Effects of an Exercise Program in Children with Cystic Fibrosis: Are There Differences between Females and Males?

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Objective To investigate the adaptive responses of an in-patient exercise program in children with cystic fibrosis (CF) and evaluate the effects of sex.

Study design In total, 158 female and 186 male subjects with CF (age, 12 to 43 years) were studied during a 6-week rehabilitation course. A maximal incremental cycling test was used to determine exercise capacity and responses after 6 weeks of exercise training. Measures included lung function, peak oxygen uptake, peak workload, and peak heart rate.

Results Lung function values were lower in males ($P < .05$). Females had a lower aerobic capacity ($P < .05$) at the beginning and at the end of the exercise training program. Similar training effects ($P > .05$) were seen between sexes in peak oxygen uptake (mL/min, mL/kg/min) and peak heart rate (beats/min) but not in peak workload (Watts, W/kg).

Conclusions The exercise program improved the fitness level similarly in females and males with CF. Basic physiological sex differences were still seen at the beginning and end of the training, despite the better lung function in females. Moreover, the finding suggested that fitness level and not lung function determined the response to training in CF, with those who were less fit at baseline having the largest response to training. (J Pediatr 2011;158:71-6).

The beneficial adaptations to an exercise program in cystic fibrosis (CF) are well recognized. Regular exercise may increase quality of life and aerobic and anaerobic capacity and may delay deterioration of lung function in children with CF. Exercise capacity may be limited in CF, but most studies have shown an increase in maximal oxygen uptake (VO$_{2peak}$) with conditioning. The improvement of VO$_{2peak}$ is of great importance in CF because a higher VO$_{2peak}$ has been associated with lower 5- to 8-year mortality. Activity levels of children with CF correlate significantly with aerobic and anaerobic capacity. Studies have shown lower exercise capacity in females with CF than in males, and in two studies girls were less active than boys of the same age and disease severity.

Orenstein et al demonstrated lower values for VO$_{2peak}$ (mL/kg/min) and peak work capacity (Watts) in females with CF compared with males with similar severity of pulmonary disease, as is also the case in non-CF-populations. In non-CF populations, females have a lower exercise capacity expressed as VO$_{2peak}$ (mL/min and mL/kg/min) and work load (Watts and W/kg). Physiologic responses to acute exercise (eg higher heart rate response in females at submaximal power output due to a lower cardiac stroke volume, lower peak blood lactate in females, females use a higher percentage of VO$_{2peak}$ at the same submaximal work load) are different between the sexes at submaximal and maximal exercise capacity.

However, with exercise training women showed the same relative increase in VO$_{2peak}$ as men. In healthy subjects, the magnitude of improvement with training seems to be influenced by the initial level of fitness. Women may have a greater response than men, but only because of lower initial fitness, perhaps related to a relatively inactive lifestyle compared with men. Furthermore, it appears that VO$_{2peak}$ has a genetic upper limit that can not be exceeded.

To date, exercise training studies in CF have concentrated on the effects of training on exercise capacity, lung function, and quality of life and have neglected potential sex effects. Children and adolescents with CF are engaged in less vigorous physical activities than their healthy peers. Selvadurai et al have shown sex differences in habitual level of physical activities after the onset of puberty. Girls and women with CF are less physically active and have a lower exercise capacity, and therefore it might be assumed that the response to exercise training might differ in magnitude between female and male subjects with CF.

BMI Body mass index
CF Cystic fibrosis
FEV1 Forced expiratory volume in one second
HRpeak Peak heart rate
MEF25 Maximum expiratory flow at 25% of vital capacity
MVV Maximal voluntary ventilation
O2-Pulsepeak Peak oxygen pulse
SaO2 Oxygen saturation
T1 Day after admission
T2 Day before completion
VC Vital capacity
VO2peak Peak oxygen uptake
PVO2 Difference between VO2 peak measurement at T2 and T1
Wpeak Peak work load

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The purpose of the present study was to evaluate the adaptive responses of an exercise program in CF and evaluate the effects of sex.

Methods

Data were collected from 344 children, adolescents, and adults with CF (158 female; 186 male; ages from 7 to 43 years) (Table I). All subjects were attending a specialized inpatient rehabilitation clinic for CF owned by the German social security organizations in Nebel. The duration of the rehabilitation course was 6 weeks. The criteria for inclusion were the following: clinically stable, no medical contraindications for exercise testing, and participating in an exercise training program. Home medication (inhaled or oral antibiotics, bronchodilators, pancreatic enzyme supplements, and vitamins) was continued unchanged throughout the time of participation. Before entering in the training program, all subjects and their guardians, if participants were younger than 18 years, had the purpose of study and the procedures explained; written informed consent was obtained. The study was approved by the Ethics Committee of the regional Medical Chamber of Schleswig-Holstein.

Pulmonary function tests and an incremental exercise test were performed on the day after admission (T1) and 1 day before completion the course (T2). Forced expiratory volume in 1 second (FEV1), vital capacity (VC), and maximum expiratory flow at 25% of vital capacity (MEF25) were measured by standard spirometric techniques (Master screen, Jaeger, Wuerzburg, Germany); values were expressed as a percentage of predicted. The lung function tests were performed according to standard spirometric techniques.

Exercise capacity was assessed by a maximal incremental exercise test on an electronically braked cycle ergometer (Examiner, Lode B.V. Groningen, The Netherlands) in an upright position to subjective exhaustion. The Godfrey protocol was used. The initial work load was adjusted for height and increased every minute (<120 cm: 10 W/min; 120 to 150 cm: 15 W/min; >150 cm: 20 W/min). Ventilation and gas exchange were measured by breath with an open circuit system (Master Screen CPX, Viaysis Healthcare GmbH, Hoechberg, Germany). Before each test, the oxygen and carbon dioxide analyzers were calibrated with gases of known concentration (O2: 21.0%, CO2: 5.0%, N2: 74%). VO2peak (L/min, mL/kg/min), Wpeak (Watts, W/kg), peak heart rate (HRpeak, beats/min), and peak oxygen pulse (O2-Pulsepeak, VO2peak/HRpeak the milliliters oxygen delivered per heart beat) were determined as the highest value in the last 30 seconds before stopping the test. Values percent predicted were determined form the reference equations of Godfrey for Wpeak (Watts) and of Orenstein for VO2peak (L/min). A 12-lead electrocardiogram was monitored continuously and heart rate was determined every 30 seconds and at peak exercise. Tests were accepted as truly maximal if any of the following criteria were met: (1) heart rate ≥90% of age-predicted maximum; (2) respiratory exchange ratio (VCO2/VO2) at test termination ≥1.0; or (3) minute ventilation at test termination ≥70% of MVV [FEV1 (L) × 40].

All subjects were given a short questionnaire asking about their habitual type of exercise, frequency per week, and problems during sport activities.

The exercise training program was supervised by a specialized sport-therapist, and each session consisted of 45 minutes of different sport activities, depending on the age of the participants (Monday: walking/jogging; Tuesday/Thursday: gymnastic hall: ball games, running games, and others; Wednesday: resistance training; Friday: swimming. Additional activities were performed Wednesday and Friday. Excursions on the island were arranged at the weekend (eg, shopping, visits to local attractions). There was no sex difference in the exercise training program. Participants exercised 4 to 5 times weekly for 6 weeks in groups of about 10 peers,

### Table I. Subject characteristics and lung function by sex

<table>
<thead>
<tr>
<th></th>
<th>Female (n = 158)</th>
<th>Male (n = 186)</th>
<th>Repeated-measures MANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SD T1</td>
<td>Mean ± SD T2</td>
<td>Mean ± SD T1</td>
</tr>
<tr>
<td>Age (y)</td>
<td>19.9 ± 8.1</td>
<td>22.0 ± 7.5</td>
<td></td>
</tr>
<tr>
<td>Height (cm)</td>
<td>159.5 ± 9.3*</td>
<td>168.6 ± 11.6</td>
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</tr>
<tr>
<td>Weight (kg)</td>
<td>47.2 ± 9.1**</td>
<td>54.3 ± 11.1</td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>18.3 ± 2.3***</td>
<td>18.9 ± 2.8</td>
<td></td>
</tr>
<tr>
<td>FEV1 (%)</td>
<td>63.3 ± 26.2†</td>
<td>55.1 ± 24.5</td>
<td></td>
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<tr>
<td>VC (%)</td>
<td>76.4 ± 21.5†</td>
<td>70.3 ± 18.8</td>
<td></td>
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<tr>
<td>MEF25 (%)</td>
<td>31.3 ± 27.5</td>
<td>26.1 ± 24.2</td>
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</tbody>
</table>

*Within groups, paired Student t test; †P < .05.
**Within groups, paired Student t test; †P < .01.
†Within groups, paired Student t test; P < .001.
‡Within groups, paired Student t test; P < .001.
§Within groups, paired Student t test; P < .001.
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Statistical Analysis

Data are presented as mean ± SD. A repeated-measures MANOVA with training as within-subjects factor and sex as between subjects factor was used to determine whether the exercise training and sex had independent or interacting effects on the changes of lung function and fitness measures. Furthermore, a MANOVA was performed with training as within-subject factor and level of fitness as between subject factor to assess differences of training effects by fitness variables. A Student unpaired t test was used to determine differences between sex groups for anthropometric values (age, height weight, and body mass index [BMI]), fitness values, and lung function values. The strength of correlation between VO2peak (mL/kg/min) and PVO2 (mL/kg/min) was determined by Pearson correlation coefficient. Statistical analyses were performed using SPSS 15.0 (SPSS, Inc. Chicago, Illinois). Significance was set at the .05 level for all tests.

Results

All participants completed the training program. Statistically significant differences were found between sexes for anthropometric data. Males were older (P < .01), taller (P < .001), and weighed more (P < .001, Table I). Weight (P < .001) and BMI (P < .001) increased after training in both male and females, and the magnitude of improvement was comparable between sexes (P > .05).

At admission and at discharge, lung function showed differences between the groups. FEV1 and VC were higher (P < .01) in females, and the same trend was observed for MEF25 (Table I), but the difference was not statistically significant (P < .05). After training, an improvement (P < .001) in all lung function values was seen in both sexes (Table I). However, the magnitude of the changes in lung function values was comparable for the two groups (T × G, P > .05).

In contrast to lung function, male participants had higher fitness measurements in absolute terms and when corrected for body mass at baseline and at the end of the training program. HRpeak was lower in males compared with females and reached statistical significance (Table II).

With the exception of HRpeak, significant improvements (P < .001) of all fitness variables were seen in both groups after training (Table II). In absolute and relative (weight-
corrected) terms, improvements were comparable between groups (Table II). No change of maximal HRpeak was found in females after training. In contrast, males with CF showed a small (2.8 beats/min) but insignificant increase (P > .05) of HRpeak.

Although both groups demonstrated a significant increase of fitness variables after training (factor training), there was a significant interaction between sex × training (P < .05) for Wpeak (Watts), Wpeak (W/kg).

A division of participants into different groups based on the initial fitness level showed different effects on trainability (factor fitness-level × training). Those with VO2peak <58% pred had a higher improvement (P < .05) in VO2peak, Wpeak, HRpeak, and O2-Pulsepeak (mL) than participants with VO2peak 59% to 81%pred and VO2peak >82%pred (Figure 1).

As in healthy people, a wide range of increase of VO2peak was observed in the present study, and a weak but statistically significant correlation (r = -0.295, P < .05) was found between the initial VO2peak (mL/kg/min) and VO2 (mL/kg/min) (Figure 2).

In the habitual exercise questionnaire, more males than females reported being engaged in a sports club.

**Discussion**

The results of this 6-week inpatient rehabilitation and exercise training study demonstrated a beneficial effect on exercise capacity and lung function in both females and males with CF. These findings are in accordance with other studies, which have also shown that an exercise training program may lead to an improvement of exercise capacity and lung function in CF.

The maximum exercise capacity, expressed as VO2peak and Wpeak in absolute and relative terms, was significantly lower in females (Table II). These differences between the sexes were similar to those seen between healthy men and women and may be explained partly by biological differences between sexes (eg, cardiac output, stroke volume, hemoglobin concentration, body composition).

Habitual physical activity seems to have an influence on pulmonary function and exercise tolerance. Those subjects with high activity levels have a better anaerobic and aerobic exercise, lung function, and quality of life. The questionnaires asking about habitual physical activities at home in this study have shown that a higher percentage of our males were members of a sport club and had more active (sessions per week) than the females. Thus, differences in habitual physical activity in the present study may explain the better exercise capacity of the males with CF, despite their lower lung function, a finding that is consistent with Selvadurai et al. and Boucher et al., both of whom found that the level of physical activity is independent of lung function in CF.

One limitation of the activity questionnaire used in this study is that intensity of the activity can not be determined. Therefore it is not possible to differentiate between moderate and vigorous physical activity and if the male subjects participated in more strenuous sporting activities than the female participants.

Female and male subjects demonstrated a 9.9% and 11.1% rise in VO2peak (mL/min), which is consistent with training studies from healthy people. There were no sex differences in the magnitude of improvement of VO2peak after the exercise program with the same training intensity, frequency, and duration. This result was somewhat surprising because the males had, in absolute and relative terms, a higher VO2peak at baseline compared with females.

It is a common observation in non-CF populations that the change in VO2peak depends on the baseline fitness level.
and those people with initially lower level of fitness had a greater increase of VO$_{2peak}$ than those with higher levels at the beginning of a training program. However, Skinner et al. have shown a wide range of improvement of VO$_{2peak}$ after a training program with low, medium, and high responders to training at all levels of fitness and for each sex.

Two recently published studies clearly demonstrated a significant association between the level of fitness and survival in CF. The classification into fitness groups according to Nixon et al. showed a positive correlation between 8-year survival and initial exercise capacity. Furthermore, a high aerobic capacity is associated with a high level of physical activities and vigorous activities.

The variation in responsiveness to exercise training in the present study might be the result of the differences in baseline fitness level and habitual physical activities. Interestingly, lung function does not seem to be a good predictor for the increase in exercise capacity in CF. It seems likely that the effect of exercise training in CF depends primarily on initial fitness level and not on lung function. Additionally, a genetically determined upper limit of VO$_{2peak}$ might help to explain the variation in training response of subjects with CF.

In the present study, the O$_2$-Pulse was used to evaluate the positive effects of the exercise program. The O$_2$-Pulse is thought to provide an indirect measure of cardiac stroke volume. An increase in cardiac stroke volume is a hallmark of improved cardiopulmonary fitness after training programs, and therefore, the improvement in O$_2$-Pulse$_{peak}$ observed after training in our subjects provides additional evidence that the participants actually increased their fitness and did not just try harder on their post-training exercise tests.

The adaptive increase in work values induced by the exercise training was more pronounced in males with CF. A possible explanation for the greater improvements in work load values are physiological and morphological differences between sexes. Females have a lower muscle mass, a lower muscle cross sectional area, a higher fat percentage, lower maximal cardiac output, and differences in fat and carbohydrate oxidation and capillarization. The greater adaptive increase in work load in response to the exercise training in the male with CF could be the result of the greater muscle mass and differences in fiber type composition.

Furthermore, enhanced capillarization may have contributed to the greater increase in work load. Another plausible explanation for the differences in the work values is the type of ergometer. In the present study an electronically braked cycle ergometer was used to determine maximal exercise capacity. There are some disadvantages when using a leg cycle ergometer (instead of a treadmill) to determine maximal exercise capacity. Cycle exercise may be unfamiliar to people who are unfit, and this may result in leg fatigue before cardiopulmonary limitation is reached. Both groups improved their body weight and BMI. This is in agreement with previous work, and it can be concluded that, despite the higher energy expended during exercise in CF, children and adults are able to maintain or increase their body weight during an exercise training program. The better nutritional status may in turn have a positive effect on lung function and exercise tolerance.

A relationship in CF has been shown for exercise tolerance, clinical status, airway obstruction, and respiratory symptoms, including dyspnea. These factors, particularly in those with worse lung function, may lead to a decrease of physical activity, and as a result muscle wasting and weakness. Little is known about the benefits of exercise training with regard to severity of disease, but there are some indications that subjects with severely impaired lung function might benefit to a greater extent from an inpatient exercise training program than those with normal lung function.

To our knowledge, there is no study dealing with exercise capacity and ABPA in CF, and it is not known if any of our subjects had ABPA. Based on published literature, it might be assumed that ABPA could have an adverse effect on physical fitness, and this should be investigated in further studies.

In summary, an exercise training program significantly improved the fitness level in both female and male with CF. The small but significant sex-based differences in work values could be ascribed to physiological and morphological differences between sexes. The fact that females had a higher lung function but lower fitness level at the beginning of the exercise program suggested that the initial fitness level and not lung function determines the magnitude of improvement.

References


