A randomized controlled trial of a 3-year home exercise program in cystic fibrosis

Jane Schneiderman-Walker, MSc, Susan L. Pollock, BPE, Mary Corey, PhD, Donna D. Wilkes, MSc, Gerard J. Canny, MD, Linda Pedder, MD, and J. Joseph Reisman, MD

Objectives: To evaluate the effects of a 3-year home exercise program on pulmonary function and exercise tolerance in mildly to moderately impaired patients with cystic fibrosis (CF) and to assess whether regular aerobic exercise is a realistic treatment option.

Study design: Seventy-two patients with CF (7-19 years) were randomly assigned to an exercise group (a minimum of 20 minutes of aerobic exercise, at a heart rate of approximately 150 beats/min, 3 times weekly) or a control group (usual physical activity participation). Pulmonary function, exercise tolerance, clinical status, hospitalizations, and compliance with therapy were monitored during scheduled visits to the hospital's CF clinic.

Results: Sixty-five patients were included in the analyses. The control group demonstrated a greater annual decline in percent of predicted forced vital capacity compared with the exercise group (mean slope ± SD, –2.42 ± 4.15 vs –0.25 ± 2.81; $P = .02$), with a similar trend for forced expiratory volume in 1 second (–3.47 ± 4.93 vs –1.46 ± 3.55; $P = .07$). Patients remained compliant with the exercise program over the study period. An improved sense of well-being was reported with exercise.

Conclusions: Pulmonary function declined more slowly in the exercise group than in the control group, suggesting a benefit for patients with CF participating in regular aerobic exercise. Consistent compliance with the home exercise program and a self-reported positive attitude toward exercise provide further evidence of the feasibility and value of including an aerobic exercise program in the conventional treatment regimen of patients with CF. (J Pediatr 2000;136:304-10)

From the Division of Respiratory Medicine, The Hospital for Sick Children, Departments of Paediatrics and Public Health Sciences, The University of Toronto, Toronto, Ontario, Canada; and the Respiratory Unit, Our Lady's Hospital for Sick Children, Dublin, Ireland.

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Reprint requests: J. Joseph Reisman, MD, Paediatric Respiratory Medicine, The Hospital for Sick Children, 555 University Ave, Toronto ON M5G 1X8, Canada.

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Advances in the treatment of cystic fibrosis, including more efficient chest physiotherapy, enzyme supplementation, and antibiotics,[1] have led to increases in life expectancy from a median survival age of 11 years in 1966 to 30 years in 1996.[2] Pulmonary function, specifically forced expiratory volume in 1 second, has been reported as the best predictor of mortality in patients with CF[3] and is a widely used clinical end point in therapeutic trials.[4] Results of investigations on the effects of an exercise training program on pulmonary function have been inconclusive.[5-20] One postulated mechanism for the improvement in pulmonary function seen with training may be the stimulation of the respiratory muscles to aid the clearance of lung secretions.[21]

See editorial, p. 279.

CF	Cystic fibrosis
FEF_{25-75}	Forced expiratory flow between 25% and 75% of vital capacity
FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
MVV	Maximal voluntary ventilation
$\dot{V}E$	Minute ventilation
$\dot{V}O_{2max}$	Maximal oxygen consumption
W_{max}	Maximal working capacity

Inconsistencies in pulmonary function results reported by various researchers may be attributed to exercise programs of varying types, duration, and intensity. Although supervised programs are likely to encourage high patient compliance and close monitoring of subjects, they are not always fea-

sible. Programs of high intensity may be difficult to maintain beyond a short-term study period. This study was proposed to determine whether a long-term home exercise program, in which subjects were offered a choice of aerobic activities, could effect a change in pulmonary function. Although other home exercise programs in patients with CF have been conducted,[8-12,17,19,20] many of these were either structured in their activity or shorter term, with the exception of a 30-month program that demonstrated no change in pulmonary function.[9]

Exercise tolerance has been shown to increase with regular aerobic training in patients with CF[8] and has been correlated with both clinical status[9] and airway obstruction[22] in these patients. Aerobic fitness has been suggested as a reliable indicator of disease status and prognosis. Nixon et al[23] reported an 83% survival rate for a highly fit group of patients, compared with 51% and 28% for moderately fit and unfit patients. This effect of aerobic fitness on mortality was present even after controlling for lung function.[23]

Previous research at The Hospital for Sick Children has examined various modes of treatment that may affect the decline in pulmonary function,[24,25] demonstrating that a minimum 2-year study period is required to detect long-term changes in pulmonary function. Therefore this 3-year randomized study was designed to determine whether an organized home exercise program of long duration, in addition to standard medical treatment and prescribed physiotherapy, would improve pulmonary status or influence its rate of deterioration in mildly to moderately impaired patients with CF. Additionally, our secondary purpose was to evaluate whether the implementation of a home exercise regimen could be a realistic complement to the current long-term treatment of CF and whether the recommended amount of exercise was enough to effect a change in exercise tolerance.

METHODS

Patients

For this investigation, 72 mildly to moderately impaired patients with CF (FEV_1 ≥40%), ranging in age from 7 to 19 years, were recruited at the CF clinic at The Hospital for Sick Children in Toronto. Although 162 patients met the eligibility criteria, not all were available to participate because of enrollment in other studies, a history of noncompliance with study protocols, or irregularity of visits to the clinic. Before commencement of the study, the protocol was approved by the Human Subjects Review Committee of The Hospital for Sick Children, and written informed consent was obtained from all patients.

Study Design

In this randomized controlled trial, the statistician (M.C.) used computerized random number assignment to allocate patients to either an exercise group (n = 36) or a control group (n = 36). A 3-year follow-up period ensued.

The study's exercise physiologists (J.S.W. and D.D.W.) educated the treatment group on the minimum requirements of aerobic activity. Activities such as running, swimming, cycling, and soccer were suggested as examples of activities that utilize large muscle groups in a continuous manner. Patients were instructed to participate in their favorite aerobic activities for a minimum of 20 minutes, at least 3 times per week. Each training session was to begin with 5 minutes of warm-up and end with 5 minutes of cool-down. Members of the exercise group were taught to monitor their pulse while exercising and advised to train at a target heart rate of 70% to 80% of their maximum rate, or approximately 150 beats/min.[26] Monitoring techniques were reviewed during phone and clinic conversations. Members of the control group were asked to maintain their usual levels of physical activity throughout the study period. All subjects were instructed to perform their usual schedule of physiotherapy and medications as prescribed by their physician. Regular telephone contact with all study participants occurred at least every 4 to 6 weeks.

Protocol

Study patients continued with their regularly scheduled clinic visits, approximately every 12 to 16 weeks. Height and weight were measured, and weight as a percentage of ideal for height was calculated by using the standards of Tanner et al.[27] Shwachman clinical[28] and Brasfield radiograph[29] (x-ray) scoring, in addition to Tanner maturity staging,[27] were also recorded during clinic visits. Forced vital capacity, FEV_1, peak expiratory flow rate, maximal voluntary ventilation, and forced expiratory flow between 25% and 75% of vital capacity (Gould Sentry System 50, Gould Inc, Dayton, Ohio) were determined annually according to standard spirometric techniques.[30] Pulmonary function values were expressed as a percent of predicted value for height and sex, based on standards previously developed in this laboratory.[31] Pulmonary function technologists were unaware of each patient's group assignment. Skinfold thickness was measured at the biceps, triceps, and subscapular and supra-iliac sites by using Harpenden skinfold calipers (John Bull British Indicators, Ltd, England). The average of 2 measures was taken, unless the difference between them was greater than 0.4 mm. If this were the case, a third measurement was performed. Lean body mass and percent fat were then calculated.[32]

On entry into the study and at yearly intervals thereafter, a maximal incremental cycling test was performed on an electrically braked cycle ergometer (Rodby Electronik AB, Enhörna, Sweden). For this progressive exercise test, the Godfrey protocol of 1-minute increases in work increments was chosen according to sex, height, and physical activity level.[33] Throughout the test,

patients breathed through a mouthpiece connected to a 2-way Y-valve of low resistance and dead space. Heart rate (lead II, electrocardiogram), arterial oxygen saturation (Hewlett-Packard 47201A ear oximeter, Palo Alto, Calif), inspired minute ventilation (Parkinson-Cowan dry gas meter, Manchester, England), mixed expired oxygen (Applied Electrochemistry oxygen analyzer, Sunnyvale, Calif), carbon dioxide (P.K. Morgan 901-MK2, Chatham, England), and respiratory rate (thermistor) were monitored continuously on an 8-channel recorder. Oxygen consumption, carbon dioxide production, tidal volume, and respiratory exchange ratio were measured continuously on-line through an automated exercise testing program developed in our laboratory. Blood pressure was measured at rest and immediately after peak exercise with a mercury sphygmomanometer. The test was considered complete when the patient reached exhaustion, based on an inability to maintain a continuous pedaling speed of 60 revolutions per minute. Maximal work capacity was recorded as percent predicted.[33]

Both the exercise and control groups recorded their physical activity in a daily diary throughout the study. Parents were involved in the completion of the activity diary as needed, depending on the age and/or maturity of the child. Date, type of activity, duration in minutes, and level of intensity from 1 to 5 (1 for "easy," 3 for "easy conversation while exercising," 5 for "too difficult to talk") were listed. Diary sheets were collected for both study groups at each clinic visit; physical activity was subsequently categorized as general play (difficult to quantify, unstructured play), inactive (consistently <3 times per week), moderately active (a minimum of 3 sessions of aerobic activity per week), or very active (a minimum of 5 sessions of aerobic exercise per week).

A final written questionnaire completed by the participants from both groups, with help from parents when needed, was used to evaluate both their attitudes toward physical activity and their perceived feasibility of a regular exercise program. The exercise group was asked how difficult it was to meet the activity requirement of 3 times per week, and both groups were asked how realistic a goal it would be if asked by their doctors to exercise aerobically that often (on a scale of 0-5, where 0 = easy and 5 = difficult or impossible).

Compliance

In addition to regular telephone contact, annual incentives, such as sports bags and T-shirts, were offered to the patients to support their continued participation. Efforts were made to contact the child's physical education teachers and to involve parents and siblings in a supportive role. Compliance with prescribed physiotherapy and with the exercise program was ranked by the exercise physiologists, according to the scoring system by Passero et al,[34] with values of 0, 1, or 2 indicating poor, partial, or full compliance, respectively. Information about compliance with physiotherapy and exercise regimens was provided by the patient, with help from the parent when needed.

Statistical Analysis

Rate of decline in FEV_1 was the primary outcome variable. Secondary outcome measures were the annual rates of change in FVC, FEF_{25-75}, maximal working capacity, and maximal oxygen consumption. These results from the pulmonary function and exercise tests were used as major determinants of the efficacy of the aerobic intervention. Brasfield radiograph score,[29] Shwachman clinical score,[28] nutritional and anthropometric parameters, and hospitalization data were also analyzed and compared by using Student *t* test. Level of significance was set at $P < .05$. For each subject, a rate of decline was computed for each variable by using least-squares regression. Student *t* test was used to compare average slopes and baseline values in the 2 study groups. Analysis of variance was used to compare mean compliance scores in different years by means of an F test. Categorical variables were compared by χ^2 analysis. Pearson's correlation coefficient was computed to assess the correlation between pulmonary function and exercise parameters.

RESULTS

Of 72 patients with CF who entered this study, 4 (3 girls and 1 boy) dropped out of the exercise group (1 moved and 3 quit) before completion of year 1, and 3 patients (2 girls from the exercise group and 1 boy from the control group) withdrew before completion of year 2 (1 had poor health, 1 was incarcerated, and 1 was pregnant). Subsequently, one girl in the control group died before completion of year 3. Data for the 7 subjects who did not complete at least 2 years of follow-up in the study have not been included in the reported analysis. Routine pulmonary function was available for these patients, and a full "intention to treat" analysis produced results similar to those reported. However, in order to present equivalent analyses of spirometry and exercise testing, results are presented for the 65 subjects who completed at least 2 years of follow-up.

Physical and clinical subject characteristics are given in Table I. Table II provides baseline values for exercise parameters, and Table III gives percent predicted pulmonary function values, showing that randomization was successful in producing groups that were balanced for all measures. Mean baseline parameters in this group of 65 were similar to those in the randomized group of 72.

At baseline, 66% (43/65) of the patients had mild pulmonary impairment (FEV_1 > 80% predicted), and 34% (22/65) of the patients were catego-

rized as moderately impaired (FEV_1 = 40%-80% predicted). The 2 groups were similar with respect to disease severity. Sixty-three percent of the control group and 70% of the exercise group had mild impairment.

The 2 groups were also similar in the proportion of patients for whom sputum cultures were positive at baseline: *Burkholderia cepacia* (control, 31.4%; exercise, 40.0%), *Pseudomonas aeruginosa* (94.3% vs 90.0%), and *Staphylococcus aureus* (71.4% vs 70.0%).

The mean annual rates of change for physical, exercise, and pulmonary function parameters are shown in Table IV. The control group demonstrated a significantly greater mean annual rate of decline in FVC over the study period than that of the exercise group (–2.42 ± 4.15 vs –0.25 ± 2.81, P = .02). A similar trend was noted for FEV_1 (–3.47 ± 4.93 vs –1.46 ± 3.55, P = .07). There were no significant differences in exercise parameter changes in the 2 groups.

A correlation analysis was conducted to determine the relationship between exercise tolerance and pulmonary function. FEV_1 and FVC were selected as indicators of pulmonary function, and W_{max} and $\dot{V}O_{2max}$ were representative of exercise tolerance. Table V shows that positive and significant correlations were demonstrated for both FEV_1 and FVC with W_{max} and $\dot{V}O_{2max}$ at all testing periods. The correlation was stronger at follow-up times than at baseline and was not different in the 2 study groups (data not shown).

Mean scores of exercise compliance (range, 0-2) within the exercise group for years 1 (1.51 ± 0.55), 2 (1.51 ± 0.60), and 3 (1.49 ± 0.62) did not differ. These scores were higher than mean scores for compliance with conventional physiotherapy, which were consistently lower, although not statistically different, for the exercise group (0.69 to 0.91) compared with the control group (0.95 to 1.44). Not surprisingly, activity diary scores were higher for the exercise group compared with the control group, indicating that the exercise group was participating in more physical activity than the control group at year 1 (P = .06), year 2 (P = .006), and year 3 (P = .01).

There were no significant differences between groups for x-ray or Shwachman scores throughout the 3-year study period. In the year before the study's onset, there were no differences between groups for either mean number of hospitalizations or mean days in the hospital, nor were there any significant differences at years 1, 2, or 3.

There was an 88% (57/65) response rate for the final questionnaire (29 respondents from the exercise group and 28 from the control group). Patients were asked how they felt when involved in regular exercise compared with when not. Of the 49 patients who answered this question (26 from the exercise group and 23 from the control group), 43 reported positive effects, ranging

Table I. Baseline subject characteristics

Characteristic	Exercise group	n	Control group	n
Age (y)	13.4 ± 3.9	30	13.3 ± 3.6	35
Height (cm)	153.3 ± 17.4	30	148.8 ± 17.3	35
Weight (kg)	45.9 ± 14.0	30	41.3 ± 14.0	35
Percent of ideal weight for height	101.3 ± 9.2	30	100.7 ± 11.5	35
Percent body fat	18.3 ± 6.9	25	16.9 ± 4.9	27
Lean body mass (kg)	38.2 ± 13.1	25	34.1 ± 11.1	27
SBP (mm Hg)	102.8 ± 10.2	29	101.9 ± 10.8	33
Shwachman score (/100)	89.2 ± 9.1	30	87.7 ± 9.5	34
X-ray score (/25)	19.6 ± 2.7	30	19.7 ± 3.1	34

Values are mean ± SD. The exercise group comprised 12 girls and 18 boys; the control group, 15 girls and 20 boys.
SBP, Systolic blood pressure.

Table II. Exercise parameters at baseline

Variable	Exercise group	n	Control group	n
Sa_{O_2} at rest (%)	95.8 ± 1.3	24	96.0 ± 2.0	31
Max HR (beats/min)	180.2 ± 11.9	30	177.8 ± 11.7	35
Max $\dot{V}_E$ (L/min)	67.1 ± 27.2	30	62.1 ± 25.5	35
SaO_2 at max (%)	94.4 ± 2.1	24	95.1 ± 1.9	31
$\dot{V}O_{2max}$ (mL/kg/min)	40.6 ± 7.6	30	40.7 ± 7.9	35
Max SBP (mm Hg)	132.3 ± 16.3	27	133.6 ± 18.6	29
W_{max} (% pred)	94.8 ± 15.0	30	93.5 ± 17.5	35
$\dot{V}_{Emax}$/MVV	83.9 ± 26.1	30	77.9 ± 20.1	35

Values are mean ± SD.
Sa_{O_2}, Arterial oxygen saturation; *Max,*parameter at maximal workload; *HR,* heart rate; *SBP,* systolic blood pressure; *$\dot{V}_{Emax}$/MVV,* ventilatory reserve.

Table III. Percent of predicted pulmonary function (for height and sex) at baseline

Variable	Exercise group (n = 30)	Control group (n = 35)
FVC	92.6 ± 15.7	90.1 ± 12.9
FEV_1	89.2 ± 19.5	87.9 ± 17.8
PEFR	89.9 ± 20.3	90.6 ± 13.2
MVV	84.9 ± 24.3	88.6 ± 17.2
FEF_{25-75}	76.3 ± 31.2	72.9 ± 29.2

Values are mean ± SD.
PEFR, Peak expiratory flow rate; *MVV,* maximal voluntary ventilation.

Table IV. Annual rates of change of physical, exercise, and pulmonary function parameters

Variable	Exercise group (n = 30)	Control group (n = 35)	*P* value
Percent of ideal weight for height	0.48 ± 2.52	–0.04 ± 2.75	.43
FVC (% pred)	–0.25 ± 2.81	–2.42 ± 4.15	.02
FEV_1 (% pred)	–1.46 ± 3.55	–3.47 ± 4.93	.07
FEF_{25-75}(% pred)	–3.07 ± 5.34	–3.87 ± 7.00	.61
Max $\dot{H}R$ (beats/min)	0.51 ± 3.68	–0.59 ± 4.33	.28
Max $\dot{V}_E$ (L/min)	3.93 ± 8.31	1.84 ± 6.57	.26
$\dot{V}O_{2max}$ (mL/kg/min)	–1.80 ± 2.21	–1.85 ± 2.51	.93
$\dot{V}_{Emax}$/MVV (%/min)	–1.58 ± 8.49	0.95 ± 7.59	.21
W_{max} (% pred)	–1.68 ± 5.16	–2.50 ± 6.08	.56

Values are mean ± SD.
% pred, Percent predicted (height and sex); *Max*, maximal; *HR*, heart rate; $\dot{V}_{Emax}$/*MVV*, ventilatory reserve.

Table V. Correlation between pulmonary function and exercise tolerance

	W_{max}			$\dot{V}O_{2max}$		
	R	n	*P* value	R	n	*P* value
FEV_1 (% pred)						
Baseline	.34	65	.005	.35	65	.005
Year 1	.55	65	.0001	.42	64	.0006
Year 2	.52	60	.0001	.44	58	.0006
Year 3	.59	63	.0001	.46	62	.0002
FVC (% pred)						
Baseline	.29	65	.02	.28	65	.03
Year 1	.54	65	.0001	.37	64	.003
Year 2	.48	60	.0001	.37	58	.004
Year 3	.59	63	.0001	.41	62	.0009

from feeling better about themselves and having more energy with exercise to having less chest congestion. Four boys from the control group and 2 boys from the exercise group reported no change in well-being with exercise. In terms of difficulty (maximum = 5) in meeting the activity requirement (3 times per week), the mean scores (mean ± SD) were 1.92 ± 1.73 for 18 boys and 1.73 ± 1.56 for 11 girls, all from the exercise group. In assessing the feasibility of an exercise program (how realistic a goal it would be if asked by their doctors to exercise aerobically that often), the exercise group (n = 28) reported a mean score of 1.54 ± 1.47, and the control group (n = 28) 2.14 ± 1.81. However, this between-group difference was not statistically significant (*P* = .17).

DISCUSSION

A 3-year program of exercise therapy slowed the rate of decline in pulmonary function for a group of mildly to moderately impaired patients with CF. Rates of decline in the exercise group were less than those of the control group, which were similar to those previously reported in another sample of patients with comparable disease severity from the same CF population.[24] In another randomized controlled trial[35] in which patients were allocated to receive either ibuprofen or a placebo, rates of decline in the placebo group were similar to those in this study.

Previous investigations have suggested that rates of pulmonary function decline can be affected by short-term, supervised training programs, indicated by changes in FEV_1 and/or FVC.[13,15,17] It is now evident that a long-term, unsupervised program has the ability to positively influence pulmonary function in mildly to moderately impaired patients with CF. Andrew et al[36] have suggested that the larger values for vital capacity seen in swimmers versus nonswimmers may result from both training during the growth period and genetic endowment, supporting the findings of Åstrand et al[37] that female swimmers had higher lung volumes in relation to height than their nonathletic counterparts. In addition, Twisk et al[38] reported that changes in physical activity positively correlated to changes in FVC. Therefore we hypothesize that training may have contributed to the favorable rate of decline for FVC in the exercise group in this study.

Improvements in exercise tolerance in patients with CF have been demonstrated in studies in which the exercise program was intense, supervised, and of a short duration.[13,17] However, other investigations,[10,12] including this study, have been unable to show improvements in exercise tolerance. Our program may have been unique in that patients were able to choose aerobic activities according to their own individual interests, in order to encourage compliance, and to begin to address the question of whether regular exercise could be feasibly incorporated into the management of CF. It may be that a minimum of 3 weekly aerobic sessions was enough to effect change in pulmonary function, however insufficient to demonstrate a training effect. In addition, the baseline exercise results of these patients with CF were comparable to those of healthy children.[26] Perhaps a training effect was not demonstrated over the study period

because of the patients' relatively high fitness levels at baseline. Establishing thresholds for a training effect in this CF population has many challenges: the start-and-stop nature of young children's physical activity patterns, the demanding daily routines of a CF family, and the potential apathy toward exercise in the adolescent group.

However, responses from the final patient questionnaire did suggest that both groups perceived benefits from regular exercise. This was demonstrated by an overall positive attitude toward physical activity. After the 3-year study period, the exercise group indicated that the prescribed exercise protocol (3 times per week for a minimum of 20 minutes) was feasible to maintain.

A direct correlation between pulmonary function and exercise tolerance has been demonstrated in the literature.[13] Our research supports this correlation. However, pulmonary function and exercise tolerance reflect different physiologic processes within the lungs and periphery. Therefore the prediction of exercise tolerance for an individual should not be based solely on pulmonary function.[39] Other investigations have demonstrated that exercise tolerance can be predicted from nutritional status,[40] resting hypoxemia,[40] and peripheral muscle function[41] in addition to lung function.

An assessment of compliance with both prescribed physiotherapy and the exercise protocol was conducted in this study. In the exercise group, compliance with exercise was demonstrated to be higher than compliance with physiotherapy throughout the study. At all follow-up times, compliance with physiotherapy was always higher in the control group. Based on these scores, the exercise group's adherence to both therapies may have been too demanding, and the perceived benefits of regular exercise, reported by the study participants, may have encouraged the exercise group to replace some physiotherapy sessions with exercise.

Regular contact with the study patients was maintained by the study physiologists, contributing to the high level of exercise compliance observed in the exercise group for the duration of the study. Holzer et al[10] hypothesized that nonsignificant changes in pulmonary function and exercise tolerance were due to diminished exercise compliance over a 3-month period. These studies suggest that CF clinic programs should encourage physical activity during all patient encounters, as well as through newsletters and special events.

This study has shown that regular aerobic exercise beyond the average CF pediatric activity patterns can contribute to a delay in the decline of pulmonary function. Many questions as to the precise role of exercise in the treatment of CF remain. Investigations must continue to address variables that may confound the relationship between exercise therapy and CF, including disease severity, duration and intensity of training, compliance with the prescribed exercise program, type of training setting (supervised vs unsupervised), genetic predisposition to aerobic endurance, type of exercise, and other therapy modalities. Research is still needed to determine whether long-term participation in regular aerobic exercise can decrease the mortality rates of persons with CF and whether a specific type and quantity (or threshold) of exercise is most effective in bringing about changes in disease status and quality of life in patients with CF.

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