems are based on the principle that the lever-arm moves at a preset angular velocity however great the turning force, or moment, applied by the user. If the user pushes harder i.e. the muscle-generated moment is increased, tending to increase the angular velocity, the machine increases its resistance correspondingly and maintains movement within very narrow margins about the preset angular velocity (Dvir 1995). The KinCom equipment has been used in previous studies to evaluate training interventions in patients with COPD (Clark, Cochrane et al. 1996; Clark, Cochrane et al. 2000; Van't Hul, Harlaar et al. 2004).

**Maximal dynamic strength in knee extension and knee flexion**

The familiarisation procedure was followed by a period of rest for 2 minutes. Thereafter the patients performed 4 maximal knee
extensions at the angular velocity of $90^\circ \text{s}^{-1}$ with the instruction to extend their knee as forceful as possible and to relax during the passive flexion downward movement. No rest was allowed at the start position between the active and passive part of the contraction cycle. After a period of rest for 2 minutes the patients performed 4 additional contractions in $90^\circ \text{s}^{-1}$ with the instructions to maximally flex their knee and relax during the passive extension phase. The highest mean force value obtained for extension and flexion, respectively, was chosen.

**Dynamic endurance in knee extension**

In the endurance test, performed 5 minutes after the maximal test, the patients were instructed to extend their knee as many times, and as forceful as possible, at an angular velocity of $90^\circ \text{s}^{-1}$. They continued until exhaustion or until 100 repetitions were attained. During all tests the patients were frequently encouraged verbally to perform maximally.

The patients rated their perceived leg fatigue, according to Borg CR10 (Borg 1982) before the test started, after every 5th extension up to 50 and thereafter at every 10th extension until exhaustion or at 100 repetitions. During all tests the patients were frequently encouraged verbally to perform maximally.

**Blood lactate**

*(Study I, II, IV)*

In study I venous blood samples were taken from a catheter in the arm to measure the blood lactate. The samples were analysed in a lactate analyser (“YSI 1500 Sport L-Lactate Analyser”, Yellow Springs, USA). The samples were drawn at three occasions during the walking tests, at rest, directly after, and 3 minutes after the test. In study II and IV a later version of lactate analyser (“YSI 2300 STAT PLUS”, Yellow Springs, USA) was used to analyse the samples taken in connection with the cycle ergometer tests. Samples were taken at rest, at every load (2 to 8 occasions), at the maximal load and 3 minutes after the test.
Methods

Oxygen saturation, \textit{SpO}_2

(Study I, II, IV)
During tests (study I, II and IV) and training (study I) the patients’ saturation was measured with a pulse oximeter ("Omeda Biox 3700e", Louisville, USA) using a finger probe or a forehead probe. During the tests in study I the pulse oximeter was connected to a recorder (Yokogawa LR 4200, Tokyo, Japan) which continuously printed the saturation.

Arterial oxygen saturation, \textit{SaO}_2

(Study I)
An arterial blood gas analyser ("IRMA Blood analysis system", St Paul, USA and "ABL 520" Radiometer, Copenhagen, Denmark) was used in study I during the walking tests. Arterial blood gases were taken from radial artery at rest and directly after each test.

Transcutaneous carbon dioxide, \textit{TcpCO}_2

(Study I)
To get a continuous measurement of TcpCO_2 during walking tests, a TcpCO_2-meter ("Tina TCM 3", Radiometer, Copenhagen, Denmark) was used. The probe was connected to the 3\textsuperscript{rd} rib or to the temple of the patient. The equipment was connected to a recorder (Yokogawa LR 4200, Tokyo, Japan) that continuously printed the levels. The pCO_2-values from the arterial blood gas tests were used to calibrate the TcpCO_2-meter.

Heart rate monitoring

(Study I-IV)
During training in study I the heart rate was continuously monitored with a pulse oximeter ("Omeda Biox 3700e", Louisville, USA) using a finger probe or a forehead probe. During the tests in study I the pulse oximeter was connected to a recorder (Yokogawa LR 4200, Tokyo, Japan) that continuously printed the heart rate. In study II, III and IV
the heart rate registration during training was monitored with portable heart rate watch (Polar Accurex Plus™, Polar Elektro Oy, Kempele, Finland).

**Perceived exertion, dyspnea and leg fatigue**

*(Study I-IV)*

Rated perceived exertion during test and training was evaluated with the Borg RPE scale. Dyspnea during test and training and leg fatigue during test were evaluated with the Borg CR-10 scale (Borg 1982).

**Body composition**

*(Study III-IV)*

Lunar dual energy X-ray absorptiometer (DXA), “Lunar DPX-L” (Lunar Co. Wisconsin USA) was used to measure the patients’ body composition. The patients are placed in supine position and scanned in a rectilinear manner using X-ray at two energies (Jebb 1997). With this method information about bone mineral density (BMD), lean body mass, and fat mass is given for the arms, legs, trunk and total body. In study III we analysed change in lean body mass of the legs and in study IV we analysed change in BMD.

**Health related quality of life**

*St George’s Respiratory Questionnaire – SGRQ*

*(Study II and IV)*

SGRQ is a self-completed questionnaire developed 1992 for measuring health in chronic airflow limitation (Jones, Quirk et al. 1992). It is a disease specific, self-completed questionnaire and has become widely used for assessing health related quality of life (HRQoL) in respiratory patients (Ferrer, Villasante et al. 2002). It consists of 50 items with 76 weighted responses divided into three component scores: symptom (problems caused by specific respiratory symptoms); activity (restriction of activity by dyspnea); and impact (impact of everyday life caused by the disease). A total score is calculated from all three components with zero indicating no health impairment and 100 representing maximum impairment. SGRQ has
been translated to, and validated for use, in several languages, among them Swedish (Engstrom, Persson et al. 1998). A decrease in score denotes an improvement in HRQoL while an increase in score denotes deterioration and a change of 4 units has been found to be a clinical significant change with treatment (Jones 2002)

**Medical outcome Short Form-36 – SF-36**

(Study II and IV)
The SF-36 is a multipurpose, short-form health survey with 36 questions. It yields an 8 scale profile of scores as well as physical and mental health summary measures. It is a generic measure and has been used in many studies to compare general and specific populations and to evaluate a wide range of different treatments (Ware, Gandek et al. 1998). SF-36 has been translated and validated for use in Swedish populations (Sullivan and Karlsson 1994; Sullivan, Karlsson et al. 1995; Persson, Karlsson et al. 1998). An increase in score denotes improvement while a decrease denotes deterioration in HRQoL. In the studies we present the changes in physical component score (PCS) and mental component score (MCS).

**Activity level questionnaire**

(Study II-IV)
To measure the activity level in the patients a questionnaire developed for use in elderly people was used (Frändin and Grimby 1994). It is designed to describe the level of physical activity and self-assessed fitness with a six graded scale. The classification system of physical activity includes household activities and was found valid in 76-year-olds.

**Statistical analysis**

SPSS was used in all studies (version 7.5 in study I and version 10.0 in II, III and IV). Level of significance was set to $p \leq 0.05$. Table 6 presents the methods used in the different studies.
Methods

Table 6. Overview of statistical methods used in studies I-IV.

<table>
<thead>
<tr>
<th>Statistics</th>
<th>Study I</th>
<th>Study II</th>
<th>Study III</th>
<th>Study IV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Non-parametrics</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wilcoxon matched-pairs signed ranks test</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
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<tr>
<td>Mann-Whitney U test</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Kruskal Wallis test</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chi square test</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td><strong>Parametrics</strong></td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Student's t-test</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Regression analysis</td>
<td></td>
<td></td>
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<td>X</td>
</tr>
<tr>
<td>Intention to treat analysis</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>

Non-parametric methods were used in study I-III. Wilcoxon matched-pairs signed ranks test for within group comparisons. In study I Mann-Whitney U test was used for between group comparisons. In study II-III, the Kruskal Wallis one way ANOVA was used in study II and III for comparisons between the three groups. When the ANOVA showed significant difference between groups the Mann-Whitney U test was used for pairwise comparisons between the groups. In the analysis of body composition, Friedman’s ANOVA was used to evaluate differences within groups over time. In study IV, the Chi-square test was used to compare the groups regarding whether or not the patients reached a change of clinical relevance in SGRQ score. Results are presented as medians along with the minimum and maximal values unless otherwise stated.

Parametric methods were used in study IV. The patients training in water and on land were analysed as one training group and not as two separate groups. Student’s t-tests were used to analyse differences within groups between the tests at baseline and 9 months and between the tests at 3 months and 9 months. Regression analysis was used to analyse differences between groups at 9 months with control for interaction between the different test occasions for the analysed parameters (walking distance, VO₂peak, work load, time cycled, SGRQ...
scores and SF-36 scores). Results are presented as means along with the standard deviations.

In studies II, III and IV an intention to treat analysis (ITT) was applied (i.e. all patients completing pre and post tests were taken into the analysis). A lower limit of training compliance was set to 50 % of the training sessions. The patients who fulfilled that criterion were also analysed separately as the on treatment group (OT).

Effect-size values (ES) were calculated in study II and IV, to describe overall treatment effects (Cohen 1988). It is calculated as the difference between before treatment (T1) and after treatment (T2) divided by the combined standard deviation for the total patient group before treatment (SD1). (ES = (T1-T2)/SD1 for the total group). ES values are preferably calculated so that a positive change gives a positive value. The most common criteria for what is considered to be a large or a small treatment effect are based on Cohen’s work. Values below 0.2 are considered as no effect, between 0.2 and 0.5 a small effect, between 0.5 and 0.8 a medium effect and values above 0.8 are a large effect (Cohen 1988).

The patients in the training groups (both land and water) in study III, who showed an improvement in any muscle performance tests of ≥ 10 %, were defined as responders of the training and patients who improved < 10 % were defined as non-responders of the training (Dvir 1995).
RESULTS

Two patients in study I were regarded as drop outs because of exacerbations. In study II, one patient in the control group and one patient in the land training group did not attend to the follow up tests at three months and were regarded as drop outs due to decline. At nine months follow up one patient in the water training group dropped out due to pancreatitis and one in the land training group dropped out due to an exacerbation of COPD.

Training attendance

In study I all patients fulfilled at least 21 out of 24 training sessions. Mean attendance rate at three and nine months was 87 % and 79 % respectively. In study II and III twelve patients in both training groups fulfilled the criteria of training attendance of at least 50 % at three months and were included in the on treatment group (OT). At nine months (study IV) eleven patients in each group fulfilled the criteria and were included in OT.

The intensity level of the training during the first three months in the water and land groups is presented in Figure 4.

Figure 4. Mean heart rate for the water and land training groups during the training sessions, in percent of peak heart rate. Peak heart rate was measured during maximal cycle ergometer test at baseline.
Physical capacity

Walking distance

The total distances walked during the first and last training week for both groups in study I are presented in Figure 5. Both groups increased the distance and OG covered a longer distance per session during the whole study.

Figure 5. Total distance walked during the first and last weeks of training (constituting of 90 minutes of walking) for the group training with air (AG, open bars) and the group training with oxygen (OG, grey bars) in study I. Values presented as median. Min-max for the first and last week respectively for AG (2112-5761), (3247-7371) and OG (2625-5194), (4924-7270). ** Significant increase in distance walked in both groups, p < 0.01.

In study I, both training groups (air group-AG and oxygen group -OG) increased the distance walked in 6 MWD after 8 weeks training with 20 and 14 % respectively when tested on air. When tested on oxygen AG increased the distance walked with 21 % while OG did not change (Table 7). Rated perceived exertion according to Borg RPE scale was decreased in AG group when the 6MWD was performed with air. In the test with oxygen, the OG decreased their ratings of both dyspnea and perceived exertion after training. The total time during which the patients desaturated below 90 % was significantly longer after training in the OG when tested on air. The
Results

time below 90 % in SpO₂ was 174 seconds (0-291) before training and 251 seconds (0-288) after training (p<0.05). In the AG there was no change.

Table 7. Distance walked and heart rate during Test A (with air) and Test B (with oxygen), before and after training in Study I. Values are presented as median (min-max). AG - patients training with air, OG - patients training with oxygen. % change is the change post training compared to pre training.

<table>
<thead>
<tr>
<th>Training groups</th>
<th>Pre training</th>
<th>Post training</th>
<th>% change</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Test A (air)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6MWD (m) AG</td>
<td>230 (110-280)</td>
<td>270 (130-390)</td>
<td>19.8 **</td>
</tr>
<tr>
<td>6MWD (m) OG</td>
<td>210 (90-360)</td>
<td>245 (140-380)</td>
<td>14.0 **</td>
</tr>
<tr>
<td>Max heart rate (bpm) AG</td>
<td>137 (102-162)</td>
<td>144 (113-155)</td>
<td>5.4</td>
</tr>
<tr>
<td>Max heart rate (bpm) OG</td>
<td>128 (104-142)</td>
<td>128 (102-140)</td>
<td>4.9</td>
</tr>
<tr>
<td><strong>Test B (oxygen)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6MWD (m) AG</td>
<td>235 (160-310)</td>
<td>290 (180-360)</td>
<td>21.3 **</td>
</tr>
<tr>
<td>6MWD (m) OG</td>
<td>245 (130-400)</td>
<td>275 (170-350)</td>
<td>9.9</td>
</tr>
<tr>
<td>Max heart rate (bpm) AG</td>
<td>130 (110-152)</td>
<td>137 (113-162)</td>
<td>4.3</td>
</tr>
<tr>
<td>Max heart rate (bpm) OG</td>
<td>122 (102-142)</td>
<td>127 (102-150)</td>
<td>2.1</td>
</tr>
</tbody>
</table>

** Significant within group, p<0.01.

In study II, the land training group increased distance walked with 20 m in ISWT (intention to treat - ITT) after 12 weeks. The water group on treatment (OT) increased the distance walked in ISWT, however not significantly, with 55 m. These changes, in the OT water and land groups, were significant compared to the control group. The water group increased the distance walked in ESWT with 164 m (ITT) and that was significant to both the land and control group. Results from both tests are presented in Table 8. There were no differences in the Borg ratings after tests within or between groups after the 12 weeks of training. The long term effect of reduced training frequency on walking distance is presented in Figure 6.
Table 8. Results from the walking tests at baseline, and after 3 months intervention in the control group and the training groups. Analysis of all patients in the study (Intention to treat) and analysis of patients fulfilling the training attendance criteria (On treatment) are presented. Median values (min-max) at baseline, at 3 months follow up, and the differences are given. Comparisons within and between group are outlined. Ns; no significance.

<table>
<thead>
<tr>
<th></th>
<th>Control group (n=12)</th>
<th>Water group (n=15)</th>
<th>Land group (n=14)</th>
<th>Between group comparisons</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intention to treat</td>
<td>On treatment</td>
<td>Intention to treat</td>
<td>On treatment</td>
</tr>
<tr>
<td>ISWT (m)</td>
<td>Baseline</td>
<td>345 (180-550)</td>
<td>350 (130-570)</td>
<td>ns</td>
</tr>
<tr>
<td>3 months</td>
<td></td>
<td>320 (200-500)</td>
<td>390 (140-590)</td>
<td>ns</td>
</tr>
<tr>
<td>Within group</td>
<td>ns</td>
<td>ns</td>
<td>p=0.008</td>
<td>p=0.003</td>
</tr>
<tr>
<td>comparison</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Difference</td>
<td>-5 (-110 – 80)</td>
<td>20 (-140 – 110)</td>
<td>20 (-20 – 130)</td>
<td>p=0.03a</td>
</tr>
<tr>
<td>Baseline/3 mo</td>
<td></td>
<td>55 (-90 – 110)</td>
<td>25 (0 – 130)</td>
<td>p=0.008b</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ESWT (m)</td>
<td>Baseline</td>
<td>1047 (116-1538)</td>
<td>576 (85-1905)</td>
<td>ns</td>
</tr>
<tr>
<td>3 months</td>
<td></td>
<td>599 (176-1446)</td>
<td>512 (209-1905)</td>
<td>ns</td>
</tr>
<tr>
<td>Within group</td>
<td>ns</td>
<td>p=0.001</td>
<td>ns</td>
<td></td>
</tr>
<tr>
<td>comparison</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Difference</td>
<td>-40 (-890 – 444)</td>
<td>164 (8 – 1454)</td>
<td>53 (-473 – 704)</td>
<td>p=0.001c</td>
</tr>
<tr>
<td>Baseline/3 mo</td>
<td></td>
<td>179 (8 – 1454)</td>
<td>53 (-473 – 704)</td>
<td>p=0.001e</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>p=0.007f</td>
</tr>
</tbody>
</table>

Wilcoxon Signed Ranks test was used for comparisons within groups. Kruskal-Wallis and Mann-Whitney U test was used for comparisons between groups. a) control and water group – on treatment, b) control and land group – on treatment, c) control and water group – intention to treat, d) water and land group – intention to treat, e) control and water group – on treatment, f) water and land group – on treatment.
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Figure 6. Walking distance in ISWT (incremental shuttle walking test) and ESWT (endurance shuttle walking test) for the three groups at baseline, after 3 and 9 months intervention. Values presented as median. a) and c): intention to treat analysis (ITT) b) and d), on treatment analysis (OT). * Significant within group, p<0.05.

In study IV, the on treatment group (OT) increased the distance walked with 31 m in ISWT at 9 months compared to baseline. The change in walking distance differed between the training and the control group in both ISWT (+16 m in ITT, -28 m in control group) and ESWT (+34 m, -208 m). The training group increased their Borg rating of perceived dyspnea with 0.6 after the ESWT at 9 months compared to baseline.

**Oxygen uptake – VO2peak**

In study II, the water group increased their VO2peak in the cycle ergometer test with 1.5 ml/kg · min (2.1 in OT) after 3 months training. Also the control group showed an increase of 0.7 ml/kg · min while the land group did not change. At 9 months compared to 3 months (study IV) all groups decreased VO2peak. Compared to baseline the training group decreased their VO2peak with 1.1 ml/kg ·
Results

min at 9 months (ITT) and the control group showed a similar decrease in VO\textsubscript{2}\text{peak}, 1.0 ml/kg \cdot min, though this change was not significant.

**Work load**

In study II, all groups increased their work load in the cycle ergometer test after the 3 months intervention with mean values of 6.7, 9.3 and 10.0 Watts in the control, water and land groups respectively (ITT). A change of 8.3 W has been suggested as a limit for clinical relevant change in patients with COPD (Lacasse, Wong et al. 1996). At 9 months compared to 3 months (study IV) the improvements had disappeared in all groups and there was no difference in any group compared to baseline.

**Time cycled**

Both training groups increased the time cycled in study II after training (ITT). The water group increased with 40 seconds (85 s in OT) and the land group increased with 25 seconds (40 s in OT) while the control group did not change. These changes had disappeared at the nine months follow up and there was no difference in any group compared to baseline (Study IV).

**Dynamic muscle strength and endurance**

In study III, the land group improved the thigh muscle strength in both maximal dynamic extension and maximal dynamic flexion, 16 % and 27 % respectively (ITT). The water group improved in maximal dynamic flexion, 40 %, and the control group in maximal dynamic extension, 7 %, Figure 7. In the analysis of the patients on treatment (OT) the water group showed an improvement of 8 % in maximal dynamic extension. At nine months the water and control group improved the knee flexion strength (Figure 7 a). The patients in the training groups (both land and water) who showed an improvement in any muscle performance tests of \( \geq 10 \% \) after 3 months of training was defined as responders and patients who improved < 10 % was defined as non-responders of the training (Dvir 1995). In two of the parameters measured at baseline difference between responders and non-responders were found. In extension the responders (n=15) had
a lower BMI at baseline than the non-responders. In flexion the responders (n=24) had a higher peak work load (mean value 68 W) than the non-responders (mean value 52 W) respectively.

In the test of muscle endurance there was no change in any of the groups after three months. All groups increased the muscle endurance after 9 months, Figure 8.

Figure 7. Maximal thigh muscle strength in flexion (a) and extension (b) in the three groups at baseline, after 3 and 9 months intervention. Intention to treat analysis. * Significant changes within groups; 1: p=0.016 baseline-9 mo, 2: p=0.001 baseline -3 mo, 3: p=0.005 baseline-9 mo, 4: p=0.011 baseline-3 mo, 5: p=0.016 baseline-3 mo, 6: p=0.013 baseline-3 mo.

Figure 8. Thigh muscle endurance in knee extension in the three groups at baseline, after 3 and 9 months intervention. Intention to treat analysis. * Significant changes within groups; 1: p=0.016 baseline-9 mo, 2: p=0.006 3 mo-9 mo, 3: p=0.004 baseline-9 mo, 4: p=0.002 3 mo-9 mo, 5: p=0.033 baseline-9 mo.
Of the 42 patients in the study, there were 27 patients who could not perform 100 repetitions in the muscle endurance test at baseline and they are regarded as low performers in this test. Fifteen patients managed to perform 100 repetitions and were defined as high performers. When analysing the results from the baseline tests, with the patients divided into high performers and low performers, there were no differences between the two groups except for rating of perceived leg fatigue after the test (mean Borg ratings 9 and 11 respectively).

**Body composition**

The results from the DXA measurements at baseline, 3 and 9 months for the three groups (ITT) are presented in Table 9. There were no changes in body weight or absolute values of bone mineral density (BMD) within groups. There were small within-group changes in total body fat, lean body mass in arms and legs. A decrease in total lean body mass was shown in the control and land groups over time. No differences were found between groups in any of the parameters.
Table 9. Body composition at base line, 3 months and 9 months in control, water and land groups, intention to treat analysis.

Values presented as median (min-max).

<table>
<thead>
<tr>
<th></th>
<th>Control (n=12)</th>
<th>Water (n=14)</th>
<th>Land (n=13)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Base line</td>
<td>3 months</td>
<td>9 months</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>76 (50-98)</td>
<td>76 (50-97)</td>
<td>75 (53-99)</td>
</tr>
<tr>
<td>BMD (g/cm³)</td>
<td>1.13 (0.88-1.28)</td>
<td>1.13 (0.87-1.32)</td>
<td>1.14 (0.87-1.32)</td>
</tr>
<tr>
<td>BMD (age %)</td>
<td>99 (89-111)</td>
<td>99 (88-112)</td>
<td>100 * (89-113)</td>
</tr>
<tr>
<td>Fat %</td>
<td>29.8 (21.6-46.1)</td>
<td>32.3 (22.8-47.4)</td>
<td>31.9 * (21.3-49.1)</td>
</tr>
<tr>
<td>Lean arm (kg)</td>
<td>4.99 (3.14-8.00)</td>
<td>5.02 (3.24-8.21)</td>
<td>4.69 (3.00-8.09)</td>
</tr>
<tr>
<td>Lean leg (kg)</td>
<td>15.64 (10.53-19.30)</td>
<td>16.03 (10.57-20.27)</td>
<td>15.93 (10.44-20.00)</td>
</tr>
<tr>
<td>Lean total (kg)</td>
<td>49.22 (33.24-65.74)</td>
<td>49.60 (34.66-64.75)</td>
<td>47.34 * (33.18-64.35)</td>
</tr>
</tbody>
</table>

* Significant within group comparison over time, p<0.05.
Health related quality of life

*St George’s Respiratory Questionnaire*

Results from SGRQ are presented in study II and IV. A decrease in score denotes an improvement in HRQoL. In study II, the water group showed a slight, non significant, improvement in total score (-3.6 units) in SGRQ (ITT). A change of 4 units is considered to be of clinical relevance. The control group showed a significant deterioration in total score (+5.3 units), and that deterioration was also significant compared to the training groups. The water group showed a significant improvement in activity score (-5.1 units), which was also significant compared to the other two groups, Figure 9. Table 10 presents the changes in the four domains after 3 and 9 months in the three groups.

![Change in SGRQ](image)

Figure 9. Change in St George’s Respiratory Questionnaire (SGRQ) after intervention. Intention-to-treat analysis. Decrease in units denotes improvement. Mean values are presented. * Significant within group, p < 0.05.
### Results

Table 10. Difference in St George's Respiratory Questionnaire at baseline compared to 3 months and at baseline compared to 9 months for the three groups, intention to treat analysis. Values presented as mean (SD). Decrease denotes improvement.

<table>
<thead>
<tr>
<th>SGRQ</th>
<th>Control (n=12)</th>
<th>Water (n=14)</th>
<th>Land (n=13)</th>
<th>Between group comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Symptom score</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline-3 mo</td>
<td>9.4 (20.4)</td>
<td>0.0 (25.7)</td>
<td>0.4 (20.4)</td>
<td>ns</td>
</tr>
<tr>
<td>Baseline-9 mo</td>
<td>7.6 (20.1)</td>
<td>3.7 (23.4)</td>
<td>10.7 (15.3)*</td>
<td>ns</td>
</tr>
<tr>
<td><strong>Activity score</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline-3 mo</td>
<td>7.6 (13.4)</td>
<td>-4.6 (9.3)</td>
<td>1.1 (9.3)</td>
<td>p=0.018</td>
</tr>
<tr>
<td>Baseline-9 mo</td>
<td>5.2 (8.6)</td>
<td>-1.8 (12.6)</td>
<td>4.1 (11.7)</td>
<td>ns</td>
</tr>
<tr>
<td><strong>Impact score</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline-3 mo</td>
<td>2.7 (5.6)</td>
<td>-3.1 (12.6)</td>
<td>-2.0 (13.9)</td>
<td>ns</td>
</tr>
<tr>
<td>Baseline-9 mo</td>
<td>5.9 (11.1)</td>
<td>1.6 (13.1)</td>
<td>-1.8 (9.0)</td>
<td>ns</td>
</tr>
<tr>
<td><strong>Total score</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline-3 mo</td>
<td>5.3 (5.8)*</td>
<td>-3.1 (10.8)</td>
<td>-0.7 (9.5)</td>
<td>p=0.038</td>
</tr>
<tr>
<td>Baseline-9 mo</td>
<td>5.9 (10.7)</td>
<td>2.8 (13.0)</td>
<td>2.1 (8.4)</td>
<td>ns</td>
</tr>
</tbody>
</table>

* Significant within group, p<0.05

In study IV, at 9 months compared to 3 months, the training group deteriorated in HRQoL, according to symptom score, with 6.9 units, and to total score, with 3.4 units. At 9 months, there were no significant differences compared to baseline within the training or the control groups. There were no significant differences in absolute values between groups, however, there were differences between groups in number of patients who improved or deteriorated in HRQoL. There were 75% of the control group (9 patients out of 12) who increased in their total score more than 4 units (deterioration) compared to 37% (10 patients out of 27) in the training group. In the training group there were 48% (13 patients out of 27) who decreased their activity score more than 4 units (improvement) compared to 8% (1 out of 12) in the control group.

**Short Form 36**

SF-36 was used in study II and IV. An increase in score denotes an improvement in HRQoL. After 3 months (study II) the water group showed a significant improvement in physical health – PCS (physical
component score) from 33 to 39 in SF-36, and this change was significant compared to the two other groups (ITT). The change in the patients who fulfilled the criteria of training (OT) attendance was slightly greater, from 34 to 42. Table 11 presents the changes in PCS and MCS after 3 and 9 months in the three groups (ITT).

Table 11. Difference in SF-36 between baseline, 3 and 9 months, intention to treat analysis. Values presented as mean (SD). Increase denotes improvement.

<table>
<thead>
<tr>
<th>SF-36</th>
<th>Control (n=12)</th>
<th>Water (n=14)</th>
<th>Land (n=13)</th>
<th>Between group comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline-3 mo</td>
<td>-1.4 (7.6)</td>
<td>5.6 (9.4) *</td>
<td>1.2 (8.3)</td>
<td>ns</td>
</tr>
<tr>
<td>Baseline-9 mo</td>
<td>-3.4 (4.6) *</td>
<td>0.9 (10.6)</td>
<td>0.5 (6.7)</td>
<td>ns</td>
</tr>
<tr>
<td>MCS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline-3 mo</td>
<td>0.0 (5.3)</td>
<td>-0.6 (9.3)</td>
<td>-0.8 (7.3)</td>
<td>ns</td>
</tr>
<tr>
<td>Baseline-9 mo</td>
<td>-4.8 (9.2)</td>
<td>0.4 (13.5)</td>
<td>-0.4 (7.0)</td>
<td>ns</td>
</tr>
</tbody>
</table>

PCS: physical component score, MCS: mental component score. * Significant within group, p<0.05.

At 9 months compared to 3 months (Study IV) the training group showed a decrease of -2.8 units in PCS. No differences were found between training and control groups. At 9 months compared to baseline the control group had a significant decrease in PCS (-3.4). The control group also decreased their mental component score, MCS, with – 4.8 at 9 months compared to baseline and that was significant compared to the training group (OT) who increased their value (+2.6).

**Activity level questionnaire**

Table 12 shows the changes in activity level after 3 and 9 months in the three groups (ITT). There was a difference between the groups OT at 9 months compared to baseline with an increased activity level in the training groups and a decreased level in the control group.
Table 12. Difference in activity level between baseline, 3 and 9 months in the three groups, intention to treat analysis. Values presented as median (min-max). Increase denotes improvement.

<table>
<thead>
<tr>
<th>Activity level questionnaire</th>
<th>Control (n=12)</th>
<th>Water (n=14)</th>
<th>Land (n=13)</th>
<th>Between group comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline-3 mo</td>
<td>-1 (-1-1)</td>
<td>0 (-2-2)</td>
<td>0 (-1-3)</td>
<td>p=0.025</td>
</tr>
<tr>
<td>(mean -0.5)</td>
<td>(mean 0.1)</td>
<td>(mean 0.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline-9 mo</td>
<td>-1 (-2-1)</td>
<td>0 (-1-1)</td>
<td>0 (-1-2)</td>
<td>ns</td>
</tr>
<tr>
<td>(mean -0.6)</td>
<td>(mean 0.0)</td>
<td>(mean 0.4)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Effect size

The effect sizes for the control, water and land groups at three months compared to baseline are presented in Table 13. The water group shows a medium positive effect in ESWT and physical component score (SF-36) and small positive effect in SGRQ. The land group shows a small positive effect in ISWT and no change in the other parameters. The control group show small negative effect in all parameters. The difference between the control and the training group is significant regarding ESWT and activity score in SGRQ.

The effect sizes for the control group and the training group (water and land analysed as one group) at nine months compared to baseline are presented in Table 14. The control group shows small negative effect in distance walked and in HRQoL. The training group (ITT) shows no change except for a negative change in symptoms score. Regarding ISWT and ESWT the change is significant compared to the control group. That is also the case in the patients in the on treatment group (OT) who show a small positive effect in ISWT and mental component score in SF-36.
Table 13. Mean effect-size values (ES) and 95 % CI for of walking tests (ISWT, ESWT) and health related quality of life, HRQoL, (SGRQ, SF-36) in the three groups at three months compared to baseline. Between group differences are presented.

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Control (n=12)</th>
<th>Water (ITT) (n=15)</th>
<th>Land (ITT) (n=14)</th>
<th>Between group comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ES 95 % CI</td>
<td>ES 95 % CI</td>
<td>ES 95 % CI</td>
<td></td>
</tr>
<tr>
<td>Walking tests</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ISWT</td>
<td>-0.08 (-0.35 – 0.19)</td>
<td>0.16 (-0.16 – 0.49)</td>
<td><strong>0.33</strong> (0.09 – 0.56)</td>
<td>ns</td>
</tr>
<tr>
<td>ESWT</td>
<td><strong>-0.30</strong> (-0.78 – 0.17)</td>
<td><strong>0.68</strong> (0.22 – 1.14)</td>
<td>0.06 (-0.23 – 0.35)</td>
<td>0.003</td>
</tr>
<tr>
<td>SGRQ</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptoms</td>
<td>-0.37 (-0.88 – 0.14)</td>
<td>-0.02 (-0.56 – 0.52)</td>
<td>-0.06 (-0.51 – 0.39)</td>
<td>ns</td>
</tr>
<tr>
<td>Activity</td>
<td><strong>-0.42</strong> (-0.88 – 0.05)</td>
<td><strong>0.28</strong> (0.00 – 0.55)</td>
<td>-0.17 (-0.52 – 0.19)</td>
<td>0.018</td>
</tr>
<tr>
<td>Impact</td>
<td>-0.14 (-0.33 – 0.05)</td>
<td><strong>0.21</strong> (-0.16 – 0.57)</td>
<td>0.07 (-0.35 – 0.48)</td>
<td>ns</td>
</tr>
<tr>
<td>Total</td>
<td><strong>-0.30</strong> (-0.50 – -0.09)</td>
<td><strong>0.20</strong> (-0.13 – 0.53)</td>
<td>0.03 (-0.36 – 0.30)</td>
<td>ns</td>
</tr>
<tr>
<td>SF-36</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCS</td>
<td>-0.14 (-0.62 – 0.34)</td>
<td><strong>0.61</strong> (0.10 – 1.13)</td>
<td>0.02 (-0.48 – 0.52)</td>
<td>ns</td>
</tr>
<tr>
<td>MCS</td>
<td>0.00 (-0.37 – 0.36)</td>
<td>-0.07 (-0.60 – 0.46)</td>
<td>-0.10 (-0.54 – 0.18)</td>
<td>ns</td>
</tr>
</tbody>
</table>

CI: confidence interval, ISWT: incremental shuttle walking test, ESWT: endurance shuttle walking test, SGRQ: St Georges Respiratory Questionnaire
The effect-size values of clinical relevance are indicated with bold style. Values < 0.2; no effect, 0.2-0.5; small effect, 0.5-0.8; medium effect (Cohen 1988).
Table 14. Mean effect-size values (ES) and 95 % CI for of walking tests (ISWT, ESWT) and health-related quality of life, HRQoL, (SGRQ, SF-36) in the Control group and the Training group (intention to treat, ITT and on treatment, OT) at nine months compared with baseline. Intention to treat and on treatment analysis. Between group differences are presented.

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Control (n=12)</th>
<th>Training (ITT) (n=27)</th>
<th>Training (OT) (n=22)</th>
<th>Between group comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ES 95 % CI</td>
<td>ES 95 % CI</td>
<td>ES 95 % CI</td>
<td></td>
</tr>
<tr>
<td>Walking tests</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ISWT</td>
<td>-0.26 (-0.52-0.01)</td>
<td>0.14 (-0.08-0.36)</td>
<td>0.28 (0.12-0.44)</td>
<td>0.032, 0.000</td>
</tr>
<tr>
<td>ESWT</td>
<td>-0.39 (-0.88-0.11)</td>
<td>0.06 (-0.14-0.26)</td>
<td>0.08 (-0.13-0.29)</td>
<td>0.038, 0.036</td>
</tr>
<tr>
<td>SGRQ Symptoms</td>
<td>-0.31 (-0.83-0.21)</td>
<td>-0.29 (-0.61-0.03)</td>
<td>-0.20 (-0.56-0.16)</td>
<td>ns</td>
</tr>
<tr>
<td>Activity</td>
<td>-0.28 (-0.57 0.01)</td>
<td>-0.06 (-0.32-0.21)</td>
<td>-0.01 (-0.32-0.29)</td>
<td>ns</td>
</tr>
<tr>
<td>Impact</td>
<td>-0.31 (-0.68-0.06)</td>
<td>0.00 (-0.23-0.24)</td>
<td>0.07 (-0.22-0.38)</td>
<td>ns</td>
</tr>
<tr>
<td>Total</td>
<td>-0.34 (-0.72-0.05)</td>
<td>-0.08 (-0.32-0.16)</td>
<td>-0.04 (-0.37-0.29)</td>
<td>ns</td>
</tr>
<tr>
<td>SF-36 PCS</td>
<td>-0.35 (-0.66-0.05)</td>
<td>0.07 (-0.28-0.43)</td>
<td>0.07 (-0.32-0.46)</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td>-0.55 (-1.21-0.11)</td>
<td>0.00 (-0.47-0.48)</td>
<td>0.30 (-0.14-0.75)</td>
<td>ns, 0.025</td>
</tr>
</tbody>
</table>

CI: confidence interval, ISWT: incremental shuttle walking test, ESWT: endurance shuttle walking test, SGRQ: St Georges Respiratory Questionnaire.

The effect-size values of clinical relevance are indicated with bold style. Values < 0.2; no effect, 0.2-0.5; small effect, 0.5-0.8; medium effect (Cohen 1988).
DISCUSSION

This thesis revealed that physical training of different modalities is of benefit for patients with COPD with regard to physical capacity and HRQoL. The training can be performed with high intensity, individually or in group in water and on land. Patients with exercise-induced hypoxaemia benefit from physical training and supplemental oxygen does not seem to further improve the training effect. If the training is performed three times per week, training in water seems to be somewhat more effective than the same training on land. However, the difference between the training modalities disappears when the training frequency is reduced. To train once a week is not enough to maintain the positive effects of a period of higher frequency of training. The combination of high and low frequency training during nine months does, nevertheless, seem to prevent decline in physical capacity and HRQoL compared to baseline.

Methodological considerations

Training programs

Both interventions in the studies described in this thesis were designed as interval training. In the first study the patients walked on a treadmill in interval form and the intensity target according to Borg score was set pretty high (7/17 in CR-10 and RPE respectively). The programs for training in water and on land were designed with intervals guided by music. The intensity target in this intervention was set to 5/15. According to personal communication with Gunnar Borg, one should not exceed these intensity targets during training (“hard is too hard”). The intensity level during training in water and on land was also monitored with heart rate monitors. These showed that the patients’ mean heart rate during the sessions stayed at 80-90 % of their peak heart rate (at baseline) which indicates that they reached a high intensity. This level also complies with the goal of 60-90 % of HR max, set by the American College of Sports Medicine for improving aerobic fitness (ACSM 1998). High intensity continuous exercise training (80 % of baseline peak work-rate (PWR)) has in COPD patients been shown to be superior to low intensity exercise
Discussion

(50 % PWR) when the same total work is performed (Casaburi, Patessio et al. 1991). Further studies reported however that the majority of COPD patients characterised by severe airflow limitation were not able to sustain prolonged high intensity exercise for the entire duration or for several weeks of rehabilitation (Casaburi, Porszasz et al. 1997; Maltais, LeBlanc et al. 1997). Interval training is a well-established alternative strategy that allows high intensity exercise to be performed for a relatively long period. Studies in healthy subjects showed that more work can be performed, before exhaustion sets in, by exercising with intervals than when the same total amount of work is performed continuously (Wilmore and Costill 2004). Studies on COPD patients comparing interval training with continuous training programs revealed no significant differences in terms of improvement in exercise tolerance (Coppoolse, Schols et al. 1999; Vogiatzis, Nanas et al. 2002), however they conclude that interval could be better for patients with more severe disease since the training is performed in shorter time.

Walking tests

In the first study the 6MWD was used to evaluate walking capacity while ISWT and ESWT were used to evaluate the second intervention (training in water and on land). There is no consensus about which test is the best to use. The 6MWD is widely used and is recommended by the American Thoracic Society (ATS). It is considered to be safe, easy to administer, well tolerated, and to reflect activities well (Enright 2003). The 6MWD requires access to a corridor of at least 30 m, free from disturbing factors. The instructions and encouragements should be standardised (2002). Normal values for the test are presented (Troosters, Gosselink et al. 1999) and minimal clinical important difference is calculated for interpretation of the results (Redelmeier, Bayoumi et al. 1997). Although attractive, there are arguments against the 6MWD protocols. They are difficult to standardise and may be influenced by motivation and encouragement (Guyatt, Pugsley et al. 1984). They also demand an undisturbed corridor of at least 30 m that might be difficult to find in the wards today. We performed the 6MWD on a non-motorised treadmill in study I because of the number of measurements with non mobile equipment during the tests. Since the patients were breathing oxygen or air during the tests it was more
appropiate to let them perform the test on a treadmill. The training in the study was performed on a motorised treadmill where the speed was adjusted by a physiotherapist. Since the 6MWD is a self paced test we chose the non motorised treadmill, which was driven by the patients own walking and enabled them to decide speed and pauses independent of the test leader. The treadmill used for the tests showed good test-retest-reliability when tested on healthy persons. A variability of 5% was found when the subjects performed two tests with one week interval. Despite the recommendations of not to use the treadmill in 6MWD (Enright 2003) we found it to be the best possible alternative.

Concerns about the methodological problems with 6MWD have led to the development of the shuttle walking test for patients with chronic airway obstruction (Singh, Morgan et al. 1992). The incremental shuttle walking test (ISWT) requires the patient to walk up and down a 10 m course. The test is progressive and has been found to produce a maximal response in patients with COPD (Singh, Morgan et al. 1994). This has led to a further development of the endurance shuttle walking test (ESWT) (Revill, Morgan et al. 1999). This test is performed on the same course as ISWT and the speed with which the patients walk is calculated from the result in the maximal test. The test is found to have good reproducibility and to be sensitive to pulmonary rehabilitation (Revill, Morgan et al. 1999). Though, one aspect is a possible ceiling effect of the test. If the patients, after intervention, manage to walk for longer than 20 minutes it may be difficult to interpret the result. The patients may have performed an even better result if they were not restricted by the time limit. However, it would be difficult, in a clinical setting, to let the patient walk until exhaustion considering the time consumed.

**Metabolic stress test**

In healthy subjects the measurement of oxygen consumption (VO₂) and carbon dioxide production (VCO₂) are standard tools of exercise physiology to assess aerobic capacity, exercise intensity and energy expenditure (1998). For many years the technique for the collection and analysis of these gases has been the Douglas bag method (Douglas 1911). In the field of sports medicine the need for quicker and smaller equipment has forced the development of different
portable systems for measuring aerobic capacity. Now there are a number of these systems on the market and they are found to be more or less valid and reliable on healthy people (Macfarlane 2001). To be able to test VO₂ and VCO₂ in functional activities (stair walking, gardening etc.), different portable devices have been developed for healthy people and athletes (Macfarlane 2001). Obviously, there is a need for light-weighted, portable and accurate equipment also for patients with COPD but their validity is not well described in the literature. We used a portable metabolic stress test system, MetaMax II, to evaluate the cardiorespiratory response to training in water and on land. This system was found to be valid in healthy subjects (Larsson, Wadell et al. 2004) and it also showed acceptable validity when tested on patients with COPD in our laboratory. However, larger studies are desirable for validation of portable equipment for use in patients with COPD.

**Muscle tests**

The isokinetic dynamometer used in study III has also been used in many other studies that evaluated interventions in patients with COPD. In our study it was responsive to changes in maximal strength in knee flexion and extension. The protocol used has also been applied in other studies on healthy elderly (Lindstrom, Lexell et al. 1997) and patients with ischaemic stroke (Lindstrom, Kristensen et al. 1999). Most subjects in these studies could attain the predetermined goal of 100 repetitions in the endurance test. However, in our study there was a remarkable portion of the study population who did not manage to perform the endurance test (to attain 100 repetitions). This influenced the analysis of data since two variables were affected by the intervention (the numbers of contractions performed and the total work performed).

**HRQoL questionnaires**

We chose to use SGRQ as the disease specific questionnaire in the second intervention, study II and IV. This questionnaire has demonstrated good reproducibility, validity and responsiveness when used in patients with COPD. There are however some results indicating that the SGRQ is more responsive to pharmacological than to rehabilitation intervention while the Chronic Respiratory Disease
Questionnaire (CRDQ) (Guyatt, Berman et al. 1987) is more responsive to rehabilitation. The CRDQ was specifically designed for assessment of change after rehabilitation. However, this instrument is not yet available in Swedish.

The SF-36 has been used in several populations which made it possible to compare the study population in our study with healthy, Swedish controls in the same age group.

The activity level questionnaire was designed for elderly people (evaluated in 76-years old). This instrument was perhaps too blunt and may explain why we did not detect any significant changes within groups.

Results

The hypothesis in the first study was that oxygen supplementation would yield a better result since previous studies have shown that oxygen during exercise is of benefit for patients with COPD (Stein, Bradley et al. 1982; Mitlehner and Kerb 1994). The oxygen group performed, as expected, a higher level of training in terms of distance walked during training sessions (Figure 5). However, this was not transferred to a better result in the test performed on air after the training period. In study I, we found that oxygen supplementation during training did not add to the positive effect of training since both groups, AG and OG, improved the distance walked after training. One explanation could be that the patients training with oxygen were not exposed to hypoxia at all. The oxygen content in the blood (PO₂) was continuously high during training and the tissues were never exposed to low blood oxygen content. A reduced oxygen supply is thought to be essential for initiating the conditioning response (Wilmore and Costill 2004). Training under conditions with a slight hypoxia is used in healthy athletes to improve oxygen uptake during work. Elite athletes can, in periods, perform physical training at high altitudes to get physiologic effect of hypoxia. The lower atmospheric pressure (hypobaric environment) means a lower PO₂, which limits pulmonary diffusion and oxygen transport to the tissues, resulting in hypoxia. Recent studies on healthy subjects, however, have come to different conclusions regarding the benefits of training.
Our conclusion from this study is that physical training in patients with COPD and exercise induced hypoxia preferably can be performed without supplemental oxygen assumed that the patients do not desaturate too much. However it is difficult to give general recommendations since the group of patients, as mentioned, is heterogeneous. The studies evaluating this issue have come to different conclusions. Two previous studies (Rooyackers, Dekhuijzen et al. 1997; Garrod, Paul et al. 2000) have reached the same conclusion as we did, that supplemental oxygen during training does not add to the effect of training with air. On the contrary, a recent, well designed study, concluded that supplemental oxygen during training yields higher intensity during training, larger decrease in breathing frequency at isotime, and larger increase in endurance after training compared to the same training with air (Emtner, Porszasz et al. 2003). The number of patients in the studies varied from 20 (our study) to 29 (Emtner et al). The patients in our study, and in the studies of Rooyacker el al. and Garrod et al., were hypoxaemic during exercise while the patients in the study of Emtner et al. did not desaturate during exercise. If this could explain the different results is hard to say. Other factors that can explain the opposite conclusions can be training intensity and test methods. In our study, the patients were stopped during the training if their saturation dropped below 90 %. This was never the case in the OG though it happened occasionally in the AG, especially in the beginning of the training period. However, after a couple of weeks almost all patients in the AG were able to perform the 30 minute sessions without desaturation and consequently without pauses. In the test with air after training, the time below 90 % in SpO₂ was significantly longer in the OG while there was no change in the AG. We therefore assume that training with oxygen does not stress the VO₂ capacity in the same way or to the same extent as training with air. However additional studies with specific design are needed to further investigate if, how, and in which patients, oxygen during training would be of benefit in COPD.

In study II we found that high-intensity group training 3 times per week performed in water gave larger positive effects in endurance and HRQoL than the same training performed on land. This was rather surprising and the reason for this result is not obvious. The design of the two training programs in water and on land was the same, with
the same amount of endurance, strength and mobility exercises. Physiotherapists directed the training and, as far as possible, the same physiotherapist supervised both land and water training to avoid the impact of different leader personalities. The mean heart rate during the training sessions shows that the intensity level complies with the goal 60-90 % of HR<sub>max</sub> set by the American College of Sports Medicine for improving aerobic fitness (ACSM 1998).

The patients training in water in the present study attained lower heart rates compared to the land group throughout the training period (Figure 4), although they rated their dyspnea and perceived exertion as high as the land group (4 and 14 on the Borg score). Head-out immersion in water leads to a central shift of blood volume from the peripheral to the intrathoracic vascular bed and studies have reported lower heart rates in water compared to the same exercise intensity on land (Avellini, Shapiro et al. 1983; Svedenhag and Seger 1992). Agostini et al (Agostoni, Gurtner et al. 1966) found that the functional residual capacity (FRC) is decreased by almost the half, the vital capacity (VC) is decreased with 9 % and the residual volume (RV) is decreased with about 16 % during head-out water immersion. In patients with COPD the FRC and RV are often increased due to pathological changes in the lungs. This augments the work of breathing and contributes to the increased dyspnea that many of the patients suffer from. The fact that FRC and RV are decreased during head-out water immersion could possibly decrease the sense of dyspnea and facilitate the accomplishment of physical exercises in water. Further studies would be of interest to investigate if this effect explains the difference in results between the water group and the land group.

The superior effect of water training disappeared when the training frequency was decreased from 3 to once per week. The land group on treatment showed a significant increase in ESWT at 9 months compared to baseline, and an increase, however not significant compared to the 3 month level. The water group, on the other hand showed preserved results in ESWT at 9 months compared to baseline but a significant decrease compared to the 3 month level. This shows that water training has to be performed more than once per week to retain the positive effect while land training seems to better preserve, and also improve, the physical capacity when the training frequency is
reduced. The similarity between the exercises in the land training program and activities performed during daily life could explain these results. It is, however, difficult to make strong conclusions of an intervention performed once per week during six months since it is such a small part of the total activities of the patients’.

We found a greater effect of training in ESWT than in ISWT in the water group in study II (effect size 0.68 and 0.16 respectively). This supports the statement that tests of endurance capacity, exhibit greater sensitivity to change than tests on maximal capacity, following rehabilitation in patients with COPD (Revill, Morgan et al. 1999). However, the result in the land group was the opposite with greater change in ISWT than in ESWT (0.33 and 0.06 respectively) which could indicate that the two different training modalities affect different capacities. The design of the walking tests could possibly also explain the results. The speed in the ESWT was derived from the result of the ISWT since it should correspond to 85 % of the predicted VO₂ achieved in ISWT. An improvement in ISWT could lead to a higher walking speed in ESWT, which in itself is an improvement. However, it could be difficult for the patient to manage the higher speed for a longer period.

The maximal muscle strength, evaluated in study III improved after training (both in flexion and extension in the land group and in flexion in the water group). This is in accordance with previous studies that showed positive effects on muscle strength after training. The total lack of effect on muscle endurance, however, is somewhat remarkable. Despite the fact that the training was not specifically designed to have an effect on muscle endurance, it is strange that no change what so ever was seen. We conclude, despite the absence of a healthy control group, that the patients studied had quite a decreased muscle endurance since such a large part of the group, two thirds, was not able to perform the test (attain 100 repetitions). The design of training program could be one explanatory factor. The programs were not specifically designed to improve muscle strength or muscle endurance but rather general muscle strengthening exercises. Since we did not specifically address these exercises it is difficult to describe the intensity of the exercises performed but a too low intensity of the muscle strengthening exercises could perhaps explain the lack of response in the endurance tests.
In the analysis of responders and non-responders of the training with regard to maximal muscle strength BMI was found to be a predictive parameter. A normal BMI was found to give an increased strength in knee extension in contrast to a high BMI. One explanation can be that a higher BMI could indicate a more passive lifestyle which can have an effect on the outcome. Though, it is difficult to say if the high BMI is a cause or a consequence. The water group had a higher BMI than the land and control groups at baseline and 8 of 14 patients in the water group were non-responders of the training.

The measurements of body composition performed at three occasions during the 9 months intervention (study II-IV) showed that the studied group had relatively well preserved bone mineral density. This is in contrast to the general view, and previous studies indicating that patients with COPD have a lower BMD and a higher incidence of osteoporosis fractures than age-matched controls (Goldstein, Fallon et al. 1999; Biskobing 2002; Sin, Man et al. 2003; Melton, Patel et al. 2004). The reason for this can be the selection of patients. The patients included in the training groups accepted to attain a high intensity physical exercise program. If all patients eligible would have been measured the result might have been different. If the patients are severely affected by the disease, with more pulmonary and/or other symptoms, they would probably deny participation in such an intervention.

In study II and IV we found, in accordance with other studies, that physical training improves HRQoL. Though, the improvement achieved after the first 3 months with high intensity, high frequency training, was not evident at the follow up after 9 months. Training once per week was not sufficient to keep the improvements in HRQoL. The participants of the land group even increased their symptom score at 9 months compared to both baseline and the level at 3 months. The water group lost the improvement achieved at 3 months and returned to the baseline level in the tests at 9 months. In the effect size analysis of the results at 9 months compared to baseline the control group showed a small decrease in HRQoL.
External validity

Since the number of patients who declined participation in the second intervention was large (60 out of 90 patients) the generality of the results might be restricted. There are several factors that might explain the decline to enter the study. One aspect is the exertional dyspnea which in patients with COPD contributes to a decreased level of physical activity. It is a great demand on a patient to join a training study, probably even larger at the time of inclusion to the study than today, thanks to increasing information in the society about the benefit of physical exercise. The form of exercise offered to the patients; training in water and in groups, could be strange for these patients. Also the lack of tradition of physical training in this age group might add to the reasons not to attend. There is, therefore a potential risk that the patients included in the intervention were more positive to physical exercise than the total group of COPD patients. Nevertheless, we interpret the results to be applicable also for COPD patients with a more severe disease than those included in our studies. Other possible aspects are our inclusion criteria which were rather strict. Among the 284 patients who did not comply with the entry criteria at study start, there are probably many who would benefit from physical training. The character of the tests used in our studies excluded patients with, for example, orthopaedic and neurologic disorders. We also chose to omit smokers, an exclusion criterion which could be questionable in clinical practice.

Clinical implications

The results of these studies show that patients with moderate to severe COPD benefit from physical training. The training intensity can be high when the training is performed in a controlled environment with skilled personnel. The training could preferably be performed as interval training. It is important for the patients to have confidence in the training situation and hence dare to perform physical activity at a high intensity. Group training has both social and economical advantages. Patients with exercise-induced hypoxaemia can benefit from training without oxygen supplementation if the training is performed with the aim to keep the oxygen saturation on an acceptable level. Different training modalities, walking on
treadmill, group training on land or in water have been found effective. Alternate periods of high frequent training with periods of less frequent training seem to be an optimal training design for COPD patients. This strategy can prevent the deterioration in physical capacity and health related quality of life.

**Future research**

It would be rewarding to investigate cost effectiveness of training interventions concerning consumption of medications, health care, number of exacerbations, frequency and length of hospitalisations. Furthermore, studies of physical training in patients with different disease severity are necessary to conduct to be able to handle this heterogeneous patient group. It would also be of interest to evaluate if, and how, nutritional supplementation during training intervention, will affect the results. Whether physical training affects the level of pro-inflammatory cytokines is also a matter of interest. To reach a consensus about oxygen supplementation during physical training, more studies in this field are required. From a patient perspective it is important to investigate what effect physical training has on wellbeing, and which training modality the patients will prefer. Interview studies on patients entering training programs ought to be performed to evaluate the effect on a more qualitative basis.
GENERAL CONCLUSIONS

In studies on patients with COPD the following conclusions are drawn:

- Physical training of different modalities is of benefit for these patients.
- In patients with exercise-induced hypoxaemia, oxygen supplementation does not seem to further improve the training effect, compared with training with air.
- High-intensity group training in water and on land is beneficial with regard to walking capacity and HRQoL, compared to a control group.
- High-intensity group training in water seems to be somewhat more effective than the same kind of training on land with regard to walking capacity and experienced physical health when performed 3 times per week.
- Physical training in water and on land increases the maximal dynamic muscle strength of the thigh but does not seem to influence the dynamic muscle endurance.
- Training once a week does not seem to be sufficient to maintain the level achieved after a 3 month period of higher frequency training.
- High-intensity/low frequency training during 6 months with a preceding 3 month period of high-intensity/high frequency training seems to prevent decline in physical capacity and HRQoL compared to baseline.
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