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Physical Exercise in Cystic Fibrosis

- studies on muscle strength, oxygen uptake and lung function in young adult patients

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“Fitness is nothing you just have”

To my beloved family

To my past brother and parents

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Abstract

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Muscular strength, lung function and exercise capacity are internationally reported to be markedly impaired in adult patients with cystic fibrosis (CF). Since 20 years physical exercise is one important part in the treatment of patients with CF in Sweden. Handgrip strength is reported to relate to nutrition and activity of daily living. Decreased handgrip strength has been found in patients with lung disease and a correlation to mortality has been claimed.

The aims of this thesis were to evaluate the effects of different type of training in young adult patients with classic CF on muscular strength, lung function and exercise capacity and to compare baseline data with matched healthy controls. One additional aim was to evaluate the effect of general resistance training (RT) of the upper extremities on handgrip strength in healthy subjects.

The effect on handgrip strength of 8 weeks of RT of the upper extremities was evaluated in healthy young adults. Muscular strength was assessed using 15 different tests representing hand-, arm/shoulder-, leg-, back- and abdominal muscles in patients with CF. Lung function was evaluated with spirometry, and exercise capacity was evaluated using an electromagnetic cycle ergometer. Serum levels of cytokines were investigated with ELISA technique and vitamin E with HPLC. The outcome of three months (m) of endurance training (ET) or RT followed by three m of mixed training performed three times weekly during 30-45 minutes was evaluated.

Healthy female (F) subjects significantly increased handgrip strength after 8 weeks of a general RT program for the upper extremities. A sample of 33 patients with classic CF showed muscular strength comparable to that of healthy age and sex matched control subjects (CS), but F patients were weaker in handgrip strength than CS and did not improve after 6 m of training. At baseline one of the leg tests in each sex and sit-ups during 30 s in male patients also showed lower values than controls. Handgrip strength correlated to $FEV_{1.0}$ in % of predicted values. In 19 patients muscular strength did not increase after 6 m, regardless of the kind of training. Three patients fulfilled the study on a lower and one on a higher frequency level and the result did not differ from the others. Maximal oxygen uptake (VO_{2max}) and work load (Watt/kg) showed significant increase by ET compared to RT after 6 m. The $FEV_{1.0}$ % predicted showed increase in M patients, who mainly performed ET. The results suggested that a 6 m program, 3 times/week of mainly ET may keep or even increase lung function but not muscular strength in young adult patients with CF.

Conclusions: General RT of the upper extremities increased handgrip strength in healthy F subjects but not in CF. Young adult patients with CF, who have regular physical exercise as part of the treatment, showed mainly muscular strength comparable to that of healthy control subjects, a well preserved lung function and good oxygen uptake. Six m of either mainly ET or RT did not increase muscular strength, exercise capacity and oxygen uptake. Lung function, after 6 m with mainly ET, showed improvement compared to RT.

Key words: Lung function, muscle strength, exercise capacity, endurance, resistance training.

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Fysisk Träning vid Cystisk Fibros

-studier av muskelstyrka, syreupptag och lungfunktion hos unga vuxna patienter

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Sammanfattning

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Patienter med sjukdomen cystisk fibros (CF) beskrivs i artiklar som muskelsvaga, med dålig lungfunktion och arbetskapacitet. I Sverige har fysisk träning utgjort en viktig del i behandlingen redan från diagnos alltsedan början av 1980-talet. Handstyrka har rapporterats ha samband med näringsstatus och till aktiviteter i vardagen Nedsatt handstyrka har visats hos patienter med lungsjukdom.

Syftet med avhandlingen var att med olika typer av träning under 6 månader undersöka effekt på muskelstyrka, lungfunktion och arbetskapacitet hos unga vuxna patienter med CF samt att jämföra basvärden med friska jämnåriga kontroller. Ytterligare ett syfte var att undersöka om ett generellt styrketräningsprogram för skuldermuskulaturen kunde påverka handstyrka hos friska unga vuxna kvinnor.

Med 15 olika test mättes muskelstyrka i händer, arm/skuldror, ben, magmuskler samt uthållighet i benmuskler. Lungfunktion bestämdes med spirometri och maximal arbets-förmåga och syreupptag på testcykel. Patienter med klassisk CF, 16 - 35 år gamla, tränade antingen kondition eller styrka, 3 gånger/vecka under 30-45 minuter med en intensitet på nivå 70-75 % av den hjärtfrekvens, som hade uppmätts vid arbetsprov. De som tränade styrka gjorde varje övning 12- 15 gånger med 1-3 upprepningar. Efter 3 månader testades deltagarna på nytt och fortsatte därefter träna under ytterligare 3månader och nu med ett blandat träningsprogram. Pulsmätare användes och dagbok fördes över träningen.

Åtta veckors styrketräning gav en ökning av handstyrka hos de friska kvinnorna, men ingen ökning noterades efter 6 mån träning hos kvinnor med CF. Patienterna visade i stort sett jämförbar muskelstyrka och uthållighet som matchade friska kontroller men 6 månaders träning gav ingen ökning av styrka. Lungfunktionen var lägre hos patienterna men ändå runt 90% av förväntat värde vilket är unikt i den åldersgruppen av patienter med CF. Även arbetskapaciteten var god och inte signifikant skild från kontrollerna. Efter 6 månader hade de som tränade huvudsakligen kondition ökat mer i maximalt syreupptag och arbetsbelastning än de som huvudsakligen tränade styrka.

Sammanfattningsvis visade studien att unga vuxna patienter med CF som varit regelbundet aktiva hade en ovanligt väl bevarad lungfunktion, muskelstyrka och arbetskapacitet. En tendens till fördel för konditionsträning kunde noteras, men avsaknaden av signifikanta förbättringar kunde antingen bero på att patienterna redan hade bra funktioner eller att det finns en tröskel hos patienter med CF som försvårar träningseffekterna.

List of papers

This thesis is based on the following publications and manuscript, which in the text are referred to by their Roman numerals.

Study I.

Magnusson Thomas E, **Sahlberg M**, Svantesson U. The effect of resistance training on handgrip strength in young adults. *Isokin Exerc Sci.* 2008; 16:1-7

Study II.

Sahlberg M, Svantesson U, Magnusson Thomas E, Strandvik B. Muscular Strength and Function in Patients with Cystic Fibrosis. *Chest* 2005; 127:1587-1592

Study III.

Sahlberg M, Svantesson U, Magnusson Thomas E, Andersson B.A, Saltin B, Strandvik B. Muscular strength after different types of training in physically active patients with cystic fibrosis. *Scand J Med Sci Sports.* 2008, Doi:10.1111/j.1600-0838.2007.00691.x

Study IV.

Sahlberg M, Eriksson B.O, Sixt R, Strandvik B. Cardiopulmonary Data in Response to 6 Months of Training in Physically Active Adult Patients with Classic Cystic Fibrosis. *Respiration. Accepted for publication.*

List of Contents

Abbreviations

ACSM	American College of Sports Medicine
ACT	airway clearance technique
ATP	adenosine triphosphate
BMD	bone mineral density
BMI	body mass index
C, CS, CSs	control/control subjects
CF	cystic fibrosis
CFTR	cystic fibrosis transmembrane conductance regulator
CO_2	carbon dioxide
ET	endurance training
FET	forced expiratory technique
FEV_1 %	forced expiratory volume in one second in percentage of predicted val
kPa	kilo Pascal
MVC	maximal voluntary contraction
N	Newton
Nm	Newton meter
P_{AO2}-P_{aO2}	alveolar-arterial oxygen tension gradient
PCr	phosphate creatine
PI	pancreatic insufficiency, pancreas-insufficient
PS	pancreatic sufficiency, pancreas-sufficient
RER	respiratory exchange ratio (V_{CO2}/V_{O2})
RR	respiratory rate
RT	resistance training
RV	residual volume
SMVC	sustained maximal voluntary contraction
$tcPCO_2$	transcutaneous carbon dioxide tension
$tcPO_2$	transcutaneous oxygen tension
TLC	total lung capacity
VC	vital capacity
V_D	physiological dead space
V_E	minute ventilation
V_E/VO_2	ventilatory equivalent for oxygen
VO_{2max}	maximal oxygen uptake
V_T	tidal volume
W	Watts, work load

Background

Cystic fibrosis (CF)

Cystic fibrosis is the most common fetal autosomal recessive inherited disease among Caucasians. Guido Fanconi first described the disease in 1936, with symptoms from both the pancreas and the lungs [1]. Dorothy Andersen [2] described the disease in infants, as *"cystic fibrosis of the pancreas"* and Paul Di Sant´Agnese reported loss of salt from the sweat glands in children [3]. In 1985 the gene was localized to chromosome 7 and 1989, the protein was identified as the cystic fibrosis transmembrane conductance regulator (CFTR) [4-6]. Today, May 2008, there are 1558 mutations (http://www.genet.sickkids.om.ca/cftr) of which ΔF508, either homozygous or heterozygous, is the most common mutation. In Sweden approximately 66% of the patients have this mutation [7]. The expression of CFTR is regulated in the epithelial cells of the salivary and sweat glands, lungs, pancreas, kidneys, intestines, gallbladder and uterus, and is causing a defect in the ion transport and an increased mucus secretion in those organs [1].

- **Diagnostic criteria**

The diagnosis of CF is present when one criterion from each of the following two groups is present [8]

1.
   - a sweat chloride concentration of >60 mmol/L, which is to be find at two occasions by a pilocarpin stimulated sweat test
   - two genetic mutations causing CF
   - a disturbed chloride transport measured as an epithelial potential difference

2.
   - a sibling with CF
   - a positive newborn screening (not available in Sweden)
   - characteristic clinical symptoms, such as weight loss, steatorrhoea, pulmonary exacerbations and coughing

- **Symptoms**

- From the pancreas

For the outcome of the CF disease a good nutritional status is one of the most important factors [1]. The function of the pancreas is production and release of enzymes for digestion, especially lipolysis. Absorption of other nutrients is also disturbed in CF. Pancreatic insufficiency (PI), found in approximately 85% of the patients at diagnosis, affects the basal metabolism and is associated with increased resting energy expenditure (REE) [9]. Studies have shown increased oxygen consumption associated to calcium transportation [10], and usually 120 – 150 % higher energy intake than in healthy subjects is recommended. Several factors are associated with this increased demand, e.g. patients having esophageal reflux, diabetes, liver involvement or frequent coughing due to respiratory problems [1]. Increase in REE is associated with deterioration of the lungs expressed as less than 75% of forced expiratory volume in one second in percentage of predicted values ($FEV_{1.0}$ % predicted) [1].

Supplementation with adequate enzymes, usually expressed as the lipase activity, 1800 – 2500 units /g fat, is prescribed for fat absorption and compliance to the prescription is monitored by a dietitian at routine follow-ups. Many patients with moderate impairment do not have increased energy intake and still have normal growth and activity [11] and some adapt to an increased REE by decreasing the physical activity level, which make them able to keep total daily energy expenditure at levels comparable to controls.

One measurement for compliance with nutritional prescription is to calculate the body mass index (BMI), the weight in kilograms divided by the square of the height in meters (kg/m^2), which in adults is normal within 18.5-24.99, age-independent, and the same for both sexes according to the World Health Organization (WHO). Patients with CF are usually reported to have low BMI. Malnutrition in patients with CF is frequently reported together with a decreased bone mineral density (BMD), lean body mass and fat mass [12,13]. During the

growth spurt in the late second decade nutritional factors, e.g. the presence of calcium, are important for the skeleton. Weight bearing activities during childhood have been reported to increase BMD in healthy prepubertal boys and girls [14]. Different kinds of exercises are included in the treatment program to our patients with CF e.g. the use of a trampoline [15, 16]. Gronowitz et al. showed good nutritional status and normal BMD in young adult men with CF at our centre, comparable with healthy controls [17]. The studies by Gronowitz et al. also showed normal lean body mass but decreased fat mass in the patients. In children and young adults with late puberty also an association between fatty acids and BMD was found [17, 18].

Crucial in the metabolism of the cells is the presence of fatty acids. Essential fatty acids deficiency is common in CF and related to the genotype [19]. It needs to be supplemented for. By physical exercise there is an oxidative stress in the body which constitutes free radical reactive oxygen species (ROS) [20]. The body has its own endogenous defense, which is reinforced by exogenous antioxidants such as vitamin C and E [21]. Vitamin E is one of the most important antioxidants. A deficiency of vitamins impairs physical performance capacity [20, 21]. Studies have suggested that vitamin C reinforces the effect of vitamin E and that regular physical activity upregulates the endogenous defense [20]. The absorption of vitamins in CF varies. Water-soluble vitamins, like vitamin C, are absorbed as in healthy subjects but fat-soluble vitamins, like vitamin E, are not adequately absorbed [1]. In CF supplementation is recommended for vitamin A, D, E and K, according to consensus reports [22].

- From the lungs

In the lungs the abnormal secretion leads to hyperabsorption of salt and water from the airway surfaces, which impairs the mucociliary clearance and promotes bacterial infection leading to airway obstruction. Chronic colonization of the airways, with bacterial pathogens particularly *Staphylococcus aureus, Pseudomonas aeruginosa, Stenotrophomonas maltophilia* and

Burcholderia cepacia contributing to tenious secretions, is common in patients with CF [1]. The presence of these pathogens causes a great demand on the patients since they can only be reduced and/or eradicated by heavy antibiotic treatment, usually as an intravenous course with intensified physiotherapy, preferentially performed at home [23]. The chronic bacterial colonization leads to increased levels of inflammatory cytokines, like TNF-α, IL-1β, IL-6 and Il-8 and lower levels of IL-10 in CF [1]. Intensive training can release cytokines and IL-6 has been reported to increase by training [24]. This was also found in patients with CF after moderate exercise by Ionescu et al. [25].

Studies in infants with CF have shown that the lung disease starts early in life with infection and inflammation of peripheral airways and with disturbed ventilation [26, 27]. The volume of trapped gas is increased in children with CF [28]. Without efficient airway clearance of mucus there is an increased risk for progressive damage by the infections behind remaining plugs, causing destruction of lung tissue. Respiratory failure accounts for more than 90% of the mortality in patients with CF [1] and the only option to increase survival is lung transplantation.

- ***From other organs***

Liver disease is present in approximately 25% of the patients and 2-5 % has liver cirrhosis. There is an increased risk of diabetes with increasing age. Sinusitis is frequently present. There is a high percentage of infertility in men (98%) caused by the absence of vas deference and tenious vaginal secretion in women results in difficulties to become pregnant. In vitro fertilizing might be necessary [1].

CF in Sweden

The incidence of CF in Sweden is 1/5000-6000 newborn [29,30]. Ninety percentages of the patients are diagnosed before 2 years of age. The prevalence in Sweden 2007 was

approximately 600 individuals with CF, of whom 60% were >18 years old. The median survival rate in Sweden is today >50 years [26]. Thirty years ago the patients were not expected to reach adulthood. There is still no cure for the disease, but the treatment strategies worldwide have undergone an enormous change during the last four decades including centralized care, pharmacological therapies, and aggressive intravenous antimicrobial therapy of pulmonary infections, more efficient mucociliary clearance and more efficient enzymes for substitution of PI [31].

At the CF centre in Gothenburg the patients are seen monthly for routine assessment and/or treatments. At the annual check-up, lasting from one to three days, the patients meet all team members for evaluation of ongoing treatments. Blood samples are taken for analysis of hematology, liver and renal function and the levels of vitamins, essential fatty acids and the presence of bacterial colonization. Lung function tests, chest radiography and exercise capacity test on a cycle ergometer are performed. Every third year thin-section computed tomography (CT) of the lungs, for a more detailed investigation of the progression of the disease, is included. Dual X-ray absorptiometry is performed every third year or at clinical indication and oral glucose tolerance test is performed every second year after 8 years of age. Liver ultrasonography or even liver biopsy is performed when indicated, as well as other investigations at symptoms.

- **The physiotherapist in the care of CF**

The physiotherapist teaches airway clearance techniques (ACT) as soon as the diagnosis is confirmed. Prescribed treatment is continuously evaluated. A mainstay for the patient with CF and a challenge for the physiotherapist are to clear the airways from the mucus. This part is for the adult patient and for the child with his/her parent also the most time consuming part of the treatment, since it has to be performed 30-45 minutes twice daily.

Throughout the years different techniques for mucus evacuation have been described [32-37]. The International Physiotherapy Group for Cystic Fibrosis (IPG/CF) presents an overview of today available and used techniques in ”Physiotherapy in the Treatment of Cystic Fibrosis (CF)” [38]. The technique with postural drainage (PD), in combination with percussion, breathing exercises and huffing has been the “gold standard” [36]. It consists of chest wall clapping in 6 to 12 different positions, interspersed with breathing exercises and evacuation of mucus with a “huff”. A “huff” is a forced expiratory maneuver, and reduces airway compression compared with coughing [32]. In the literature it is also named forced expiratory technique (FET). The PD technique is thought to make it easier for the mucus to evacuate from the lungs, by gravity assistance and by shaking the patient. Today the hypothesis is that mucus is moved by airflow. Studies aiming to evaluate and compare different ACT [16, 32-37, 39-41] have not found evidence that the above-mentioned technique is more efficient than others described by the IPG/CF. Furthermore that technique makes the patient dependent and inactive.

In the early 1980´ s, PD, percussion and FET was compared with physical exercise and FET in studies of children with CF in Sweden [16, 41]. No difference in lung function outcome was seen between the two techniques. Physical exercise increases ventilation and thereby sputum clearance. Another explanation for the benefits of physical exercise is the production of catecholamine, that although increasing mucus production, also increase the speed of the cilia beats and together with increased airflow enhances evacuation of the mucus [42]. Furthermore the children and their parents preferred the treatment model with physical exercise and FET [16, 41]. These studies resulted in exclusion of PD with percussion, breathing exercises and FET in the treatment package for children and have not later been recommended.

From the time a child gets the diagnosis of CF, inhalation therapy and physical exercise are prescribed, on a daily individual and regular basis. The aim of the exercise is to influence breathing pattern and increase minute ventilation. The ACT, which is taught to the parents, includes one passive maneuver: thoracic compression to facilitate mucus evacuation. The exercise program includes exercises for joint mobility, especially the thoracic part, balance, coordination, muscular strength and endurance. Weight-bearing exercises are always included [14]. The patients are encouraged to intersperse with huffs for mucus evacuation. For infants, children and adults the treatment is similar, although always individually tailored. This technique is often referred to as the "Swedish technique" [38]. Current international practice in the treatment of infants and young children with CF is described by Lannefors et al. [43].

With increasing age the airway clearance techniques are changed to suit each individual. During adolescence other ACTs are focused on independence and participation in the physical education at school is mandatory. To find a sport outside school which can be continued up in adulthood is encouraged and important. The described treatment policy is used also when a patient is diagnosed later in life, comprising ACT and exercises appropriate to medical status.

Physical fitness

Physical activity and exercises contribute to, what is called "fitness", and are considered beneficial from a wide range of aspects, physiological as well as from a psychosocial viewpoint in healthy people, as well as in people with different diseases. Instead of, or in combination with medication, exercise as therapy is now prescribed to patients with various diagnoses as diabetes, high blood pressure, heart failure and overweight [44] . Regular weight bearing activities, especially before puberty, are beneficial to increase peak bone mass [14]. This is crucial as one part to prevent the risk of osteoporosis.

Muscles

Our 600 muscles are working in a constant acting /relaxing mode. The muscles contain contractile and metabolic properties. Muscle cells or muscle fibers, containing thousands of myofibrilles, build a skeletal muscle. The basic functional unit of the myofibril is the sarcomere with the protein filaments of actin and myosin. Their sliding mechanism creates force resulting in a muscle contraction. The muscle fibers are grouped together, 10-20, in fascicules that are separated by the perimysium. A motor unit consists of a motor neuron, its axon with branches and the muscle fibers connected to these branches. The initiation of a muscle action comes via an impulse from the α-motor neuron, transmitted by the axon to the muscle fiber at the motor endplate, the neuromuscular synapse, creating an action potential. This causes the sarcoplasmatic reticulum to release calcium ions (Ca^{2+}). The Ca^{2+} binds to the protein troponin on the actin filaments initiating the myosin heads to attach to the actin filaments, building cross-bridges by the energy from adenosine triphosphate (ATP) resulting in muscle shortening [20].

- ***Muscle fibers***

Burke et al. identified and classified three different fiber types found in mammalian skeletal muscles; type I fibers, which are slow twitch fibers and type IIA and IIX, which are fast twitch fibers [46]. An individual´s fiber type composition has an influence on the muscles´ functional characteristics. Type I fibers are suitable for sustained oxidative work (= endurance activities). The fast IIA and IIX twitch fibers are more suitable for explosive work (= strength and explosive activities) [47]. The fiber composition is to 45% determined by genetics, and to 40% by environmental factors [48]. Among the environmental factors the single most important is *training* according to Åstrand [48].

- ***Energy***

The muscles are the body´s largest consumer of oxygen. A solid muscle action needs energy. The food we ingest is converted to energy through different chains. ATP and phosphocreatine (PCr) are the energy sources being used in the beginning of a muscle action and ATP is also needed for the transport within the muscle cells. The ATP is generated through three energy systems, the ATP/PCr system, the glycolytic system and the oxidative system. In the ATP/PCr system, the inorganic phosphate (P) is separated from PCr and together with adenosine diphosphate (ADP) it forms ATP. This system is anaerobic and its function is to maintain the ATP level. In the glycolytic system glucose or glycogen is broken down to pyruvic acid via glycolytic enzymes. Pyruvic acid is converted to lactic acid, when conducted without oxygen. The oxidative system is the final system being used in energy production. This is an aerobic process because oxygen is being used. The oxidative production of ATP occurs in the mitochondria within the muscle cell [20]. The main sources, during prolonged exercise at an intensity < 50% of $VO_{2max,}$ are from fat and at intensities > 50 % of VO_{2max} from carbohydrates [48].

- ***Performance***

Muscle actions are static (isometric), when no movement takes place; the contractile force equals the resistance force for a movement. When the contractile force exceeds the resistance a concentric muscle action is achieved. An eccentric muscle action takes place when the contractile force is less than the resistance i.e. an elongation of the muscle. Both concentric and eccentric actions are dynamic, a movement occurs [48].

- ***Measurements of strength***

Muscle strength can be measured with manual muscular technique (MMT) [49], by functional tests, hand held dynamometry and computerized equipment. In the clinical work as physiotherapist the most commonly used technique is the MMT, with an evaluation rate from

0 to 5. Among functional tests, sit-ups and push-ups, are widely spread in clinical practice as well as in sports and are recommended in the guidelines by the American College of Sports Medicine (ACSM) and by Eurofit, a European test battery. Computerized equipments are used in research laboratories.

Exercise capacity

Physical training increases oxygen uptake, increases cardiac output, reduces heart rate at rest and at a given load and increases the facility for utilization of fat as an energy resource. To reach these effects the organ has to be exposed to overload or stress which is a catabolic process [48]. It is important to regulate the balance between breakdown and replacement. The intensity of the load increases as the performance improves because of the adaptation to a given load. Training enhances oxygen supply to the active muscle cells in order to exercise more aerobically. The opposite increases lactic acid more rapidly and reduces the time able to exercise. In athletes, training results in slower and deeper breathing pattern and this lower rate indicates a training effect [48]. Measurements of physiological responses to exercise are performed using ergometers either a cycle or a treadmill [20, 48].

Physical fitness in CF

- ***Muscular strength***

Reduced muscular strength has been reported in children [50-53] and in adults [12, 54-56] with CF. The reported dysfunction has not yet been explained. One explanation that cannot be excluded is inactivity [12, 13]. The use of corticosteroids, in treating inflammatory tissue of the lungs, is an explanation that was reported by Barry et al. [54] as the main reason for muscle impairment and reduced strength in patients with CF. Both Selvadurai et al. [50] and de Meer et al. [53] proposed mitochondrial deficiency in CF. Elkin et al. assumed that the decreased muscle strength was due to reduced muscle mass from malnutrition [12].

Training studies in children have shown increased muscular strength after a training period [52, 56-58]. Until now only one longer resistance training study, for 6 months, has been performed in adults with CF, and muscular strength in half of the tested muscles, that at baseline were weaker, was reported increased after variable weight training [49].

- ***Exercise capacity***

Peak exercise capacity (VO_{2max}) and anaerobic capacity have been studied in children [52, 53, 59-64] and adults with CF [65-70]. Most of those studies have been performed in patients with moderate (<70% $FEV_{1.0}$ % predicted) to severe (<40% $FEV_{1.0}$ % predicted) impaired lung function. The results have indicated reduced aerobic and anaerobic capacity, similar to results in patients with chronic obstructive pulmonary disease (COPD) [71].

Also in female athlete girls with CF and normal lung function, significantly reduced peak anaerobic capacity and reduced leg muscle strength have been reported [50]. These patients also showed a greater fatigue index measured with magnetic resonance spectroscopy, compared with matched control subjects. The authors hypothesized that a dysfunctional muscle metabolism would explain the results.

- ***Physical training***

There has not been consistency about the benefits of physical training as added to the care package [72, 73]. Stanghelle et al. were the first to report on lung function and exercise capacity in 16-year-old boys, who participated in regular training compared with controls without training, and they stated in the early 1980´s the importance of physical training included in the treatment policy [63]. The results showed significantly higher values in lung function and exercise capacity in the boys, who had been trained. Some of the reported training studies have been carried out during hospital stay due to acute exacerbations or routine assessments [58, 74, 75]. Some of the reported studies have lasted 6 months or more [16, 41, 49, 52, 76, 77]. In a recent review on “Physical exercise in CF” by Bradley and

Moran [73], only 7 studies met the criteria for a randomized controlled trial (RCT). The authors concluded that there was "some limited evidence from both short- and long- term studies that aerobic or anaerobic physical training has positive effect on primary outcomes (exercise capacity, strength and lung function) but improvements are not consistent between studies." In addition they proposed that physical training today should be a part of the care package offered in the treatment of CF. Only one of the studies was performed in adults [76] and the lung function, expressed as $FEV_{1.0}$ (L), was 2.27 L in the participating adult patients. A slower yearly decline in pulmonary function was a positive outcome after one year of the physical training program. Encouragement to continue with physical exercise after discharge from the hospital was not stressed in the conclusions in any of the studies.

Deterioration was registered in pulmonary function after a three months run-in period preceding a 6 month training study in 9 patients. The authors reported significant increase in pulmonary function after the intervention even if the patients did not reach baseline values [49].

Modalities for training

- ***Resistance training (RT)***

The one repetition maximum (1 RM) is the mode that is used for resistance training. One RM is defined as the weight you possibly can lift once but not twice through the range of motion. From this weight you choose appropriate intensity, duration and frequency for the training, depending on the goal that is set up. An increase in muscular endurance strength, which is of importance for activity of daily living, is achieved by low weights and many repetitions. Explosive strength, which is needed in weight lifting or in a 100 m race, is reached by heavy weights and few repetitions [78], but is of less interest for improving daily life. Gain in muscular strength before puberty is caused by neuromuscular adaptation [20], which results in

a better motor control and technical skill. Also in adults, gain in muscular strength during the first weeks of training is mainly due to neuromuscular adaptation [20].

- ***Endurance training (ET)***

There are four important factors to take into consideration when designing a program for endurance training aiming to increase maximal oxygen uptake (VO_{2max}), namely the type, the intensity, the frequency and the duration of the training. The training can be performed as interval training with different modalities such as 70/20, 15/15 seconds or 4/2 minutes of work/rest, respectively [48]. Another model of aerobic training is continuous training. To increase exercise capacity, the intensity of the training should be approximately 75-85 % of the individual´s maximal heart rate, the frequency of the training should be three times per week and the duration each time at least 30 minutes, according to Åstrand [48]. Willmore & Costill proposed that optimal training frequency is 3-5 times per week with duration of 20-30 minutes and an intensity level of 60% of VO_{2max} [20]. Types of activities that engage large muscle groups are recommended e.g. walking, jogging, running, cycling and swimming but also aerobics and racket sports are included. Individual preferences and motivation are important considerations to take in to account when designing a program [20].

Aims of the study

The aims of the study were:

- To assess reference values of handgrip strength in healthy subjects 20-29 years old and to evaluate 8 weeks of general resistance training of the upper extremities on handgrip strength in healthy females (Study I).
- To assess muscular strength in young adult patients with CF (Study II) in comparison with age and sex matched healthy controls and to evaluate the effect of 6 months of different training programs on muscular strength in CF (Study III).
- To assess lung function and exercise capacity in young adult patients with CF and to evaluate the effect of 6 months of different training programs on those parameters (Study IV).
- To have a gender perspective when analyzing all the data.

Study design

Study I: a cross-sectional, randomized controlled single blinded study

Study II: a cross-sectional study

Study III: an intervention study

Study IV: a cross-sectional and intervention study

Subjects and Methods

Subjects

- ***Study I***

Forty-one (27 F) students were recruited, by advertising at the University of Gothenburg, to a study on handgrip strength. Inclusion criteria were subjectively healthy 20-29 years old subjects with no skeletal injuries of the upper extremities during the last year. Exclusion criteria were exercise and/or competition on an elite level. The F were randomized to a study evaluating handgrip strength after 8 weeks of general resistance training of the upper extremities, 15 to a training group and 12 to a control group. Randomization used was opaque envelopes and the investigator was blinded.

- ***Study II-IV***

One-hundred-and-forty patients with CF attended the CF unit in Gothenburg during 2002. Forty seven (25 F) patients, who met the inclusion criteria of age 16-35 years, were invited to participate in a 6 months training study. Exclusion criteria were lung transplantation (2), being on the lung transplant list (2), oxygen need during sleep and/or exercise (2) and pregnancy (2). Fourteen (9 F) rejected participation. Thirteen (8 F) patients accepted to perform only baseline tests. Twenty patients (8 F) accepted to participate in the training study. The inclusion process for the patients is shown in Figure 1.

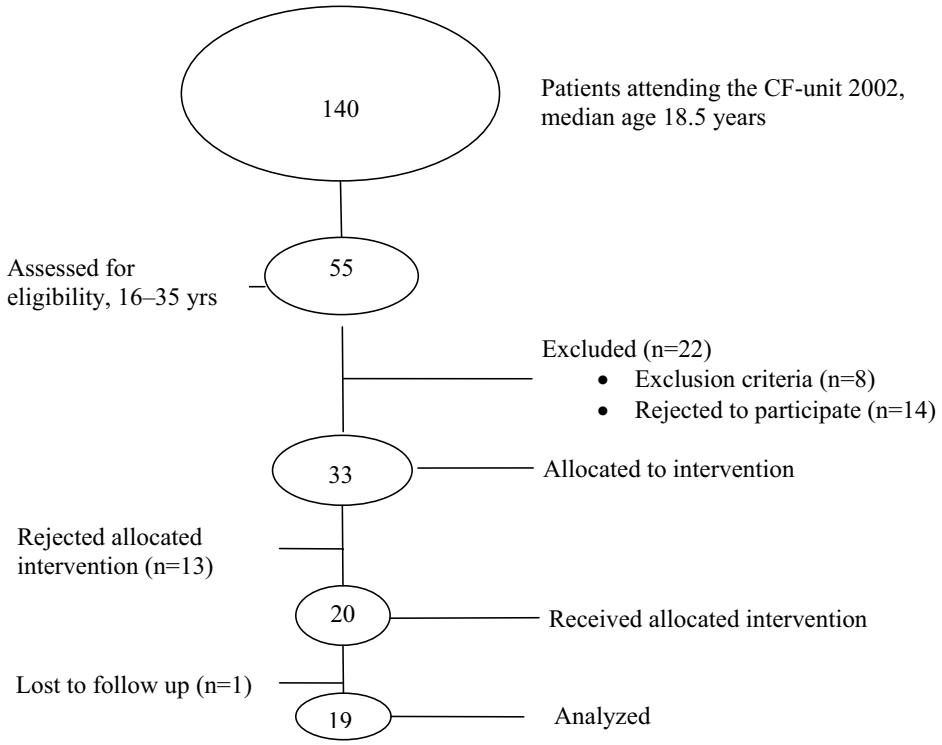


Figure 1. The inclusion process for the patients with CF attending the West Swedish CF centre in Gothenburg (study II-IV).

Fifteen of the 33 patients were homozygous and 12 were compound heterozygous for the mutation ΔF508. In the latter group a severe second mutation was identified in 7 patients. In total 24 (11 F) patients had severe mutations and were PI. Twenty-two patients were chronically colonized with *Pseudomonas aeruginosa*. Six patients had CF related diabetes mellitus. Six patients had mild liver involvement and one patient had liver cirrhosis. These 7 patients were treated with ursodeoxycholic acid since some years. One patient was periodically prescribed oral corticosteroids. Lean body mass and fat mass was measured in 28 patients and were reported normal. Two women with CF had each given birth to two children. All patients were non-smokers. The patients reported regular physical training 2-3

times/week, representing an activity score of median 6 on an activity scale ranged between one and 8; one representing no activity and 8 training and competition on an elite level [79]. Control subjects were recruited among friends to the patients and from the staff at the hospital and their relatives. Twenty healthy age and sex matched control subjects were enrolled. The inclusion criteria were selected to match the indexed patient by age (within one year), sex, height (within 5 cm), weight (within 5 kg), number of children and the physical activity level. Exclusion criterion was eczema, as it could interfere with the transcutaneous measurements of oxygen saturation during the maximal cycle ergometer test. None of the control subjects reported eczema. All controls were non-smokers.

A flow chart is showing all participants in the studies I-IV (Figure 2)

Anthropometric data of the participants in the four studies is given in Table 1.

Table 1. Demographic data in 41 healthy participants (HP) (Study I), 20 healthy control subjects (CS) (Study II-IV) and 33 patients with CF (Study II-IV), split by gender.

	Females			Males		
Variables	HP (n=27)	CS (n=8)	CF (n=16)	HP (n=14)	CS (n=12)	CF (n=17)
Age (yrs)	24.6 (2.6)	26.9 (6.6)	23.6 (6.2)	25.9 (3.0)	26.7 (5.8)	25.0 (5.0)
Height (cm)	168.2 (4.3)	164.9 (5.3)	165.5 (4.6)	180.9 (5.5)	178.2 (6.4)	179.1 (7.4)
Weight (kg)	60.6 (7.5)	61.2 (7.5)	60.3 (7.0)	77.4 (10.1)	73.7 (4.9)	72.6 (7.3)
BMI (kg/m^2)	21 (2.3)	23 (2.4)	22 (2.2)	24 (3.1)	23 (2.2)	23 (3.0)
$FEV_{1,0}$ % (of predicted)		114 (9.8)	94 (19.2) ‡		107 (9.9)	90 (23.2)†

Values are mean (±SD); †$p<0.05$; ‡ $p=0.01$ compared with healthy CS in study II-IV

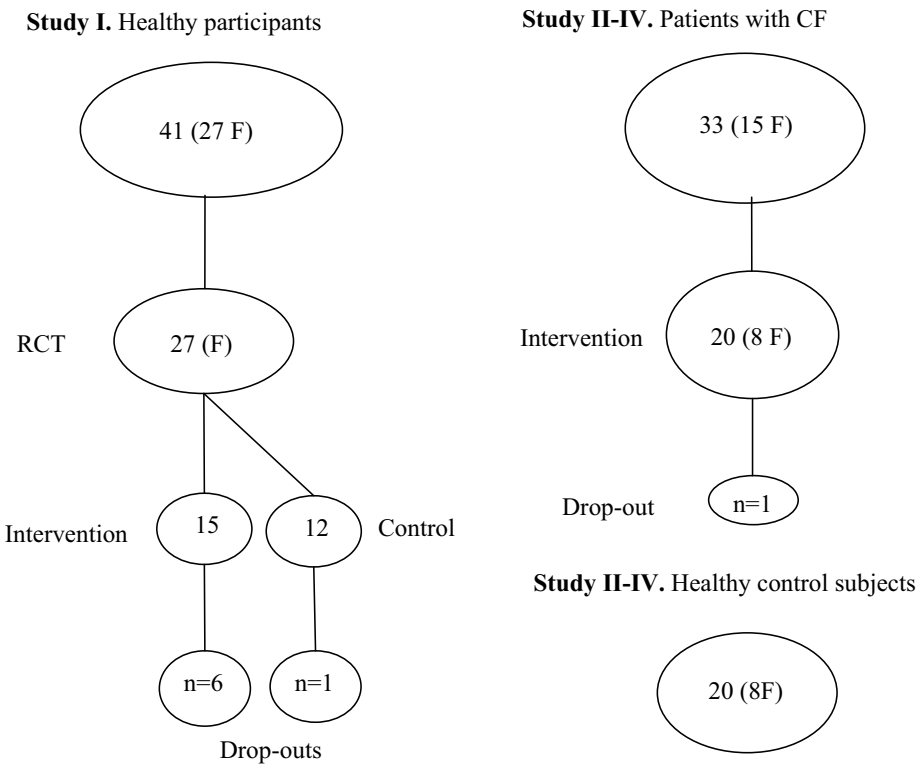


Figure 2. Flow chart over the participants (study I), the patients with CF (study II-IV) and healthy control subjects (II-IV)

Individual values of $FEV_{1.0}$ % predicted in the patients with CF and the control subjects are presented in a histogram in Figure 3.

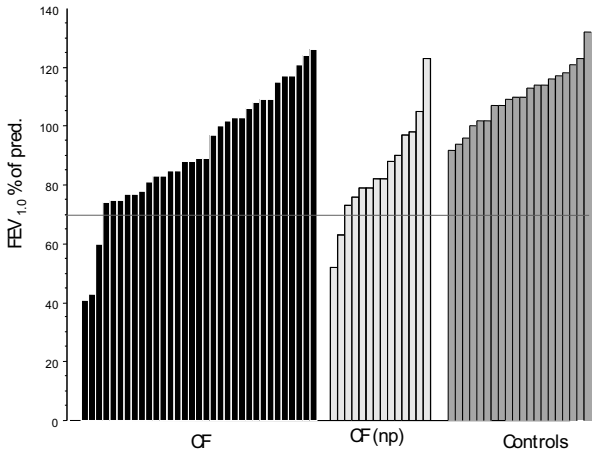


Figure 3. Individual values of $FEV_{1.0}$ % predicted in 33 patients with CF participating in study II-IV, 14 patients with CF not participating (np) in the study, and 20 controls. The horizontal line represents the limit between mild and moderate lung disease. Pancreatic insufficiency (PI) was present in 37 of the 47 patients. No significant difference in $FEV_{1.0}$ % predicted was found between patients, who were PI or PS.

The Ethic Committee at the University of Gothenburg had approved the studies, S 482-02 and Ö 504-01 (study II-IV) and AD Ö 504-01 T 099-03 (study I). Informed consent was obtained from healthy subjects, patients and parents (participants < 18 years).

Methods

- ***Tests of Muscular Strength***

Counter Movement Jump (CMJ) (Bosco 1999) (*Study II and III*) a vertical jump that was performed on a mat, Time-it®, (Eleiko Sport, Halmstad, Sweden). The time in the air was transformed into centimetre (cm) by an electronic timer (Ergojump), which was connected to

the mat. The jump was performed with both legs and started in an upright position. Free arm swings were allowed. The movement started with a bending of the knees, directly followed by an upward movement ending with a maximal vertical jump and landing on both feet. The highest value in cm out of three maximal tests was registered.

Figure 4. The maximal vertical jump position for Counter Movement Jump

Handgrip strength (*Study I – III)* was measured with Grippit® (AB Detector, Gothenburg, Sweden) an instrument with arm support and a grip device that allows the fingers and palm to be completely clasped around. The force is exerted against the transducer and is displayed in Newton (N). It registers the maximal voluntary contraction (MVC), and the mean value of 10 s registers the sustained maximal voluntary contraction (SMVC). Three trials, with one-minute rest between each trial, were recorded. Both hands were tested. The test always started with the right hand. The trial with the highest value of the MVC was registered.

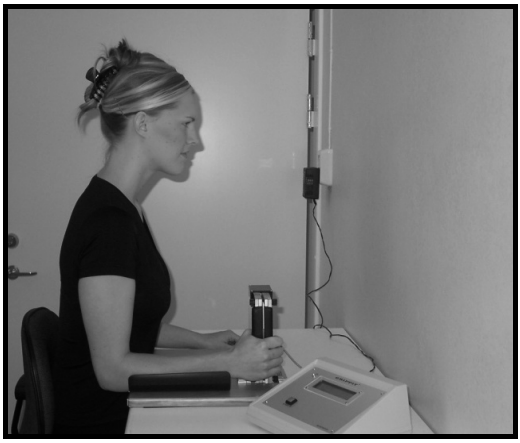


Figure 5. Starting position for measuring hand grip strength of the right hand

Abdominal muscular strength *(Study II and III)* was measured with sit-ups. The sit-up was performed from a supine position on a mat, with the knees bent at 90˚ and the feet flat on the mat, 10 cm apart. With the hands held together behind the neck, the subject raised and touched the knees with the elbows and lay back with scapulae on the mat. The test leader held the feet and the subject was informed to do the sit-ups as fast as possible until exhaustion. The test was interrupted if two sit-ups were performed incorrectly. The number of sit-ups during 30 s and the total number of sit-ups were recorded.

Figure 6. The end position for the sit-up test

Arm/shoulder muscular strength *(Study II and III)* was measured with push-ups. The subject was in prone position on a mat, with the arms straight, the hands were placed under the shoulder joint and the fingers pointed forward. The head and the body were held in a straight position and the toes, 10 cm apart, on the mat. The subject bent the elbows to 90˚, with the body still in a straight position, and pushed up to the start position. If two incorrect push-ups were performed the test was interrupted. The total number of push-ups was registered.

Figure 7. Starting position for the push-up test

Quadriceps muscular strength *(Study II and III)* was measured with a KINetic COMmunicator II® (Chattanooga Group Inc, Chattanooga, TN, USA). The equipment operates both in an isokinetic (dynamic) and an isometric mode and is hydraulically driven and microcomputer controlled. The subject was seated with an angel of 120˚ of the hip and the axis of the knee joint was approximated to the axis of rotation of the dynamometer. The subject was stabilized with a strap around the waist. Stabilization of the leg was placed distal of the tibia, allowing full dorsal flexion of the ankle and the arms were crossed in front of the

chest. All measurements had gravity compensation applied. The subject made three sub maximal concentric muscle actions of the knee joint for familiarization. Thereafter three maximal concentric muscle actions were performed with 30 s rests between the trials, at both 60˚/s and 180˚/s. Three maximal isometric muscle actions in knee extension, were performed at an angle of the knee joint of 60˚. The highest values were recorded. Both legs were tested and starting leg was randomized. The force was given in Newton meter (Nm) and in Newton (N).

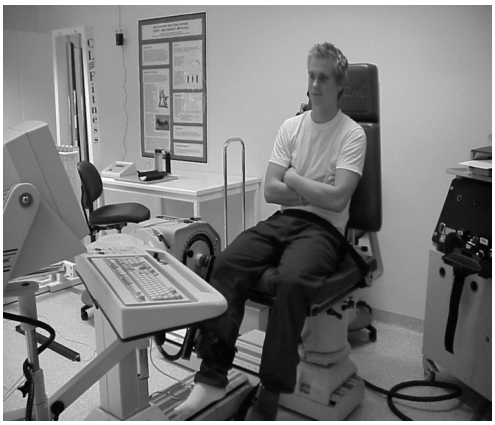


Figure 8. Starting position for measuring quadriceps dynamic muscle strength in 60˚/s and 180˚/s

A functional knee-bending test *(Study II and III)* was created to measure leg muscle endurance. The subject was standing on the floor with the hips flexed in 90˚ and the knees bent in 70-90˚. The feet were 10 cm apart, the arms hanging, the back and neck were held in a straight position. The level of the distal part of digit three was marked on the leg in that position. The distance between the lateral knee joint spring and the lateral malleolus was measured and half of the distance was marked. With the back kept in a straight position the subject was instructed to do as many knee bending as possible touching the two marks. With a standardized velocity, using a metronome set to 120 beats per minute, corresponding to one

Hz, the test was performed until exhaustion. If the standardized procedure could not be kept, the test was interrupted. The total number of knee bending was recorded.

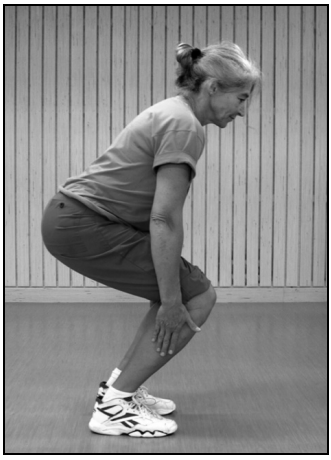


Figure 9. End position of the leg endurance muscle test

Testing procedure

Study I – III

The subjects were tested at a research laboratory by a physical therapist accustomed to the testing procedure (EMT), blinded to group assignment. After standardized instructions the subjects were allowed to familiarize with each specific test. Verbal encouragement was not used but an instruction to perform with a maximum of effort was given in advance to the subjects. The test procedure was equal for all participants.

Study III and IV

No recovery time was given except for time to move between the tests and the time for instructions. All subjects wore a t-shirt, shorts and fitness shoes. The subjects warmed up on a cycle ergo meter for five minutes, with a workload of 100 Watts, and performed 20 sub maximal push-ups against a wall. The total time for the tests was 1 hour and 15 minutes, equal for all subjects.

The tests were repeated at the same time of the day and by the same test leader after three and six months for the patients participating in the training study.

- ***Tests of pulmonary function (Study II-IV)***

Pulmonary function tests, including body plethysmography (Figure 10) and dynamic spirometry (Master Screen Body®; Erich Jaeger GmbH, Wűrzburg, Germany) were performed at the Department of Paediatric Physiology.

Figure 10. Measurement of lung volumes in a Jaeger body pletysmograph

The static lung volumes vital capacity (VC), residual volume (RV) and total lung capacity (TLC), and the dynamic lung function values, forced vital capacity (FVC) and forced expiratory volume in one second ($FEV_{1.0}$), were expressed in absolute values in litres (L). The dynamic values were also reported in percentage of predicted values. All values were related to reference values, for subjects <18 years to Solymar et al. [80] and for adults (>20 years) to Quanjier et al. [81]. The pulmonary tests were familiar to all the patients. The CSs were given standardized instructions.

- ***Test of exercise capacity (Study IV)***

The peak exercise capacity test was performed on an electromagnetically braked cycle ergometer, Vmax 229 (Sensor Medics, Yorba Linda, CA, USA). The system was calibrated according to the manufacturer's instructions. The participants rested for 5 minutes in a supine position before an electrocardiogram, and for another 10 minutes before baseline values were measured. Familiarization with the equipment was allowed since neither patients nor CS had any previous experience with this equipment. Baseline data were registered after 2 minutes on the cycle with a nose clip and a mouthpiece connected to a breath-by-breath computerized analyzer, Vmax 229 (Figure 11).

Figure 11. Exercise capacity tested on a cycle ergometer connected to a breath-by-breath computerized analyzer (Vmax 229).

Blood pressure and heart rate were registered at rest and continuously during the test, as were transcutaneous oxygen tension ($tcPO_2$) and transcutaneous carbon dioxide tension ($tcPCO_2$)

using a TCM^{TM}4 radiometer (Radiometer, Copenhagen, Denmark). Transcutaneous saturation ($tcSO_2$) was measured using a pulse oximeter (MasimoSET Radical; Masimo Corp, Irvine, CA, USA). The starting load, in watt (W), and the progression was equal to the most recent annual individual protocol for the patients. The CS followed a protocol identical to that of the indexed patient. The increase in W was continuous, ranging from 10 to 30 W/min. Workload, oxygen uptake (VO_{2max}), ventilation (V_E) and respiratory exchange ratio (RER = V_{CO2}/V_{O2}) were registered. The anaerobic (ventilatory) threshold was determined, according to the values from the computer, and defined as the point at which the rise in carbon dioxide production was higher than the rise in oxygen consumption. Alveolar oxygen and CO_2 tension were achieved from end tidal values from the equipment and the ratio of the physiological dead space and tidal volume (V_D/V_T) was estimated. Ventilatory equivalent for oxygen (V_E/VO_2) was calculated. The alveolar-arterial oxygen tension differences (P_{AO2}– P_{aO2}) at rest and at peak were calculated using the transcutaneous values [82]. Rating of perceived exertion (RPE) according to the Borg scale [83] was indicated on a scoring board, every second minute during the exercise capacity test.

All measurements continued two minutes after the end of the cycling. At four and 8 minutes after the end of the cycling, flow volume curves, were registered (Figure 12).

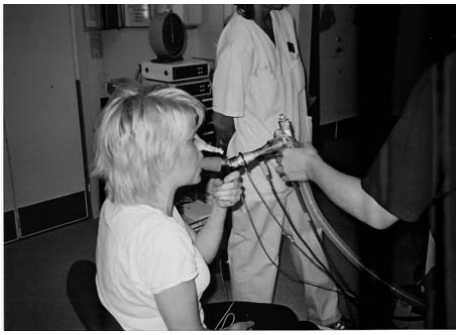


Figure 12. A participant performing a flow volume curve which is needed after 3 and 6 monyhs after four and 8 minutes after the cycle ergometer test.

One F patient with *Burkholderia cepacia* infection used another cycle ergometer (Rodby, Enhörna, Sweden) for the test and so did her indexed control. This cycle was calibrated according to the manufacturer's instructions and registered the same data except oxygen uptake.

The participants were encouraged to continue until exhaustion maintaining a pedal frequency of 60 revelutions · min^{-1}. The reason why the participant stopped was documented.

For patients who were prescribed bronchodilators, inhalation was performed within one to two hours before the test. The participants were not allowed to perform any physical training during the 24 hours preceding the test, or to have food intake within two hours prior to the test.

The tests were repeated after three and six months for all patients at the same time of the day as the first test and by the same investigators.

- ***Blood analyses (Study II-III)***

At baseline and after three and six months, blood samples were collected after overnight fast for assessing vitamin E with HPLC, serum phospholipid fatty acids with GLC and cytokines with ELISA kits. Further detailed descriptions are provided in study III.

- ***Dual x-ray absorptiometry (Study II)***

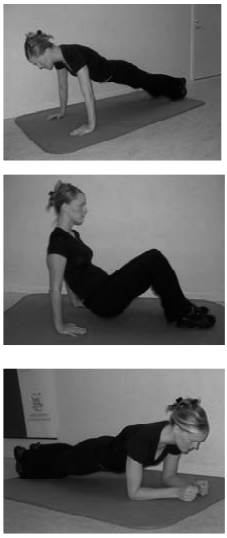
Dual X-ray absorptiometry (DXA) was performed in 28 patients with CF with a Hologic QDR 2000 (Hologic Inc., Bedford, MA, USA) in association with another study [18].

- ***Interventions***

Study I A resistance training (RT) program for 8 weeks including three different exercises for the upper extremities were performed. The frequency was three sessions per week. The subjects own body was used as load. The intensity during the first four weeks was 12

repetitions in 3 sets, followed by 15 repetitions in 3 sets during the last 4 weeks. Training diaries were used and adherence to the training was investigated and reported. Training criterion for the period was ≥75% of the requested program/week.

For starting positions of the exercises see Figure 13



Push-ups in the prone position

Push-ups in the supine position

Shoulder stabilization in the prone position

Figure 13. Starting positions of the three exercises performed in the resistance training program in study I

Study III – IV Twenty patients with CF (8 F) participated in an intervention with endurance training (ET) or RT for three months and thereafter a mixed training program for another three months (Figure 14). The participants entered the study conceptually between September and November. The geographic area, from where the patients with CF were coming, was large and facilities for physical training were not the same everywhere. Some of the participants were studying, were part or full time working and had families of their own with one or two children. The training program had to fit into their regular life. The patients were allowed to choose the base of the exercise program according to interest and availability. For

both programs the *frequency* was set to three times per week and the *duration* of each session should be 30-45 minutes. Time for warming up, 10 minutes, and stretching was added to the programs. Evaluation of training effects on muscular strength is presented in study III and on lung function and cardiovascular outcome in study IV.

– *Endurance training (ET)*

The intensity level of ET was set to 70-75 % of achieved HR reported at VO_{2max} from the cycle ergometer test. Aerobics, dance, playing tennis, ice hockey or soccer, running or cycling were some of the chosen exercises among the participants.

– *Resistance training (RT)*

The intensity level of RT was based on the principles of progressive resistance training, where adaptation to a greater load, aiming to increase muscular strength, is crucial. The intensity was expressed as percentage of one RM. The progression was achieved, with the participants starting with 12 repetitions followed by an increase to 15 repetitions in one to three sets, being approximately 70-75% of one RM. The participants chose free weights, machines or body pump classes. For the participants who were not able to visit a gymnasium, a RT program based on the individual's own body as load was designed by a registered physiotherapist and an educated instructor. All programs included training of arm/shoulder-, leg-, abdominal- and back- muscles and were instructed to the participants.

After three months one session in each program was exchanged to the type of training that was not performed during the first three months, resulting in a mixed program (Figure 14).

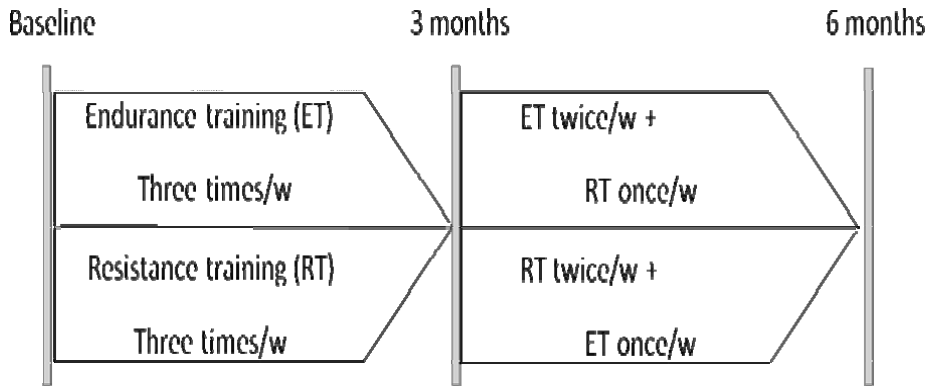


Figure 14. The design of the intervention (Study III-IV) with endurance training (ET) or resistance training (RT) for three months and thereafter with a mixed training program for three months.

- ***Compliance***

All participants were given a Polar a5® (Polar Electro Oy, Kempele, Finland) for registration of the pulse. The equipment was a tool for help to reach and control the training pulse. Training diaries for recording of frequency, duration and intensity were used. Two investigators independent of each other evaluated the diaries.

Appointments during the monthly visits to the CF clinic were used for check-up of the programs and to facilitate adherence to the training programs, which were unsupervised due to the risk of cross contamination of bacterial pathogens when training in groups. Occasionally contacts were made in-between regular visits.

Statistical methods

Data were analysed using Stat View for Windows version Xp (SAS Institute Inc, Cary, NC, USA). In presenting anthropometric data, descriptive statistics were used with mean

±standard deviation (± SD) and standard error of the mean (SEM), median and range. The Mann Whitney´s U test was used to assess differences between groups. The Wilcoxon signed rank test and ANOVA for repeated measurements were used for evaluating the interventions. Statistical significance was set at p-value <0.05. An intention to treat analysis was used in study I.

Results

- **Study I**

Measurements of handgrip strength in 41 (27F) students (20-29 years) showed significantly higher values in the right hand compared to the left hand ($p<0.001$). The males were significantly stronger ($p<0.001$). There was an increase in maximal voluntary contraction of the right hand in the TG compared to the CG after 8 weeks of RT ($p=0.03$). Six participants in the TG and one in the CG did not meet the training criteria of > 75 % completed training sessions. An intention to treat analysis confirmed the significance ($p=0.02$).

- **Study II**

We found comparable values in clinical data between 33 patients (16F) with CF and 20 (8F) healthy control subjects (CS). Significantly lower values were found in $FEV_{1.0}$ % predicted with a mean (±SD), in F and M with CF being 94 (19.2) and 90 (23.2) % of predicted, respectively. Of the 15 tests of muscular strength, F patients had decreased hand-grip strength, MVC right and left, ($p=0.02$ and $p=0.001$, respectively) and SMVC left ($p=0.002$) and performed fewer knee-bending compared with the F control subjects. In the M patients the isokinetic quadriceps strength (180°/s) was decreased ($p=0.02$) as were the number of sit-ups during 30 sec compared with CS ($p=0.03$). The latter correlated with $FEV_{1.0}$ % predicted ($p<0.05$). Differences were not associated to PI or PS.

- **Study III**

Fourteen (7F) patients started with ET and six (one F) with RT. One F patient who chose ET interrupted the study soon after start. The remaining 19 patients performed all the tests after three and six months. Fifteen patients followed training instructions, five of each sex who started with ET and five M who started with RT. Three (one F) had training frequency of two sessions/week and one F patient had a frequency of 4-5 sessions/week according to the training diaries and clinical contacts. Left isometric quadriceps strength, in F starting with ET, was decreased after six m ($p<0.05$). No other change was found in muscular strength. No difference was found in $FEV_{1.0}$ (L) between patients and controls. $FEV_{1.0}$ in % of predicted was respectively in CF and CS, F 90 (19.1) and 114 (9.8) ($p<0.01$) and in M 92 (22.4) and 107 (9.9) ($p<0.05$). No change was found after three months. The M patients who started with ET and fulfilled the stipulated training frequency of three sessions per week (n=5) had an increased $FEV_{1.0}$ % predicted after 6 m compared with baseline ($p=0.04$). Serum levels of vitamin E increased in the group starting with ET ($p=0.02$). IL-6 was increased at baseline and after three and 6 m compared to reference values and tended to increase further in the group with mainly RT (not significant). An opposite pattern was seen in the ET group.

- **Study IV**

Exercise capacity was performed at baseline in all 33 subjects**.** After three and six months the tests were repeated in the patients participating in the training study.

Differences in work load expressed in Watts was found between patients and CS, being in F 170 (31.3) and 200 (25.7) ($p<0.05$) and in males 273 (54.2) and 320 (47) in M ($p=0.05$), respectively, but was not significant when expressed in $W \cdot kg^{-1}$. After six months the work load increased by ET and decreased by RT, the difference being significant ($p<0.05$) (Study IV, Table 4).

At baseline, respiratory rate was higher and tidal volume lower in the M patients with CF compared with the controls ($p<0.05$). The physiological dead space to tidal volume ratio (V_D/V_T) was increased in the patients of both sexes at peak work ($p<0.01$). In the M this was found also at rest ($p<0.01$). At baseline no difference was found in VO_{2max} expressed in $L \cdot min^{-1}$ or in $ml \cdot kg^{-1} \cdot min^{-1}$ between CF and CS, split by sex. After six months of mainly RT, VO_{2max} ($ml \cdot kg^{-1} \cdot min^{-1}$) had decreased compared with baseline values ($p<0.05$). The difference at six months to baseline showed improvements of VO_{2max} for patients performing ET ($ml \cdot kg^{-1} \cdot min^{-1}$ and $L \cdot min^{-1}$) $p<0.01$ and $p<0.05$, respectively. Baseline values of transcutaneous oxygen tension ($tcPO_2$) was significantly higher at rest ($p=0.03$) and lower at peak work ($p<0.01$) in the M patients compared with the controls. After three months an increase was found in the M performing RT ($p=0.04$).

Discussion

To the best of our knowledge, these studies are the first reporting muscular strength and oxygen uptake in an unselected sample of young adult patients with CF, who have good lung function and nutritional status.

In study I, we found good handgrip strength in young physically active healthy subjects, both in F and M of ages comparable with the patients with CF, and also comparable to the study of that age group by Nordenskiöld et al. [84]. Eight weeks of a general RT program for the upper extremities significantly increased handgrip strength, even if the use of the handgrip was not involved in the exercises. This indicated that the upper extremity work as a complex system. In our training study for 6 months, the patients with CF did not improve handgrip strength even though exercises for arm/shoulder were included in the RT program. The baseline values of handgrip strength in the F patients for both right and left hand was lower

compared to CS, and it was unexpected that no improvement was found. Handgrip strength has been related to upper extremity strength [85], and found to be related to the pulmonary function in COPD patients [86] although one study did not find decreased muscle strength in severely impaired COPD patients if correction was made for fat–free mass [87]. Our female patients had good lung function and lean body mass, but still showed decreased handgrip strength also after the six months of training. Handgrip strength is also reported to correlate to malnutrition and to mortality [88, 89]. The nutritional status was good in the patients with CF, all with BMI >18.5, why a relation to malnutrition cannot be applied.

There is a great demand on the patients with CF to keep a good posture of the upper body for good thoracic expansion for optimal airway clearance [90]. It may be speculated if early provided training in the patients with CF according to study I, would improve their handgrip strength in the patients to secure good strength of the upper extremities. The Grippit® Instrument for measuring handgrip strength is easy to handle, have high reliability [84] and is therefore suitable for longitudinal studies evaluating the effect of a RT program, also carried out without any equipment. Even our results from study II with general good muscular strength give support for a good posture in the participating patients. At present it is therefore difficult to conclude if the impaired handgrip strength in the F patients might be a sensitive indicator of impairment in muscle function.

Except for handgrip strength, lower values were found in one of the leg tests each in the F and M patients and in sit-ups for 30 s in the M compared to sex matched CS. The training period of five months did not improve muscle strength in any of the tests. How much strength can increase is dependent of the status at start of the training period [20]. In a sedentary person the increase in strength is large why in already well trained an increase is harder to achieve [48]. One reason to the absence of improvement would be that the patients

were not sedentary at start. On the other hand, impairment in quadriceps strength has repeatedly been reported in COPD, but mainly referred to inactivity or increase of inflammation [91, 92]. None of these explanations was relevant for the decrease we found both at baseline and after the 6 months of training. Barry et al. [54] reported decreased muscle strength and a strong correlation to the use of corticosteroids and prescribed dosage. The absence of improvements of muscle strength in our study could not be due to corticosteroids since they are seldom prescribed to our patients. Only one patient, who was participating in the training study, was prescribed oral corticosteroids during the last part of the study due to airway inflammation. Selvadurai et al. [50] and de Meer et al. [53] proposed mitochondrial deficiency being the reason to muscle impairment in CF.

Only the study by Strauss et al. [49] have reported resistance training as the only type of training in 9 adult patients with CF. MMT was used to evaluate the strength of 36 muscles. A loss of normal strength, where normal was defined as "a movement you can perform against resistance 5 times without fatigue", in more than half of the tested muscles was reported. By six months of variable weight training an increase in muscle strength was achieved in more than 50% of the weaker muscles. $FEV_{1.0}$ (L) was 40% of predicted in the participating patients. In our study the patients started on a level comparable with healthy controls in both muscle strength and $FEV_{1.0}$ % predicted, thus having more difficulties to increase strength.
In the one year RCT by Moorcroft et al. [76] 30 patients were assigned for training and performed weekly weight training for upper body 3*20 minutes together with or separated from endurance training 3*20 minutes. The outcome of weight training was assessed with arm ergometry while comparison with our study is not possible. The baseline lung function values were also notably low with $FEV_{1.0,}$ 2.27(L), not split by gender, compared to the values in our study, presenting $FEV_{1.0}$ of 3.6 L (F 2.8 and M 4.0). Selvadurai et al. [58]

studied muscle strength in children during admission to hospital, where with a mean stay of 19 days increased leg strength was found in the children who performed RT compared to those with ET.

Hickson [93] reported that when endurance training was added to resistance training during the same training session (=concurrent training), there was a plateau in muscular strength after two months and no further increase was achieved. He also showed that a mixed programme with ET and RT had disadvantages compared with one programme with ET and another with RT in the outcome of training. In our design we changed one whole session out of the three during the week to reach a mixed program during the last three months of the study. We do not consider that the model in Hickson´s study is comparable to ours and would therefore not explain why the patients in our study did not improve muscular strength. The training design in our study was in line with what today is recommended by the ACSM.

In progressive resistance training adaptation is of great importance to achieve an increase in strength [78]. The overload is progressive, as in our design from 12 to 15 repetitions and from one to three sets as well as an increased load due to increased strength. If only the initial load level is kept no increase could occur [78] which might be a risk when training is unsupervised. This would be one reason why no improvement in muscular strength was found by three months of RT in our study. At start of the study we only had the patient´s report on the activity scale about training. The patients had the responsibility to increase load, repetitions and sets due to evaluated increase in strength and we did not find any reason to doubt the diaries. The results of the exercise tests supported that we could exclude the above concern as a reason for no strength gain.

In study IV we evaluated exercise capacity in 33 (17F) patients with CF and compared the outcome with control subjects. The oxygen uptake ($L \cdot min^{-1}$) % of predicted was in F and M with CF 86% and 93%, respectively. The corresponding values in CS were 106% and 104%. Moorcroft et al. [66] recently reported that 38/104 young adult patients with CF showing mild lung disease, had a mean $FEV_{1.0}$ % predicted of 77% (±13.6) and "peak VO_2" in % predicted values 75.6% (±12.9), not split by gender. The remaining 2/3 of the included patients showed values far below the ones in our study group (cf Figure 3). From the RCT study by Moorcroft et al. [76] no data on exercise capacity comparable to ours are given. In their study data on lactate levels were given showing decreased values indicating a training effect. Also the decline in $FEV_{1.0}$ (L) of 67 ml at 12 months was evaluated as an indication of better preserved lung function. In that context the well preserved lung function and exercise capacity in our study would further support that the patients followed the program. We found it difficult to compare our results with those others since the sex difference is usually not reported but prominent as illustrated in fig 15.

The commonly used classification of the lung disease states that $FEV_{1.0}$ % predicted >70% corresponds to mild impairment, moderate impairment is 40-70% of predicted and severe impairment is <40% of predicted. Only three of our patients had lung function below 70%, which would be rather unique. Exercise capacity (VO_{2max} $L \cdot min^{-1}$) was also well above reported values (Figure 15). Good aerobic fitness in CF is associated with prolonged survival reported by Nixon et al. [68] and Pianosi et al. [59]. Pianosi found that the rate of decline in VO_{2max} was a predictor of mortality [59]. With our annual test of exercise capacity followed by training recommendations concerning training, we hopefully contribute to prevent deterioration of exercise capacity in the patients.

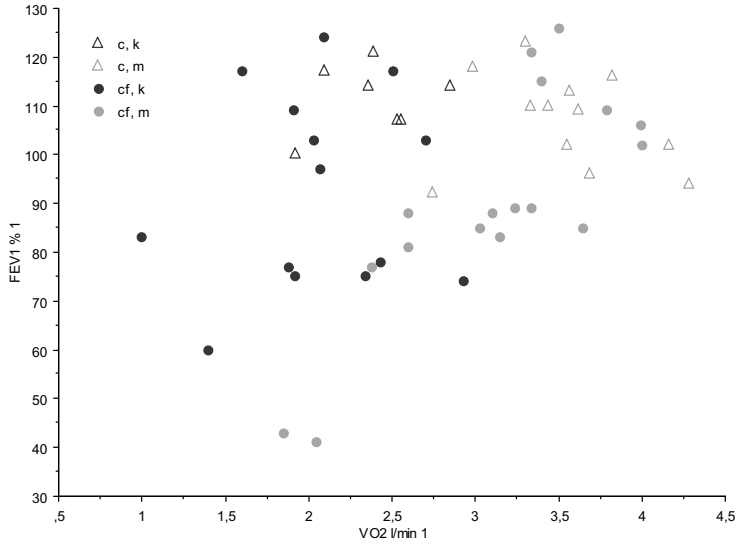


Figure 15. Maximal oxygen uptake (VO_{2max} $L \cdot min^{-1}$) and $FEV_{1.0}$ % predicted in 32 (15 F) patients with CF and in 20 (8 F) control subjects (C) at start of the study.

In study IV we did not find any change after three months of ET or RT in pulmonary or cardiovascular data. At the end of the study there were improvements in Watts, VO_{2max} $L \cdot min^{-1}$ and $ml \cdot kg^{-1} \cdot min^{-1}$ in the patients, who mainly had performed ET compared to those mainly performing RT. (Study IV, Table 4). An increase between 15 and 20% in VO_{2max} is expected in a sedentary person following the above mentioned and recommended training intensity [20, 48]. Since our patients were not sedentary at start of the study we could not expect such an improvement. Åstrand reported that already from results in 1931, Christensen et al. concluded that, "the fitter the person, the more it will take to improve that fitness" [48]. The patients with CF showed already from start good exercise capacity, which did not improve by training, even if there was a significant difference in the change between the

groups performing ET and RT. Maybe it was the mixed program during the last three months when RT was added to ET that made this difference? Future studies with appropriate design for evaluation of this might give the answer.

Increased physiological dead space (V_D) and the ratio of V_D to tidal volume V_T (V_D/V_T) are reported in CF [94]. We also found a significantly higher V_D/V_T ratio at baseline in the M patients with CF at rest ($p<0.01$). At peak exercise performed on a cycle ergometer we found increased values in both the F and the M patients with CF ($p<0.01$) compared to healthy CS confirming earlier results [94] and the presence of lung disease. The V_D/V_T ratio showed more often a decrease than an increase after training, but all changes were to small to allow any conclusions (Figure 16).

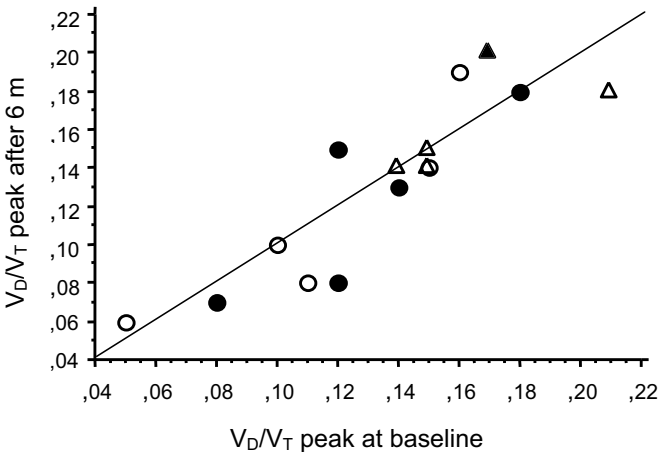


Figure 16. The V_D/V_T ratio at peak exercise test on a cycle ergometer at baseline and after 6 months of training in 15 patients with CF, who strictly followed a program with training frequency of three sessions per week.

The high ventilatory equivalent for oxygen (V_E/VO_2) indicated a real peak work and that the lungs were not a limiting factor. A further support that the lungs not were limiting during

maximal exercise was the alveolar-arterial pressure gradient ($P_{AO2-aO2}$) achieved at maximal peak exercise, which was comparable to the controls.

Methodological Considerations

The six months training study in patients with CF could unfortunately not be formed as a RCT. This was primarily due to our 25-year treatment policy with physical training included in the care package. By ethical reasons one group of patients could not have been abandoned to exercise and designed to controls. We did not manage to get recruited CS to follow a strict training program.

At the start of the study we invited all the patients that met the inclusion criteria (n=47). All did not accept to participate. The histogram in Figure 3 with $FEV_{1.0}$ % predicted in all patients that met the inclusion criteria shows that there was no selection bias due to medical status in the study group. There are though personal interests in an acceptance to participate in a study, which might be a bias.

To standardize measurements of muscular strength is crucial for comparisons between results and to repeat studies. For measuring muscular strength we used standardized functional tests and computerized equipments (Study I-III), which are well documented and used. We question the MMT method used by Strauss et al. (49) since there are concerns with internal reliability and validity when judging muscular strength in a manual way especially in strong muscle groups like those of the legs. In our study we used the same test person and strictly standardized methods with a minimum of subjective judgement.

We evaluated lung function with static and dynamic tests. To assess the obstruction of the airways we chose forced expiratory values in one second ($FEV_{1.0}$) expressed in absolute value (L) and in percentage of predicted values (% predicted). For comparison of clinical data in patients in other studies and in other countries, the $FEV_{1.0}$ % predicted is frequently and mostly used. Gustafsson et al. [28] have in recent pulmonary studies in children, using multiple-breath inert gas washout, shown abnormalities in the peripheral airways and increased volumes of trapped gas. These study results may lead to the use of more precise measurements and values confirming obstruction and to evaluate the degree of the lung disease in patients with CF.

Exercise capacity was evaluated using a cycle ergometer, which is standard at the Department of Paediatric Physiology in Gothenburg. Studies have shown 5-11% higher values of VO_{2max} when using a treadmill with an uphill inclination of $\geq 3°$ during the test [48]. We start with the cycle ergometer test for assessment of exercise capacity in the children with CF at 6-7 years of age and there is a need for continuity at the annual check-up for yearly comparisons.

- Design of the study

Significant training effects by an intervention are reported but the effect does not stay very long [33]. It has been suggested that a study program often is quite new for the participants and does not belong to the daily life. To our knowledge it has not been reported that the participating patients with CF have been encouraged to continue with physical exercise when the study time was over. One reason to the design of our study with the patients allowed to choose the exercises to be performed was to reach a high adherence in the study and to have continuity with training also afterwards, which also is in line with recommendations from

Moorcroft et al. when designing training programs [67]. Some of the patients continued with already ongoing training but had it systemized by the design of frequency, intensity, and duration. Also the monitoring was new to them.

One reason for not supervising the patients was the large area the patients were coming from. There were distances of more than 200 km. The risk of bacterial contamination between the patients gave us not the choice to have the patients in a training group, which also was a reason why they were unsupervised. Compliance in studies is a challenge and especially in unsupervised ones (76). The use of telemetry, diaries and personal contacts and monthly visits hopefully gave a true picture of reported adherence. Without adherence the good values, though not improved, would not have been present, since muscle strength and fitness is perishable (20, 48).

The level of intensity during endurance training, 70-75 % of achieved heart rate at VO_{2max}, was chosen as it is regarded the best indicator of cardiorespiratory endurance capacity [20] and with most of the energy demand coming from carbohydrates. At a lower pulse rate more energy is used from fat [20, 48]. Due to an already low fat mass in CF [17] this might have been negative. There would be concerns as we compared the results from different types of endurance exercises making them equivalent, like spinning and aerobics, jogging and frisbee golf. During the ET the pulse rate was the main standard for measuring training intensity. The pulse monitoring gave training interval and total time at that interval why we decided that the choice of exercise belonged to patients.

One objection to the RT program might be that the training performed at a gymnasium with free weights was compared with a home maid program with the own body as load in the exercises. This would be questioned but training instructions were the same.

Conclusions

- Resistance training of the upper extremities for 8 weeks significantly improved handgrip strength in young adult females.
- Thirty-three (16 F) young adult patients with classic CF showed comparable muscle strength to age-and sex matched control subjects.
- Three months of endurance (ET) or resistance training (RT) followed by three months of a mixed training program did not further improve muscular strength.
- The absence of improvement in muscle strength might be due to metabolic impairment since the lung function and oxygen uptake was not limiting factors in this study.
- Young adult patients in our treatment policy had close to normal lung function and exercise capacity.
- Physiological dead space to tidal volume ratio, V_D/V_T, was significantly increased in the patients, reflecting the presence of a lung disease.
- ET seemed to give a small advantage to RT, but the effect might be due to combination of training modalities.

Clinical relevance

To find tests, with high reliability, that are easy to use in clinical practise are of importance to ensure evidence based medicine. The Grippit® is a good instrument to use to assess handgrip strength and for follow up of interventions in both prevention and rehabilitation.

In patients with CF standardized tests of muscle strength would be of great importance when designing training programs, for evaluation of an intervention and for comparisons since the patient population is small at each clinic in Sweden.

Future studies

Our study has led to the hypothesis that metabolic limitation might explain the absence of improvement in muscle strength. There is a need for further studies including muscle biopsies.

To ensure good muscular strength into adulthood it would be a challenge to regular assess muscular strength and to design training programs in children. To reduce small sample size and selection bias multicenter studies would be preferable.

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