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Long-term effects of a partially supervised conditioning program in cystic fibrosis

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ABSTRACT

Little is known about the long-term persistence of positive effects induced by a physical conditioning program. Therefore, this study determined the effects of a 6-months conditioning program on peak oxygen uptake (primary outcome), and other markers of fitness, physical activity, anthropometry, lung function, and quality of life (secondary outcomes) 18 and 24 months after the program was initiated.

Patients with CF aged 12-40 years were randomly assigned to an intervention (n=23) and a control (n=15) group. The intervention group consented to add three hours of sports per week for at least six months to their previous activities. Controls were asked to maintain their level of activity for 12 months. Patients were seen at baseline and after 3, 6, 12, 18, and 24 months.

There was no significant difference between groups at baseline. The intervention induced positive effects on peak oxygen uptake (difference in changes from baseline to the 18- and 24-months assessments between groups: +3.72±1.23 $ml \cdot min^{-1} \cdot kg^{-1}$, $p<0.01$), maximal work load (+0.37±0.11 $W \cdot kg^{-1}$, $p<0.01$), vigorous physical activity (+1.63±0.82 $hours \cdot week^{-1}$, $p<0.05$), FVC (+6.06±2.87 %predicted, $p<0.05$), and perceived health (+9.89±4.72, $p<0.05$).

A home-based partially supervised physical conditioning program can improve physical fitness, lung function and perceived health long after the intervention has ended.

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Key words: Cystic fibrosis, pulmonary rehabilitation, exercise capacity, quality of life. lung function

INTRODUCTION

Several studies have demonstrated favourable effects of exercise programs in children and adults with cystic fibrosis (CF) (1-5). Specifically, an increase in physical activity was associated with a gain in exercise capacity (1;3;5), a stabilisation or even an improvement in lung function (1;2;4) and a higher quality of life (1;5). However, it is unclear whether the benefits induced by an exercise program are maintained for a time period longer than three months.

Supervised conditioning programs (1;3;5) and home-based approaches (2;4) were both effective at inducing positive health effects in patients with CF. Yet, a home-based individualised conditioning program has several conceivable advantages: 1) the program can be easily implemented, 2) the patients can chose activities based on their personal preferences, 3) the accessibility of the activities in respect to location and time is much greater, and 4) activities can be planned together with family members or friends. Therefore, we hypothesised that activities initiated as part of a home-based program might be maintained beyond the end of the program.

Peak oxygen uptake (VO_2peak) has been used as a marker of aerobic fitness and physical activity (6). In CF, VO_2peak has been shown to be related to physical activity (7) and responded to physical conditioning within two weeks of an intense in-patient program (1), or within three months of a supervised outpatient program (3). Furthermore, VO_2peak seems to be an important predictor of CF related mortality (8).

The primary objective of this randomised controlled trial was to determine the effects of a home-based, individualised, partially supervised conditioning program on VO_2peak 12 to 18 months after the program had ended. Secondary outcome measures included other markers of exercise capacity, physical activity, body composition, lung function, and quality of life (QoL).

METHODS

Details on the sample size justification, the randomization procedure and the study´s design and procedures are provided in an online supplement.

Subjects

Patients with CF were recruited from the German CF centres at Frankfurt, Hannover, and Würzburg. Inclusion criteria for this study were a confirmed diagnosis of CF (i.e. a typical clinical picture and at least two positive sweat tests or CF-relevant mutations on both allels of the CFTR gene), an age of at least 12 years, a forced expiratory volume in 1 second (FEV1) of at least 35% of predicted (9), and the ability to perform physical activity. Exclusion criteria were non-CF related chronic diseases and CF-related conditions posing an increased risk on the patient when exercising. These were specifically oesophageal varicosis, pulmonary bullae, drop in arterial oxygen saturation with exercise <80%, and signs of pulmonary hypertension in ECG and/or echocardiogram.

40 patients agreed to participate. Written informed consent was obtained from the patients and their guardians, if the patients were under 18 years of age. The ethics committees of the medical faculties of all participating centres approved the study protocol and procedures.

Figure 1 summarises the flow of patients through the study. Two patients were excluded from the study at the baseline visit due to a FEV1 below 35% predicted. No patient had to be excluded for one of the other specified exclusion criteria.

FIGURE 1 about here

At the end of the baseline assessments, patients were randomly assigned to the intervention or the control group. The procedure allocated 60% of all patients to the intervention group since

we expected more drop-outs in this group. In the process of the study, five patients decided to discontinue their participation. One male control patient moved to a town far away and was not willing to travel; one female patient in the intervention group decided to join another study. For the remaining drop-outs reasons were not given.

Due to exacerbations, some patients could not be tested on all scheduled visits. During the time period between baseline and 6 months, 22 patients of the intervention group and all 15 patients of the control group were seen at least once. The number of patients investigated at 12 months was 19 in the intervention group and 12 in the control group. During the 18- to 24-months period, 20 patients of the intervention group and 13 of the control group were assessed at least once.

Study design and procedures

Patients were seen in their respective center at baseline, and after 3, 6, 12, 18, and 24 months. At each visit, VO_2peak (primary outcome) was determined as highest VO_2 over 30 s during a continuous incremental cycling task to volitional fatigue (10). Wmax was taken as the power maintained over the final completed 1-minute stage. A Wingate test was employed to determine muscle power (peak power – PP and mean power – MP) (11). Engagement in vigorous physical activity was determined by accelerometry over 7 days. Height and body mass were measured, and skinfold thickness was determined at four sites. Percent body fat (%BF) was calculated using age-specific equations (12,13). FEV_1, forced vital capacity (FVC), and residual volume relative to total lung capacity (RV/TLC) were determined and expressed as %predicted (9,14,15). Quality of life was assessed by questionnaire (CFQ-14+) (16).

Intervention

Patients in the intervention group consented to increase their sport activities by a minimum of 3 times 60 minutes per week for the first six months of the study. All patients of the intervention group received activity counselling at the baseline visit and at those after 3 and 6 months. First, an exercise specialist and the patient discussed options about incorporating intense physical activities in daily life. Based on the results of the exercise tests and clinical data, an individual activity plan was generated which incorporated the patients' preferred physical activities and their availability near their homes. Patients were equipped with a heart rate monitor (Accurex plus, Polar Electro GmbH, Büttelbron, Germany) and provided with a target heart rate for endurance type activities which was just below the heart rate at the individual gas exchange threshold (17). Patients were also encouraged to perform strength enhancing exercises since strength building activities and interval training have been shown to be effective for conditioning and improving health in CF (18).

Four of the 23 patients of the intervention group chose to engage exclusively in endurance type sports (cycling, jogging, swimming) while three chose ball games (squash, badminton, soccer). Five patients combined weight training with endurance training in a fitness centre while the remaining 11 patients of the intervention group engaged in a variety of activities combining endurance type sports with ball games and strengthening exercises.

Some logistic support and, if needed, financial help (maximum: Euro 200) was offered to the patients to foster the realization of the activity plan. For example, the specialist called the director of a fitness centre in order to facilitate admission of a patient and to stimulate specific supervision and guidance. Alternatively, the patient received financial support to become a sports club member. Patients of the intervention group were called several times during the first 6 months of the study to check on their activity behaviour and, if necessary, to offer

additional help. After the first six months, patients in the intervention group were encouraged to maintain or further increase their activity level.

Patients in the control group were told to keep their physical activity level constant for the first 12 months of the study. Thus, the assessment at 12 months marked the end of the controlled follow-up period. During the second year of the study, the open follow-up period, control subjects were free to change their physical activity behaviour.

Data analysis and Statistics

The intervention and control groups were compared for baseline characteristics using t-test for continuous and Chi^2-statistics for dichotomous data. Groups were compared for the reported incidence of reported febrile infections at each visit using Chi^2-statistics. The rank sum test was used to assess group differences in attitude towards sports activities at each visit while changes from baseline were analyzed separately for each group using the matched signed rank test.

For primary and secondary outcome variables, changes from baseline to subsequent visits were calculated. To assess the long-term effects of the intervention, the changes from baseline to 18 months and 24 months were compared between groups using ANOVA for unbalanced repeated measures allowing for missing data. In case of a significant group difference, two subsequent analogous tests were performed: for the main intervention period up to 6 months, and for the 12-months visit. Estimates of the effects of the intervention and their standard errors were obtained from the ANOVA analyses.

All analyses were performed using BMDP statistical software release 7 (Statistical Solutions Ltd., Cork, Ireland). Statistical significance was accepted at $p<0.05$. Data are reported as means±standard deviation if not stated otherwise.

RESULTS

Physical characteristics and activity behaviour of the study population are summarised in table 1. At baseline, there were no significant differences between the groups. There was also no difference between the groups in any QoL domain (data not shown).

TABLE 1 about here

Relative to baseline and the control group, the intervention group reported a significant increase in sports activities of 2.16±0.49 h·week^{-1} during the first 6 months of the study. For the same time period, the increase in vigorous physical activity in the intervention group measured objectively by accelerometry was 1.05±0.43 h·week^{-1} (non significant). There was no difference between the groups in the reported number of infections with fever at any time during the study. There was also no difference between the groups in the reported attitude towards sports activities at baseline and during the follow-up visits and no change in the reported attitude over time.

Primary outcome

Figure 2 shows the effect of the intervention on the primary outcome variable VO_2peak. There was a significant intervention effect on the change in VO_2peak during the long-term, open follow-up period 12 to 18 months after the 6-months intervention (Table 2). Subsequent analyses showed significant group differences for the main 6-months training period, but not for the assessment at 12 months (Table 2).

FIGURE 2 about here

Secondary outcomes:

Results of secondary outcomes with significant effects of the intervention at 18 to 24 months are documented in Table 2.

Work capacity. A significant effect was observed for Wmax at long-term follow-up and during the initial 6-months training period (Table 2).

Muscle power. There was no effect of the intervention on PP and MP at 18 to 24 months.

TABLE 2 about here

Physical activity. The change in time spent in vigorous activities as assessed by accelerometry was significantly different between the groups during the open, long-term follow-up period (Table 2). Although there was a trend for vigorous activities in favour of the intervention group throughout the initial 12 months of the study, the effect was not significant.

Anthropometry. There was no effect of the intervention on either changes in height or body mass. However, a significant group difference in the change of skinfold thickness occurred between baseline and the assessments at 18 to 24 months (Table 2). Relative to the control group, the intervention group experienced a decrease in skinfold thickness, which was also evident at the 12-months visit. There was no significant difference between the groups in the change of percent body fat or lean body mass.

Lung function. As shown in table 2, the difference in FVC change from baseline to 18 to24 months between groups was about 6 %predicted favouring the intervention group while no

differences between groups were observed during the first year of the study. No effects of the intervention were evident for FEV1 and RV/TLC.

Quality of life. There was no significant effect of the intervention on QoL scales except for the scale "Subjective health perception". Here, the intervention group profited during the 18- to 24-months follow-up and the main 6-months intervention period (Table 2).

DISCUSSION

This study documents that positive health effects of a 6-months home-based partially supervised conditioning program can be observed 12 months and more after the end of the intervention. These favourable long-term health effects were obtained for aerobic fitness, vigorous physical activity, and FVC which are important and relevant determinants of health in CF (8;19). Furthermore, the patients´ subjective health perception remained positively affected by the intervention long after the program had ended.

The difference in change of aerobic fitness (i.e.VO_2peak and Wmax) between the intervention and control group at long-term follow-up was about 10% of baseline values. This positive effect was reached right after the 6-months partially supervised intervention period, but more importantly, was also evident at long-term follow-up without any further formal intervention and supervision. This novel finding is promising and shows that a 6-months partially supervised and individualised physical activity program might suffice to induce persisting changes in activity behaviour and health. This increase is clinically relevant when considering that VO_2peak is an important predictor of mortality (8).

Surprisingly, no effect of the intervention on VO_2peak and Wmax was evident at the 12-months visit despite significant effects during the 6-months training period and at the long-term follow-up after 18-24 months (Figure 2 and Table 2). This phenomenon is not easily explained. It does not reflect differences in sample composition among time periods since an

analysis including only patients with complete data revealed the same pattern. A potential reason might be that the 12-months assessments took place during winter times where most health problems occur (20). Although there was no difference between the groups in the reported number of febrile infections between the 6-months and the 12-months assessment, subclinical exacerbations inducing a transient reduction in vigorous activities might have occurred in the intervention group reducing the patients´ physical activity. This hypothesis is in line with the intervention groups´ perception of health which was lowest at the 12-months visit. Another possible explanation for the non-significant effect of the intervention on aerobic fitness at 12 months could be an intermittent decline in exercise adherence due to the cold winter season.

Skinfold thickness decreased more in the intervention group compared with the controls. At first, this seems alarming since a poor nutritional status has been associated with higher mortality in CF (21). However, there were no differences in changes of height or weight between the groups and no significant effect of the intervention on percent body fat. A significant increase in muscle mass was not reached, possibly because the intervention was rather mild.

In line with other studies evaluating the effects of a conditioning program in CF lasting at least 6 months we found positive effects of the intervention on FVC, but not on FEV1 (2;4). Our data suggest that the beneficial effect on FVC is not caused by a decrease in pulmonary hyperinflation since no effect of the intervention on RV/TLC was observed. We can only speculate that the regular exercise might have resulted in a concomitant training of respiratory muscles, thereby increasing FVC (22-25).

Concordant with the significant long-term effects of the intervention on aerobic fitness and lung function, patients of the intervention group perceived significant and long lasting benefits to their health compared with control patients. However, no effect on any other scale

of the QoL questionnaire was demonstrable. This is somewhat surprising since training-induced changes in physical fitness have been associated with changes in the physical functioning scale, another QoL domain assessed with the CF questionnaire used in the present study (5). We can only speculate that factors other than physical fitness affect the QoL scales in such a way that the effects of increased aerobic capacity were clouded in the present study.

For long-term benefits, an intervention program involving physical conditioning should be able to modify exercise behaviour towards an active lifestyle. The long-lasting effects of the intervention observed in the current study suggest that a partially supervised, individualized, home-based approach may be sufficient to change activity behaviour in patients with CF. The lasting effects of a 6-months home-based condition program are of major clinical importance since such a program can be realized relatively easily. The practical implementation of such a program requires the assessment of exercise-related risks based on the patient´s medical status, his preferred physical activities, and – in some patients – the results of an exercise test to rule out exercise induced hypoxemia or arrhythmia (26;27). With respect to beneficial effects, the type of activity chosen by the patient for his or her exercise routine probably does not matter at large. At least in the short run, anaerobic (5), and aerobic exercises (1-3), as well as strength training (1) or a combination thereof (4) have been effective in enhancing fitness and health in CF.

There are some limitations of this study to be addressed. First, although not statistically significant, the control group appeared somewhat healthier and more active at baseline than the intervention group (Table 1). We cannot exclude that this differences might have favoured a positive change in health-related outcomes in the intervention group that were not related to the intervention itself. However, there is some evidence that patients who did not do well in the past might have a faster decline of health status in the future (28). Thus, the somewhat better health status of the controls in our study at baseline could also strengthen our results.

Second, there might have been a bias towards positive effects of the intervention for VO_2peak and skinfold measurements since the outcome assessors were not blinded for these parameters. However, great care was taken that each individual measurement was administered following standardized procedures and criteria and – in case of the exercise tests – was performed to exhaustion irrespective of group allocation. Third, engagement in vigorous activities was, on average, not increased by the intended extent (2.16 instead of 3 h/week) which might reflect underreporting or – most likely – an insufficient compliance with the intervention. Yet, the effects of the program were still significant in favour of the intervention. At last, the incomplete long-term patient follow-up, an inheritant feature in intervention studies of 2-years duration, might somewhat compromise the validity of the results. However, the percentage of patients tested at each scheduled assessment was similar in the intervention and control group (figure 1) and we were able to assess more than 85% of all patients recruited at least once in the 18- to 24-months follow-up period.

In conclusion, a 6-months home-based partially supervised and individualized physical conditioning program lead to long-lasting beneficial effects on physical fitness, activity and lung function in patients with CF more than one year after the intervention has ended. This finding indicates that persisting changes of activity behaviour can be initiated by such a program.

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Table 1) Subject´s characteristics at study entry

	Intervention Group	Control Group
N	23	15
Male/female	13/10	6/9
Age (years)	19.5±6.4	19.4±5.3
Height (cm)	165.6±11.6	165.7±11.3
Body mass (kg)	55.5±13.7	56.8±13.3
Sum of 4 skinfolds (mm)	37.4±13.9	35.3±12.1
Body fat (%)	17.8±7.4	17.2±6.5
Lean body mass (kg)	45.3±11.0	47.0±11.7
FVC (%predicted)	81.5±13.1	88.2±16.3
FEV1 (predicted)	69.1±17.2	75.6±21.9
RV/TLC (%predicted)	172.1±46.8	161.6±68.3
Vigorous physical activity ($h \cdot week^{-1}$)	4.31±2.68	6.27±2.93
VO_2peak ($ml \cdot min^{-1} \cdot kg^{-1}$)	37.2±8.9	39.4±6.9
Wmax ($W \cdot kg^{-1}$)	2.81±0.58	2.98±0.62
PP ($W \cdot kg^{-1}$)	9.50±1.51	8.89±1.63
MP ($W \cdot kg^{-1}$)	6.59±1.19	6.38±1.16

Table 2) Effects of the intervention on changes in outcome variables from baseline at different time intervals during the 2-year study period. The reported effects are estimated regression coefficients and their asymptotic standard errors. Positive values indicate that the intervention group had a larger increase or a smaller decrease in the respective parameter than the control group. Mean changes from baseline for the control group (CON) and the intervention group (INT) are also given for each time period of the study.

	Estimated effect of training					
	18-24 months		3-6 months		12 months	
	Mean effect±SE (group means)	P	Mean effect±SE (group means)	P	Mean effect±SE (group means)	P
ΔVO_2peak ($ml \cdot min^{-1} \cdot kg^{-1}$)	3.73±1.23 CON: -1.25; INT: 2.48	0.002	2.04±1.00 CON: 0.18; INT: 2.22	0.041	0.70±1.18 CON: 0.01; INT: 0.71	0.551
$\Delta Wmax$ ($W \cdot kg^{-1}$)	0.37±0.11 CON: -0.06; INT: 0.31	0.001	0.25±0.11 CON: -0.08; INT: 0.17	0.033	0.19±0.11 CON: 0.02; INT: 0.21	0.078
ΔVigorous physical activity ($h \cdot week^{-1}$)[$]	1.63±0.82 CON: -2.47; INT: -0.84	0.047	1.05±0.87 CON: -1.12; INT: -0.06	0.225	2.08±2.00 CON: -1.29; INT: 0.79	0.299
ΔSum of 4 skinfolds (mm)	-7.10±3.20 CON: 2.63; INT: -4.47	0.027	-1.19±1.92 CON: -0.41; INT: -1.60	0.536	-5.68±2.63 CON: 0.74; INT: -4.94	0.031

ΔFVC (%predicted)	6.06±2.87	0.035	0.50±2.45	0.837	2.71±3.61	0.453
	Con: -6.44; INT: -0.38		CON: -1.32; INT: -0.82		CON: -3.15; INT: -0.44	
Δ subjective health	9.89±4.72	0.036	9.91±4.60	0.031	-2.31±6.71	0.730
perception	CON: -10.73; INT: -0.85)		CON: -5.68 INT: 4.23		CON: -0,76 INT: -3,07	

ΔVO_2peak – change in peak oxygen uptake from baseline; ΔWmax – change in maximal work load during an incremental cycling task; ΔFVC – change in forced vital capacity from baseline.

FIGURE LEGENDS

Figure 1) Outline of study design and flow of patients through the study.

- Outcome variables assessed at each study visit: quality of life, anthropometry, lung function, muscle power, maximal aerobic power, peak oxygen uptake, physical activity

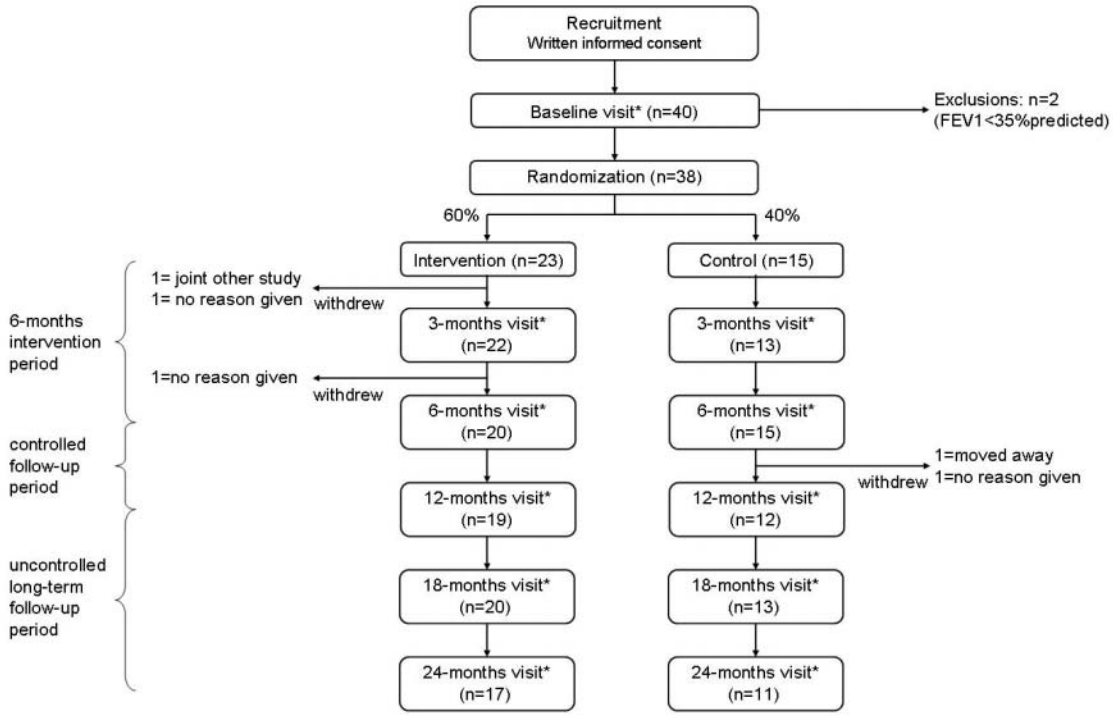
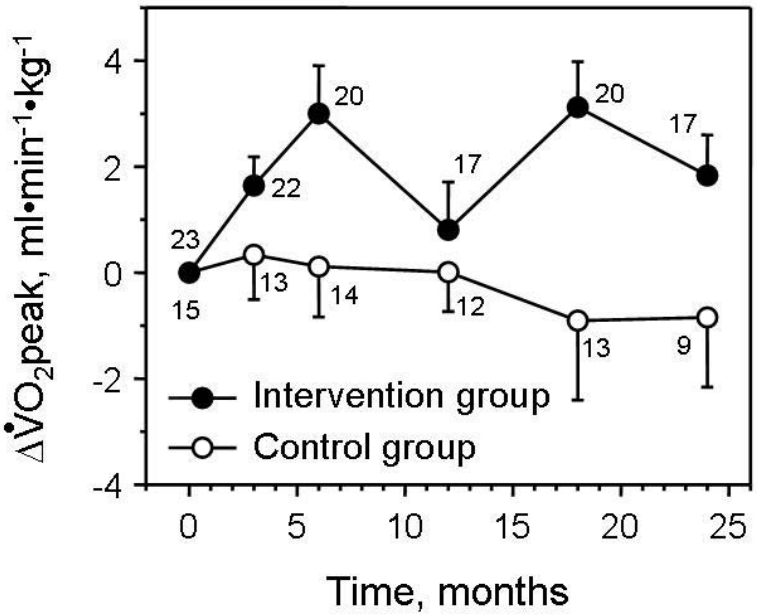


Figure 2) Change in VO_2peak from baseline in the intervention and the control group. Data are represented by means (dots), standard errors (whiskers), and respective numbers of patients. There was a significant difference between groups ($p<0.01$) and a significant group x time interaction ($p<0.01$) in the repeated measures ANOVA involving all 5 follow-up time points.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25
Time, months
$\Delta\dot{V}O_2$peak, ml•min^{-1}•kg^{-1}
Intervention group
Control group
23
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