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Thesis for doctoral degree (Ph.D.) 2008 Adjuvant strategies in exercise performance for patients with chronic obstructive pulmonary disease - COPD **Gun Faager**

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Adjuvant strategies in exercise performance for patients with chronic obstructive pulmonary disease - COPD

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When I do not move I feel cured, if I move I feel diseased,

but how can I exist without moving?

Expressed by a patient with COPD

ABSTRACT

Chronic obstructive pulmonary disease (COPD) is a multicomponent disease which affects both the lungs and organs outside the lungs. Patients with moderate to severe COPD are restricted by dyspnoea, especially during physical activities. This results in the patient avoiding such activities only to further impair physical capacity and to exert a negative effect on quality of life. It is, therefore, of great importance to establish strategies that can optimise the effect of physical exercise and enhance physical activity among these patients.

This thesis is based on four studies that investigate the effects of a physiotherapy programme on patients requiring long-term oxygen therapy (LTOT) as a result of COPD and chronic hypoxia. In addition, it explores the effects of creatine supplementation in combination with physical training and the effects of the oral intake of glucose on arterial oxygen tension, exercise endurance and oxygen consumption in patients with moderate to severe COPD. It also looks at the influence of spontaneous pursed lips breathing (PLB) on oxygen saturation and walking endurance.

To evaluate the effects of a physiotherapy programme (n=20) and the combination of creatine supplementation with physical training (n=23) two different walking tests were used. Activity of daily living and health related quality of life were also assessed. To determine whether or not pursed lips breathing influences exercise endurance (n=32), an endurance shuttle walking test and transcutaneous oxygen saturation were conducted. The effect of oral glucose intake (n=13) was evaluated in respect of arterial blood gas analysis, oxygen uptake, carbon dioxide production, ventilation and endurance time on a bicycle ergometer.

Patients with chronic obstructive pulmonary disease receiving long-term oxygen treatment may improve their walking distance, experience less dyspnoea and improve their ability to perform daily activities after a physiotherapy programme. Creatine supplementation in combination with physical training showed no significant improvement in physical performance, muscle strength, pulmonary function and health related quality of life in patients with severe to moderate COPD when compared with physical training alone. However, the creatine group showed significant increased walking time after the eight-week training programme.

When spontaneous pursed lips breathing was used the patients walked longer, with a significant difference in oxygen saturation in favour of spontaneous PLB. The technique can be useful to increase walking endurance and reduce oxygen desaturation during walking in patients with moderate to severe COPD. Oral intake of glucose may increase the arterial oxygen tension in COPD patients with slight to moderate hypoxia at rest, paralleled with increased blood lactate.

When an oral glucose solution is taken before a bicycle exercise test there appears to be no increase in endurance or improved oxygen saturation. On the contrary, glucose intake may be associated with reduced ventilatory reserves and higher ratings of dyspnoea.

Key words: Chronic obstructive pulmonary disease, Long-term oxygen therapy, Physiotherapy, Creatine supplementation, Pursed lips breathing, Arterial oxygen tension, Glucose, Exercise endurance

SAMMANFATTNING

Kroniskt obstruktiv lungsjukdom (KOL) är en systemsjukdom som leder till konsekvenser i både lungor och andra organ i kroppen. Patienter med måttlig till svår grad av KOL är begränsade av andfåddhet särskilt vid fysisk aktivitet. Till följd av detta undviker patienten fysiska aktiviteter som leder till andfåddhet, vilket i sin tur försämrar patientens fysiska kapacitet och allt sammantaget leder detta till en sänkt hälsorelaterad livskvalitet.
Det är därför av stor vikt för patienten att finna strategier som kan optimera effekter av fysisk träning och på detta sätt förbättra förmågan till fysisk aktivitet hos patienter med måttlig till svår KOL.
Denna avhandling är baserad på fyra studier och har undersökt effekten av ett sjukgymnastiskt program för patienter med svår KOL och kronisk syrebrist och med kontinuerlig syrgasbehandling i hemmet; effekten av ett tillägg av kreatin kombinerat med fysisk träning för patienter med medelsvår till svår KOL; effekten av spontan sluten läppandning på transkutan syremättnad och gångsträcka och effekten av ett intag av glukos på arteriellt syrgastryck, uthållighet på cykel och syreupptag hos patienter med medelsvår till svår KOL.
För att utvärdera effekterna av ett sjukgymnastiskt program (n=20) och kombinationen av kreatinintag och fysisk träning (n=23) gjordes två olika gångtester. Daglig aktivitet och hälsorelaterad livskvalitet mättes också. Påverkan av sluten läppandning eller inte på fysisk uthållighet (n=32) mättes med gångtest och transkutan syremättnad. Effekten av glukosintag (n=13) mättes med arteriella blodgaser, syreupptag, koldioxidproduktion, ventilation och uthållighet på en ergometercykel.
Patienter med svår KOL och kontinuerlig syrgas behandling i hemmet kan förbättra sin gångsträcka, minska andfåddhet och förbättra sin dagliga aktivitet. Ett tillägg av kreatin i kombination av fysisk träning ledde inte till någon säkerställd skillnad i fysisk förmåga, muskelstyrka, lungfunktion eller hälsorelaterad livskvalitet jämfört med enbart fysisk träning. Dock, i jämförelsen inom gruppen som fick kreatin så ökade gångtiden signifikant efter åtta veckors träningsprogram.
När spontan sluten läppandning kunde användas så ökade patientens gångsträcka och det blev också en säkerställd skillnad i syremättnad till fördel för spontan sluten läppandning. Detta kan vara en användbar andningsteknik vid gång för patienter med medelsvår till svår KOL.
Ett intag av glukos kan höja det arteriella syrgastrycket, parallellt med ett förhöjt laktatvärde i blodet hos patienter med lätt till måttlig syrebrist. Slutligen, när patienterna intog en glukoslösning före ett cykeltest kunde ingen ökad uthållighet eller syremättnad visas. I motsats till detta verkar glukosintag ha samband med en minskad ventilatorisk reserv och högre skattad andfåddhet.

Key words: Kroniskt obstruktiv lungsjukdom, kontinuerlig syrgasbehandling, kreatin, sjukgymnastik, sluten läppandning, arteriellt syrgastryck, glukos, fysisk uthållighet

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II. Faager G, Söderlund K, Rundgren S, Tollbäck A, Sköld CM, Jakobsson P. Creatine supplementation and physical training in patients with COPD. A double blind, placebo-controlled study. Int J of Chron Obstruct Pulmon Dis. 2006;1(4) 445-53.

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CONTENTS

LIST OF ABBREVIATIONS

A-a diff	Calculated alveolar-arterial oxygen difference
ADL	Activity of daily living
ATP	Adenosine triphosphate
BE	Base excess
COPD	Chronic obstructive pulmonary disease
CrP	Creatine phosphate
CR-10	Category ratio scale
CRDQ	Chronic respiratory disease questionnaire
ECG	Electrocardiogram
ESWT	Endurance shuttle walking test
$FEV_{1.0}$	Forced expired volume during one second
GOLD	Global initiative for chronic obstructive lung disease
H_2O cm	water pressure
HAD	Hospital anxiety and depression scale
HAQ	Stanford health assessment questionnaire
HRQL	Health related quality of life
ISWT	Incremental shuttle walking test
kPa	Kilo Pascal
LTOT	Long-term oxygen therapy
NPPV	Non-invasive positive-pressure ventilation
PAO_2	Estimated alveolar oxygen tension
PaO_2	Arterial oxygen tension
$PaCO_2$	Arterial carbon dioxide tension
PEF	Peak expiratory flow
PEP	Positive expiratory pressure
PLB	Pursed lips breathing
RPE	Ratings of perceived exertion
RM	Repetition maximum
RQ	Respiratory exchange ratio
SaO_2	Arterial oxygen saturation
SD	Standard deviation
SGRQ	St Georges respiratory questionnaire
SpO_2	Transcutaneous oxygen tension
Stb	Standard bicarbonate
VC	Vital capacity
V_E	Minute ventilation
V_T	Tidal volume
VCO_2	Carbon dioxide production
VO_2	Oxygen uptake
W	Watt
WHO	World health organisation

1 INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a condition with increasing prevalence, closely associated with smoking and air pollution. According to the WHO´s Global Burden of Disease Study, COPD will be in the third place as a cause of death by 2020 (1, 2).

1.1 CHRONIC OBSTRUCTIVE PULMONARY DISEASE - COPD

Chronic bronchitis, bronchiolitis and emphysema of varying degrees are included in the condition, which gradually impairs pulmonary function. The clinical picture is one of productive cough, dyspnoea, general fatigue and for some, weight loss. With progression and time, respiratory tract infections will be associated with brief respiratory insufficiency which may become permanent later on (3). COPD is a multicomponent disease and will consequently affect not only the lungs, but also organs outside the lungs. The most common systemic effects of COPD are skeletal muscle dysfunction, weight loss, cardiovascular and nervous system abnormalities and osteoporosis (4).

Patients with COPD are limited by dyspnoea, especially during physical activities. As a result the patient avoids physical activities that induce dyspnoea, thus further impairing his/her physical capacity (5).

Progression of COPD is associated with increased dyspnoea, decreased physical performance, skeletal muscular weakness and high hospitalisation rates - all with a negative impact on quality of life (6).

1.2 COPD AND INTERMITTENT HYPOXIA

Oxygen desaturation is often observed during walking tests in patients with COPD or during other exercise tests (7). It has been described that hypoxemia is associated with reduction in oxygen delivery from blood to muscles in patients with moderate to severe COPD and it worsens during exercise (8). In combination with other multiple mechanisms of dyspnoea, hypoxia reduces the daily physical activity for persons with COPD (9).

Intermittent hypoxia during sleep and sleep disturbance in persons with COPD are common and an important condition to treat, as for other groups of patients (10). Hypoxia is probably one of the most important factors for developing pulmonary hypertension in patients with COPD (11).

1.3 COPD AND CHRONIC HYPOXIA

Brief respiratory insufficiency may become permanent in some patients (12). Respiratory insufficiency is defined as arterial oxygen tension (PaO_2)< 8 kPa with or without arterial carbon dioxide tension ($PaCO_2$)> 6,7 kPa during air breathing. The prognosis is worse when persons with COPD have developed chronic hypoxia and hypercapnia (13).

1.4 PERIPHERAL SKELETAL MUSCLES DYSFUNCTION IN COPD

Peripheral muscle strength has been shown to decrease in individuals with COPD (14). The weakness seems to be more concentrated in arm and leg muscles than in other muscle groups (15). Patients with COPD have been shown to have impaired skeletal muscle endurance during physical activity and Huges et al (16) demonstrated that patients with moderate COPD suffered type II fibre atrophy in quadriceps muscles and experienced a decrease in body weight. Another study showed that patients with severe COPD had an increased proportion of type II b fibres in their quadriceps, while type I fibres were reduced (17).

An early onset of lactate production during submaximal physical activity in persons with moderate to severe COPD leads to decreased pH in the muscles which may contribute to earlier exhaustion during physical activity (18, 19).

Patients with COPD have a lower content of high energetic phosphates in their skeletal and respiratory muscles than healthy individuals (20). The concentrations of adenosine triphosphate (ATP) and creatine phosphate (CrP), lactate and glycogen in the quadriceps are related to arterial blood gases - the lower the arterial PaO_2 and the higher the arterial $PaCO_2$, the lower the energy status (17).

1.5 TREATMENT

Several guidelines present recommendations for the standard care of patients with COPD, including non-pharmacological treatment such as pulmonary rehabilitation and non-invasive ventilation and pharmacological treatment such as like short/long-acting inhaled bronchodilators, inhaled/oral steroids and supplemental oxygen (21-23). Long-term oxygen therapy (LTOT) has been proven to prolong survival but, in order to be successful, oxygen must be administrated at least 16 hours/day (24).

1.6 PULMONARY REHABILITATION

It is of great importance that therapy for patients with COPD treats not only the symptoms experienced by the lungs, such as dyspnoea, but also the multi-component nature of the disease (4). Rehabilitation forms an important component of the management of patients with COPD and includes education in respiratory training, physical training, nutrition, energy-saving techniques and psychosocial support. Several meta-analysis and review articles conclude that rehabilitation relieves dyspnoea and fatigue, improves emotional function and enhances patients' sense of control over their condition (25-27).

1.7 MEASURE OF PHYSICAL CAPACITY IN PATIENTS WITH COPD

Measures to detect changes in physical capacity for patients with COPD are often based on walking tests on the floor or the treadmill (23, 28).

Exercise training and self-management education are core components of pulmonary rehabilitation and have been shown to be beneficial in improving health-related quality of life (HRQL) in patients with chronic respiratory disease (25) . Exercise training can also help to reduce the deconditioning of the muscles that follows when a patient's physical activity is restricted by his/her dyspnoea and fatigue. This is often associated with an increase in the patient's HRQL. As Health Related Quality of Life is closely linked to ability to perform physical activity in patients with COPD, this demonstrates how important activity is to human beings. One way to illustrate the effects of physical training may therefore be to measure HRQL.

As far as dynamic muscle strength is concerned, ordinary measuring techniques like a grip test or determining one repetition of maximum (1 RM) can be used in this group of patients. For elderly persons with COPD there are recommendations to modify 1 RM to 6 RM for example. If the patient can perform 6 RM with heavier weights after an exercise programme, this shows improvements (29).

1.8 EXERCISE TRAINING IN COPD

Patients with COPD gradually suffer lower physical capacity and muscle strength (30). Exercise training is, therefore, a cornerstone in pulmonary rehabilitation and has been shown to decrease dyspnoea, increase physical capacity, muscle strength and health-related quality of life (22, 31).

The optimal duration of exercise training has not yet been defined (28) but programmes lasting from four to twelve weeks have shown improvements (32, 33). However, the

more sessions the programme includes and the longer the duration of the programme, the better the improvements (34-38). To achieve optimal physiological effects from a training programme, studies have shown that patients must exercise more than one, and preferably three sessions, per week and that it is possible to combine supervised and unsupervised sessions to attain improvements (39-43). Research shows that the higher the intensity of the training programmes, the higher the physiological effects, but disease severity and motivation must also be taken into account (44). Patients with COPD cannot be exposed to the same training intensity that works for healthy adults as they are already limited in respect of respiration capacity before reaching the anaerobic threshold. An intensity that achieves approximately 60 percent of peak exercise capacity is therefore recommended (45, 46). Clinical symptom scores can be used to adjust the workload and an estimated dyspnoea in the range of "4 to 6" according to Borg's Category Ratio Scale (CR-10) (47)during exercise is recommended (47-50).
In order to be effective, training programmes must include both endurance and strength training, but walking or cycling are still the most used forms of exercise training among this group of patients (46, 51, 52).
The optimal duration of training is reported to be at least 30 minutes, but not all patients with COPD can achieve this duration (31, 53). Interval training may, therefore, be an alternative to endurance training (41, 54, 55).
Resistance or strength training is reported to be valuable for patients with COPD as it improves muscle mass and power (56-59). The recommended number of repetitions per session are two to four sets of 6 to 12 repetitions at an intensity of 50 to 85 percent of one repetition maximum (1 RM), i.e. the heaviest weight that can be lifted once with a good technique (56). Strength training is often better tolerated with regard to dyspnoea and therefore an alternative for patients who do not tolerate aerobic training (60). Clinical guidelines mostly recommend a combination of endurance and strength training as this is aimed to increase both muscle strength and whole body endurance (28, 58, 61).
Patients with COPD and LTOT are advised to use their prescribed dose of oxygen flow during exercise and to increase the flow if needed (28). Studies in exercise training with supplemental oxygen amongst patients with COPD with or without exercise induced hypoxemia have shown different results (62-64). One study of non-hypoxemic patients with COPD showed higher exercise intensity and increased exercise capacity with oxygen supplementation than without and another study showed no improvement in exercise capacity with or without oxygen supplementation (65, 66). No current clinical

guidelines recommend oxygen supplementation as it is unclear if this has any positive clinical outcome (22, 28, 37).

Non-invasive positive pressure ventilation (NPPV), which has been shown to increase minute ventilation and tidal volume and to reduce inspiratory effort and the sensation of dyspnoea in addition to reducing respiratory acidosis, can assist during exercise (67-70). NPPV is, however, not an easy intervention and present clinical guidelines recommend it only for patients who really enjoy a true benefit from non-invasive positive pressure ventilation (28).

It is evident from some studies among patients with decreased inspiratory muscle strength that inspiratory muscle training as an adjunct to exercise training improves inspiratory muscle strength and exercise capacity more than exercise alone (28, 71, 72). Despite divergent study results in this field, it is recommended in practice guidelines for patients with respiratory muscle weakness (28).

1.9 PURSED LIPS BREATHING

Pursed Lips Breathing (PLB), one of several breathing strategies, is often used spontaneously by patients with COPD. The technique prevents dynamic airway compression and has been shown to increase tidal volume, decrease respiratory rate, increase oxygen tension and saturation, and decrease carbon dioxide level at rest (73-76).

Spahija et al (77) studied the effects of PLB on respiratory mechanics and dyspnoea during exercise and concluded that PLB has a variable effect on dyspnoea during exercise. Even if the technique has not yet been proven to increase exercise capacity, it is listed in most pulmonary rehabilitation programmes, and patients are instructed on the use of PLB technique at rest, during physical activity and in situations that may cause panic.

1.10 PHARMACOLOGICAL INTERVENTIONS COMBINED WITH EXERCISE TRAINING

Pharmacological supplementation such as anabolic steroids and creatine supplementation may have an addictive effect on exercise training in patients with COPD (78-82). Some studies using anabolic steroids show positive results in respect of increased fat mass and fat-free mass, which may improve the outcome of exercise training. Among athletes, oral supplementation with creatine has been associated with an increase in exercise capacity during brief periods of physical training (83).

Moreover, creatine supplementation has been shown to increase muscular strength and volume. However, recent reports have shown that if combined with physical training, creatine supplementation does not have an addictive effect on exercise capacity in patients with COPD (80, 84). Nevertheless, existing guidelines inform that there are ongoing studies that investigate safety and indications of anabolic and nutritional treatments (28).

1.11 RATIONALE FOR THE THESIS

COPD is a chronic and progressive disease strongly associated with dyspnoea and exercise limitation in activities of daily life. So far there is no cure for the disease, only efforts to alleviate the symptoms. It is, therefore, of great importance to define effective training models and breathing techniques to relieve symptoms and to motivate patients to exercise. It is also crucial to optimise different training models and to investigate what can really help this group of patients to increase their level of physical activity, capacity and quality of life.

2 AIMS

The general aim of this thesis was to study the effects of different strategies to enhance physical activity in patients with moderate to severe chronic obstructive pulmonary disease (COPD).

The specific aims were

- To evaluate if a special eight-week physiotherapeutic training programme improved walking distance, health related quality of life and activity of daily living in patients with COPD who have recently been put on long-term oxygen therapy (LTOT).
- To evaluate if oral creatine supplementation in combination with physical training over a period of eight weeks may increase physical performance as opposed to physical training on its own among patients with COPD.
- To evaluate if spontaneous pursed lips breathing (PLB) would influence walking endurance and oxygen saturation in patients with moderate and severe COPD.
- To evaluate if the oral intake of glucose would influence arterial oxygen tension at rest and, if given before a bicycle test, would influence the oxygen saturation and exercise endurance in patients with moderate/severe COPD.

3 METHODS

3.1 PATIENTS

For Study I a succession of patients with severe COPD were recruited from the Department of Pulmonary Medicine, Karolinska University Hospital in Solna when a need for LTOT was established. The criterion for oxygen therapy was a PaO_2 <7.3 kPa on repeated examinations at rest during three infection-free weeks. The inclusion criteria constituted a diagnosis of COPD, established need for LTOT, ability to move about with or without a walking frame and willingness to participate in the study. Criteria for exclusion were symptomatic cardiac disease, or neurological orthopaedic mobility impairments.

For Study II patients with moderate to severe COPD participating in the pulmonary rehabilitation programme including exercise training at the Karolinska University Hospital, Solna or at the University Hospital in Linköping were recruited. All patients had COPD according to the British Thoracic Society's guidelines (22) ($FEV_{1.0}$ < 80 % of predicted, $FEV_{1.0}/VC$ < 70 %) and were in a clinically stable phase. Exclusion criteria were symptomatic cardiac disease and neurological or orthopedic disability with mobility impairments.

For Study III patients participating in the pulmonary rehabilitation programme at the Karolinska University Hospital in Solna were recruited. As a routine, all patients participating in the rehabilitation programme performed an incremental shuttle walking test (ISWT) one week before starting the programme. The inclusion criteria were clinically stable COPD, physical performance limited by dyspnoea and oxygen desaturation to less than 95% at the end of the ISWT. Exclusion criteria were symptomatic cardiac disease and neurological or orthopaedic mobility impairments.

For Study IV patients with moderate to severe COPD participating in a rehabilitation programme or in a maintaining rehabilitation phase at the Karolinska University Hospital in Solna were recruited. Inclusion criteria were clinically stable COPD, oxygen saturation (SpO_2) after 10 minutes' rest between 89 to 95 %, no symptomatic cardiac disease, neurological or orthopaedic mobility impairments and no diabetes mellitus. Exclusion criteria were symptomatic cardiac disease and neurological or orthopaedic mobility impairments.

Baseline characteristics for the patients included in Studies I-IV are presented in Table I.

Table I. Characteristics of patients with chronic obstructive pulmonary disease (COPD) included in Studies I-IV. Values are presented as mean with one standard deviation (SD).

	Study I (n=20)	Study II (n=23)	Study III (n=32)	Study IV (n=17)
males/females	6/14	10/13	12/20	3/14
age	71±8	66±6	66±5	71±6
VC (l)	1.9±0.5	2.6±0.8	2.7±0.7	2.4±0.8
VC (% of pred)	63±13	73±17	83±18	71±15
$FEV_{1.0}$ (l)	0.6±0.1	1.2±0.6	0.9±0.5	0.9±0.4
$FEV_{1.0}$ (% of pred)	27±7	43±18	37±18	38±12
PaO_2, kPa	[1]9.4±1.6	9.6±1.5	9.8±1.7	10.1±1.3

VC= Vital Capacity; $FEV_{1.0}$ =Forced expired volume during one second; PaO_2= arterial oxygen tension, [1]With oxygen supplementation.

3.2 STUDY DESIGN

Study I was a randomised controlled study where patients with recent onset of LTOT either completed an eight-week physiotherapy programme (Group A) or engaged in no exercise training at all (Group B). A six-minute walking test, activity of daily living and health related quality of life were the objectives.

Study II was a double-blind placebo-controlled study and patients were randomised to either a training group with creatine supplementation (the creatine group) or without (the placebo group). Both test leaders and patients were blinded to which group the patients belonged to. Objective: Endurance walking time, hand grip and quadriceps muscle strength and health related quality of life.

Study III had a crossover design, with patients randomly alternating two walking tests with pursed lips breathing (PLB) and without (no PLB). Objectives: Endurance walking time and oxygen saturation (SpO_2) at end of exercise.

During the first phase of Study IV patients' arterial blood gas analysis was determined during a glucose tolerance test at rest. This was designed as before-after. The second phase had a crossover design where two exercise tests on a bicycle with glucose (G) and without glucose (no G) supplementation were performed at random orders.

3.3 PROCEDURE

3.3.1 Physiotherapy programme (Study I)

On discharge from the hospital, patients were randomised to the physiotherapy programme or simply informed about the importance of daily physical activity. The physiotherapy programme consisted of one session of exercise training per week over a period of eight weeks. Three of the eight training sessions also included a 60-minute lesson in the anatomy and physiology of the respiratory organs, breathing-cough/huff techniques, methods for freeing secretions, functional rest postures and energy-saving techniques.

During the exercise training each patient was given his or her permanent oxygen prescription. The duration of exercise training was 90-120 minutes and consisted of eight different components: ergometer cycling, arm muscle training with dumbbells, rising from a stool, Theraband® exercises for the shoulder girdle, thigh muscle training with weight cuffs, getting up onto a low stool, stomach muscle training and movement exercises for the thorax and adjacent joints. Each part was performed with individually tested repetitions and loads. The aim of the cycling component was to succeed at cycling without a break for 15 minutes and the load was based on the degree of estimated dyspnoea and leg fatigue according to Borg's Category Ratio scale (CR-10 scale) (47). The maximum permitted degree of dyspnoea and leg fatigue during this part of the programme was set at 7. The load was increased when the patient had achieved the aim of cycling, i.e. being able to cycle without interruption for 15 minutes. The remaining components of the exercise programme were set to be 70% of one 1 RM, i.e. the heaviest weight that could be lifted once with good technique. Transcutaneous oxygen saturation and heart rate were recorded before, during and at the end of cycling, rising from a stool and getting up onto a low stool.

In addition to the supervised training session, patients performed an exercise home-training programme at least three times a week, documenting the training in a training diary.

3.3.2 Pulmonary rehabilitation and creatine supplementation (Study II)

In Study II patients were randomised to either an exercise training programme with oral creatine supplementation or with oral placebo supplementation. All involved investigators were blinded to which patient that was receiving creatine supplementation. The eight-week rehabilitation programme was designed as described above (3.3.1), but with two supervised training sessions per week and ergometer

cycling for 30 minutes. Each patient also performed the exercises in 15 repetitions repeated 3 times. In the exercises, which required different loads such as weight cuffs, the physiotherapist guided the patients to identify the weight that after 15 repetitions was too heavy to be lifted one more time. The educational programme was more extensive than described above, and the patients participated in 8 sessions about lung physiology, pulmonary disease, breathing techniques, secretion clearance techniques, psychosocial issues, medications and nutrition.

The patients received the supplementation powder (placebo or creatine) in small tubes and were informed before the programme started how to dissolve the powder in hot liquid. Patients were scheduled to take the powder in individual doses during eight weeks.

3.3.3 Endurance shuttle walking test with and without pursed lips breathing (Study III)

In Study III the patients performed two endurance shuttle walking tests (ESWT) which either allowed Pursed Lips Breathing (PLB) or prevented it (no PLB) at random orders. In the walking test with PLB, patients started to use the technique spontaneously and kept on doing so until the end of the test. A mouthpiece that prevented patients from using PLB was placed between the teeth and close to the lips. Walking time, oxygen saturation and pulse were recorded and dyspnoea and leg fatigue were estimated according to Borg CR-10 (47).

3.3.4 Endurance bicycle test with or without oral intake of glucose (Study IV)

In Study IV patients were scheduled to visit the hospital on four occasions for the following: an arterial blood analysis during an oral glucose tolerance test, an incremental bicycle exercise test and two endurance bicycle tests with or without oral glucose intake before cycling.

During the glucose tolerance test arterial blood gases, blood glucose, lactate and s-insulin were analysed. The incremental bicycle exercise test was symptom limited and all patients started at a workload of 10 W which was increased by 10 W every minute. Patients' blood pressure, SpO_2, heart rate and respiratory rate were recorded and dyspnoea, leg fatigue and perceived exertion were rated according to Borg's CR-10 scale and RPE (47, 85).

The patients performed two endurance bicycle tests with oral glucose or water taken at random orders 60 minutes before the start The period between the two tests varied from 1-3 weeks. The test leaders were blinded to what solution the patients had taken before cycling. The work load was set at 60% of the maximum load during the incremental bicycle test. The patient's working time, blood pressure, SpO_2 and ratings of dyspnoea, leg fatigue and perceived exertion, oxygen uptake (VO_2), carbon dioxide production (VCO_2) and ventilation (V_E) were recorded.

3.4 MEASUREMENTS

3.4.1 Six-minute walking test

The six-minute walking test is a reproducible field test adapted from the 12-minute walking test (86, 87). In Study I patients walked along a 30-metre corridor and were instructed to go as far as possible in six minutes without encouragement (88). Distance in metres was recorded. All patients used a walking frame (Staffan model, LEBER, AB, Sweden) with the oxygen tube in a basket. The test was completed twice on the same day before the physiotherapy programme started and with a recovery time of 10 minutes in between. Oxygen saturation and heart rate were measured with a pulse oximeter before, during and directly after the walking test. (Model 8500, Nonin Medical Inc, MN, USA). Dyspnoea and leg fatigue were estimated on Borg's CR-10 scale (47).

3.4.2 Incremental shuttle walking test (ISWT)

This test is a standardised, paced field walking test with an incremental and progressive structure to assess functional capacity in patients with chronic airways obstruction (89). The patient walks around two cones placed 10 metres apart in a corridor and the speed is dictated by a timed signal played back by a cassette recorder. The test ends if the patient is unable to continue due to breathlessness or any other reason. In Study II and III patients performed the ISWT before they were included in order to calculate their walking speed levels in the Endurance Shuttle Walking tests (ESWT). Oxygen saturation (SpO_2), heart rate and rated dyspnoea and leg fatigue (Borg's CR-10 scale) were recorded before and directly after the test (47).

3.4.3 Endurance shuttle walking test (ESWT)

In the endurance shuttle walking test patients walk in the same way as for ISWT, but the speed is constant and calculated at 85% of the maximum performance in ISWT

(90). In Study II the patients performed ESWT before the eight-week pulmonary rehabilitation programme and directly after. Oxygen saturation and heart rate were measured using pulse oximeters (Model 8500, Nonin Medical Inc, MN, USA/Model 512 and Novametrix Medical inc. Wallingford, CT, USA) (91). The patients rated their dyspnoea and leg fatigue according to Borg's CR-10 scale (47).

In Study III the participating patients performed two ESWTs, one with PLB and one without. To prevent PLB in the one test, a plastic ring, 2,2 cm deep with an oval hole of 3 cm x 1,7 cm in diameter was placed between the teeth and close to the lips. In both tests the patients also had a standard nose clip for spirometry investigations. The recovery time between the walking tests was at least 15 minutes for all patients. Oxygen saturation (SpO_2) and heart rate were measured using a pulse oximeter with a finger probe (Model 8500, Nonin Medical Inc, MN, USA). Heart rate and oxygen saturation were recorded before the tests, every two minutes during the tests, directly after the patient stopped walking and again after five and ten minutes. The patients carried the pulse oximeter in a small bag with a window allowing the investigator to read the values.

3.4.4 Knee muscle strength and fatigue

In Study II maximal voluntary strength and fatigue in right knee extensors muscles were measured with an isokinetic dynamic dynamometer, (Kin-Com 500H, Chattecx Corp., Chattanooga TN, USA) before and after the rehabilitation programme (92). The isokinetic dynamometer has been used for patients with COPD and is valid and reliable for assessing strength and fatigue (59, 93).The patients were sitting with 90° hip and knee flexion and the arms crossed in front of the chest. Maximal voluntary concentric strength was measured at 30°/s angular velocity in a movement range from 90° to 30° knee flexion. After a five minutes rest, muscle fatigue was evaluated by 3 bouts of 30 maximal consecutive concentric repetitions at 180°/s angular velocity in a movement range from 90° to 30° knee flexion (93). One learning-session was performed at least two days or within one week before the actual baseline testing.

3.4.5 Grip test

In Study II grip strength was measured with a Jamar Dynamometer/Grippit (Jamardynamometer standard, BB44JR, WS Routband Comp LTD, Albionmille, Helmshore, Rossendale, UK and Grippit type G100, serial number 197100, AB

detector, Gothenburg, Sweden) at baseline and after eight weeks. Measuring grip strength has been used in several studies for patients with COPD and has been shown to correlate with whole body strength (30, 94, 95).
The patients were told to squeeze at maximum strength for 5 seconds. After resting for one minute, the patients repeated the test with the same instructions for the second and third trial. The mean value of the three trials was recorded (96).

3.4.6 Health- related quality of life

In Study I and II health related quality of life was assessed using the Chronic Respiratory Disease Questionnaire (CRDQ) and the St. George's Respiratory Questionnaire (SGRQ) (97, 98). The Chronic Respiratory Disease Questionnaire is based on interviews following the chronic respiratory disease and is divided into four components: dyspnoea, fatigue, emotional disturbance and feeling of mastery over the disease and its effects. The higher the component scores, the better the function. All patients in Study I were interviewed before the physiotherapy programme started, eight weeks after the programme ended and then six months after the programme started. SGRQ is also a disease-specific questionnaire, but a self-administered form with 76 weighted responses and three component scores – Symptoms, Activity and Impacts and one total score –are also calculated. A decrease in score means better health related quality of life and a change of four units is considered clinically relevant (99). In Study II the patients answered the questionnaire at baseline after eight weeks of training.

3.4.7 Anxiety and depression

Anxiety and depression were measured by interview using the hospital anxiety and depression scale (HAD) in Study I (100). The HAD consists of 12 statements each with four answer alternatives. It is intended to reflect how the patient has been feeling during the previous week. The higher the points are the more anxiety and depression. The patients answered the questionnaire before starting the programme, at 8 weeks at the end of the programme and 6 months from the start of the programme.

3.4.8 Activity of daily living ability (ADL)

The Stanford Health Assessment Questionnaire (HAQ) was used before the programme started, at the end of the programme, at eight weeks and after six months for Study I (101). The questions are categorised in eight areas: dressing, standing up, eating, walking, hygiene, reaching things, opening various things, and managing activities

outside the home. The patient answers questions regarding degree of difficulty, i.e. how their dyspnoea is affected when they do different activities in their daily lives. The lower the points, the better ADL ability.

3.4.9 Symptom limited exercise bicycle test

In Study IV patients performed one symptom limited incremental exercise test and two symptom limited endurance tests on a bicycle model Rodby ergometer/RE 820/830. The ECG used was a model Siemens Electra MegaCarc/R/E and the workload, which started with 10 W for the endurance tests and was constantly at 60 % of the maximum work load reached during the incremental test. The patient's blood pressure, SpO_2, heart rate and respiratory rate were recorded with Respons Optovent (Optovent AB, Täby, Sweden) and the patient's rated dyspnoea, leg fatigue and perceived exertion according to Borg's CR-10 scale and RPE (85, 102). The patients were instructed to exercise for as long as possible until they reached a level of dyspnoea, leg fatigue or exertion that prevented them from continuing in both the incremental and the endurance test. The period between the two endurance tests varied from 1-3 weeks.

3.4.10 Metabolic stress test

During the endurance tests in Study IV the patient's oxygen uptake (VO_2), carbon dioxide production (VCO_2) and ventilation (V_E) were measured with a metabolic stress test system (Metamax® II, Cortex, Biophysik GmbH, Leipzig, Germany). It is a portable cardiopulmonary exercise system for pulmonary gas exchange measurements based on a mixing chamber technology. Throughout the exercise test patients breathed through a face mask and the exhaled air was measured every10^{th} second. The baseline values were calculated as an average of the patient's ventilation one minute before the start and the final value as an average of the last half minute before they ended the test.

3.4.11 Spirometry

In Studies I and III the forced exhaled volume during one second ($FEV_{1.0}$) was determined on the basis of the best of three flow volume curves. In Study II spirometry was performed by a Vitalograph Compact C (Förbandsmaterial AB, Gothenburg, Sweden). In all three studies normal values were calculated according to European Coal and Steel Union guidelines (103, 104).

In Study IV spirometry was performed by a Vitalograph Alfa (GP Supplies Limited, Units 1 and 2, AMC Business Centre 12, Cumberland Avenue, London - NW10 7QL, United Kingdom) and normal values were calculated according to Berglund (105).

3.4.12 Blood analyses

In Studies I and II the arterial blood samples were taken with the patient seated and spontaneously breathing and the samples were analysed within 15 minutes (IRMA, Blood analysis system, Series, Diametrics Medical, MN, USA).

In order to establish whether oral glucose influences arterial oxygen tension, a blood gas analysis at rest was performed as a first phase in Study IV. Arterial blood samples were taken from a short catheter placed in the radial artery while the patient was seated and breathing spontaneously. This intervention was done by a specially trained research nurse, assisted by the physiotherapist responsible for the study. Blood gases were analysed using an ABL 800 FLEX (Radiometer, Denmark).

The arterial glucose concentration (mmol/l) was analysed by a Glucosanalyser 2® (Beckman Instruments Inc., Brea, Ca, USA).

The arterial plasma lactate was analysed according to Beckman LX manual and the normal range established in our laboratory for arterial P-lactate was 0,3-2,3 mmol/l.

Arterial serum insulin was analysed using an immunometric ("sandwich") method with two monoclonal antibodies and detection with ECLIA (Electrochemiluminescence Immunoassay).

3.4.13 Transcutaneous oxygen saturation and respiratory rate

In Studies I, II and III oxygen saturation and heart rate were measured with a pulse oximeter (Model 8500, Nonin Medical Inc, MN, USA). In study II the research group in Linköping used a Model 512, Novametrix Medical inc. Wallingford, CT, USA. In Study IV transcutaneous SpO_2, heart rate and respiratory rate were measured with Respons Optovent (Optovent AB, Täby, Sweden).

3.4.14 Perceived dyspnoea, leg fatigue and exertion

Studies I-IV rated patients'dyspnoea and leg fatigue according to Borg's CR-10 scale during training and exercise capacity tests (102). In Study IV patients rated their perceived exertion according to Borg's RPE scale (85) during the endurance exercise bicycle test.

3.4.15 Statistical methods

Results of Studies I-IV were either presented in respect of mean and/or median values, with either a standard deviation (SD) and/or range and 95% confidence interval (CI). The statistical analysis used in Studies I-IV is presented in Table II.

Table II. Statistical methods used in Studies I-IV

Method	Study I	Study II	Study III	Study IV
Friedman test	X			
Student´s unpaired t-test		X		
Student´s paired t-test		X	X	X
Mann Whitney U-test	X			
Wilcoxon rank sum test		X		X
Wilcoxon matched pairs test			X	

The statistical analysis was performed using Statsoft Statistica 6.0 in Studies I, II and III and SPSS 15.0 for Windows in Study IV.

3.4.16 Ethical approval

The studies were approved by the Local Ethics Committee at the Karolinska University Hospital, the Local Ethics Committee at the University Hospital in Linköping and all patients gave their verbal or written informed consent to participate in the studies.

4 RESULTS

In Study I, three patients were excluded from the group that performed the physiotherapy programme and three patients from the control group due to lack of strength and serious infections of the airways. At the six-month follow-up five patients in the intervention group and three in the control group were able to perform the tests. There were no dropouts in Study II or III. In Study IV, four patients were excluded: one male who developed a brain tumour that was discovered between tests III and IV, one female who did not tolerate the face mask during the exercise endurance test, and two females who developed ECG changes during the first exercise test.

4.1 STUDY I

Patients who started the physiotherapy programme (Group A) shortly after commencing oxygen therapy significantly increased their distance walked ($p<0.01$) in the six-minute walking test compared to the control group (Group B) (Figure 1).

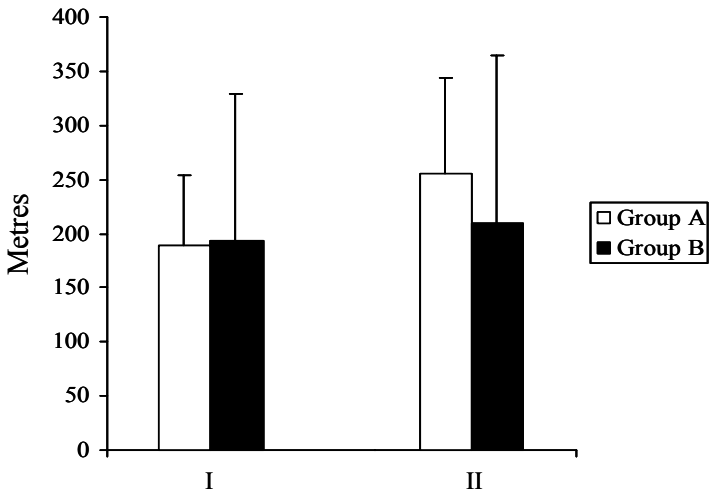

Figure 1: Measurement occasions I and II. Group A's (training programme) walking distance during six-minute walking test versus Group B's (control group) walking distance. Group A: I vs. II; $p<0.01$. Group B: I vs. II; ns. I: Group A vs. Group B; ns. II: Group A vs. Group B; $p<0.05$.

Group A also improved in the dimension dyspnoea ($p<0.05$) in the CRDQ and the dimensions for fatigue, emotion and mastery also tended to improve in the CRDQ. ADL ability measured with HAQ improved ($p < 0.01$) in comparison with the control group (Table III).

Table III. Effects of the physiotherapy programme on patients with chronic obstructive pulmonary disease (COPD) and long-term oxygen therapy (LTOT). Group A (physiotherapy programme) is compared with Group B (control group) in respect of health related quality of life (HRQL), measured with the chronic respiratory disease questionnaire (CRDQ) and the hospital anxiety and depression scale (HAD), and activity of daily living (ADL) ability, measured with the Stanford assessment activity questionnaire (HAQ) (m, range). Increased score on the CRDQ = improvement. Decreased score on the HAD and HAQ = improvement. The values are presented as mean (range).

	Group A (physiotherapy programme)		Group B (control group)	
	Measurement I n=10	Measurement II n=7	Measurement I n=10	Measurement II n=7
CRDQ				
Dyspnoea (5-35)	18 (10-23)	21 (18-26)*	16 (12-21)	17 (12-25)
Fatigue (4-28)	16 (10-24)	19 (14-22)	14 (7-23)	16 (12-19)
Emotional (7-49)	31 (19-49)	35 (21-34)	33(18-47)	32 (17-47)
Mastery (4-28)	22 (16-26)	23 (19-28)	19 (8-28)	20 (11-26)
HAD				
Anxiety (0-18)	5 (1-17)	4 (1-7)	5 (0-12)	6 (3-10)
Depression (0-18)	5 (1-11)	4 (1-7)	4 (1-8)	5 (1-12)
HAQ				
ADL score (0-3)	1.2 (0.5-1.8)	0.9 (0.3-1.4)**	1.3 (0.4-2.1)	1.3(0-2.3)

* $p<0.05$ within group comparison of dyspnoea in CRDQ, ** $p<0.01$; group comparison of ADL-score

4.2 STUDY II

Patients with COPD participating in the physical training programme and taking creatine supplementation (n=13) increased their average walking time by 61%: from 320 (173-825) to 515 (215 -1200) seconds in the ESWT ($p<0.05$) after eight weeks of training. The group with placebo treatment (n=10), on the other hand, increased their walking time by 48%: from 372 (161-1114) to 552 (123-1200) seconds (ns). The difference between the two groups before and after 8 weeks was not statistically significant (Figure 2).

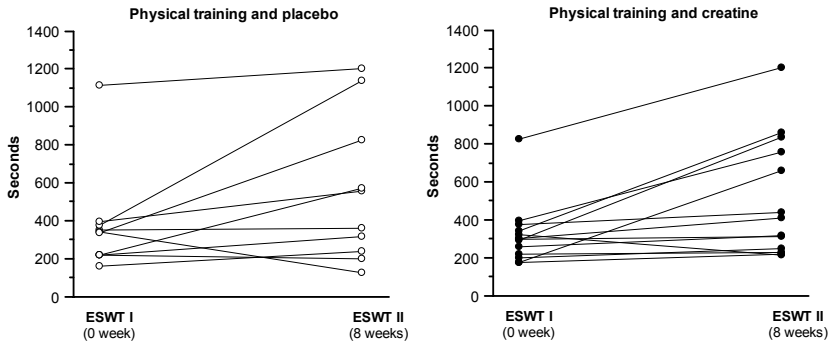

Figure 2: Individual walking time during endurance shuttle walking test (ESWT) for the creatine (n=13) and placebo (n=10) groups before and after creatine/placebo supplementation and the training programme. Within the placebo group: difference (ns); within the creatine group: $p<0.05$. Creatine group vs. placebo group: (ns).

The patients' median estimated dyspnoea directly after the ESWT, before and after the eight- week training programme decreased significantly from 7 to 5 ($p<0.05$) in the creatine group. In the placebo group the dyspnoea index decreased from 5 to 4 ($p=0.28$).

The difference in grip strength between the creatine group (n=12) and the placebo group was not significant; neither before nor after the eight-week exercise programme. Within each group, grip strength increased significantly ($p< 0.05$); by 3% from baseline in the creatine group and by 6% in the placebo group.

There was no difference in maximal knee extensor strength within or between the creatine (n=7) and placebo (n=5) groups before or after the exercise programme (Figure 3). Maximal knee extensor strength for the total group was 131±38 Nm and 138 ±42 Nm respectively before and after the training programme ($p=0.260$).

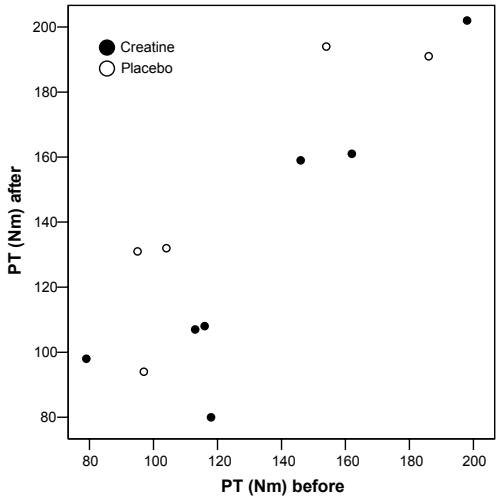

Figure 3: Knee extensor peak torque (PT)(Nm) at 30 °/s for the creatine (n=7) and the placebo group (n=5) before and after an eight-week training programme.

As far as HRQL is concerned, there were no significant differences between the two groups in respect of the various dimensions (symptoms, activity and impacts) or in total score after the exercise programme. The dimension of symptoms decreased significantly ($p<0.05$) within the placebo group, as two patients showed a difference of 40 units from baseline compared to a mean change of 7 units for the rest of the group. With a mean value of 5 units, the creatine group also decreased in this dimension, but failed to show a significant difference. The change in units, before and after the training programme, regarding the dimensions and total score are shown in Figure 4.

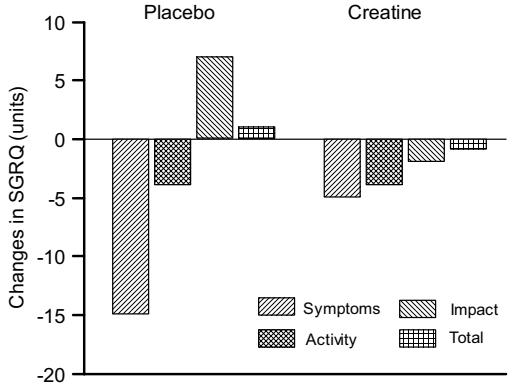

Figure 4: Change in St George's respiratory questionnaire (SGRQ) among the creatine group (n=9) and placebo group (n=8) after oral supplementation of creatine/placebo and the training programme. Mean values are presented. The symptom dimension $p < 0.05$ within the placebo group.

4.3 STUDY III

When the patients with COPD used PLB during the ESWT they walked 37 seconds (16%) longer ($p<0.01$) on average than when the technique was prevented. Oxygen saturation dropped considerably during both tests, but the absolute difference in oxygen saturation was 1.2 % ($p<0.01$) in favour of PLB measured at the end of the walking tests. The results of the ESWT are shown in Table IV.

Table IV
SpO_2, heart rate, PEF (mean, SD); ratings of dyspnoea and leg fatigue (median, range) in 32 COPD patients breathing without pursed lips technique (PLB) during endurance shuttle walking test (ESWT I) and with PLB (ESWT II).

	ESWT I Walking time 235 ±66 seconds			
	At rest	After test	5 min after test	10 min after test
SpO_2 (%)	96 ±2	86 ±5	95 ±2	96 ±2
Heart rate (bpm)	83 ±13	108 ±15	86 ±13	84 ±13
PEF (l/min)	247 ±85	238 ±85	240 ±87	244 ±86
Borg CR 0-10				
Dyspnoea	0.5 (0-3)	5 (3-9)	1 (0-4)	0.5 (0-3)
Leg fatigue	0 (0-3)	1.5 (0-7)	0 (0-4)	0 (0-3)
	ESWT II Walking time 272 ±110 seconds **			
	At rest	After test	5 min after test	10 min after test
SpO_2 (%)	96 ±2	87 ±5**	95 ±2	96 ±2
Heart rate (bpm)	84 ±11	109 ±12	85 ±14	85 ±13
PEF (l/min)	248 ±84	240 ±86	248 ±83	248 ±86
Borg CR 0-10				
Dyspnoea	0.5 (0-3)	5.5 (4-9)	1 (0-5)	0.5 (0-3)
Leg fatigue	0 (0-3)	2 (0-7)	0 (0-4)	0 (0-3)

SpO_2 = transcutaneous oxygen saturation; PEF = Peak Expiratory Flow; COPD=chronic obstructive pulmonary disease, bpm = beats per minute.
** $p<0.01$; group comparison of walking time and SpO_2 % between ESWT I and II.

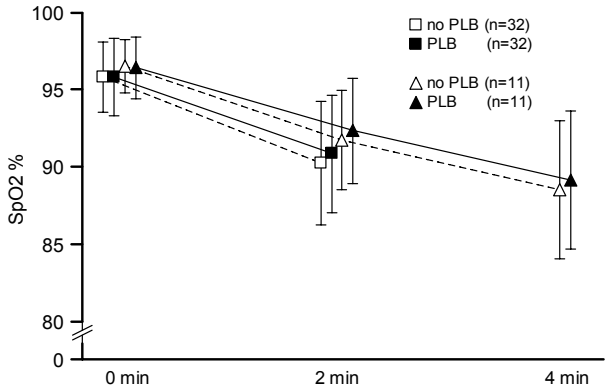

Figure 5: Mean (SD) value of oxygen saturation (SpO_2) in 32 patients with chronic obstructive pulmonary disease (COPD) during the endurance shuttle walking tests I (ESWT I) and II on two occasions, i.e. before the test and at two minute during the test. During the ESWT I patients could not use spontaneous pursed lips breathing (PLB) and during ESWT II they were allowed to use PLB. SpO_2 with PLB vs. no PLB at two minutes ($p<0.05$). Mean (SD) value of SpO_2 in 11 COPD patients during ESWT I and II on three occasions, i.e. before the test and at two and four minutes.

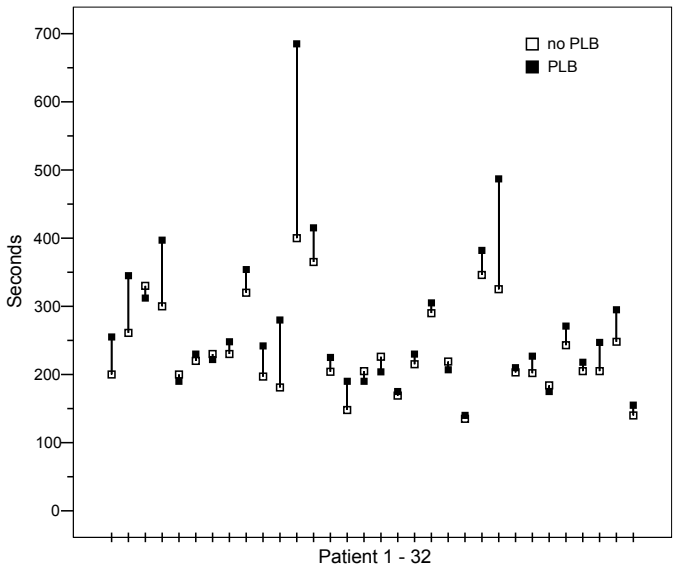

Figure 6: Individual walking time in endurance shuttle walking test (ESWT) of 32 patients with chronic obstructive pulmonary disease (COPD) on two measured occasions. During the ESWT I patients could not use spontaneous pursed lips breathing (PLB) and during ESWT II they were allowed to use PLB.

There was also a significant difference in oxygen saturation with or without PLB measured at 120 seconds and at 240 seconds ($p<0.05$) during ESWT I and II (Figure 5). Twenty-five out of the 32 patients walked for a longer period when they used PLB compared to when they were prevented to use the technique (Figure 6).
Characteristics and results in responders and non-responders (walking longer or shorter time with PLB) are presented in Table V.
When the degree of dyspnoea was analysed at the end of ESWT II (with PLB) it showed that four patients rated less dyspnoea, 20 patients rated no change in dyspnoea and eight patients rated higher dyspnoea compared to ESWT I (no PLB). In those who rated less dyspnoea when using PLB (n=4) the mean $FEV_{1.0}$ was 37 ± 12 % of predicted value and in those who rated more dyspnoea when using the technique (n=8) it was 32 ± 21 % of predicted value. The mean walking time was 437 ±168 seconds in the less dyspnoeic patients and only 237 ± 37 seconds in those who rated more dyspnoea. The mean oxygen saturation was 91 ± 5 % in the less dyspnoeic patients (n=4) and 88 ± 5 % in those who rated more dyspnoea (n=8) at the end of the test.

Table V. Characteristics and results in responders to pursed lips breathing (PLB) (n=25, walking longer time with PLB) and non – responders (n=7; walking shorter time with PLB). Values are presented as mean ± SD, ratings of dyspnoea and fatigue as median and range.

	Responders		Non-responders	
	n=25		n=7	
Age (years)	66±5		68±6	
Males/females	8/17		4/3	
$FEV_{1.0}$ (% of pred)	38 ± 19		30 ± 15	
	PLB-	PLB+	PLB-	PLB+
Walking time (seconds)	238 ± 71	288 ± 118***	227 ± 48	214 ± 45
SpO_2 (% end of test)	86 ± 5	87 ± 5 **	86 ± 5	87 ± 4
Borg CR 0-10				
Dyspnoea, end of test	5(3-9)	6(4-8)	5(5-8)	5(4-8)
Leg fatigue, end of test	1(0-7)	2(0-7)	2(0-5)	3(0-3)

Abbreviations: $FEV_{1.0}$ = Forced expired volume during one second; SpO_2 = transcutaneous oxygen saturation; (*** $p<0.001$; ** $p<0.01$; within-group comparison in responders).

Table VI. Arterial blood gases, blood glucose, P-lactate and S-insulin levels, before and every 15 to 75 minutes after oral glucose intake for 10 COPD patients at rest. Values are presented as mean ± SD.

	pH	BE, mmol/l	Stb mmol/l	PCO_2, kPa	SaO_2,%	PaO_2 kPa	PA O_2 calculated	A-a diff kPa	Blood glucose, mmol/l	P-Lactate mmol/l	fS-Insulin pmol/l
Before glucose intake	7.41±0.02	0.3±1.7	24.7±1.4	5.35±0.5	95.4±1.5	10.1±1.2	13.3±0.7	3.2±1.3	5.3±0.7	(n=8) 0.73±0.3	54±29
15 min	7.41±0.02	1.1±2.2	25.3±1.9	5.42±0.6	95.3±2.1	10.1±1.5	13.2±0.8	3.0±1.4	8.6±1.2	0.75±0.3	346±144
30 min	7.40±0.01	0.7±2.2	24.9±1.8	5.49±0.6	95.3±1.7	9.9±1.0	13.1±0.8	3.2±1.1	10.1±0.9	1.17±0.4	408±42
45 min	7.40±0.02	0.2±2.2	24.6±1.9	5.48±0.6	95.4±1.9	10.3±1.2	13.1±0.8	2.9±1.3	10.6±1.3	(n=9) 1.61±0.5	509±189
60 min	7.40±0.02	0.2±2.3	24.6±1.9	5.33±0.6	95.6±1.9	10.6±1.4*	13.3±0.8	2.8±1.4*	*** 10.2±2.5	*** 1.79±0.5	*** 536±167
75 min (n=9)	7.40±0.02	0.2±2.3	24.6±2.0	5.46±0.6	95.3±1.9	10.2±1.0	13.2±0.9	2.9±1.2	10.5±2.4	1.78±0.5	371±197

BE = Base excess; Stb = Standard bicarbonate; $PaCO_2$ = arterial carbon dioxide tension, SaO_2 = arterial oxygen saturation, PaO_2=arterial oxygen tension, PA O_2 = estimated alveolar oxygen tension, A-a diff = Calculated alveolar-arterial oxygen difference.*$p< 0,05$, ***$p<0,001$: for the difference before glucose intake and 60 minutes after intake.

4.4 STUDY IV

During the first part of the study, when arterial blood gases, plasma-lactate and serum-insulin were analysed, ten out of 17 patients could finish the test. Four were not able to participate early in the morning after 12 hours of fasting and three of the 13 patients´ blood tests failed due to clotting of the catheter. Mean PaO_2 increased by a maximum of 0.5 kPa during the glucose tolerance test, 60 minutes after glucose intake ($p<0.05$). Both the lactate and insulin mean levels increased significantly ($p<0.001$) until 60 minutes after glucose intake. Insulin began to decrease after 60 minutes. The alveolar-arterial oxygen difference (A-a diff.) before and after an intake of glucose showed a significant decrease after 60 minutes. The results of the remaining 10 patients' blood tests are shown in Table VI.

All 17 patients performed the symptom limited incremental bicycle test and the average peak work load was 59±21 W.

As mentioned, four patients were excluded during this phase of the study and the remaining 13 patients performed two endurance bicycle tests with glucose (G) or water (no G) taken 60 minutes before exercise. The average work load during the endurance exercise test was 35 W±12.

The average endurance time on the bicycle, with or without glucose intake was similar: 7.4 (2.1-21.4) min with glucose and 7.9 (3.9-30) without. The patients' oxygen saturation monitored at the end of the endurance exercise tests with or without glucose were 90±4% and 90±4% respectively, with no statistically significant difference. At the end of the exercise test and after glucose intake, mean rated dyspnoea significantly increased compared to after water intake $p<0.01$.

Before the test, i.e. 60 minutes after the patients had their water/glucose solution, heart rate, respiratory exchange ratio (RQ), VCO_2 and V_E increased significantly after glucose intake.

The results of ventilation and oxygen consumption before and at the end of the endurance exercise test with glucose (G) or water (no G) are shown in Table VII.

Table VII. Ventilation and oxygen consumption before and at the end of a symptom limited endurance bicycle test with oral intake of glucose (G) and without (no G) among 13 patients with COPD. The intake of glucose or water was 60 minutes before cycling. The values are presented as mean ±SD. Rated degree of exertion, dyspnoea and leg fatigue are presented as median and range.

	Start/ no G	Start/G	End/ no G	End/G
Heart rate, b/min	72±13	77±14*	109±16	111±18
SpO_2, %	95±2	96±2	90±4	90±4
Respir. rate, [1]b/min	20±5	20±5	30±6	31±7
RQ	0.85±0.05	0.92±0.05**	0.91±0.04	0.95±0.06*
VO_2, l/min	0.32±0.03	0.36±0.07	0.90±0.15	0.94±0.17
VCO_2, l/min	0.27±0.04	0.31±0.04*	0.83±0.16	0.9±0.2
V_E, l/min	11.0±2	12.3±3*	28.0±7	29.7±8
V_T, l	0.62±0.3	0.65±0.3	1.00±0.34	1.00±0.37
V_E/ VO_2, %	34±5	35±7	32±7	32±8
V_E/ VCO_2, %	40±6	40±5	35±7	34±9
Ventilation spare, %	67±12	63±13*	19±20	15±19
Rated dyspnoea (Borg CR-10)	-	-	7(0-10)	8.5(5-10)*
Rated exertion (Borg 6-20)	-	-	17(15.5-19)	17(15-19)
Rated leg fatigue (Borg CR-10)	-	-	4.5(0-10)	4(0-10)

b/min= beats per minute, SpO_2 = transcutaneous oxygen saturation, [1]b/min = breaths/minute, RQ= respiratory exchange ratio, VO_2 = Oxygen uptake, VCO_2 = carbon dioxide production, V_E = minute ventilation, V_T = tidal volume, * $p<0.05$ ** $p<0.01$ for the difference between no Glucose (no G) and intake of Glucose (G).

Nine out of 13 patients had increased oxygen uptake at the end of the endurance test after glucose intake (p=0.07) compared to water intake. Individual VO_2 at the end of the endurance tests with glucose or water intake is shown in Figure 7.

The calculated ventilatory reserve was significantly lower before the test than after the test. Nine out of 13 patients' calculated ventilation reserve was lower at the end of the test after glucose intake (Figure 8).

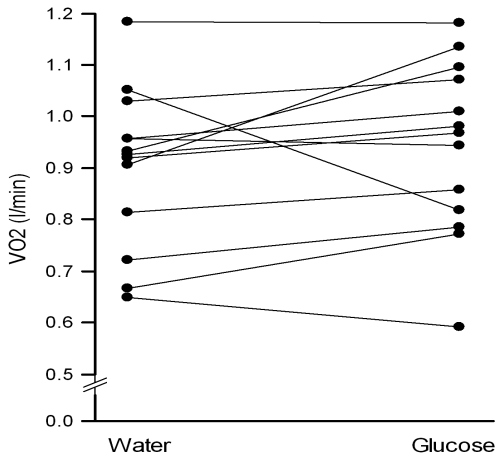

Figure 7: Oxygen uptake of 13 patients with chronic obstructive pulmonary disease (COPD) at the end of a symptom-limited endurance bicycle test with water and glucose intake 60 minutes before cycling. Nine out of 13 patients had increased their oxygen uptake after glucose intake at the end of the test (p=0.07).

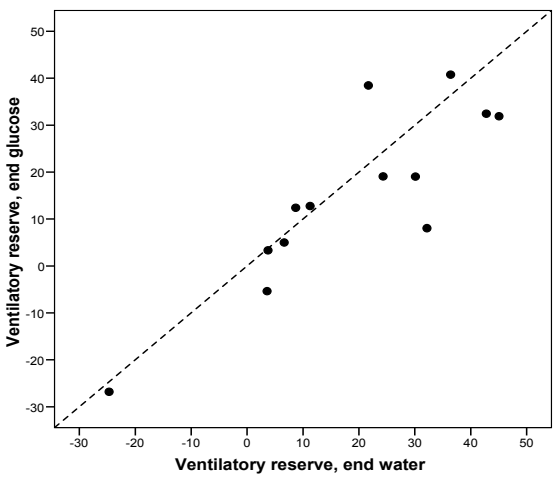

Figure 8: Ventilatory reserve in 13 patients with COPD at the end of the endurance bicycle test with water and glucose intake. Nine out of 13 patients had decreased ventilatory reserve after glucose intake at the end of the endurance exercise test.

5 DISCUSSION

5.1 GENERAL DISCUSSION

Pulmonary rehabilitation, with physical training as a cornerstone, has been proven to decrease dyspnoea and increase health related quality of life in patients with COPD (28). COPD is not possible to cure but is, from a humane perspective, of great importance to relieve symptoms that are caused by the disease. From a societal perspective the positive effects and improvement in functional capacity are clear, as rehabilitation renders the patients more physically active and thereby less dependent on care.

This thesis has shown that even patients with severe COPD and LTOT can increase their physical capacity, decrease dyspnoea and increase daily activities after participating in a physiotherapy programme based on physical training and supplementary education on the disease and how to cope with it. Participation in the physiotherapy programme not only improves physical capacity, but also ability to cope with symptoms related to physical activity, which may lead to less fear during exertion and consequently to a more physically active life.

Many patients with COPD (and their physicians) think of LTOT as a terminal condition which impedes participation in physical training or more strenuous daily activities. It is, therefore, of great importance to show that this stage of COPD must not lead to increased isolation at home and decreased daily physical activity, as was shown in Study I.

Many patients with COPD ask for “something more” to increase their capacity to grow in strength during physical training. Creatine supplementation has been shown to increase maximal muscle strength and muscle volume in healthy individuals. As patients with COPD have lower quantities of energy substrate in their skeletal muscles, these patients may benefit from creatine supplementation during exercise and training. However, no significant increase in physical capacity or skeletal muscle strength were seen in those patients treated with oral creatine supplementation during training (Study II) and these results have recently been confirmed by two other studies (80, 84).

Pursed lips breathing (PLB) is a strategy that many patients with obstructive pulmonary diseases use spontaneously. PLB prevents dynamic compression and has positive effects on breathing control. The technique is scheduled in every rehabilitation programme for patients with COPD to facilitate breathing, especially during exertion or

exacerbation, as PLB has been shown to have positive effects in these situations. However, the technique not yet has been proven to increase physical capacity.
Once a patient with COPD has adopted the technique and incorporated it into his/her breathing strategy, it is difficult to prevent the use of PLB. This was obvious in Study III, and all patients spontaneously used PLB when walking. However, when a mouth piece prevented them from using the technique, their walking capacity was lower than when using PLB.
Patients with COPD often desaturate during physical activity and this, among others, limits the patient's ability to be physically active and to exercise. Glucose infusion has been shown to increase blood oxygen tension in COPD patients at rest. If this is also true after oral intake of glucose it may, most likely, positively influence exercise capacity and, in the longer term, training intensity in patients with COPD. Study IV showed no positive impact on exercise capacity after oral intake of glucose. On the other hand, it is important to verify if oral intake of glucose may have negative effects on physical capacity for this group of patients, as there is a demand for alternative methods to improve physical capacity in COPD patients.

5.2 EXERCISE TESTING IN PATIENTS WITH COPD

5.2.1 Walking tests

Exercise capacity was evaluated by the six-minute walking test in Study I. All patients included in the study had severe COPD with LTOT and had to transport the oxygen tubes when they moved outside their home. Therefore all patients used a walking frame with a basket for their oxygen bottles. The six-minute walking test was chosen instead of an incremental shuttle walking test (ISWT), as the six-minute walking test correlates more closely with daily activities than an incremental test such as ISWT and may, therefore, better reflect the patient's normal capability (106). ISWT is more standardised than the six-minute walking test, but in this test patients walk up and down a 10-m course with many turns. This was not considered safe enough for the patients as they all used their walking frame during the test situation.
The six-minute walk test is a simple field test with standardised instructions and good reproducibility (106). In Study I no encouragement was used and all tests were supervised by the same test leader (88). At the time the study was performed, the recommendation was two learning tests (87) but, considering the patient's status we decided to perform only one learning test. However, the seven patients in Study I increased their mean walking distance by 66 metres, an increase which cannot only be

due to learning (87), but may also be explained by a decreased fear to move, to dare to be more active during dyspnoea after having participated in the training programme, i.e. a better coping strategy with the symptoms during exertion.

The Endurance Shuttle Walking Test (ESWT) was used in Study II and III as this is a more sensitive test to detect changes in physical capacity than the ISWT (89, 90). ESWT is a standardised walking test which has developed from ISWT. In Study II ESWT was used to detect a possible additional effect of creatine supplementation in physical capacity linked to physical training. Within-group changes in physical capacity, measured with ESWT, increased significantly in the creatine group, but not in the placebo group. This result was unexpected, as many studies have shown the positive effects of physical training and as all patients were exposed to training (23, 28). This may be due to a lack of power, as the number of participating patients and the in-between-groups comparison was relatively low. However, two other recently published studies have arrived at the same conclusion (80, 84) as we did and Deacon et al (84) in particular showed, the same result as our Study II with a large number of patients.

In Study II and III there was "no learning test" as the ISWT, which is always performed before the ESWT, has been shown to be sufficient (107).

5.2.2 Symptom limited exercise test on a bicycle

In Study IV we used a bicycle test to measure physical capacity after oral intake of glucose in patients with exercised induced hypoxia. As patients with COPD are often limited in their daily life, an endurance test was chosen to investigate if intake of glucose positively influences endurance exercise capacity. We estimated that 60 percent of maximal capacity would be a suitable level for an endurance test for this group of patients. To calculate the 60 percent level of peak exercise capacity, the patients performed a symptom-limited incremental exercise test on a bicycle (108). Considering COPD patients' low level of capacity, patients started on 10 W with an increase of 10 W every minute. The mean load in the bicycle test in Study IV was 59 ±21 W. If the endurance exercise test had started at 30 W, which is the traditional way of an incremental bicycle test, some patients would only have been capable of exercising for a few seconds and, with this in mind, the starting load was set at an adequate level.

During the endurance test oxygen uptake and ventilation were measured online and all patients were wearing a face mask. Wearing a face mask may be uncomfortable and

could, therefore, impact the results. There was also the small risk that patients could become used to the mask and would therefore be more comfortable with the mask in the second test. However, when data were analysed there was no difference between the first and second endurance tests.

5.2.3 Muscle strength and fatigue

Grip strength was measured in Study II as it has been shown to correlate with whole body strength (94, 95). Study II was performed in two places: Stockholm and Linköping. Unfortunately, the only available instruments for measuring grip strength were the Jamar Dynamometer in Stockholm and the Grippit in Linköping. Instruction for the tests followed the recommendations of Mathiowetz et al (96) and as these two instruments have been shown to be valid and reliable (96), we do not think that this has influenced the results.

In Study II maximal voluntary strength and fatigue were measured with an isokinetic dynamometer, Kin-Com, and with a protocol used in other studies with patients in the same age group, but with coronary heart disease (92, 93). Although this test is rather time-consuming and tiresome for patients, our patients could comfortably manage the number of repetitions and follow the instructions. However, no significant difference was found between the placebo or creatine group.

5.3 HEALTH RELATED QUALITY OF LIFE

We used the Chronic Respiratory Disease Questionnaire (CRDQ) in Study I, as CRDQ seems to be more responsive to rehabilitation than other health related quality of life questionnaires (HRQL) among patients with COPD. Individuals with COPD have been shown to suffer from depression to a higher degree than healthy individuals (109), and being dependent on LTOT may have a negative impact on depression and anxiety. We therefore completed HRQL assessments in Study I with the Hospital Anxiety and Depression Scale (HAD) (100) to establish if our patients with very severe COPD were suffering from depression and if this may influence the results. However, no increase in depression or anxiety, whether within the respective groups or between the groups, was found. We then concluded that the anxiety and depression grade of patients in Study I may not have influenced the HRQL results. In Study II we used St George's Respiratory Questionnaire (SGRQ), also a disease specific HRQL questionnaire available in Swedish which has been tested for validity (98). There were no significant differences between the creatine or the placebo group after the exercise programme.

Within the placebo group, in the dimension of symptom, there was a significant difference ($p<0.05$) as two patients had 40 units in difference from baseline compared to a mean of 7 units change for the rest of the group. We speculate that these two patients had exarcerbations shortly before the programme started and recovered during the training programme.

5.4 PULSE OXIMETRY

Transcutaneous oxygen saturation has inherent limitations, but valid trends can be followed and even a small improvement in oxygen saturation may be of clinical relevance in exercise capacity in patients with moderate to severe COPD (91).

5.5 RESULTS

Participation in a pulmonary rehabilitation programme based on physical training and supervision by a physiotherapist is beneficial, even for patients with severe COPD and LTOT, This is evident from an increase in physical capacity, HRQL and ADL. These results are encouraging not only for this group of severely ill patients, but also for other patients with COPD. The fact that patients increased their walking distance, estimated a higher grade of dyspnoea and higher heart rate at the end of the programme may be due to the fact that they were more used to physical activity and less fearful of increased exertion, as shown by a higher grade of dyspnoea and heart rate. The group that participated in the physiotherapy programme showed a mean increase of 66 metres in walking distance. To a healthy individual this may not seem like an impressive improvement, but for these patients it is indeed clinically significant (110). The increase in ADL ability is, from the patient's perspective, very important as small differences in daily activities for these severely ill patients are of great value.

Even if there were many dropouts in our study we still think that our results may have been the same with a larger number of patients as other studies have confirmed our results (111).

Even if the large number of dropouts in Study I is considered, the results are still encouraging as other studies have confirmed our results (111).

When the patients recruited for Study II started, no other study on this subject had been published to our knowledge, but while Study II was in progress Fuld et al (80) concluded that exercise training and creatine supplementation resulted in an increase in fat-free-mass, upper and lower limb muscle strength and endurance, but not in whole body exercise capacity. This was confirmed by the results of Study II, showing no

significant improvement in walking time (measured by ESWT), grip strength, maximal knee muscle strength or fatigue and HRQL in relation to exercise training and placebo. As patients with moderate to severe COPD are limited in their daily activities, one of the aims of pulmonary rehabilitation in conjunction with exercise training is to increase endurance capacity. The exercise training in our programme was designed to reach that goal and the ESWT was therefore chosen as the most appropriate and sensitive test to study endurance capacity in Study II. However, no significant difference in walking endurance was found when comparing the creatine and the placebo group. The reason for this lack of improvement may be that creatine supplementation has been shown to influence maximal muscle strength and not endurance exercise capacity after exercise training in healthy individuals. This proves how important it is to choose the proper method for the evaluation of trainings effects.

Knee maximal voluntary muscle strength and fatigue were only assessed at one of the two study sites for Study II as the Kin-Com equipment was only available in Stockholm. The sample size was therefore reduced to only a few patients. This could explain the lack of effect on muscular strength and fatigue in Study II. On the other hand Deacon et al, working with a much larger sample size, showed that creatine supplementation does not enhance the effect of training; neither in respect of exercise capacity - measured with the ISWT - nor muscular strength (84).

The exercise training programme followed the present guidelines and seems to have the same level of intensity and duration as programmes in other studies with creatine supplementation (80, 84).

The St. George's respiratory questionnaire, a disease-specific instrument, was chosen to measure any difference in HRQL in Study II (98). Within-group comparison in the creatine group showed a significant increase in exercise endurance in the ESWT, but this was not reflected in the SGRQ, although all dimensions showed a positive change in direction. On analysis of the data it was found that the placebo group showed a substantial decrease in the symptom dimension, with two patients displaying a change of 40 units on completion of the programme. This may be due to exacerbations unknown to the study leaders prior to the programme and recovery on completion of the programme. It could also be that these two patients did not really understand the questions the first time around. The SGRQ is a self-completed questionnaire and if patients answer all questions without asking for help, there is no support from the leaders.

As patients with COPD often desaturate during physical activity, PLB as a strategy for breathing may decrease oxygen desaturation and therefore positively influence physical ability. The most important finding of Study III was that most patients could walk for a longer time during the endurance shuttle walking test, experiencing a reduced decrease in oxygen saturation with spontaneous PLB when compared with using open-mouth breathing as a result of a mouthpiece.

The focus in Study III was the effect of PLB on walking endurance and not on maximal capacity. The ESWT was therefore chosen to assess walking endurance. All patients performed an ISWT before they were registered at the department of Pulmonary Rehabilitation and we also used this test to recruit patients for our study. Since an ISWT needs to be done before an ESWT we considered the ISWT as a learning test (107). As all our patients used PLB spontaneously, it was impossible to prevent them from applying the technique. A mouthpiece was therefore included which, although not a natural way of breathing, is as close as possible to a natural breathing pattern.

The patients walked longer when using PLB and experienced a reduced decrease in oxygen saturation, but felt no relief in respect of graded dyspnoea. This may be due to the fact that they walked a longer distance and reached a higher grade of exhaustion using PLB or that the mouthpiece or nose clip influenced the estimated dyspnoea. However, to our knowledge no other study has showed significant decreased dyspnoea in patients with COPD using PLB during exercise. Dyspnoea is a very individual experience and perhaps there is a need for more sensitive measurements than those available at present.

Oxygen saturation decreased during the ESWT, both with and without PLB, but the decrease at the end of the tests was lower with PLB. Even a slight improvement in oxygen saturation may be of clinical relevance in this group of patients with COPD. During the later stage of the walking tests the recorded oxygen saturation was well below 90%, which indicates that the patients were operating on the steep part of the dissociation curve for oxygen.

Patients in Study III increased their walking time with 37 seconds (approximately 44 meters). This increase may have a significant clinical benefit for the group of patients that suffers from severe exercise limitations. However, to our knowledge there is no study that shows how many seconds/metres the ESWT needs to be improved to become clinically significant. Reidelmeier et al (110) found that the smallest clinically significant increase in the six-minute walking test was 54 m and Singh et al (112)

recently identified two important minimum clinical levels in ISWT: 47.5 m and 78.7, if patients were able to distinguish an additional benefit.

Glucose and insulin infusion in patients with COPD and hypoxia has been found to increase the oxygen tension at rest (113). It has been suggested that intravenous infusion of glucose and insulin under euglycemic conditions increases carbon dioxide production and therefore alveolar ventilation and arterial oxygen tension in hypoxic COPD patients (114). Patients with COPD often decrease their oxygen saturation and if oral glucose intake - not infusion - can increase the PaO_2 in these patients, this may lead to increased physical capacity. This may therefore be viable for use during physical training and result in COPD patients enjoying more benefits from physical training. This hypothesis was investigated in Study IV. During the oral glucose tolerance test in Study IV mean PaO_2 increased significantly by 0.5 kPa with parallel increased lactate concentrations in patients with COPD and moderate hypoxia. Another finding was that intake of glucose 60 minutes before a symptom-limited endurance bicycle test did not improve endurance time or oxygen saturation when compared to drinking ordinary water.

Patients in Study IV had light hypoxia at rest, but became hypoxic during exercise. Apparently increased oxygen tension and glucose supply before exercise was not enough to overcome the undesired effects of CO_2 production. Early lactic acidosis has been reported in patients with mild to severe COPD during sub-maximal exercise when compared to healthy individuals (115, 116). The increased lactate leads to a higher level of pH in the muscles, and this may contribute to earlier muscle fatigue and exercise limitation in patients with COPD. This early release of lactate may be due to decreased oxidative metabolism in the muscles (17).

The reason for the unexpected increase in lactate levels at rest during the oral glucose intolerance test could be that some glucose will still descend down the glycolytic pathway even though most of the glucose absorbed by the muscle is converted to glycogen and the muscle does not really require ATP. However, activity in the mitochondria of the muscle is low when at rest and the overload of glucose will probably accumulate and produce some lactate that will be released into the blood. As patients already had a higher lactate level after the intake of glucose as opposed to only water when they started their exercise, this may have contributed to the absence of increased exercise endurance.

Before the start of the exercise test with glucose there was a significant increase in mean minute ventilation and carbon dioxide elimination compared to water intake,

which may have been as a result of the glucose combustion, but on completion of the tests these differences were less obvious. However, when the patients started to exercise after their glucose intake they experienced a higher degree of breathing related to minute ventilation. This, in combination with the other results, may also explain the unchanged endurance time after oral glucose intake compared to no glucose.
All patients in Study IV estimated their level of dyspnoea, exertion and leg fatigue at the end of all exercise tests with or without glucose and reported a significant increase in dyspnoea with glucose. The calculated ventilatory reserve after an intake of oral glucose was significantly lower at the start of the endurance test compared to when the patients had only water. This may also explain the higher grade of dyspnoea at the end of the exercise test with glucose.
Oxygen uptake changed at the end of the exercise test with glucose, but did not reach the previously set significant level or improve the exercise capacity in time or in oxygen saturation. It could be that the patients needed more oxygen for the same level of work when they had also taken glucose orally.
The already higher level of lactate in comparison with healthy individuals before the start of the exercise endurance test may also have contributed to the default in respect increased exercise capacity, as we had expected.
Based on these findings, we cannot yet recommend a high intake of fast-acting carbohydrates for patients with COPD.

5.6 FUTURE STUDIES

It would be of great interest to follow a larger group of patients with COPD and LTOT for a longer period and to study the persistence of the effects after a supervised exercise programme. It would also be of great interest to establish if the exercise training has any long-term effects on quality of life, morbidity and mortality.
Why some of the patients naturally chose the Pursed Lips Breathing strategy is another question for future research; so too the underlying reasons why some patients experience less and others more dyspnoea when using the technique. Another interesting matter that could be pursued would be to establish which kind of supplementation could have addictive effects when patients with COPD exercise and which type of patient that would benefit most from the supplementation in question.

6 CONCLUSIONS

Supervised training during eight weeks increases walking distance improves health related quality of life and improves activities of daily living in severely ill patients with COPD and those recently instituted for long-term oxygen therapy.

Oral creatine supplementation in combination with physical training shows no significant improvement in physical performance measured as endurance shuttle waking test in patients with COPD when compared to physical training alone.

Spontaneous pursed lips breathing can be a useful technique to increase walking endurance and reduce oxygen desaturation during walking in patients with moderate to severe COPD.

Oral intake of glucose may increase the arterial oxygen tension in COPD patients, even with slight to moderate hypoxia at rest. When a glucose solution is taken before a bicycle exercise test there appears to be no increase in endurance capacity or improved oxygen saturation. On the contrary, glucose intake may be associated with reduced ventilatory spare and higher ratings of dyspnoea during exercise.

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