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Physical Training and Testing in Patients with Chronic Obstructive Pulmonary Disease (COPD)

RAGNHEIÐUR HARPA ARNARDÓTTIR





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Abstract

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The overall aims of the studies were to investigate the effects of different training modalities on exercise capacity and health-related quality of life (HRQoL) in patients with moderate or severe COPD and, further, to explore two of the physical tests used in pulmonary rehabilitation.

In study I, the 12-minute walking distance (12MWD) did not increase on retesting in patients with exercise-induced hypoxemia (EIH) whereas 12MWD increased significantly on retesting in the non-EIH patients. In study II, we found that the incremental shuttle walking test was as good a predictor of peak exercise capacity (W peak) as peak oxygen uptake (VO, peak) is. In study III, we investigated the effects of two different combination training programmes when training twice a week for eight weeks. One programme was mainly based on endurance training (group A) and the other on resistance training and callisthenics (group B). W peak and 12MWD increased in group A but not in group B. HRQoL, anxiety and depression were unchanged in both groups. Ratings of perceived exertion at rest were significantly lower in group A than in group B after training and during 12 months of follow-up. Twelve months post-training, 12MWD was back to baseline in group A, but significantly shorter than at baseline in group B. Thus, a short endurance training intervention delayed decline in 12MWD for at least one year. Patients with moderate and severe COPD responded to training in the same way. In study IV, both interval and continuous endurance training increased W peak, VO2 peak, peak exhaled carbon dioxide (VCO2 peak) and 12MWD. Likewise, HRQoL, dyspnoea during activities of daily life, anxiety and depression improved similarly in both groups. At a fixed, submaximal workload (isotime), the interval training reduced oxygen cost and ventilatory demand significantly more than the continuous training did.

Keywords: chronic obstructive pulmonary disease, pulmonary rehabilitation, physical training, endurance training, interval training, health-related quality of life, exercise testing, walking tests, physiotherapy

Ragnheiður Harpa Arnardóttir, Department of Medical Sciences, Akademiska sjukhuset, Uppsala University, SE-75185 Uppsala, Sweden

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ISSN 1651-6206 ISBN 978-91-554-6815-6 urn:nbn:se:uu:diva-7632 (http://urn.kb.se/resolve?urn=urn:nbn:se:uu:diva-7632) To my family: Guðjón, Örn, Erla and Atli and to the true heroes in this book: My patients.

> "The essence of optimism is that it takes no account of the present, but it is a source of inspiration, of vitality and hope where others have resigned; it enables a man to hold his head high, to claim the future for himself and not to abandon it to his enemy" Dietrich Bonhoeffer

List of papers

This thesis is based mainly on the following original papers, which are referred to in the text by their roman numerals:

I	Arnardóttir RH, Larsson K, Sörensen S, Ringqvist I. No increase in walking distance on repeated tests in COPD-patients with exercise-induced hypoxemia. Submitted
Π	Arnardóttir RH, Emtner M, Hedenström H, Larsson K, Boman G. Peak exercise capacity estimated from in- cremental shuttle walking test in patients with COPD: A methodological study. Respir Res. 2006 Oct 17;7:127
III	Arnardóttir RH, Larsson K, Sörensen S, Ringqvist I. Two different training programmes for patients with COPD: A randomised study with 1-year follow-up. Respir Med. 2006 Jan;100(1):130-9
IV	Arnardóttir RH, Boman G, Hedenström H, Larsson K, Emtner M. Interval training compared with continu- ous training in patients with COPD. Respir Med. 2006 Dec 22; [Epub ahead of print]

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Abbreviations

6MWD	Distance walked in a 6-minute walk test
12MWD	Distance walked in a 12-minute walk test
ADL	Activities of daily living
ATS	American Thoracic Society
BMI	Body mass index
BTS	British Thoracic Society
COPD	Chronic obstructive pulmonary disease
CPET	Cardiopulmonary exercise test
CR-10	Category-ratio scale (Borg)
CRDQ	Chronic Respiratory Disease Questionnaire
DALŶs	Disability-adjusted life years
DLCO	Diffusion capacity for carbomonoxide
EIH	Exercise-induced hypoxemia
ERS	European Respiratory Society
FEV ₁	Forced expiratory volume in one second
FFM	Fat-free mass
FVC	Forced vital capacity
GOLD	Global initiative for chronic obstructive lung disease
HAD	Hospital Anxiety and Depression scale
HRQoL	Health-related quality of life
ICT	Symptom-limited incremental cycle test
ISWT	Incremental shuttle walking test
MVV	Maximum voluntary ventilation
Pack-years	Number of cigarette-packets/day multiplied by years of smoking
PaCO ₂	Partial pressure of oxygen in arterial blood
PaO ₂	Partial pressure of carbon dioxide in arterial blood
PEF	Peak expiratory flow
REE	Resting energy expenditure
RPE	Ratings of perceived exertion (Borg)
RV	Residual volume
SaO ₂	Oxygen saturation measured in arterial blood
SF-36	The Medical Outcome Short Form-36 Health Survey
SGRQ	St.George's Respiratory Questionnaire
SpO ₂	Oxygen saturation measured by pulse oximeter
TLC	Total lung capacity
VC	Vital capacity
VCO ₂	Carbon dioxide production
VO ₂	Oxygen uptake
VE	Minute ventilation
W peak	Peak exercise capacity (Watt)

Introduction

Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality in the world (1,2). It is the fourth leading cause of death in Europe and the USA and the impact of COPD has grown immensely during the last 20 years, especially among women (3). As COPD is an incurable disease, treatment aims towards preventing progression, minimising the negative effects of the disease and, hence, adding both years to the patient's life and life to his/her years. Pulmonary rehabilitation is a cornerstone in modern care of patients with COPD, and exercise training is one of its key components.

Chronic obstructive pulmonary disease

Definition, diagnosis and staging

There are some slightly different definitions of COPD. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) definition of the disease from 2006, states:

"COPD is a preventable and treatable disease with some significant extrapulmonary effects that may contribute to the severity in individual patients. Its pulmonary component is characterized by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lung to noxious particles or gases." (1)

The common task force statement of The American Thoracic Society (ATS) and The European Respiratory Society (ERS) adds to this definition that: *"COPD is....primarily caused by cigarette smoking"* (4). Both GOLD and

ATS/ERS agree that COPD is to be suspected when there is a history of exposure to risk factors for the disease, chronic cough, sputum production and/or dyspnoea and that diagnosis must be confirmed by spirometry. When forced expiratory volume in one second (FEV₁) divided by forced ventilatory capacity (FVC) is < 70%, even after administration of a bronchodilator, the diagnosis is confirmed (1). In patients older than 70 years a somewhat lower ratio (< 65%) has been suggested (5). Some guidelines claim that besides FEV₁/FVC < 70%, the FEV₁ should be < 80% of predicted value for diagnosis of COPD (6).

Various stages of the disease have also been classified, this classification being somewhat different in different countries and at different times (1,6-8). Three of these staging systems are shown in Table 1. The classification used previously in the Swedish guidelines for diagnosis and treatment of COPD was similar to the classification by The British Thoracic Society (BTS, Table 1) (6), but has recently been updated to resemble the GOLD 2006 (1,5). In recent years, it has been criticised to use FEV₁ as the dominating factor in staging COPD. Although COPD is primarily a lung disease, the literature has revealed various functional and systemic effects of the disease (9). Those effects, along with other co-morbidities of COPD, have emerged as important contributors to the severity or impact of COPD. The staging of disease severity by FEV₁ alone has therefore been criticised and in the future more multidimensional grading systems could become the dominant way of staging disease severity in COPD (10,11).

	BTS	GOLD	ATS/ERS
	1997	2001	2004 and
			GOLD 2006
Definition of COPD	$FEV_{1}/VC < 0.7$	$FEV_1/FVC < 0.7$	$FEV_{1}/VC < 0.7$
	and		
	$FEV_1 < 80\%$ pred		
Severity staging, according to FEV ₁ % of predicted value	-		
I Mild	$60 < FEV_{*} < 80$	$FEV_{c} > 80$	$FEV_{2} > 80$
	00 1 1 1 1 00	$1 L V_1 \ge 00$	$\Gamma L V \ge 00$
II Moderate	$40 \le \text{FEV}_1 < 60$	$30 \le \text{FEV}_1 < 80$	$50 \le \text{FEV}_1 < 80$
III Severe	$FEV_1 < 40$	$FEV_1 < 30$	$30 \leq \text{FEV}_1 < 50$
IV Very severe			$FEV_1 < 30$

Table 1. Three different definitions of diagnosis and stages of disease severity in COPD

BTS: British Thoracic Society, GOLD: Global Initiative for Chronic Obstructive Lung Disease, ATS: American Thoracic Society, ERS: European Respiratory Society, FEV₁: forced expiratory volume in one second, VC: vital capacity, FVC: forced vital capacity, % pred.: percent of predicted value.

Prevalence

The prevalence of COPD is estimated from one to ten percent in the adult population worldwide, largely dependent on the criteria used (12). Prevalence differs in different age groups, as COPD is primarily an illness of the later half of life. In a Swedish population study the prevalence was 14% after the age of 45 and as high as 50% in smokers \geq 75 years (13). COPD is underdiagnosed, especially in the more moderate forms of the disease, but even in patients with severely impaired lung function. The prevalence of COPD is still increasing worldwide and it is predicted that in the next decades it will continue to increase (14). Disability-Adjusted-Life-Years (DALYs) means the sum of years lost because of premature mortality and years of life with disability, adjusted for the severity of the disease. In 2020, COPD is expected to be the fifth leading cause of DALYs worldwide (14).

Previously, most COPD-patients were men, but in recent years the prevalence amongst women has increased and in the Nordic countries there is hardly any difference in COPD prevalence between men and women (13). As smoking is the largest risk factor in industrialized countries, it is reasonable to believe that this development is linked to the change in the smoking pattern of the genders in the last decades.

Risk factors

Tobacco smoke is by far the largest risk factor for developing COPD in the developed countries (4). There is a dose-response relationship with increased risk of developing COPD with increased number of pack-years. Cigarette smoke seems to be a stronger risk factor than pipe or cigar smoke (1,15). There is some evidence that women are more easily harmed by smoking than men, as they develop COPD earlier (fewer pack-years) than men (16,17).

Other air-pollutants also increase the risk of COPD, both outdoor and indoor. As not all smokers develop COPD, it is reasonable to believe that some genetic factors are important as well, but this needs to be studied further. As it is, the only known genetic risk factor is the alpha-1-antitrypsin deficiency (18). Besides being a risk factor for smoking, low socio-economic status has been found, per se, to increase the risk of COPD (19).

Pathology and pathophysiology

The pathology of the lungs in COPD involves the airways, the lung parenchyma and pulmonary vasculature, variably presented in individual patients. Inhaled noxious particles and gases cause inflammatory response in the lungs which leads to pathological lesions in the airways and lung tissue characteristic for COPD. The main physiological abnormalities in COPD include mucous hyper-secretion and ciliary dysfunction; airflow obstruction and hyperinflation; gas exchange abnormalities and pulmonary hypertension (4). Besides the pathology in the lungs, there are significant systemic effects (extrapulmonary abnormalities) in COPD (9,20). The systemic effects contribute significantly to the impact of COPD on the patients' health. The main systemic effects are systemic inflammation, nutritional abnormalities and weight loss as well as skeletal muscle dysfunction. Systemic oxidative stress is considered to be an important factor and facilitator in the systemic effects of COPD, especially during exacerbations (9,21). Frequent exacerbations are common in COPD and are often the main factor, except for continued smoking, to cause progression of the disease over the years (22).

Clinical hallmarks

Dyspnoea and reduced exercise capacity

The most common and at the same time the most distressing symptom in COPD is dyspnoea: "I just can't get enough air any more" or "I get so terribly out of breath" are common phrases when the patients are describing their problems. The lung function impairment is most often experienced by the patients as if they cannot get enough air into their lungs, especially during activities. In spite of this, total lung capacity is usually normal or larger than normal. However, expiratory airflow is limited because of the obstruction, leading to air trapping and hyperinflation. This accentuates when the minute ventilation or respiration rate is increased, for example during exercise (23,24). The hyperinflation induces increased strain on the respiratory muscles, which are forced to work in a limited range of movement with negative pressure/effort relationship, leading to fatigue and increased dyspnoea (25-27). To avoid the distressing feeling of dyspnoea, the patients with COPD tend to avoid physical exertion and adapt a more sedated lifestyle than healthy elderly subjects (28). This, in turn, leads to a vicious cycle of reduced exercise capacity inducing increased dyspnoea during exercise which leads to a further avoidance of exercise and so on (Fig. 1).

Exercise capacity is impaired in COPD, both peak exercise capacity and functional exercise capacity. Besides lung hyperinflation and physical inactivity, ventilation-perfusion mismatch, hypoxemia, cardio-vascular problems and muscular changes contribute to the reduced exercise capacity. Functional exercise capacity is one of the key prognostic factors of morbidity and mortality in COPD (10) and correlates strongly with physical activities in daily life (28).



Figure 1. The vicious spiral of dyspnoea and exercise avoidance in COPD

Body composition and peripheral muscle changes

Weight loss and tissue depletion are common problems in COPD. Its prevalence has been found to vary from 20-27% in clinically stable out-patients up to 35% in patients eligible for pulmonary rehabilitation and is more common in women than men suffering from COPD (29-31). Decreasing body mass index (BMI) is an independent prognostic factor in COPD and associated with increased mortality (32-34). Resting energy expenditure (REE) and total daily energy expenditure has been found elevated in COPD patients compared to healthy people, in spite of COPD patients leading a more sedative life (35-37). Systemic inflammation, tissue hypoxia and drug affects (β_2 agonists) are considered to contribute to this (38-40), but the vast increase (10-20 fold) in the energy cost of breathing in severely ill patients with COPD is considered to be the main reason for elevated REE (41-43).

Besides weight reduction, depletion of fat-free mass (FFM) is an independent predictor of mortality in patients with normal BMI (31,44,45). Skeletal muscles are the main bulk of the FFM in the human body. The muscle wasting in COPD is more pronounced in the lower extremities, contributing to reduced exercise capacity (46-50). In studies on the quadriceps muscle in patients with COPD, it is evident that muscle mass and muscle properties are altered, with decreased total cross-sectional area of the muscle and a proportional shift from type I to type II muscle fibres (51-53). This leads to impaired strength and endurance of the thigh muscles in COPD, especially in women (54-56). The mechanisms associated with the changes in skeletal muscles in COPD are not fully understood, but are considered to be complex. Malnutrition, systemic inflammation, hypoxemia, oxidative stress, medication effects (oral corticosteroids) and abnormal hormonal factors (testosterone and growth hormones) are amongst the factors that contribute to impaired skeletal muscle function in COPD (20,55,57,58). However, the most obvious factor is deconditioning and, in a recent review article, Decramer et al claimed that "physical inactivity is currently the only convincing factor that is known to contribute to muscle weakness in COPD" (20).

Osteoporosis

Osteoporosis is common in patients with advanced COPD, leading to fractures and pain, which restrict physical activity even further. As in the depletion of muscles, osteoporosis is a problem of complex factors; systemic inflammation, physical inactivity, oral corticosteroids, current or previous smoking history and is associated with loss of FFM (59-61).

Anxiety and depression

The prevalence of anxiety and depression is higher in patients with COPD than in healthy people (62-64). This prevalence increases with increased severity of COPD (65). The low exercise capacity and frequent sensations of dyspnoea seem to make patients with COPD susceptible to panic and anxiety, dyspnoea being a central symptom of both COPD and panic (66). It may be assumed that being deprived of performing interesting leisure activities and experiencing a struggle to carry on with every day life would cause depression. In a recent review article, 12 out of 17 studies showed increased prevalence of depression in patients with COPD (63). Several studies confirm an inverse relationship between physical function and psychiatric disturbance in COPD (62,65,67,68), while others do not (69,70).

Health-related quality of life (HRQoL)

HRQoL is an individual's satisfaction or happiness with domains of life that are or can be affected by health or health care (71). HRQoL is considerably decreased in patients with COPD compared to healthy people (72,73). The domains considered important for HRQoL in COPD patients are mainly respiratory symptoms, dyspnoea, physical function, health perceptions, emotions, mastery, fatigue and overall impact of illness on health (74-76). In a qualitative study it was claimed that family relationships and local opportunities for independence in activities of daily living (ADL) were the most important factors for quality of life (77). Correlation has been found between HRQoL and physical function and/or lung function, but the relationship is weak to moderate (r-values from 0.14 to 0.50) (78-80). HRQoL correlates better with functional exercise capacity than with lung function or peak exercise capacity, but the correlation is moderate and an improvement in exercise capacity does not correlate with improvement in HRQoL (81,82). Low HRQoL is associated with increased mortality risk in COPD, especially in combination with anxiety (83,84).

Hypoxemia during exercise

Many patients with moderate or severe COPD become hypoxemic during exercise, although not hypoxemic at rest. This has been shown during common, daily activities (85). Exercise-induced hypoxemia (EIH) is more pronounced during walking than cycling (86). As chronic episodic hypoxemia may have adverse effects on, for example, the pulmonary vascular system (and thus the heart) (87), the skeletal muscles (88) and the central nervous system (89), there is a consensus on supplying oxygen during exercise training in patients with COPD if oxygen saturation measured by a pulse oximeter (SpO₂) falls below 90% (90).

Exacerbations

In patients with COPD exacerbations are frequent and correlate to disease severity. The most severely ill patients usually suffer from 3-4 exacerbations per year (91). Frequent exacerbations increase annual decline in lung function and in HRQoL (92,93). Exacerbations that lead to hospitalisation are demanding for the patient and costly for society. Approximately 60% of patients attended for exacerbation in a hospital will be readmitted within a year (84,94). Although low FEV₁ correlates with increased readmission rate, low exercise capacity, low physical activity and/or low HRQoL associated with anxiety, each are much stronger predictors of rehospitalisation than FEV₁ (84,94,95).

Treatment, other than pulmonary rehabilitation

Smoking cessation

The single most important intervention to prevent disease progression and increase survival is to stop smoking (1,96).

Pharmacological treatment

The most common medicines prescribed to stable patients with moderate or severe COPD are inhaled bronchodilators and corticosteroids. As reflected in the definition of COPD with a chronic and not fully reversible bronchial obstruction, the effects of pharmacological treatment are limited. However, their use can increase exercise capacity and HRQoL by reducing bronchial obstructivity and lung hyperinflation, and there is evidence that pharmacological treatment can reduce exacerbations (97-100).

Supplemental long-term oxygen therapy is prescribed when resting arterial oxygen tension is < 7.3 kPa. This therapy improves survival, sleep, exercise and cognitive performance in hypoxemic COPD patients (4).

Androgene supplementation (testosterone) and growth hormone therapy are amongst the pharmacological agents that have been tested to increase BMI, exercise capacity and muscle mass in patients with COPD (101-103), but their use is somewhat controversial and still at the experimental stage.

Surgery

In highly selected patients, lung volume reduction surgery, bullectomy or lung transplantation may result in improved lung function, exercise capacity and HRQoL (4,104-106).

Pulmonary rehabilitation

History

Although pulmonary rehabilitation, as we now know it, was not common in Sweden until the 1990's, the world history of pulmonary rehabilitation in some form goes back to the late 19th century. In those "pre-COPD days" the main threat to pulmonary health was infectious diseases, especially tuberculosis. In the book "Principles and Practice of Pulmonary Rehabilitation", Dr. Thomas Petty mentions that in 1895, Dr. Charles Denison in Denver, USA wrote a monograph entitled "Exercise for Pulmonary Invalids", which included breathing exercises and an exercise programme for tuberculosis convalescents (107). Across the Atlantic Ocean, Dr. Marcus Paterson introduced "graduated labour" into the treatment at the Sanatorium at Frimley, England in 1904 (108). This was considered most useful for the patients but could also be beneficial for the economy of the sanatorium and ranged from Grade 1, designated as Small Baskets: "a weight of about 10 lbs is carried a distance of about 10 yards; total weight carried about 8.5 cwt.; distance travelled to and fro, about 7 miles..." to Grade 6: "using large shovel and pick; digging with a large fork. Pulling down trees and trenching ground 3 feet deep... ...doing generally heavy work" (108). Gradually the awareness of the usefulness of physical exercise in pulmonary diseases other than tuberculosis increased. In 1918 the Swedish Dr. Henrik Berg wrote in his revised Läkarebok: "Physiotherapy is an excellent treatment for chronic bronchitis. This includes: movements of respiration, frontal or dorsal tapping of the thorax, and movements of the extremities; for the weak ones passive movements, for the stronger ones active movements" (109). In the 1950's some form of pulmonary rehabilitation was applied in parts of the USA and England and oxygen administration during exercise for patients with advanced

stages of emphysema had started in a few clinics both in the USA and in England (110,111). It took however 25-30 more years for pulmonary rehabilitation to develop into a well-recognised treatment for patients with emphysema and chronic bronchitis, the disease now known as COPD.

Definition and application

The first authoritative definition of pulmonary rehabilitation was published in 1981 (112) and was based on the final statement of the Pulmonary Rehabilitation Committee of the American College of Chest Physicians in 1974 (107). Since then, several updated versions of the definition of pulmonary rehabilitation have been published, the latest one by ATS/ERS (90):

"Pulmonary rehabilitation is an evidence-based, multidisciplinary, and comprehensive intervention for patients with chronic respiratory diseases who are symptomatic and often have decreased daily life activities. Integrated into the individualized treatment of the patient, pulmonary rehabilitation is designed to reduce symptoms, optimize functional status, increase participation, and reduce health care costs through stabilizing or reversing systemic manifestations of the disease". (ERS/ATS, 2006)

Pulmonary rehabilitation is thus not defined specifically for any single diagnosis, but, as stated above; *"for patients with chronic respiratory diseases who are symptomatic and often have decreased daily life activities"*. However, the main focus in pulmonary rehabilitation in the latest decades has been on patients with COPD. The multidisciplinary approach is important and is a central issue in all definitions of pulmonary rehabilitation. The main components of pulmonary rehabilitation are exercise training, nutrition and patient education. Psychological and sociological interventions may also be needed (90). Pulmonary rehabilitation is an effective treatment for patients with COPD (Fig. 2), more effective in improving HRQoL and exercise capacity than pharmacologic treatment (113). Pulmonary rehabilitation is also cost-effective for patients with high health-care utilisation and the number needed to treat for improved HRQoL is approximately three (114-117).

In spite of the evidence, pulmonary rehabilitation has, until recently, been utilised in clinical practice mostly as "the last resort" for patients with advanced COPD. In the step-by-step management of COPD guidelines, pulmonary rehabilitation was moved in year 2005 to the same step in treatment as regular pharmacologic treatment (long-acting bronchodilators or inhaled corticosteroids) and for patients with moderate as well as severe disease (GOLD stage II-IV) (1). Although pulmonary rehabilitation is, at its best, a tightly woven net of different factors to support the health of the patient, it is necessary to separately investigate the different parts of the programme. Nutrition and patient education are important factors of pulmonary rehabilitation (90). This thesis focuses, however, mainly on the effects of exercise training in patients with moderate or severe COPD.



Figure 2. Pulmonary rehabilitation fights deterioration in COPD and can reverse the vicious spiral to a considerable extent.

Nutrition

For malnourished patients, nutritional intervention can be considered vital, as there is a clear association between underweight and increased mortality risk in patients with COPD (33,34). In patients with COPD it is difficult to induce weight gain by nutritional supplementation alone (118). During physical training, energy demands increase and the ATS/ERS guidelines on pulmonary rehabilitation recommend that caloric supplementation should be given during periods of physical training when BMI < 21 kg/m², or if involuntary weight loss has been noted in the near past (1-6 months) (90). The combined intervention of physical training and nutritional supplementation is more successful than the nutritional intervention alone and can lead to weight gain with approximately twice as much gain in FFM as in fat mass (119,120).

Patient education

In COPD, like in other chronic diseases, self-management education is important. There is a broad consensus on this, although it has been difficult to measure effects of patient education per se (90). However, a recent study showed a decreased usage of rescue medication, number of physician consultations and health care costs for one year after patient education (121).

Physical training

There is a large amount of evidence on the effectiveness of physical training in COPD and it is recognised as the most important component of pulmonary rehabilitation (90). However, to find "the optimal" exercise mode, intensity, setting and duration for different COPD patients, much work is still to be done. A true optimum will hardly be found, because of the large variety of symptoms, needs and wishes of the patients with COPD. All the same, a better understanding of the impact of different aspects of physical training on exercise capacity and HRQoL is needed to improve the options and quality of exercise training available to the patients. The American College of Sports Medicine recommends that a programme for healthy, elderly people should include endurance training, strength training and flexibility training (122). The latest ATS/ERS practice guidelines on pulmonary rehabilitation recommend a combination programme of endurance and strength training (90).

Endurance training

The body of scientific evidence on the positive effects of endurance training in COPD is impressive (113,123-132). However, even in endurance training there are questions to be answered regarding endurance training modality, intensity, duration and frequency. Most studies have used cycle training but walking training on treadmills, in level corridors or outside are other useful alternatives, as well as free standing or water aerobics (126,127,133-135). High-intensity training has more effect on exercise capacity than lowintensity training (126), but in patients with severe COPD it can be difficult to sustain high-intensity by the continuous training modality (124,136). Dynamic hyperinflation, i.e. a progressive increase in end-expiratory lung volume during continuous exercise, limits exercise tolerance in patients with COPD (24,137). Methods that induce less dynamic hyperinflation on exercise have thus been proposed, such as hyperoxic inhalation (138), heliox (oxygen mixed with helium) inhalation (139,140), non-invasive positive pressure support (141) and interval exercise (142,143). Of these methods, interval exercise is the only method that is not associated with extra equipment and costs. Studies show inconsistency as to whether the effects of endurance training programmes can be enhanced by hyperoxic inhalation

(128,144). More consistency is on the positive effects of non-invasive positive pressure support, although the studies are small and the method is considered of value only for the most severely ill patients (141,145,146). In one, small study, a training programme with heliox inhalations showed no benefits over training with room-air breathing (147). Few studies have compared interval training with continuous training in patients with COPD and the results are somewhat inconsistent (148-150). In some studies both interval and continuous training have increased exercise capacity to a similar extent (149), whereas others have found more increase in exercise capacity by interval training (148). Comparable changes in peripheral muscle adaptations by continuous and interval training have been reported (150). Interval training can be conducted in various ways. Some evidence suggests that long intervals are more efficient than short intervals in healthy, young people (151). More studies are needed on the effects of different length and intensities of intervals for patients with COPD.

Resistance training

As peripheral muscle strength and endurance are impaired, resistance training is considered to be important for patients with COPD (90). The scientific evidence for resistance training in COPD is, however, not yet as strong as it is for endurance training. Resistance training undoubtedly improves muscle strength (152,153), though there is some inconsistency whether this leads into increased exercise capacity as well. Resistance training has been found to improve exercise capacity in a few studies (152,154), but only one study has found this to be at the same magnitude as from endurance training (152). When comparing endurance training with a combination of resistance and endurance training, however, no added benefits from the resistance training have been found, except more increased muscle strength (131,155,156). HRQoL improves quite similarly from resistance training as from endurance training (130,152), but there are no added benefits in HRQoL when combination programmes are used (131,155). As muscle endurance has been found to be more decreased than muscle strength (56) it could be proposed that a resistance training programme with lighter weights and increased number of repetitions would be more effective for the COPD patients. It seems though that quite a high proportion of weight is needed for effects on exercise capacity (152). This, however, is still unclear, as no randomised studies of different resistance training programmes have been done in patients with COPD. As most COPD patients are elderly and osteoporosis is quite common, resistance training can even be important because of its positive effects on bone mineral density and fall prevention among the elderly (157,158).

Other training modalities

In COPD patients with severely impaired exercise capacity and muscle strength, neuromuscular electrical stimulation on leg muscles has in some studies been found to increase muscle strength and walking ability (159,160). This could be an alternative for patients too weak to participate in other exercise programmes or during exacerbations (159), but further studies are necessary.

Specific inspiratory muscle resistance training (threshold resistance) has been recommended for COPD patients with decreased respiratory muscle strength (90). There is, however, inconsistency in the literature as to whether this type of training adds to the effects of whole-body physical training or not (161-164).

Pursed lips breathing aims to improve expiration. It is a moderately active expiration technique through half-opened lips, inducing slower breathing and slightly increased expiratory mouth pressure (165). Pursed lips breathing improves dyspnoea, resting blood gases and even functional exercise capacity (166-168). Some COPD patients use this technique instinctively during exercise, while others need instructions.

Thoracic movement is limited by hyperinflation of the lungs in COPD. It is important to prevent additional musculo-skeletal stiffness in the thorax. In this context, flexibility exercises for the thorax and shoulder girdle can be useful. As many muscles of the thorax, neck and shoulder girdle are used as accessory muscles of breathing, they tend to become stiff and sore and need extra stretching.

Progressive relaxation (169) saves energy and induces rest by e.g. lowering heart rate and blood pressure (170,171). In COPD patients it has also been found to decrease respiratory rate, anxiety and dyspnoea (172).

Duration, frequency and setting of the intervention

Intervention training programmes vary from 10 days (173) to 12-15 months (116,153,174,175). Most programmes have, however, been conducted for six to twelve weeks (46,123-131,133-135,144,152,154-156,176-183). When comparing similar interventions for different time periods, a longer period of intervention provides greater improvements in HRQoL and exercise capacity (175,184,185).

Training frequency from two to five times a week has been reported (126,133,154,156,186,187), usually most frequent sessions when programmes only last for two or three weeks. A "rule of thumb" in exercise for healthy people is that a minimum of three sessions per week are needed to increase exercise capacity (122,188). Some authors report exercise twice weekly as sufficient to improve exercise capacity in patients with COPD, even without home-training programmes between the sessions (130,149). This is, however, not confirmed by others (176). Consensus reports recommend exercise training for patients with COPD at least three times per week for at least six weeks (90,189). Meanwhile, in Sweden, the standard outpatient training offered hitherto has been twice a week at most clinics.

Most studies on exercise training in COPD are performed in an outpatient setting, either at a hospital or in the community (primary care) (180). Inpatient training at a hospital and home-based training without supervision has also been described (123,190,191). Outpatient training is performed in a safe clinical environment with trained staff and is cost-effective compared to the in-patient training. Home-based training supposedly has its greatest value in prolonging the effects of other training forms, i.e. as maintenance training after a rehabilitation period (192). Supervised training is more effective than unsupervised training (191,193). In many studies the patients exercise side by side in groups of four to ten patients (114,125,128,135). Training in a group of fellow patients is considered more effective both for the patients' psychosocial well-being (194) and for the cost-effectiveness of the training programme (114).

Selection of patients

COPD patients with varying disease severity benefit from exercise training. Most studies include patients with moderate or severe COPD. However, whether the same training protocols are equally beneficial for the patients with severe COPD as for the patients with moderate COPD has not been well established. Recent studies show that even patients with mild COPD benefit from exercise training (185). Exercise studies in COPD patients have included mainly men (195). As there are some gender differences in physiologic adaptations to the pathology of COPD and to exercise training, more studies on women with COPD are needed. Most studies only include clinically stable COPD patients, but in recent years even exercise directly after or during exacerbations has been tried with promising results (196). Some clinics only include patients who have stopped smoking, while others include even current smokers as smoking has not been found to affect the effects of training (90). As exercise training in malnourished patients can induce further catabolism, there is a consensus to give supplementary nourishment to all patients with BMI < 21 kg/m². Exercise training can, on the other hand, induce an anabolic response in normal-weight COPD patients (197).

Long-term effects

As COPD is a progressive disease, functional exercise capacity decreases with time. An annual decline of ≥ 26 m in 6-minute walking distance (6MWD) has been found in patients with severe COPD on usual medical

treatment (198). After intensive exercise training, exercise capacity returns to pre-training level after ten weeks to eight months of detraining in healthy people (122). There is some inconsistency in the reports on long-term effects after exercise training in COPD patients. By home-training protocols and reinforcement exercise sessions at the clinic once a month, some of the gain of the initial exercise programme can be preserved for up to one year (116,134,174,199,200) or even two years (116). Others have found that the initial gains of the training programme were lost, in spite of some maintenance training, but exercise capacity and HRQoL were preserved at pretraining levels while deterioration was observed in control groups at one year follow-up (179,201,202). Even unsupervised home-training alone has been effective in preserving pre-training levels of exercise capacity and HRQoL in patients who have participated in exercise programmes compared to controls (203). Two studies of exercise programmes that lasted ≥ 6 months revealed sustained effects for at least one year post training, despite no hometraining protocols (116,153). Whether there can be any long-term effects of shorter interventions, without home-training programmes, is not known.

Walking distance, physical activity and HRQoL are inversely related to the risk of re-hospitalisation and mortality (94,95,198,204), whereas depression correlates positively with re-hospitalisation (84). As exercise training improves walking distance, physical activity, HRQoL and depression, it is not surprising that exacerbations and days spent in hospital have been found to decrease after pulmonary rehabilitation (116,203).

Testing

The tests used to evaluate the physical and mental well being of the COPD patients as well as the effects of interventions can be split into three main groups: physical tests, questionnaires that measure mental health, dyspnoea with daily activities and HRQoL and, thirdly, lung function tests.

Physical exercise tests

Measurements of exercise capacity are important and widely used in rehabilitation of patients with COPD. Exercise testing in COPD varies from maximal laboratory tests, requiring advanced technical equipment, to simple field tests (Table 2). Maximal laboratory tests are mostly constructed to measure peak exercise capacity (W peak), and/or peak oxygen uptake (VO₂ peak) whereas field tests have been considered to reflect functional capacity (205-207). Cardiopulmonary exercise test (CPET) is considered "goldstandard" as it allows for more thorough scrutiny of physical adaptation or mal-adaptation to exercise than any other test as well as revealing comorbidities (208). The symptom-limited incremental test is not as informative as the CPET, but it can detect co-existing heart disease and it establishes peak exercise capacity which is useful for setting target exercise intensity. Excellent as they are, the laboratory tests are not always feasible in pulmonary rehabilitation as they are expensive and sometimes not available in clinical practice. Besides, peak tests do not reflect as well as field tests how active the patient is in every-day life.

Incremental shuttle walking test (ISWT), endurance shuttle walking test (ESWT) and the timed walk tests (12- and 6-minute walk tests), are the most commonly used field tests in COPD. The ISWT resembles the laboratory tests as it is externally paced and progressive (209). During ISWT there is a linear relationship between VO₂ and walking speed, similar to the relationship between VO_2 and work rate in incremental laboratory testing (210,211). VO_2 peak can be estimated from distance walked on ISWT (210). This was established by comparing two different walking tests (treadmill and ISWT) and it is unclear whether a similarly strong relationship would be found between ISWT and cycle performance. In laboratory testing, the treadmill test evokes slightly higher ratings of VO_2 peak than the cycle tests (212,213), whereas different protocols of cycle tests usually result in similar VO₂ peak but different W peak, depending on the slope of increased load during the test (214-216). Body weight is an important contributor to the work load during walking, whereas it is of minor importance during cycling. Thus, the correlation between performance on timed walk tests and VO₂ peak from a cycle test becomes stronger if distance walked is multiplied by body weight (distance x weight = work of walking at horizontal level) (217,218).

Recent findings indicate that metabolic and ventilatory responses to walking may differ from the responses to cycling in patients with COPD (213,219,220). In pulmonary rehabilitation, many exercise programmes are conducted on ergometer cycles and target training intensity expressed as a percent of W peak measured by an incremental cycle test. From a known VO₂ peak it is possible to estimate W peak (221,222). As VO₂ peak can be estimated from an ISWT (210) it seems reasonable to assume that W peak could be estimated from ISWT through the estimated VO₂ peak. An estimation of W peak directly from the performance on ISWT would, however, be preferable. This could be of clinical interest when expensive laboratory tests are not accessible.

Laboratory-tests	Variables measured (most common)	Equipment/ Requirements	Main use
Cardiopulmonary exercise test (CPET)	VO ₂ , VCO ₂ , V _E , heart rate, breathing frequency, W peak, dyspnoea, exertion, dynamic hyperinfla- tion, SpO ₂	Electronic cycle or treadmill, ECG, er- gospirometer, Borg- scales, pulse oximeter, ≥ 2 staff members	Detecting co- morbidities, peak and target exercise intensity, measure true physiologic effects of interven- tion (peak and isotime values)
Symptom-limited incremental test	W peak, heart rate, dyspnoea, exertion, SpO ₂	Electronic cycle or treadmill, ECG, Borg- scales, pulse oximeter, ≥ 1 staff member	Detecting co- morbidities, peak and target exercise intensity, measur- ing effects of intervention
Endurance test	Time until exhaus- tion, heart rate, dyspnoea, exertion, SpO ₂	Electronic cycle or treadmill, ECG, Borg- scales, pulse oximeter, timer, ≥ 1 staff mem- ber. Incremental test must be performed first, to establish level of intensity	Measuring effects of intervention
Field tests			
Incremental shuttle walking test (ISWT)	Distance walked, walking speed, dyspnoea, exertion, SpO ₂ , manual meas- urements of heart rate and breathing frequency	Level corridor: 10m, a cassette- or CD-player, 2 cones, pulse oxime- ter, Borg-scales, 1 staff member	Measuring effects of intervention, prognostic value, assessment of desaturation
Endurance shuttle walking test (ESWT)	Distance and time walked, dyspnoea, exertion, SpO ₂ , manual measure- ments of heart rate and breathing fre- quency	Level corridor: 10m, a cassette- or CD-player, 2 cones, pulse oxime- ter, timer, Borg-scales, 1 staff member ISWT must be per- formed first, to dictate speed	Measuring effects of intervention
12-min. walk test and	Distance walked, SpO ₂ , dyspnoea, exertion, manual measurements of	Level corridor: ≥ 25 m, pulse oximeter, timer, Borg-scales, 1 staff member	Measuring effects of intervention, prognostic value, assessment of
6-min. walk test	heart rate and breathing frequency		desaturation

Table 2. The most used physical exercise tests in pulmonary rehabilitation

The timed walk tests differ from the ISWT in that they are self-paced and therefore perhaps the timed walk tests reflect functional, every-day exercise capacity better than the ISWT. Timed walk tests have been used for patients with COPD for many years. A 12-minute walk test was modified from a running test (223) and evaluated for COPD-patients in 1976 (207). Six years later a shorter variant of the test was presented, the 6-minute walk test (224). The two tests are identical in all aspects except for the duration of the test, though the 12-minute test is considered more discriminating than the 6minute test (224,225). Learning-effects in the timed walk tests have been demonstrated and patients with COPD improve walking distance on the second test compared to the first test by 3-17% (226-228). Some authors have found significant improvement even between the second and the third test (226,229,230), though these findings are not confirmed by all (231,232). Improvement decreases with increased number of repetitions, and most authors have regarded it sufficient to perform only one practice test before assessment of walking distance. The increase on retesting is more prominent when tests are repeated on the same day than on different days or weeks apart (226,233). Encouragement during testing improves walking distance and has also been found to enhance the difference between test one and two (234) The ATS has published guidelines for the 6-minute walk test where they recommend standardized encouragement (206) but some authors have refrained from using encouragement to minimize the risk of examiner bias (235,236). Walk tests are more effective than cycle tests to detect exerciseinduced hypoxemia (EIH) (86). It is of importance to detect EIH when entering pulmonary rehabilitation, as supplementary oxygen should be given during sessions of physical training to patients with EIH (SpO₂ < 90%) (189). EIH may reduce exercise capacity (237,238) but it is not known whether the presence of EIH influences the improvement in walking distance on repeated walk tests. In older studies, pulse oximetry was not used (207,233,234) and in more recent papers patients with EIH often receive supplementary oxygen on retesting (198,227,232).

Questionnaires

For measuring HRQoL in patients with COPD, it is recommended to use both generic and disease-specific questionnaires (239). The Medical Outcome Short Form (36) Health Survey (SF-36) is a generic HRQoL questionnaire (240,241). It is valid and responsive to change in a variety of patient groups, including patients with COPD (203). The St George's Respiratory Questionnaire (SGRQ) (74) and the Chronic Respiratory Disease Questionnaire (CRDQ) (76) are the most widely used disease-specific questionnaires in patients with COPD. Of these three questionnaires, CRDQ has the most sensitivity for changes (242). Questions on anxiety and depression are partly addressed by some HRQoL instruments, but it is recommended to measure those items separately as well. The Hospital Anxiety and Depression Scale (HAD) is a reliable, short and widely used questionnaire for this purpose (240,243).

Lung function

Spirometry is the most important measurement to diagnose and stage the degree of COPD (1). Dynamic spirometry includes the flow-dependent measurements of FEV_1 and FVC, whereas static spirometry allows measurements and estimations of the static lung volumes. Physical training usually does not affect lung function in COPD. For inclusion/stratification and because the disease is progressive, it is common procedure to measure lung function before and after training intervention.

Aims

The overall aim of this thesis was to investigate the effects of different physical training modalities on exercise capacity and health-related quality of life in patients with moderate or severe COPD and, in addition, to explore two of the physical tests most used in pulmonary rehabilitation.

Specific aims were:

- to investigate retest-effects in the 12-minute walk test when three tests are performed on separate days within one week (I)
- to investigate whether exercise-induced hypoxemia affects the retest-effects in the 12-minute walk test (I)
- to investigate whether maximal exercise capacity (W peak) can be estimated from an Incremental Shuttle Walking Test (ISWT) (II)
- to compare the effects of a resistance training programme with a combined programme of endurance and strength training on exercise capacity and health-related quality of life after training twice a week for eight weeks (III)
- to investigate whether patients with moderate and severe COPD benefit equally from the same type of training (III)
- to investigate whether there are any long-term effects of a short training intervention (III)
- to compare the effects on exercise capacity, dyspnoea, mental health and health-related quality of life of two different endurance training modalities; training with 3-minute intervals and training with a constant load (IV)
- to compare the effects of interval and continuous training on oxygen cost at sub-maximal exercise (IV)

Ethics

All participants gave their informed consent. The Ethics Committee of Uppsala University approved the studies.

Patients and methods

Patients

Patients with moderate or severe COPD according to the BTS guidelines (6) were consecutively invited to participate in the study when being referred to training at the Physiotherapy Unit of the Pulmonary Section at the Akademiska Hospital, Uppsala or at the County Hospital in Västerås, Sweden. All were smokers or ex-smokers.

Inclusion criteria were COPD with a FEV₁/FVC-ratio < 0.7 and a FEV₁ <60% of predicted value after bronchodilatation. Exclusion criteria were other diseases that could interfere with training, such as ischemic cardiac disease or musculo-skeletal problems. In study I and III an increase of FEV₁ > 20% following inhalation of a bronchodilator was also an exclusion criteria. For baseline characteristics of the participants in all four studies, see Table 3.

Study I

Fifty-seven COPD patients were included in Västerås. The patients were divided into two groups, those with EIH, defined as a fall in SpO₂ below 90% at the first walk test and those without EIH, i.e. $SpO_2 \ge 90\%$ throughout the first test. After baseline tests, including dynamic spirometry, symptomlimited incremental cycle test (ICT), arterial blood gas analysis and measurements of HRQoL, each subject performed a 12-minute walk test on three separate days within one week. All three tests were performed at the same time of day, two or three days apart, with the same supervisor.

Study II

Ninety-three COPD patients were included in Uppsala. After baseline lungfunction measurements (dynamic and static spirometry) the patients performed an ICT and a CPET as well as an ISWT (Table 4). The two different ergometer cycle tests were performed on the same day, while the lung function tests and the ISWT were conducted on separate days. The three test days were separated by 1-3 resting days. Fifty-two of the patients repeated the ISWT within a week.

	Stuc	ly I	Study II	Study	III	Study	⁷ IV
	EIH n = 19	Non-EIH n = 38	All n = 93	Endurance n = 20	Strength n = 22	Interval n = 28	Continuous n = 32
Gender f/m	11/8	19/19	67/26	10/10	11/11	25/3	26/6
Age years	65 (50-79)	66 (47-84)	64 (43-80)	65 (49-77)	68 (52-84)	65 (52-80)	64 (43-77)
BMI kg/m²	22.6 ± 4.8	23.3 ± 4.4	23.4 ± 4.3	23.0 ± 3.8	22.8 ± 3.8	24.1 ± 5.0	23.5 ± 4.4
Pack-years	32 ± 13	30 ± 16	36 ± 21	29 ± 14	30 ± 16	33 ± 17	35 ± 19
VC liters	2.6 ± 0.8	2.6 ± 0.8	2.6 ± 0.9	2.7 ± 0.8	2.6 ± 0.9	2.3 ± 0.6	2.6 ±1.0
VC % prd.	77 ± 16	76 ± 14	67 ± 16	78 ± 13	76 ± 15	70 ± 16	69 ± 22
FEV ₁ liters	0.9 ± 0.3	1.0 ± 0.3	0.9 ± 0.3	1.0 ± 0.3	1.0 ± 0.3	0.9 ± 0.3	0.8 ± 0.3
EV1 % prd	35 ± 10	39 ± 11	32 ± 11	37 ± 11	38 ± 10	35 ± 13	32 ± 10

Table 3. The baseline characteristics of the subjects who completed participation in each of the four studies, mean \pm SD or (range)

fm: female/male, BMI: body mass index, Pack-years: packets/day x years, VC: vital capacity, FEV₁: forced expiratory volume in 1 second, % prd: percent of predicted value

Study III

Sixty-three COPD patients were included in Västerås (including the 57 patients from study I). Forty-two patients attended the minimum amount of training sessions (Fig 3). After dynamic spirometry and arterial blood gas analysis each patient underwent an ICT, 12-minute walk tests and HRQoL as well as anxiety and depression were measured (Table 4). At the pre-trial tests eight patients were excluded from the study because of cardiac problems or a bronchodilator response (FEV₁) of more than 20%. The remaining 63 patients were divided into those with severe disease (FEV₁< 40% of predicted value) and moderate disease (FEV₁ 40-59% of predicted value) (6). After the stratification, the patients with moderate and severe disease, respectively, were blindly randomised (in blocks of four) to an exercise programme including endurance training, resistance training and callisthenics (group A) or a programme of only resistance-training and callisthenics (group B). All patients trained for eight weeks, twice a week in groups of three to six patients. Each session lasted for about 75 minutes. After eight weeks of training, the pre-trial tests were repeated. A criterion for fulfilling the training was participation of at least 12 of the 16 sessions. Pre- and post-training tests were performed less than two weeks before and after the exercise period, respectively. Follow-up measurements were made at six and twelve months post-training. Measurements during follow-up were dynamic spirometry, blood-gas analysis at rest, 12-minute walk test and HRQoL.

Study IV

One hundred patients from Uppsala and Västerås were included (including 88 patients from study II), 60 patients attended the minimum amount of training sessions (Fig. 3). At baseline and after 16 weeks of training the following tests were performed: lung function tests, ICT, CPET, 12-minute walk tests as well as HRQoL (Table 4). Patients were stratified according to disease severity and randomised (as in study III) into training with either interval (I-group) or continuous (C-group) load. Training sessions were twice a week for 16 weeks, session duration approximately 90 minutes. A criterion for completing the training was participation in at least 24 of the 32 sessions.



Figure 3. A flow-chart of the participation in studies III and IV. n: total number of patients at the given time, s: number of patients with severe COPD, group A: endurance training, group B: resistance training, I-group: interval training, C-group: continuous training.

Testing

Table 4 shows an overview of the tests performed in the different studies.

Incremental cycle test (ICT) (Studies I-IV)

Peak exercise capacity (W peak) in studies I and III (Table 4) was determined by an ICT (RE 830, Rodby Elektronik AB, Enhörna, Sweden) with continuous ECG registration (Megacart, Siemens Elema AB, Solna, Sweden). After one minute of pedalling at a work rate of ten watts, the work rate was increased by ten watts per minute until exhaustion. In studies II and IV the ICT-apparatus was different (Case 8000 Exercise Testing System, GE Medical Systems, Milwaukee, USA) and the patients started pedalling at 20 W and the load was increased by 10 W every minute until exhaustion. Oxygen saturation was measured by a pulse oximeter (SpO₂, Optovent Respons, Optovent, Linköping, Sweden) and heart rate and breathing frequency were registered every minute during exercise. Systolic blood pressure, subjective ratings of perceived exertion (Borg RPE scale) and dyspnoea (Borg CR-10 scale) were recorded every second minute (244,245). All variables were measured before as well as one, two, four and ten minutes after exercise.

Cardiopulmonary exercise test (CPET) (Studies II and IV)

A semi-steady-state cardiopulmonary exercise test with breath-by-breath gas exchange analysis (ergospirometry) was performed by all patients in study II and the patients from Uppsala in study IV. Measurements of heart rate, SpO₂ and ratings of perceived exertion and dyspnoea were made as described above. The patients wore a mask with a turbine for gas exchange analysis (Oxycon Sigma, Jaeger, Germany) measuring VO₂, VCO₂ (carbon dioxide) and V_{E} . After recording steady-state measurements at rest (approximately four minutes of registration at rest) the patient began pedalling at 20 W. The load was kept constant until the ventilation and oxygen uptake reached a plateau, on average three to four min. at each level (hence semi-steady-state, as conventional steady-state requires at least six min. at each level). To keep testing time within reasonable limits (10-15 min) the load was increased by 5, 10, 20 or 30 W depending on the outcome of the first test. This was continued until exhaustion. The test procedure was identical (same steps of load) before and after the training intervention for each patient. The test was performed 30 min after the ICT (later if needed for all resting parameters to be stable at pre-exercise levels).

	Study I	Study II	Study III	Study IV
ICT	\checkmark	\checkmark	\checkmark	✓
CPET		\checkmark		\checkmark
ISWT		\checkmark		
12 min walk test	\checkmark		\checkmark	\checkmark
SGRQ	\checkmark		\checkmark	
SF-36				\checkmark
CRDQ -dyspnoea				\checkmark
HAD	\checkmark		\checkmark	\checkmark
Dynamic spirometry	\checkmark	\checkmark	\checkmark	\checkmark
Static spirometry		\checkmark		\checkmark
Blood-gas analysis	\checkmark		\checkmark	

Table 4. An overview of the tests performed in the different studies

ICT: incremental cycle test, CPET: cardiopulmonary exercise test, ISWT: incremental shuttle walking test, SGRQ: St George's Respiratory Questionnaire, SF-36: Medical Outcome Short-Form 36, CRDQ: Chronic Respiratory Disease Questionnaire, HAD: Hospital Anxiety and Depression scale.

Incremental shuttle walking test (ISWT) (Study II)

The ISWT was performed in a level corridor. Two cones were placed 9 m apart comprising a 10 m track as described by Singh et al (209). Instructions to the patient and the pace of the test were played from a tape recorder. The test commenced at a speed of 30 m/min. which then was increased by 10 m/min. every minute. The patients continued walking until they were not able to reach the next cone in time for the signal or got too exhausted to con-
tinue. The total distance walked was the main outcome of the test. Before and directly after walking, SpO₂, heart rate, peak expiratory flow (PEF), perceived exertion (Borg RPE-scale) (245) and dyspnoea (Borg CR-10scale) (244) were registered. The patients carried a pulse oximeter (Optovent Respons, Optovent, Linköping, Sweden) with a shoulder strap throughout the test. In 52 of the patients the test was identically repeated within a week.

Twelve-minute walk test (Studies I, III-IV)

The 12-minute walk tests were performed in a 34 m level corridor as described by McGavin (207). No encouragement was given and the supervisor did not walk alongside the patient. The patient was asked to cover as much ground as possible in 12 minutes in his own speed, pausing if necessary. The patient was told the time after 4, 6, 8, 10 and 11 minutes. In studies I and III two tests were done for practice and a third test served as baseline, all tests within one week at the same time of day, with the same supervisor (233,234,246). After training and during follow-up only one test was performed each time. In studies II and IV the test was performed twice within one week and the best of two tests was used for analysis. This was done both before and after training intervention (IV). During the test a non-invasive pulse oximeter was carried by the patient in a shoulder strap (Nellcor Incorp., Hayward, USA in studies I and III, Optovent Respons, Linköping, Sweden in studies II and IV). PEF, heart rate, SpO₂ and breathing frequency were measured and the patients rated their exertion and breathlessness on the Borg scales RPE and CR-10 (244,245) before starting, after six minutes, at the end of the walk (12 min.) and five minutes after walking, respectively.

Health related quality of life (HRQoL) (Studies I, III-IV)

The HRQoL was assessed by the SGRQ (74) (I and III) and the SF-36 (240) (IV) (Table 4). The SGRQ has three domains: symptoms, activity and impact and, in addition, a total score is calculated. The highest (worst) possible score for every component is 100. The SF-36 has eight domains: physical function, role physical, bodily pain, general health, vitality, social function, role emotional and mental health. For each domain the score is from 0 to 100 (most healthy). Mental health was assessed by the Hospital Anxiety and Depression scale (HAD) (243). The score-range in HAD is 0-21, a higher score indicating deteriorating mental state. All the above questionnaires are self administered. Dyspnoea during activities of daily life was measured by the dyspnoea scale from the Chronic Respiratory Disease Questionnaire (CRDQ) (76) in study IV. The patient scores on a 7-graded scale the dyspnoea usually experienced during five self-chosen activities of his life. A higher score indicates less dyspnoea.

Lung function (Studies I-IV)

Lung function was measured in accordance with the ATS guidelines (247). Swedish reference values were used (248,249). In study I and III a dynamic spirometer (P K Morgan Ltd., Rainham, England) was used, while in study II and IV a Masterlab Trans spirometer, a Masterlab Body Plethysmograph and a Masterlab Transfer (Erich Jaeger AG, Würzburg, Germany) were used for both dynamic and static spirometry (Table 4). In studies I and III a blood sample was taken from arteria radialis at rest and *PaO*₂, *PaCO*₂ and SaO₂ were analysed (Bergman and Beving, Copenhagen, Denmark).

Physical training intervention

All training was conducted on a hospital outpatient basis. Training sessions were twice weekly. All patients were taught to use pursed lips breathing during exercise. The patients were encouraged to be physically active at home during the weeks of intervention though no special home-training programmes or diaries were used. Patients with EIH (SpO₂ < 90%) were administered supplementary oxygen by a nasal cannula while exercising, just enough to keep the saturation \geq 90%. SpO₂ was monitored with non-invasive pulse oximetry during exercise.

Training in study III

The endurance training consisted of interval training on an ergometer cycle (Monark, Varberg, Sweden). After six minutes warm up at a low work load (20-30% of W peak) ten 3-minute intervals followed with reciprocal high/low work loads (total ergometer time 36 min.). The lower work rate was 30-50% and the higher work rate was $\geq 80\%$ of baseline W peak. After every interval, perception of exertion and breathlessness were assessed using the Borg-scales RPE and CR-10, respectively. After the higher work load intervals, target ratings were ≥ 15 (RPE) and/or ≥ 5 (CR-10). The patients' ratings and the therapist's observations were used to choose the appropriate level of work load for the next interval, according to the above limits. After cycling the patients stretched their leg muscles. Once a week, the endurance training was followed by resistance training (30 min.), alternatively with callisthenics for 15 minutes and 15 minutes of relaxation.

During resistance training, the patients exercised at their own rate for about 30 minutes, taking breaks as needed. The David Back Clinic apparatus (David Fitness and Medical, Helsinki, Finland) and a usual treatment bench were used. The programme consisted of exercises for the arms and shoulders (David 400, 420 and 610), legs (David 200 and 300) and abdominal muscles (sit-ups). Resistance was initially chosen so that the patients were able to perform 15 lifts (approximately 65% of one repetition maximum).

When 20 lifts were accomplished, resistance was increased. Sit-ups were done on a bench in the supine position with knees bent (soles on mattress).

The callisthenics were done in the sitting position for approximately 15 minutes. The main emphasis was on unsupported arm exercises (shoulder flexion and circumduction, scapular elevation and depression), mobility exercises for thorax and neck (flexion, extension, rotation and lateral flexion; including stretching) and breathing exercises. The callisthenics were followed by 15 minutes relaxation ad modum Jacobson (169).

In conclusion, endurance training was performed twice a week in group A, resistance training and callisthenics were performed once a week in group A and twice a week in group B (Table 5).

	Study III		Study IV	
	Group A	Group B	I- group	C- group
Endurance - interval	2		2	
Endurance - continuous				2
Resistance training	1	2	1	1
Callisthenics and	1	2	1	1
relaxation	1	2	1	1

Table 5. The number of sessions per week the different modalities of training were a part of the training in each group in studies III and IV.

Training in study IV

All sessions started with ergometer cycling. In the interval group (I-group) the target training intensity was $\geq 80\%$ of the baseline W peak in the "uphill" intervals and 30-40% of the baseline W peak in the "downhill" intervals. All intervals in the I-group were three minutes, i.e. the high- and low-intensity intervals were equally long. In the group with a constant load (C-group) the target training intensity was $\geq 65\%$ of baseline W peak. For warming up and cooling down both groups cycled at 30-40% of baseline W peak for six minutes in the beginning and at the end of each session. Total cycle time each session was 39 minutes in both groups to allow for five "uphills" in the Igroup, separated by four "downhills" and with warming up before and cooling down afterwards. Consequently, the C-group cycled for 27 minutes each session at their effective training load. In both groups, exercise load was kept as high as tolerated at all times, above the target values when possible. All patients scored their dyspnoea and perceived exertion on the Borg scales CR-10 and RPE every three minutes. Target scores for dyspnoea and exertion were ≥ 5 and/or ≥ 15 , respectively, after the "uphill" bursts and at the end of the continuous load. Target intensity, patients' score and the physiotherapist's observation of the patient steered the adjustment of exercise load.

After cycling, the session proceeded once a week with callisthenics and relaxation and once a week with resistance training (Table 5). The callisthenics were done in the sitting position and consisted of flexibility exercises for thorax, neck and shoulders. The relaxation was ad modum Jacobson (169). The resistance training included exercises for upper and lower limbs as well as the abdominal muscles (two sets of ten repetitions at about 70% of 1 repetition maximum). Callisthenics, relaxation and resistance training were identical in both groups.

Statistical analysis

For objective, normally distributed data the statistical methods used were Pearson's correlation coefficient, Student's t-test for paired and unpaired comparisons and ANOVA repeated measures (one and two way). For subjective data and data not normally distributed the methods used were Spearman's correlation coefficient, Wilcoxon's signed rank test, Mann-Whitney U-test and Friedman's ANOVA. In the two methodological studies (I and II), Bland-Altman scatterplots (250) were used for additional measurement comparisons. Results are presented as mean \pm SEM in studies I and III, except for results from the questionnaires that are presented as median (range). In studies II and IV the results are presented as mean \pm SD or 95% confidence intervals in tables and text, as mean and SEM in figures. A p-value of < 0.05 was regarded as statistically significant. Power-analysis was made for studies III and IV: For study III to detect significant difference between the groups, if one group increased their 12MWD by 35% and the other by 5%, a group size of 21 patients would yield a power of 80% if α =0.05. Calculating with an inter-group difference of training-induced W peak difference of 5 W, 35 patients in each group in study IV would yield a power of 80% if α = 0.05. The statistical analyses were performed on a personal computer using StatView 5.0 (SAS Institute Inc., Cary, NC, USA) and Statistica (Statsoft Inc., Tulsa, Oklahoma, USA).

Results

Study I

In the EIH group, no increase in 12-minute walking distance (12MWD) was found on repeated testing (Fig. 4). The 12MWD increased significantly on repeated testing in the non-EIH group by $12 \pm 1\%$ from test one to test two (p<0.0001) and further by $4 \pm 1\%$ from test two to test three (p<0.001). The 12MWD was significantly shorter in the EIH group than in the non-EIH group at test two (p<0.05) and three (p<0.01, Fig. 4). The 12MWD did not significantly predict the increase on repeated testing in either group (Fig. 5).



Figure 4. The 12-minute walking distance (12MWD) on three tests within one week. White dots: patients with EIH (SpO2<90%, n = 19). Black dots: non-EIH patients (SpO₂ \geq 90%, n = 38). Significant difference from the previous test : ****: p<0.0001. NS: not significant compared with test one. There was a significant difference in walking distance between the groups at test two (p<0.05) and three (p<0.01). Mean and SEM

The 12MWD correlated with W peak both in the EIH group (r = 0.82; p<0.0001) and in the non-EIH group (r = 0.55; p<0.001). This correlation was significantly stronger in the EIH than in the non-EIH group (p<0.05).

Significant drop in SpO₂ during walking (Δ SpO₂) was found in both groups at all three tests (p<0.0001, Fig. 6). In the EIH group, the Δ SpO₂ was

 8.4 ± 0.3 at test one and no significant increase in Δ SpO₂ was found on retesting. In the non-EIH group the Δ SpO₂ was 3.8 ± 0.3 , 4.4 ± 0.4 and 4.9 ± 0.5 at test one, two and three, respectively, significantly larger at test two and three compared to test one (Fig.6). No significant difference was found between SpO₂ at 6 minutes compared to 12 minutes, except at test one in the non-EIH group.



Figure 5. Scattergrams (Bland-Altman) of the differences between 12MWT on tests I and III plotted against the mean value of 12MWD from the two tests. Solid lines: mean difference, dotted lines: \pm 2SD. White dots: patients with EIH, black dots: non-EIH patients. 12MWD: distance walked (meters) in a 12-minute walk test.

In the EIH group the only sign of increased effort on retesting was an increased dyspnoea (CR-10 score) at 12 min. (p<0.05). In the non-EIH group, along with the increased Δ SpO₂, the post-walking heart rate, RPE score and CR-10 score were significantly higher on retesting (p<0.05). In both groups, post-walking breathing frequency was 25 ± 1 breaths/min. and did not change on retesting. Significant differences emerged between the groups for RPE and CR-10 at the end of walk, already at test one (p<0.05). A multiple regression analysis of post-walking measurements for all subjects revealed SpO₂ post-walking at test one as the only predictive variable for the increase in 12MWD (r = 0.53; p<0.0001 for test one to three, r = 0.41, p<0.01 for test one to two).



Figure 6. Oxygen saturation (SpO₂) at rest before walking, after 6 minutes of walking and at the end of test (12 min.) on the three walk tests. White dots: subjects with EIH (n=19), black dots: non-EIH subjects (n=38). **:p<0.01; ***:p<0.001 compared with test I. At all time points there was a significant difference between the groups; at rest p<0.01, at 6 and 12 minutes p<0.0001. Mean and SEM.

The pre-walking measurements of SpO₂, PEF, heart rate, breathing frequency, exertion (RPE) and dyspnoea (CR-10) did not differ significantly between the three days and could not predict the variation in 12MWD in a multiple regression analysis (p = 0.1, all subjects together) although there was a significant correlation between pre-walking SpO₂ and the variation in 12MWD (r = 0.34; p<0.05). Pre-walking SpO₂ differed significantly between the groups (p<0.01) on all three test days.

Study II

There was a significant correlation (r = 0.88, p<0.0001) between ISWT distance × body weight and the measured W peak from the incremental cycle test: W peak = $0.0025 \times \text{distance}$ (m) × body weight (kg) + 10.19. W peak estimated from performance on ISWT by this equation was 62 (57-66) W and did not differ significantly from the measured W peak (62 (57-68) W, p = 0.7). For comparison, W peak was estimated from the measured VO₂ peak by the equation derived from Åstrand (221), resulting in an estimated W peak of 61 (56-66) W. This was not significantly different from the measured W peak or the estimated W peak from ISWT above. A strong agreement was found between the measured and estimated values of W peak with a minor tendency to overestimation at the lower range and underestimation

at the higher range of performance, both when estimated from ISWT and from VO_2 peak (Fig.7). There was one outlier where ISWT clearly underestimated W peak (Fig.7). This was the only patient who would have been able to run at the end of the ISWT, which is not allowed in a walk test.

No significant differences were found between women and men regarding the relationship between the different exercise tests.

There were significantly lower peak heart rate, SpO₂, ratings of perceived exertion and dyspnoea at the end of the walking test compared to the cycle tests (p<0.0001). The reported reasons for cessation were identical in the two cycle tests; 39% because of dyspnoea, 35% because of a combination of dyspnoea and exertion, 20% because of exertion and 6% because of leg fatigue. In the ISWT the reason for cessation was dyspnoea in 3%, a combination of dyspnoea and exertion in 12% and inability to increase or keep up the speed to reach the next cone in time in 85% of the cases.



Figure 7. Scatterplots (Bland-Altman). On the left, the difference between measured maximum exercise capacity (W peak) measured by incremental cycle test (ICT) and estimated W peak from performance on incremental shuttle walking test (ISWT) against the mean values of those two. On the right, the difference between measured W peak from ICT and estimated W peak from measured maximum oxygen uptake on semi steady-state cardiopulmonary exercise test (CPET) against the mean of those two. Whole line: mean difference, dotted lines: ± 2 SD.

Fifty-two subjects repeated the ISWT within a week. The difference between the two tests was not significant for any variable measured, mean difference in walking distance being 9 ± 38 m or $3\% \pm 12\%$ (p = 0.09). All calculations were therefore based on the first ISWT. This subgroup did not differ from the larger group in any baseline characteristics.

Study III

Twenty patients in group A and 22 in group B completed the trial (Figure 3). There were no baseline differences between the groups. Twenty-one patients (11 in group A) did not complete the training intervention, 10 due to exacerbations, eight due to lack of motivation or psychological problems, and three due to back pain. The drop-outs had lower PaO_2 (8.8 kPa) and a shorter 12MWD (700 m) than those who completed the trial (9.6 kPa and 831 m, respectively, p<0.05). Otherwise no differences were found between drop-outs and other participants. During the 12-month follow-up, 10 patients dropped out (three in group A) (Fig.3). Three patients died, one moved from the area and six patients got other diseases.

In group A, peak exercise capacity increased by 7 W \pm 2 W (11%, p<0.001) (Fig.8) and 12MWD increased by 50m \pm 72m (6%, p<0.01). Group B did not improve significantly in any of these variables. The difference in peak Watt (Δ W) differed between the groups (p<0.05), whereas the difference in improvement of 12MWD (Δ 12MWD) did not reach statistical significance between groups (p=0.07). After eight weeks of training, the ratings of perceived exertion and the ratings of dyspnoea at rest were significantly lower in group A than in group B (p<0.01 and p<0.05, respectively).



Figure 8. Peak exercise capacity in watt (W peak) before and after 8 weeks of training in group A and B. Mean and 95% confidence interval. ***: p<0.001 difference in group A, \dagger : p<0.05 for difference between the groups in pre-post training W peak (Δ W). Black dots: group A, white squares: group B

The SGRQ and HAD scores did not change significantly by training in any of the groups, although a tendency towards lower scores (improvement) emerged in group B for the SGRQ item "activity" (-3.6 \pm 4.5 points, p=0.07) and total score (-2.0 \pm 3.2 points, p=0.08). There was no correlation between the change in W peak or 12MWD and the changes in SGRQ.

Lung function and blood gases were not influenced by the training period in either group.

Twenty-seven patients (13 in A) had severe and 15 (7 in group A) moderate disease (Fig. 3). Apart from spirometry they differed significantly only in W peak at baseline (56 ± 3 W vs 72 ± 8 W, p<0.05). There was no difference in the effect of training between patients with severe and moderate disease (Fig. 9).



Figure 9. The effect of training on peak exercise capacity in watts (W peak), in group A, for subjects with severe and moderate COPD. Black dots: moderate COPD, black squares: severe COPD. Mean and 95% confidence intervals.

At six months the 12MWD did not differ significantly from baseline level in either group. There was a further decline in 12MWD from six to twelve months in group B (p<0.05) and not in group A (p=0.09). At 12 months post-training the 12MWD was not significantly different from baseline in group A (p = 0.19) whereas it had declined in group B (-79 m \pm 24 m, p<0.05) (Fig. 10) but the difference between the groups was not significant. The difference between groups in CR-10 scores for dyspnoea at rest was still evident six months post-training (p<0.05) but not after 12 months, whereas the difference in RPE at rest persisted throughout the follow-up (p<0.05). At 12 months post-training there was a tendency towards lower scores in SGRQ-symptoms in group A compared to baseline (-7.5 \pm 4.3, p=0.07). Neither group showed other changes in SGRQ or HAD during follow-up.



Figure 10. The 12-minute walking distance (12MWD) for the 32 patients which were followed-up for 12 months after training. Black dots: group A, white squares: group B. Means and 95% confidence intervals. *: significant difference from base-line p<0.05.

Lung function showed a small, but significant decline in VC at 12 months post-training in group A (-0.2 L, p<0.05) compared to baseline. There was no correlation between changes in 12MWD and lung function during the study. There were no changes in PaO_2 , $PaCO_2$ or SaO_2 during the time of the study (14 months).

Men and women were equally represented in the training groups and there was no difference between the genders in response to training.

Study IV

One hundred patients were included and 60 patients completed the programme (Fig.3). The range in FEV₁ % pred. was 14% - 59%. The patients who completed the programme had a mean attendance rate of 29 ± 3 of 32 possible sessions (no difference between the two training groups). The 40 patients who did not complete 24 sessions (and were thus excluded) had higher functional residual capacity ($5.5 \pm 1.2 l vs 4.8 \pm 1.3 l$; p<0.05), residual volume ($4.3 \pm 1.2 l vs 3.8 \pm 1.1 l$; p<0.05) and total lung capacity ($7.0 \pm 1.3 l vs 6.2 \pm 1.3 l$; p<0.01) than those who completed the programme, indicating a more severe disease in the drop-outs. No other baseline values were different from the patients who completed the programme. The reason for drop-out were exacerbations (n = 24), lack of motivation or transport problems (n = 10), other diseases (n = 5) and family problems (n = 1).

Exercise training

As the pattern of exercise was different, consequently the exercise intensity between the two groups was significantly different (p<0.05; Fig. 11A).



Figure 11. The progression in exercise load during the study. Every second session is shown. Black dots: I-group, n = 28, white dots: C-group, n = 32. A: The exercise load expressed as percent of baseline W peak during the high-load bursts in the I-group and during continuous load in the C-goup at the different sessions throughout the study. B: The total work in each group. Mean and SEM.

Target exercise intensity was reached at session 5 ± 5 for the I-group ($\geq 80\%$ of W peak) and at session 9 ± 7 for the C-group ($\geq 65\%$ of W peak), with a tendency of difference between the groups in time to reach target intensity (p = 0.06). The exercise workload in the high-intensity bursts in the I-group reached 100% of baseline W peak at session 14. Furthermore, during high-intensity intervals at the last sessions, exercise W exceeded baseline W peak (p<0.05) (Fig.11A). At the last high-intensive interval of cycle training sessions, mean exertion rating was 15.8 ± 1.4 in the I-group and 15.1 ± 2.1 in the C-group (p = 0.08). Ratings of dyspnoea at the same time were 5.8 ± 1.4 and 5.2 ± 1.4 , respectively (p = 0.14). There was no significant difference between the second and the last week of training in these ratings, indicating

adequate progression in exercise load as exercise capacity increased during the study.

Total cycle-workload (the sum of watts \times minutes) per session revealed no significant difference in total workload between the groups, though a tendency towards a higher total work in the C-group was observed (p = 0.07). Total workload increased significantly with time (p<0.0001) in both groups (Fig.11B).

In the resistance training part (the same procedure in both groups) both groups increased the resistance loads successively during the study (p<0.001) both for arm and leg exercises, with no difference between the groups.

	I-group n = 28		C-group n = 32	
	Baseline	16 weeks	Baseline	16 weeks
Incremental cycle test				
W peak (watt)	61 ± 20	72 ± 22***	64 ± 22	75 ± 27***
Heart rate peak	$131 \ \pm 2$	$132 \ \pm 20$	134 ± 17	$133 \ \pm 19$
Breathing freq. peak	31 ± 4	30 ± 6	30 ± 7	30 ± 8
Dyspnoea (CR-10)	$7.9 \hspace{0.2cm} \pm 2.0 \hspace{0.2cm}$	$7.2 \pm 1.4*$	7.9 ± 1.6	7.2 ± 1.6
Exertion (RPE)	17.3 ± 1.5	17.0 ± 1.2	$17.3 \hspace{0.1 in} \pm 1.3$	16.7 ± 1.3
Walking test				
12MWD (m)	$834 \ \pm 185$	$909 \pm 203^{***}$	$870 \hspace{0.1in} \pm \hspace{0.1in} 165$	964 ± 155***
Ergospirometry	n	= 25	n =	= 28
VO ₂ peak (ml/min.)	$988\ \pm 286$	$1041 \pm 299*$	$973 \hspace{0.1in} \pm \hspace{0.1in} 292$	$1119 \pm 297 ***$
VCO ₂ peak (ml/min.)	$944\ \pm 326$	$999 \pm 363*$	$942 \hspace{0.2cm} \pm \hspace{0.2cm} 346$	$1091 \pm 349 **$
V _E peak (l/min.)	36.9 ± 10.8	36.0 ± 11.3	$34.8\ \pm 10.1$	$38.4 \pm 9.3*$

Table 6. Results from incremental cycle tests, 12-min. walk tests and the semisteady-state tests with ergospirometry. Mean \pm SD.

I-group: interval-group, C-group: continuous-group, Watt: exercise capacity on incremental cycle test, breathing freq: breathing frequency, dyspnoea: dyspnoea score on the Borg CR-10 scale, exertion: score on the Borg -RPE-scale, 12MWD: 12-min. walking distance, VO₂ peak: oxygen uptake, VCO₂: carbodioxide in exhaled air, V_E : minute ventilation. Difference from baseline within group: *: p<0.05, **: p<0.01, ***: p<0.001.

Exercise capacity

Peak exercise capacity increased significantly (p<0.001) in both groups after 16 weeks of training by 11 ± 7 W in the I-group and by 11 ± 12 W in the C-

group. Peak levels of heart rate, breathing frequency, SpO_2 and subjective ratings of dyspnoea and exertion did not change. VO_2 peak and VCO_2 peak increased in both groups whereas V_E peak increased significantly in the C-group only (Table 6). No difference between the groups was found in any post-exercise peak values or in the change from baseline peak values.

Measurements at isotime, i.e. at identical work rates before and after training, showed significantly lower heart rate, perceived exertion and dyspnoea after training in both groups. Significantly lower VO₂ (-77 ± 158 ml/min., p<0.05), VCO₂ (-110 ± 169 ml/min., p<0.05), V_E (-3.6 ± 5.6 l/min., p<0.01) and breathing frequency (-3 ± 3 breaths/min., p<0.01) compared to baseline emerged in the I-group only and these changes from baseline differed significantly between the groups (p<0.05; Fig. 12).

Functional exercise capacity, i.e. 12MWD, increased significantly in both groups, with no significant difference between the groups (Table 6).



Figure 12. The change from baseline at peak performance and at isotime after training, expressed as percent (mean and SEM). Black bars: interval-group, white bars: continuous-group. All shown bars indicate a significant change within group, except those labelled "NS". \dagger : p<0.05 between the groups. 12 MWD: 12-minute walking distance, Watt: exercise capacity, VO₂: oxygen uptake, VCO₂: carbon dioxide in exhaled air, V_E: minute ventilation, CR-10: dyspnoea, RPE: perceived exertion.

Dyspnoea, mental health and HRQoL

Dyspnoea during daily activities decreased significantly after training in both groups (Table 7). Anxiety and depression were also significantly improved by training in both groups. The domains "vitality" and "mental health" from SF-36 significantly improved in both groups, whereas "social function" and "general health" improved significantly in the I-group only (Table 7). There was, however, no significant difference between the groups in the change from baseline in any of the questionnaires.

	I-group		C-group	
	Baseline	16 weeks	Baseline	16 weeks
Dyspnoea (CRDQ)	16.5 ± 4.1	$19.2 \pm 5.2*$	14.8 ± 3.0	$18.5 \pm 4.9^{**}$
Anxiety (HAD)	7.2 ± 4.5	$5.2 \pm 4.3^{**}$	6.9 ± 3.5	$4.8 \pm 3.9^*$
Depression (HAD)	5.8 ± 3.6	$4.3 \pm 3.6*$	5.4 ± 3.2	4.0 ± 3.0**
SF-36				
Physical function	37.0 ± 14.2	41.1 ± 22.4	41.7 ± 19.6	38.3 ± 19.5
Role physical	32.6 ± 35.7	35.4 ± 39.6	35.6 ± 41.9	33.7 ± 40.0
Bodily pain	68.9 ± 16.5	79.2 ± 22.9	69.6 ± 23.9	75.7 ± 23.9
General health	33.4 ± 16.5	$41.2 \pm 20.2 $ **	39.5 ± 17.2	46.3 ± 21.9
Vitality	46.7 ± 23.8	$54.8 \pm 24.7*$	44.8 ± 21.4	$56.9 \pm 21.2 **$
Social function	66.0 ± 26.1	$75.0 \pm 23.6*$	70.7 ± 23.4	73.0 ± 24.4
Role emotional	48.4 ± 44.7	61.3 ± 40.5	$53.8 \hspace{0.1in} \pm 45.3$	64.0 ± 45.1
Mental health	65.1 ± 25.0	$75.8 \pm 17.3^*$	$69.1 \hspace{0.1in} \pm \hspace{0.1in} 19.5 \hspace{0.1in}$	$75.7 \pm 16.9^{\ast\ast}$

Table 7. Health-related quality of life at baseline and after 16 weeks of training. Mean \pm SD.

I-group: interval-group, C-group: continuous group, CRDQ: Chronic Respiratory Disease Questionnaire dyspnoea scale (0-35), HAD: Hospital Anxiety and Depression Scale (0-21), SF-36: Short Form 36 (0-100). *: p<0.05, **: p<0.01 within group.

Lung function

Spirometry did not change during the study.

Discussion

Retest-effects on the 12-minute walk test and the effects of exercise-induced hypoxemia

In study I it was demonstrated that 12MWD did not increase in the EIH group on retesting, whereas a significant increase was observed in the non-EIH group. To our knowledge, this is the first time a group of patients has not increased walking distance when tests were repeated within two or three days. In previous studies on timed walk tests, the walking distance has increased on repeated testing in COPD patients (207,224-228,231,233,234), in cardiac patients (251-253) as well as in healthy, elderly people (254). The absence of improvement at retesting in the EIH group in the present study indicates a somewhat different testing behaviour compared to other groups of patients. Our results for the non-EIH patients with COPD are, however, in line with previous findings (226,229,232).

In the EIH group, the increased dyspnoea at retesting showed an increased effort without a consequent increase in 12MWD. This indicates that the EIH group performed near their maximum already at the first test and could not walk further on retesting, in spite of increased effort. The strong correlation between the 12MWD and W peak in the EIH group at the first walk also supports the interpretation that this group performed close to peak performance already at test one. In the non-EIH group, several indicators of increased effort were observed on repeated testing as the increase in heart rate, RPE and CR-10 as well as the decrease in SaO₂ during (6 minutes) and after walking were greater at the second and third tests compared to the first test. The non-EIH group walked consequently further with increased effort on repeated testing and no patient in that group walked shorter at test three than at the first test. This led to significant differences in 12MWD between the groups at the second and third tests while no difference was found at the first test. The significant improvement of 12MWD between test two and three in the non-EIH group suggests that two tests at baseline might not be enough to eliminate learning effects at retesting. The day to day variability in 12MWD was not explained by pre-walking parameters.

The finding of a different pattern at retesting in the two groups in the present study might partly be an explanation to the variable size of increase in walking distance on retesting patients with COPD in previous studies (207,227,229,233,255). There is a tendency towards a smaller increase in walking distance in studies including patients with severe COPD (227,228). In some previous studies, walk tests of different duration (228,233,234) and with different time-intervals between the tests (207,233) have been investigated, which makes direct comparisons uncertain. Knox et al pointed out that the learning effect seemed to be most prominent when the test was repeated on the same day (233). No encouragement was given in the present study which might have reduced the size of increase in 12MWD as it has been shown that performance increases more on retesting when encouragement is given (234). The ATS guidelines do not stress the issue of a training test in most clinical settings (206) and in clinical practice it is tempting to perform only one test to save time. Our results show that a training test might be redundant in COPD patients with EIH, while at least one training test is needed in non-EIH COPD patients. Although we have studied the 12-minute walk test, the results are probably applicable to the 6-minute walk test as both tests are performed in the same way and the drop in SpO₂ was similar at 6 and 12 minutes during walking.

Most subjects in the EIH group were hypoxemic (SpO₂ < 90%) after a few minutes walking, indicating repeated episodes of hypoxemia in daily life.

Incremental Shuttle Walking Test for estimation of peak exercise capacity (W peak)

In study II, ISWT distance \times body weight was a good predictor of W peak in patients with moderate or severe COPD. The fact that W peak estimated from ISWT was as accurate as W peak estimated from VO₂ is of clinical importance, as the ISWT is much simpler and cheaper than a laboratory cycle test.

Those results confirm previous findings that there is an excellent correlation between performance on ISWT and laboratory testing (210,211,256). Although the correlation in our study between VO_2 and distance walked was almost identical with the findings of Singh et al (210), applying their equation in our material resulted in a significant underestimation. One likely explanation to this could be the difference in the number of patients (19 versus 93 patients). As Singh et al performed two ISWT and used the second test in their analysis, it could explain some of the inconsistency between their equation and our, even though no significant improvement on retesting was found in our material. The majority of patients in the study by Singh et al were men while study II was dominated by women. Gender did not significantly affect the relationship between the different tests in our analysis, but this might need further investigation, as only 26% of our patients were men. The fact that Singh et al compared two walking tests whereas we compared walking and cycling might also explain the difference to some extent, as there is a known difference in metabolic adaptations during walking and cycling (213,220). However, as VO₂ peak measured on a treadmill test has been found to be higher than (213) or equal to (257) VO₂ peak measured on a cycle test in patients with COPD, a regression equation derived from a treadmill test could be expected to overestimate VO₂ peak on a cycle rather than the opposite.

Heart rate, RPE and CR-10-scores were significantly lower in ISWT than in the cycle tests. The cycle tests were mainly limited by breathlessness and/or exertion whereas the ISWT was, in most cases, limited by the incapability to increase the speed of walking. During walking it is difficult to increase walking speed above a certain level. Some treadmill test protocols are therefore constructed to increase inclination rather than speed (258).

SpO₂ decreased more by walking than cycling, quite in line with previous findings (213,219,256). It has been speculated that the positional differences between walking and cycling could lead to less effective breathing during walking and thus more desaturation (220). In spite of the above differences between walking and cycling it was possible to estimate cycle performance from an ISWT quite as accurately as when estimating performance from one laboratory cycle test to the other. As equations work both ways, our findings also make it possible to estimate distance walked (and thereby walking speed) on ISWT from W peak in patients with moderate or severe COPD. This could be useful in clinics where laboratory cycle testing is routine practice but walking is the main exercise training prescription. As the outlier in our study illustrates, the ISWT can be expected to mimic performance in a symptom-limited cycle test only in patients that reach their exercise limit by brisk walk, i.e. are unable to run, as otherwise the patients would not be close to their peak capacity during the test. Being able to run is, however, a very rare condition in COPD patients referred to rehabilitation, implying that this does not undermine the use of ISWT in patients with COPD.

We used the first ISWT (no training test) for our analyses. Due to the patient's poor condition or because of time constraints it is often not feasible to perform a training test in clinical practice. Thus, it was clinically relevant to present our calculations based on the first ISWT. This was also supported by the finding that the walking distance did not increase at the second test performed within a week. Control calculations were done by using results (not shown) from the second ISWT (n = 52) in our material and no differences were found. Significant difference in walking distance has previously been found on repeated testing with ISWT in patients with COPD (209,259). It is not clear why our results are inconsistent with previous studies regarding the repeatability of ISWT, but, as noted above, the number of patients and gender distribution is somewhat different from the other studies, and this might affect the repeatability.

Being able to estimate W peak by ISWT for clinical purposes does not make ISWT a perfect substitute for the incremental cycle test or other forms of laboratory tests. There is, of course, some variation between estimated and measured peak values on an individual basis, but most importantly the safety aspect of the laboratory tests is beyond the ISWT. However, for COPD-patients at minor risk of cardiovascular incidents, and where laboratory tests are scarce, the ISWT could be used as an alternative for estimating W peak.

Effects of different modes of physical training on:

- Exercise capacity and physiologic adaptation

In study III, two training sessions a week for eight weeks of a combined exercise programme, including endurance training, increased exercise capacity in patients with severe or moderate COPD. A programme of resistance training and callisthenics alone was not sufficient to affect exercise capacity. The increase in functional exercise capacity by the endurance training programme was lost 6 months post-training, but decline from baseline was prevented for at least 12 months post-training. Significant difference between groups after the intervention was found in increase in W peak and in dyspnoea and perceived exertion at rest.

Five studies of supervised exercise, three times a week for 8-12 weeks comparing the effects of strength training with controls, endurance training with resistance training or a combination of both, found that endurance training increased exercise capacity whereas the effect of resistance training on exercise capacity varied (131,152,154-156). Some authors found that resistance training could increase endurance but did not affect peak exercise capacity or 6MWD (154,156) while others found that even resistance training could increase peak exercise capacity (152). The resistance training was more intensive in the above quoted studies than in our study and it could be argued that the intensity of the resistance training was too low and/or the sessions too few to influence W peak or 12MWD (152). The intensity of the endurance training was, however, similar to previous studies, but was performed only twice a week instead of the more customary three times a week (90,131,152,156). Thus, the relatively small effects of endurance training.

Study IV showed that 3-minute interval training is an efficient endurance training mode for COPD patients. This is clinically relevant, as 3-minute intervals are easily conducted in group training sessions for patients with COPD. Interval and continuous training equally improved W peak, on average by 11 W. The improvement was similar to previous studies (128,153) and larger than the 5.5 W which was the weighted mean difference of the 15 studies included in a meta-analysis by Lacasse et al (113). The improvement in W peak was consistent with the findings of Vogiatzis et al (149) but differed from the results of Coppoolse et al, as W peak increased only in the Igroup in their study (148). In both our groups, peak values of VO₂ and VCO₂ increased significantly, whereas V_E peak increased in the C-group only. This is not in agreement with the findings of Vogiatzis et al, who found no increase in peak values of VO₂ or VCO₂ in either group, but increased V_E peak in both groups (149). Functional exercise capacity (12MWD) increased similarly in both our groups. In the majority of studies on physical training for COPD patients, the 6-minute walk test was used and therefore our results could not be directly compared with other studies. In a meta-analysis, the mean weighted difference in 6MWD before and after training was 49 m (113). In study IV, 12MWD increased by 75 m and 94 m, respectively in the two groups and we consider this increase to be close to the increase in the 6minute test quoted above.

At isotime, VO₂, VCO₂ and V_E were significantly more decreased in the I-group, indicating that the interval training resulted in a larger reduction in oxygen cost and ventilation at sub-maximal exercise than the continuous training. No decrease in VO2, VCO2 or VE was found in the C-group at isotime. This is in line with the findings of Coppoolse et al (148), who found that only interval training decreased the VO₂/W ratio, but differs from Vogiatzis et al, who found that VO₂, VCO₂ and V_E decreased significantly in both groups at isotime (no difference between the groups), as well as breathing frequency (149). Isotime breathing frequency decreased only in the Igroup and we consider this to be the most likely explanation for the decreased V_E at isotime. Markedly decreased dyspnoea, perceived exertion and heart rate were found in both groups at isotime, in agreement with Vogiatzis (149). As shown above, our study confirms several findings from the quoted studies, but there are some prominent inconsistencies as well (148-150). We can only speculate about the reasons for these inconsistencies. Firstly, the length and intensity of the intervals differed between our study and others quoted above (148-150) which might affect the results, as changes in peak oxygen uptake and ventilatory demand during exercise are larger after training with intervals lasting 3-5 min than after short-interval training in healthy people (151,260). Secondly, in our study, training sessions included resistance training once a week, which might have enhanced the response to training (152,156). Thirdly, 85% of our patients were women, whereas in the other studies 83-100 % of the patients were men (148-150). Recent studies indicate that the skeletal muscles adapt to COPD differently in men and women (56,261). As both interval and continuous training induce changes in peripheral muscle (150), the different gender distribution between the studies might make a difference.

- Health-related quality of life, anxiety and depression

Two recent meta-analyses conclude that multidisciplinary pulmonary rehabilitation improves physical function and HRQoL (113,262). In some of the papers included in the meta-analyses, HRQoL improvement was found after physical training intervention alone (131,152). In study III, no improvement in HRQoL, depression or anxiety scores were found in group A, although physical function improved. HRQoL improved in most of the studies included in the meta-analysis by Lacasse et al (15 studies), although the increase in W peak was similar to our study (113). The lack of effect on HRQoL in study III indicates that the relationship between peak exercise capacity and HRQoL is not strong. This is in line with previous findings (82,239,263). The increase in 12MWD in group A, although statistically significant, was small, or 50 m. In the meta-analysis by Lacasse et al a weighted mean difference of 49 m (95% CI 26-72 m) was found in 6MWD (113). A test of a longer duration (12 min.) would need a larger absolute improvement for a similar effect, therefore the improvement in 12MWD in study III can be considered inferior to what was described in the metaanalysis. HRQoL has been shown to correlate better with walking distance than with W peak (81). The small difference in walking distance in study III might explain the lack of effect on HRQoL (suboptimal dose of training). Another possible explanation to lack of effect in HRQoL is that the groups were small and that the study was not powered with HRQoL as a primary outcome. An important difference between our and previous trials is that we have used SGRQ (74) while in all the above studies the CRDQ (76) was used to evaluate HRQoL. These two instruments focus on different aspects of HRQoL in COPD and SGRQ is less sensitive to small changes than the CRDQ (242).

Both interval and continuous training in **study IV** improved dyspnoea during ADL, anxiety, depression and HRQoL. The improvement in dyspnoea was above the clinically significant difference for this domain (82,264). Anxiety in combination with low HRQoL is an important factor for rehospitalisation in COPD (84,265). As training improved anxiety and HRQoL in both groups, training after hospitalisation may decrease the risk of readmissions. This is supported by Man et al who recently showed that early rehabilitation after hospitalisation is safe and effective (266). The main changes in SF-36 scores were similar in both groups, with improvements mainly in the more psychological domains. The absence of improvement in the physical domains of the scale was not in line with increased physical performance,

confirming that HRQoL correlates only partly to physical performance (82,239).

- Patients with moderate or severe COPD

Study III revealed that patients with severe disease responded to training similarly to patients with moderate disease. This finding is particularly interesting in the view of a recent meta-analysis in which it was concluded that no effects of rehabilitation could be expected with a shorter intervention than six months in patients with severe COPD, whereas patients with moderate COPD responded even to shorter programmes (262). Casaburi et al found that patients with severe COPD improved their exercise capacity after a sixweek programme (5 days/week) (127). The intensity of the endurance training of their and our studies was higher than in most of the studies on patients with severe disease included in the meta-analysis (127,262). The different outcomes between studies analysing effects on patients with severe COPD per se, might therefore be caused by a difference in the intervention.

- Long-term effects

The small, but significant increase in functional exercise capacity (12MWD) in group A (**study III**) during the eight weeks of training wore off with time during follow-up. COPD is a progressive disease and without rehabilitation intervention, patients with severe COPD have been found to decrease their 6MWD on average by at least 26 m a year (198). In study III, at twelve months post-training (14 months from baseline) group A had returned to baseline 12MWD whereas in group B, 12MWD was significantly shorter than baseline. Although 12MWD was not significantly different between the groups during follow-up, there was a significant difference between the groups with regard to the RPE-score at rest. This strengthens the impression that the subjects in group A preserved their physical function throughout the study better than the subjects in group B. These findings indicate that short, physical training interventions may have effect in the long run by holding back annual decline.

Dose of training

We noticed a much larger training effect in **study IV** than in **study III**, indicating that the total number of training sessions might be as important as the number per week. In study IV the training intensity was still increasing after 24 sessions, implying that the subjects might have improved even further with more prolonged training. The optimal training duration is still not known for these patients and possibly the limited training time offered might contribute to somewhat poor long-term results after training in follow-up studies (179,202). As HRQoL, anxiety and depression improved in study IV but not in study III, it might indicate that a larger dose of training is needed to affect HRQoL than exercise capacity.

Progression of work load

The successive increase in workload shown in study IV is an example of the usefulness of the Borg scales for dosing exercise. Initial workloads were not chosen in order to obtain the same total workload in both groups as we wanted to investigate the effects of the two different training modalities when both groups were exercising as hard as possible. However, total workload was not significantly different between the groups throughout the study and the intensity increase ratio was similar in both groups.

Validity

The participants in this thesis can be considered representative of the population of COPD-patients currently referred to out-patient physiotherapy at specialist clinics in Sweden. Only a handful of patients declined participation in our study during the years of data collection, indicating that the patients were motivated already when they accepted the doctor's invitation of a referral to training. A few patients could not be included because of comorbidities hindering them from participating in the planned activities.

The large drop-out rate is the main threat to the validity of our intervention studies. This problem was partly expected as this has been reported in some other studies including patients with severe COPD, even with stricter exclusion criteria than in our studies (174,176,178,267). As most of our drop-outs attended a number of training sessions, an intention-to-treat analysis could have reduced the damage of the large drop-out. As the patients who dropped out were not tested post-intervention, this analysis was not possible. The drop-out may have affected the power in study IV, as less than 35 patients in each group completed the study. In study III the response to training was smaller than predicted, so the power was possibly too low to detect differences between the groups.

The choice of tests and statistic analysis affects the validity of studies. We have used well established laboratory and field tests to assess exercise capacity and valid questionnaires to measure HRQoL, dyspnoea, anxiety and depression. The sensitivity to change in the different HRQoL instruments has been discussed and as the SGRQ is not sensitive to small changes, this could have affected the results in study III. Care has been taken to use non-

parametric statistics whenever the requirements for parametric statistics have not been fulfilled, as when the groups have been very small.

Conclusions

- A small increase in 12-minute walking distance is to be expected even at the third test in patients with COPD who do not desaturate below 90% during walking (SpO₂ ≥ 90%) when tested three times in one week.
- In COPD patients with exercise-induced hypoxemia (SpO₂ < 90%), a training walk test may be redundant, as they do not increase their 12-minute walking distance on repeated testing.
- Peak exercise capacity (W peak) can be estimated from an Incremental Shuttle Walking Test (ISWT) with similar accuracy as when estimated from peak oxygen uptake (VO₂ peak) in patients with COPD.
- Exercise capacity in patients with moderate or severe COPD improves by an eight week training programme, two sessions a week, only when intensive endurance training is included in the programme. Health-related quality of life seems less responsive to training than exercise capacity is.
- Patients with moderate and severe COPD respond to training in the same way.
- A short-term improvement in exercise capacity after training slows down annual decline in functional exercise capacity for at least one year in patients with moderate or severe COPD.
- Interval endurance training (3-minute intervals) and continuous endurance training are equally potent in improving exercise capacity, functional exercise capacity, dyspnoea, mental health and healthrelated quality of life in patients with moderate or severe COPD.
- Interval training is more effective than continuous training in lowering the oxygen cost of sub-maximal exercise in COPD.

Clinical application and future tasks

Physical training is a most important factor in the treatment of COPD. It improves HRQoL and helps prevent decline in physical function. Pulmonary rehabilitation, with physical training as one of the cornerstones, is now clearly recommended at a fairly early stage in the GOLD guidelines for treatment of COPD. The challenge now is to apply the guidelines in the health system, which includes increasing the opportunities for COPD patients to exercise. Our results show that the clinical model of exercising in groups twice a week is effective if the training mode, intensity and total number of sessions are adequate. A skilled physiotherapist can easily handle eight patients at a time. Exercise training in COPD can be considered a costeffective treatment that should not be neglected. The initial cost of rehabilitation will be paid off with interest due to slower deterioration with time and less total health care utilisation.

More research is needed on whether repeated, short interventions of physical training, i.e. annually or every second year, would be most beneficial in the long run or whether a form of maintenance programme would be preferable. Perhaps both models need to be available, due to different needs and circumstances. Physiotherapists in primary care and the patient organisations could be utilised more in the future as resources and co-workers in a network of pulmonary rehabilitation. As simple field tests and HRQoL questionnaires can be used at any clinic, it is possible to follow-up the patients' physical function over time at different levels in the health care system.

What the patients really feel about physical training and what type of training they would prefer needs to be studied further. This could improve the short and long-term effects of training and minimise the number of patients who turn down proffered physical training or lack the motivation to continue training.

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