Intrahospital Weight and Aerobic Training in Children with Cystic Fibrosis: A Randomized Controlled Trial

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European University of Madrid, Madrid, SPAIN; Academic Medical Center, University of Amsterdam, Amsterdam, THE NETHERLANDS; Department of Pneumology, Hospital Infantil Universitario Niño Jesús, Madrid, SPAIN; and Sport Science Department, Colorado College, Colorado Springs, CO

ABSTRACT

SOSA, E. S., I. F. GROENEVELD, L. GONZALEZ-SAIZ, L. M. LÓPEZ-MOJARES, J. R. VILLA-ASENSI, M. I. BARRIO GONZALEZ, S. J. FLECK, M. PÉREZ, and A. LUCIA. Intrahospital Weight and Aerobic Training in Children with Cystic Fibrosis: A Randomized Controlled Trial. Med. Sci. Sports Exerc., Vol. 44, No. 1, pp. 2–11, 2012. Purpose: The purpose of our study was to assess the effects of an 8-wk intrahospital combined circuit weight and aerobic training program performed by children with cystic fibrosis (of low–moderate severity and stable clinical condition) on the following outcomes: cardiorespiratory fitness (VO₂peak) and muscle strength (five-repetition maximum (5RM) bench press, 5RM leg press, and 5RM seated row) (primary outcomes) and pulmonary function (forced vital capacity, forced expiratory volume in 1 s), weight, body composition, functional mobility (Timed Up and Down Stairs and 3-m Timed Up and Go tests), and quality of life (secondary outcomes). We also determined the effects of a detraining period (4 wk) on the aforementioned outcomes. Methods: We performed a randomized controlled trial design. Eleven participants in each group (controls: 7 boys, age = 11 ± 3 yr, body mass index = 17.2 ± 0.8 kg m⁻² (mean ± SEM); intervention: 6 boys, age = 10 ± 2 yr, body mass index = 18.4 ± 1.0 kg m⁻²) started the study. Results: Adherence to training averaged 95.1% ± 7.4%. We observed a significant group × time interaction effect (P = 0.036) for VO₂peak. In the intervention group, VO₂peak significantly increased with training by 3.9 mL·kg⁻¹·min⁻¹ (95% confidence interval = 1.8–6.1 mL·kg⁻¹·min⁻¹, P = 0.002), whereas it decreased during the detraining period (−3.4 mL·kg⁻¹·min⁻¹, 95% confidence interval = −5.7 to −1.7 mL·kg⁻¹·min⁻¹, P = 0.001). In contrast, no significant changes were observed during the study period within the control group. Although significant improvements were also observed after training for all 5RM strength tests (P < 0.001 for the interaction effect), the training improvements were not significantly decreased after the detraining period (all P > 0.1 for after training vs detraining). We found no significant training benefits in any of the secondary outcomes. Conclusions: A short-term combined circuit weight and aerobic training program performed in a hospital setting induces significant benefits in the cardiorespiratory fitness and muscle strength of children with cystic fibrosis. Key Words: PEDIATRIC PATIENTS, EXERCISE, VO₂PEAK, MUSCLE STRENGTH

Cystic fibrosis (CF) is a progressive hereditary disease, affecting 1 of 2500 Caucasian newborns. Because of a defect in the CF transmembrane conductance regulator gene, excess mucous is produced in the lungs, liver, pancreas, and reproductive organs; pulmonary function is impaired; absorption of nutrients is suboptimal; and bacterial infections frequently occur (27). In children with CF, exercise capacity and cardiorespiratory fitness are often limited because of several reasons: obstruction of bronchioles impairs gas exchange, respiratory muscles are weakened (21), and lung tissue is inflamed (21), all of which decrease pulmonary function. Heart function can be altered mainly by an increase in the right ventricular afterload imposed by hypoxic vasoconstriction and increased pulmonary vascular resistance (21). Peripheral muscles are also affected because of systemic inflammation, oxidative stress, malnutrition, and lack of vigorous physical activity (17). Given the above, it is not surprising that pulmonary function, expressed as forced

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The potential participants included intrahospital program, the aerobic program resulted in greater gains in VO\textsubscript{2peak} physical activity levels, and quality of life (QoL), whereas the former intervention resulted in greater increases in children’s weight, lung function, and leg muscle strength. The results of their study suggest an exercise program composed of both aerobic and resistance training may positively affect more physiological factors negatively affected by CF than either training type alone. However, no previous RCT has assessed the effects of a combined intrahospital program, i.e., including both resistance (weight lifting) and endurance exercises, on the functional capacity of children with CF. We recently built an intrahospital pediatric gymnasiunm (including weight training machines especially designed for the body size of children and cycle ergometers). This provides an ideal setting for intrahospital exercise interventions in chronically diseased children and adolescents, as recently shown (6,29).

The main purpose of the current RCT was to assess the effects of an 8-wk combined circuit weight and aerobic training program on pulmonary function (FVC, FEV\textsubscript{1}), cardiorespiratory fitness (VO\textsubscript{2peak}), dynamic muscle strength, body composition, functional mobility, and QoL in children with CF. Concurrent training of both aerobic and strength abilities was chosen as the training type to enhance both VO\textsubscript{2peak} and strength, both of which are negatively affected by CF. Circuit weight training was chosen as the resistance training type because it has been shown to significantly increase both muscle strength and VO\textsubscript{2peak} (4). We also determined the effects of a detraining period on the aforementioned outcomes. We hypothesized that the combined training program would result in increases in the aforementioned variables in children with CF compared with a control group performing no physical training.

METHODS

Study Design

The present study is an RCT and was designed to be compliant with the recommendations of the Consolidated Standards of Reporting Trials statement of 2010 (32,35). The Medical Ethics Committee of the Children’s Hospital Infantil Universitario Niño Jesús (Madrid, Spain) approved the study design, study protocols, and informed consent procedure. The subjects and their parents or caregivers provided written informed consent. After baseline measurements, subjects were randomly allocated to one of the two groups of this study, i.e., the control (standard therapy) or intervention (exercise) group, as explained below. The intervention group performed an 8-wk exercise training program that was followed by a 4-wk detraining period. All participants were evaluated at baseline and at the end of the 8-wk exercise and 4-wk detraining periods in the same setting (Hospital Infantil Universitario Niño Jesús) and by the same investigators. The study was performed between January 2010 and January 2011, following the ethical guidelines of the Declaration of Helsinki (last modified in 2000).

Study population. The potential participants included 111 children previously diagnosed using a genetic test detecting CF and treated at the Children’s Hospital Niño Jesús in Madrid. The inclusion criteria were being a boy or girl age 5 to 15 yr and living in the Madrid area (to be able to attend training sessions). Exclusion criteria were having severe lung deterioration, as defined by an FEV\textsubscript{1} <50% of what is expected, having an unstable clinical condition (i.e., hospitalization within the previous 3 months), having a Burkholderia cepacia infection, and having a skeletal muscle disease or any other disorder impairing exercise.

Randomization and blinding. Participants were randomly assigned to either the control or the training group with a block on gender on the basis of a randomization sequence. The staff in charge of outcome assessment was blinded to the participant randomization assignment, but the staff involved with training was not. Participants and their parents or caregivers were explicitly informed to which group they were assigned as well as the study hypotheses and told not to discuss their randomization assignment with assessment staff.

Familiarization and Reliability of Outcome Assessment

Before the start of the study, all participants underwent a familiarization period with all the tests for outcome assessment that are described below. The familiarization period included one session for treadmill testing and two ~30-min sessions for functional/strength tests. Each session was preceded by a warm-up and ended with a cool-down of the same activities and duration used during the training period. All familiarization, testing, and training sessions took place in the afternoon/evening (4:00–7:00 p.m.). Children consumed their usual lunch approximately 3 h before all sessions. We also assessed test–retest reliability for the tests that are described below. A high intraclass correlation coefficient (reliability analysis) between repeated tests was demonstrated (R consistently ≥0.99, P < 0.001). Previous research from our group has demonstrated a high test–retest reliability for the strength tests that are described below in diseased children (29).
Standard Therapy (Control) Group

During the intervention period, participants in the control group were instructed on the positive effects of regular physical activity. They were instructed to maintain their usual chest physiotherapy sessions (twice a day), which consisted mainly of postural drainage and chest percussion and vibration manually performed by parents/caregivers following previous instructions by an experienced physical therapist.

Intervention (Training) Group

Besides performing the same chest physiotherapy sessions as the control group (twice a day), the participants allocated to the intervention group enrolled in three weekly nonconsecutive training sessions (Monday–Wednesday–Friday) for 8 wk (i.e., 24 sessions in total) during the year 2010. All training sessions took place during the afternoon/evening (4:00–7:00 p.m.) in the intrahospital gymnasia of the Children’s Hospital Niño Jesús, equipped with weight training machines (Strive, Inc., McMurray, PA) and cycle ergometers (Rhyno Magnetic H490; BH Fitness Proaction, Vitoria, Spain) specifically built for the body size of children and adolescents. Each exercise session was individually supervised by trained exercise physiologists, i.e., one supervisor per participant. To minimize the risk of lung infection, each child trained alone. Each patient was instructed about staying hydrated during the training sessions (i.e., ≥500 mL of water or sport drink per session).

All children wore a portable HR monitor during the sessions to monitor their exercise intensity. The training started with a 10-min warm-up period (cycle ergometer), followed by the 20- to 40-min aerobic cycle ergometer training. The workload was set for each session so that it corresponded to the HR eliciting the ventilatory threshold (VT) during the baseline exercise test (see below). The second part of the training session consisted of three circuits of the following 11 strength exercises (which are listed in the order they were consistently performed): bench press, shoulder press, leg extension, leg press, leg curl, abdominal crunch, low back extension, arm curl, elbow extension, seated row, and lateral pulldown. For each exercise, the participants performed one set of 12–15 repetitions (total of ~20-s duration) with no rest periods between exercises. The load was gradually increased as the strength of each child improved, i.e., from 40% of five-repetition maximum (5RM) lifting ability at the start of the program to 60% of 5RM at the end of the program.

Detraining

After the intervention period, participants in the intervention group underwent a 4-wk detraining period, during which they did not perform any of the training sessions that are described above. During this period, participants in both the intervention and control groups performed the aforementioned chest physiotherapy sessions, twice per day, and were instructed on the positive effects of regular physical activity.

Participant Retention and Adherence

To reduce participants’ dropout and to maintain adherence to the training program, all sessions were accompanied with music. We assessed adherence to training in every session. We considered a session completed when at least 90% of the prescribed exercises were successfully performed. Make-up sessions were allowed if a session was missed (because of hospitalization, illness, or any other reason).

Outcome Measures

Primary outcomes: cardiorespiratory fitness and dynamic muscle strength. In all children, cardiorespiratory fitness was assessed in the pediatric exercise physiology laboratory of the aforementioned hospital, equipped with a treadmill and a metabolic cart (see below). After a familiarization session, all children performed a graded exercise test on a treadmill (Technogym Run Race 1400HC; Gambettola, Italy) for the determination of \( \dot{V}O_{2\text{peak}} \) and VT. Treadmill speed began at 1.5 km·h\(^{-1}\) (for the smaller children, height <120 cm) or 2.5 km·h\(^{-1}\) (if children’s height was >120 cm), with a grade of 0.5%. Thereafter, both treadmill speed and inclination were increased (by 0.1 km·h\(^{-1}\) and 0.5%, respectively) every 15 s. The tests were terminated upon volitional fatigue of the children, when they showed loss of ability to maintain the required workload, or when they had severe coughing. During the tests, the children could not see their parents but were given verbal encouragement by the investigators. Gas exchange data were measured by breath by using open-circuit spirometry and specific pediatric face masks (Vmax 29C; SensorMedics, Yorba Linda, CA). The \( \dot{V}O_{2\text{peak}} \) was recorded as the highest value obtained for any continuous 20-s period (29). The VT was determined using the criteria of an increase in both the ventilatory equivalent of oxygen (\( \dot{V}E/\dot{V}O_{2} \)) and end-tidal pressure of oxygen with no increase in the ventilatory equivalent of carbon dioxide (\( \dot{V}E/\dot{VCO}_{2} \)) (29). A finger pulse oximeter (TruSatTM; General Electric Finland Oy, Helsinki, Finland) was used for determination of peripheral oxygen saturation (\( \text{SpO}_{2} \)).

We measured children’s dynamic upper and lower body muscle strength endurance using the same seated bench, seated row, and seated leg press machines that were used for training (Strive, Inc.). The 5RM value was measured in kilograms and is defined as the maximum strength capacity to perform five repetitions until momentary muscular exhaustion. The testing protocol consisted of three warm-up sets at 50%, 70%, and 90% of the perceived 5RM separated by 1-min rest periods (16). A 2-min rest period followed the last warm-up set after which a 5RM attempt was made at 100%–105% of perceived 5RM depending upon the effort needed to perform the last warm-up set at 90% of the perceived 5RM. If the first 5RM attempt was successful, the resistance was increased by 2.5%–5%, and after 2 min of rest, another 5RM attempt was made. If the second 5RM attempt was successful, a second testing session was
scheduled after 24 h of rest. If the first 5RM attempt was not successful, the resistance was decreased 2.5%–5%, and after 2 min of rest, another 5RM attempt was made. If the second 5RM attempt was successful, the weight used was considered the 5RM. If the second 5RM attempt was not successful, another testing session was scheduled after 24 h of rest. Each subject was instructed to perform each exercise to momentary muscular exhaustion. Any repetitions not performed with a full range of motion were not counted.

**Secondary outcomes: pulmonary function, functional mobility, body composition, and QoL.** Spirometry tests preceded treadmill evaluations. We determined the participants’ FVC and FEV1 following the spirometry protocol by the American Thoracic Society (1). We also measured the participants’ maximal inspiratory pressure (PImax) using a mouth pressure meter (CareFusion 232 Ltd., Chatham Maritime, Kent, United Kingdom). We measured the PImax at residual volume, and the best result from three inspiratory attempts was taken. At least 1 min was allowed between attempts to minimize the effects of muscle fatigue. Testing of PImax was performed in accordance with established standards (2).

To measure children’s functional mobility, we used the Timed Up and Go (TUG) tests of 3 m and the Timed Up and Down Stairs (TUDS) test (10). Both tests have been shown to be reliable and valid in healthy children and also in children with various diseases or disabilities (10,19). The TUG test of 3 m is a measure of the time needed to stand up from a seated position in a chair, walk 3 m, turn around, return to the chair, and sit down. For the TUDS test, the time it took to ascend and descend 12 stairs was measured (10). All children used a handrail in the TUDS test to diminish the risk of falling. Performance time in all the tests was measured by the same investigator with the same stopwatch to the nearest 0.1 s.

Standing height was measured to the nearest 0.1 cm with a clinical stadiometer (Asimed T2; Barcelona, Spain) while children were standing barefoot. Body mass was determined to the nearest 0.05 kg using a balance scale (Ano Sayol SL, Barcelona, Spain) with the participant in his or her underwear. Body mass index (BMI) was calculated as weight/height (kg·m−2). Skinfold thickness was measured with a Harpenden caliper (Holton, Crymych, United Kingdom) at the biceps, triceps, subscapular, abdominal, suprailiac, thigh,

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**FIGURE 1**—Flow diagram of study.
and calf areas on the left side of the body following the criteria described elsewhere (18). We estimated children’s percentage body fat (34) from their body density values using age- and gender-specific equations, i.e., for boys and girls age <11 (5), 12–15 (7), and 16–18 yr (8).

We determined children’s QoL with the Spanish version (1.0) of the CF Questionnaire-Revised (CFQ-R) (20). The ≤11-yr-old group completed the CFQ-R through an interview, whereas the 12- to 13-yr-old group completed the same CFQ-R themselves, and adolescents age ≥14 yr completed the CFQ-R version 14+. In addition, in children age ≤13 yr, a parent or caregiver completed the parent version of the CFQ-R. Response choices included ratings of frequency, likelihood, or difficulty on four-point scales of different domains, i.e., physical functioning, social functioning, emotional functioning, treatment burden, eating disturbances, body image, digestive symptoms, and respiratory symptoms. Individual scores were standardized on 0- to 100-point scales, with higher scores indicating better QoL, and we computed a total QoL score on the basis of the sum of the scores of each domain. To minimize the risk of children memorizing the responses to the questionnaire in the evaluation after detraining (just 4 wk elapsed since the posttraining evaluation), we only used pre- and posttraining data.

### Statistical Analysis

To assess the training effects on the study outcomes, we analyzed the data according to the intention-to-treat principle (13), that is, when posttest (or detraining) data were missing, baseline scores were considered posttest (or detraining) scores. For parametric data (i.e., all except QoL), we used a two-factor (group and time) ANOVA with repeated measures. We repeated the analysis using baseline values as a covariate. For each outcome variable, we reported the level of significance corresponding to the main group (between subjects), time (within subjects), and interaction (group × time) effects. To minimize the risk of a type I error, we only performed within-group comparisons, when a significant time or group × time effect was present. We adjusted multiple comparisons for mass significance (14). For nonparametric data (i.e., QoL scores), we compared the mean change over time (after training – before training) in the two groups with the Mann–Whitney U test. The level of significance was set to 0.05.

### RESULTS

The study’s flow diagram is shown in Figure 1. Eleven participants in each group started the study. The main demographic and clinical characteristics at baseline of the two groups are shown in Table 1.

We could not assess one boy of the training group after the intervention period because of hospitalization for the treatment of gastroenteritis. At detraining, we could not assess another boy of the training group because he moved to a different city. We could not assess three children in the control group at detraining owing to (i) hospitalization for

**TABLE 1. Main demographic and clinical characteristics of the two groups at baseline.**

<table>
<thead>
<tr>
<th>Demographic characteristics</th>
<th>Intervention</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (% boys)</td>
<td>55</td>
<td>64</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>11 ± 3 (range = 5–15)</td>
<td>10 ± 2 (range = 6–14)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>147.3 ± 4.8</td>
<td>140.6 ± 3.6</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>39.9 ± 3.5</td>
<td>34.0 ± 2.6</td>
</tr>
<tr>
<td>BMI (kg m⁻²)</td>
<td>18.4 ± 1.0</td>
<td>17.2 ± 0.8</td>
</tr>
<tr>
<td>Clinical conditions (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthma</td>
<td>36</td>
<td>0</td>
</tr>
<tr>
<td>Allergic bronchopulmonary</td>
<td>18.2</td>
<td>0</td>
</tr>
<tr>
<td>aspergillosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cor pulmonale</td>
<td>18.2</td>
<td>0</td>
</tr>
<tr>
<td>Dehydration</td>
<td>18.2</td>
<td>0</td>
</tr>
<tr>
<td>Meconial ileum</td>
<td>9.1</td>
<td>9.1</td>
</tr>
<tr>
<td>Gastroesophageal reflux</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Rectal prolapse</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Biliary lithiasis</td>
<td>18.2</td>
<td>18.2</td>
</tr>
<tr>
<td>Gastrostomy</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Distal intestinal obstruction</td>
<td>0</td>
<td>9.1</td>
</tr>
</tbody>
</table>

Demographic data are in mean ± SEM. No significant between-group differences at baseline were found for age (P = 0.299), height (P = 0.239), weight (P = 0.199), or BMI (P = 0.320).

**FIGURE 2.—Results of VO₂peak by group. Data are mean ± SEM.** The numbers of participants who were actually evaluated before and after training and during detraining were 11, 10, and 10 in the intervention group and 11, 11, and 9 in the control group. The P values for group, time, and group × time interaction effect were 0.375, 0.198, and 0.036, respectively. *P = 0.002 for the before versus after training comparison within the intervention group; **P = 0.001 for the after training versus detraining comparison within the intervention group; †P = 0.023 for the between-group comparison at baseline. Range (min–max) values (mL·kg⁻¹·min⁻¹) for VO₂peak in our total study population were 22.9–46.8.
treatment of lung exacerbations (one boy, one girl) and (ii) parents declining evaluation (one boy).

Adherence and exercise adverse effects. Adherence to training in the intervention group averaged 95.1% ± 7.4%. Eight children (73% of total) completed the 24 planned sessions as originally planned, i.e., Monday–Wednesday–Friday. Two participants (both girls) did not perform two nonconsecutive training sessions, and two participants (two boys) did not perform one training session. Reasons for missing one or more sessions were school examinations (n = four sessions) and dehydration not associated with exercise (same girl, n = two sessions). Make-up sessions were possible for one girl and one boy so that they both completed 24 sessions in total. We noted no major adverse effect or health problem attributable to the testing sessions or prescribed training sessions.

Primary outcomes. The results of VO2peak are shown in Figure 2. Baseline levels of VO2peak were significantly higher in the control than in the experimental group (P = 0.023).

We observed a significant group × time interaction effect (P = 0.036, effect size (η²) = 0.153, statistical power = 0.634) for this variable. In the intervention group, VO2peak significantly increased with training by 3.9 mL·kg⁻¹·min⁻¹ (95% confidence intervals (CI) for the mean difference = 1.8–6.1 mL·kg⁻¹·min⁻¹, P = 0.002), whereas it decreased during the detraining period by a comparable magnitude of −3.4 mL·kg⁻¹·min⁻¹ (95% CI = −5.7 to −1.7 mL·kg⁻¹·min⁻¹, P = 0.001). In contrast, no significant changes were observed during the aforementioned period within the control group (training period, mean decrease of −2.2 mL·kg⁻¹·min⁻¹ (95% CI = −5.3 to 0.1 mL·kg⁻¹·min⁻¹, P = 0.155); detraining period, mean decrease of −0.7 mL·kg⁻¹·min⁻¹ (95% CI = −4.4 to 5.9 mL·kg⁻¹·min⁻¹, P = 0.758)). All of the 10 participants in the intervention group who were actually assessed after training reached higher VO2peak after the intervention compared with baseline assessment. Only one child showed desaturation during the tests (SpO2 of 86%, 88%, and 83% before and after training and during detraining, respectively). Mean values of SpO2 before and after training and during detraining averaged (mean ± SEM)
95.7% ± 0.5%, 96.4% ± 0.4%, and 96.1% ± 0.5% (control group) and 94.9% ± 0.9%, 95.6% ± 0.8%, and 94.5 ± 1.2% (intervention group).

The results of the strength tests are shown in Figure 3. We found significantly higher values of bench press (P = 0.007), leg press (P = 0.014), and seated row 5RM at baseline in the intervention than in the control group (P = 0.009). We observed a significant group × time interaction effect (P < 0.001, $\eta^2 = 0.440$, power = 1.000) for the 5RM bench press (Fig. 3). In the intervention group, the 5RM bench press significantly increased with training by 10.5 kg (95% CI = 7.0–14.0 kg, $P < 0.001$), whereas it was maintained during the detraining period (−1.2 kg, 95% CI = −3.6 to 3.0 kg, $P = 0.588$). Likewise, we found a significant group × time interaction effect for both the 5RM leg press and the 5RM seated row ($P < 0.001$ in both; $\eta^2 = 0.496$ and 0.610, respectively; power = 1.000 in both). In both tests, performance increased significantly with training (leg press: +24.9 kg, 95% CI = 14.3–34.4 kg, $P = 0.001$; seated row: +12.7 kg, 95% CI = 9.2–16.0 kg, $P < 0.001$) and was retained with detraining (leg press: −1.0 kg, 95% CI = −4.1 to 3.3 kg, $P = 0.807$; seated row: −0.2 kg, 95% CI = −3.6 to 3.2 kg, $P = 0.894$). In the control group, bench press, leg press, and seated row performance changed significantly during the study period (all $P > 0.1$). For illustrative purposes, the percent changes with training and detraining of the primary study outcomes in the two groups are shown in Figure 4.

**Secondary outcomes.** The results of secondary outcomes are shown in Table 2. There were no between-group differences at baseline ($P > 0.05$). We found no significant group × time interaction effect for any of the variables indicative of pulmonary function, i.e., $\text{FEV}_1$ ($P = 0.769, \eta^2 = 0.016$, power = 0.088), $\text{FVC}$ ($P = 0.920, \eta^2 = 0.005$, power = 0.062), or $\text{P}_{\text{Imax}}$ ($P = 0.797, \eta^2 = 0.012$, power = 0.083) (Table 2). Likewise, we found no significant group × time interaction effect for functional mobility (TUDS: $P = 0.196, \eta^2 = 0.078$, power = 0.336; 3-m TUG: $P = 0.928, \eta^2 = 0.004$, power = 0.061) or for anthropometric variables (weight: $P = 0.723, \eta^2 = 0.017$, power = 0.098; BMI: $P = 0.959, \eta^2 = 0.002$, power = 0.056; fat-free mass and percentage body fat: $P = 0.115, \eta^2 = 0.113$, power = 0.437).

The aforementioned results on primary and secondary outcome variables that we obtained with the ANOVA test (i.e., significant interaction effect for $\text{VO}_{2\text{peak}}$ and all strength tests) remained unchanged when the baseline levels of the aforementioned variables were entered as a covariate. Finally, we found no significant difference between the two groups in the post- versus pretraining scores of QoL, whether reported by children (Mann–Whitney $U = 14.0, P = 0.257$) or by their parents (Mann–Whitney $U = 8.5, P = 0.143$) (Table 1).

**DISCUSSION**

The main finding of our study was that a short-term (8 wk) combined circuit weight and aerobic training program performed inside a hospital setting induces significant benefits in the cardiorespiratory fitness and muscle strength of children with CF of moderate severity and stable clinical condition. Although gains in $\text{VO}_{2\text{peak}}$ decreased to pretraining values after the 4-wk training cessation period, gains in muscle

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**Table 2. Comparison between the two groups in the secondary study outcomes.**

<table>
<thead>
<tr>
<th>Parametric Variables</th>
<th>Group</th>
<th>Baseline</th>
<th>After Training</th>
<th>Detraining</th>
<th>$P$ for Group Effect</th>
<th>$P$ for Time Effect</th>
<th>$P$ for Interaction (Group × Time) Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary function</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\text{FEV}_1$ (L·s$^{-1}$)</td>
<td>Control</td>
<td>1.77 ± 0.17</td>
<td>1.87 ± 0.15</td>
<td>1.79 ± 0.19</td>
<td>0.756</td>
<td>0.263</td>
<td>0.769</td>
</tr>
<tr>
<td></td>
<td>Intervention</td>
<td>1.87 ± 0.24</td>
<td>1.94 ± 0.23</td>
<td>1.90 ± 0.25</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\text{FVC}$ (L)</td>
<td>Control</td>
<td>2.29 ± 0.19</td>
<td>2.36 ± 0.20</td>
<td>2.40 ± 0.24</td>
<td>0.685</td>
<td>0.024</td>
<td>0.920</td>
</tr>
<tr>
<td></td>
<td>Intervention</td>
<td>2.41 ± 0.24</td>
<td>2.49 ± 0.25</td>
<td>2.58 ± 0.29</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\text{P}_{\text{Imax}}$ (cm H$_2$O)</td>
<td>Control</td>
<td>65.1 ± 6.9</td>
<td>72.2 ± 7.2</td>
<td>76.4 ± 7.5</td>
<td>0.966</td>
<td>0.005</td>
<td>0.797</td>
</tr>
<tr>
<td></td>
<td>Intervention</td>
<td>64.0 ± 5.5</td>
<td>69.8 ± 6.8</td>
<td>75.2 ± 6.2</td>
<td></td>
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<td></td>
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<tr>
<td>Functional capacity</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TUDS test (s)</td>
<td>Control</td>
<td>6.2 ± 0.3</td>
<td>6.1 ± 0.4</td>
<td>6.2 ± 0.4</td>
<td>0.877</td>
<td>0.006</td>
<td>0.196</td>
</tr>
<tr>
<td></td>
<td>Intervention</td>
<td>6.5 ± 0.5</td>
<td>6.1 ± 0.3</td>
<td>6.2 ± 0.3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3-m TUG test (s)</td>
<td>Control</td>
<td>3.8 ± 0.1</td>
<td>3.6 ± 0.1</td>
<td>3.6 ± 0.1</td>
<td>0.263</td>
<td>0.061</td>
<td>0.928</td>
</tr>
<tr>
<td></td>
<td>Intervention</td>
<td>3.6 ± 0.2</td>
<td>3.4 ± 0.2</td>
<td>3.5 ± 0.2</td>
<td></td>
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<tr>
<td>Anthropometric variables</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Weight (kg)</td>
<td>Control</td>
<td>34.0 ± 2.6</td>
<td>35.1 ± 2.8</td>
<td>36.2 ± 3.0</td>
<td>0.222</td>
<td>0.001</td>
<td>0.723</td>
</tr>
<tr>
<td></td>
<td>Intervention</td>
<td>39.9 ± 3.5</td>
<td>40.5 ± 3.4</td>
<td>41.4 ± 3.4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI (kg·m$^{-2}$)</td>
<td>Control</td>
<td>17.2 ± 0.8</td>
<td>17.1 ± 0.8</td>
<td>17.4 ± 0.9</td>
<td>0.288</td>
<td>0.705</td>
<td>0.959</td>
</tr>
<tr>
<td></td>
<td>Intervention</td>
<td>18.4 ± 1.0</td>
<td>18.3 ± 0.7</td>
<td>18.5 ± 0.7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fat-free mass (%)</td>
<td>Control</td>
<td>81.1 ± 2.5</td>
<td>80.9 ± 2.1</td>
<td>81.1 ± 2.2</td>
<td>0.527</td>
<td>0.319</td>
<td>0.115</td>
</tr>
<tr>
<td></td>
<td>Intervention</td>
<td>78.1 ± 2.7</td>
<td>79.4 ± 2.8</td>
<td>78.8 ± 2.9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body fat (%)</td>
<td>Control</td>
<td>18.9 ± 2.5</td>
<td>19.1 ± 2.1</td>
<td>18.9 ± 2.2</td>
<td>0.527</td>
<td>0.319</td>
<td>0.115</td>
</tr>
<tr>
<td></td>
<td>Intervention</td>
<td>21.9 ± 2.7</td>
<td>20.6 ± 2.8</td>
<td>21.2 ± 2.9</td>
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</tr>
</tbody>
</table>

Data are mean ± SEM for parametric variables and median (min–max) for QoL. $\text{P}_{\text{Imax}}$, maximal inspiratory pressure; 3-m TUG, Timed Up and Go test of 3 m.

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strength were virtually maintained. This finding is in agreement with previous research on other diseased children (29). However, the program was possibly not long enough to induce significant gains in children’s pulmonary function or functional mobility. The children’s QoL was also unaffected by training.

Five studies using an RCT design have assessed the effects of exercise training in several health and fitness phenotypes in CF patients. Schneiderman-Walker et al. (31) studied the effects of a 3-yr home-based exercise program (≥20 min of aerobic exercise, thrice weekly) in patients age 7–19 yr. Pulmonary function (FVC and FEV₁) declined more slowly in the exercise group than in the control group. Klijn et al. (15) studied the effects of a 12-wk “anaerobic training” intervention (two 30- to 45-min weekly sessions, each consisting of different types of 30-s exercise bouts (sprints, jumps, throws, ball games), interspersed with longer (by three times) recovery bouts) in Dutch CF patients (mean age = 13–14 yr). Compared with the control group, participants in the intervention group significantly improved their anaerobic (assessed with the Wingate test) and aerobic performance (VO₂peak) and QoL. Hebestreit et al. (12) reported the effects of a home-based mixed-sports intervention (duration ≥ 6 months) on patients age 12–40 yr. They found significant increases in the VO₂peak, levels of vigorous physical activity, FEV₁, and perceived health after training. Orenstein et al. (24) compared the effects of a 1-yr home-based semisupervised upper body strength training regimen (where patients were encouraged to exercise at least three times per week) and a similarly structured aerobic training regimen, in patients age 8–18 yr. No standard therapy (control) group was assessed. They found both training procedures were associated with significant increases in strength and peak work capacity during cycle ergometry testing. Selvadurai et al. (33) compared the effects of two different types of training programs, i.e., five weekly sessions of aerobic (treadmill/cycle ergometry) versus resistance exercises (upper and lower limb machine exercises) performed by children with CF (age 8–16 yr) during hospitalization for intercurrent pulmonary infection (mean duration = 18–19 d). Compared with resistance training, the aerobic program resulted in greater gains in VO₂peak, physical activity levels, and QoL, whereas the former intervention resulted in greater increases in children’s weight, lung function, and leg muscle strength. The results of this last study suggest that an exercise program combining both aerobic and resistance training may be suitable for maximizing training gains in children with CF. In regard to this, our short-term intervention combining aerobic and resistance exercises in a circuit fashion induced significant improvements in both cardiorespiratory fitness and muscle strength.

Our findings showing a positive training effect on children’s VO₂peak are in agreement with the findings of previous RCTs (12,15,33). The increase we found in VO₂peak (+~11%) after only 24 exercise sessions performed during an 8-wk period is of clinical relevance. Mean levels of VO₂peak are usually lower in CF patients compared with their healthy referents (22,25). In most child patients of ages similar to that of our study participants (<17 yr), VO₂peak inevitably decreases over time, by ~2 mL·kg⁻¹·min⁻¹ per year on average (26). The aforementioned rate of decline was observed in our controls during the 3-month study period. Further, VO₂peak (as well as FEV₁) is an important predictor of mortality in CF patients (23,26). Mortality is very high in those children with VO₂peak values <32 mL·kg⁻¹·min⁻¹ (i.e., 60% after 8 yr), whereas it is null in those with VO₂peak levels >45 mL·kg⁻¹·min⁻¹ (26). In regard to this, our training program increased the VO₂peak of two children from a value <32 mL·kg⁻¹·min⁻¹ to a value above this threshold after only 8 wk. In addition, only one study participant had a VO₂peak value above 45 mL·kg⁻¹·min⁻¹; this further supports the need to prescribe exercise interventions for patients with CF during early phases of life, including patients with stable clinical conditions and low–moderate disease severity as the ones we studied. Furthermore, VO₂peak decreased to pretraining levels in the 4-wk detraining period; this indicates that exercise training to increase or at least maintain VO₂peak levels needs to be performed regularly by CF patients.

Our findings showing a significant increase in the children’s muscle strength after training are in agreement with previous research in the field using this exercise mode (24,33). Here, we showed that early increases in muscle strength can occur despite no concurrent increases in muscle mass, suggesting that neuromuscular factors (i.e., improved motor unit recruitment) were largely responsible for the gains we observed in muscle strength. We believe an emphasis should be placed in the prescription of combined aerobic and resistance exercise for CF patients beginning in early childhood owing to the fact that muscle weakness is prevalent (56% of total) among adults with CF (36). Further, adults’ muscle strength impairment is in excess to that expected from physical inactivity only and is not associated with VO₂peak levels (36). Despite earlier concerns regarding the safety and efficacy of youth strength training, current public health objectives now aim to increase the number of boys and girls (age 6 yr and older) who regularly participate in physical activities that enhance and maintain muscular strength (9). If appropriate training guidelines are followed (i.e., qualified instruction, competent supervision, and appropriate progression of the volume and intensity of training as we did here), regular participation in a strength training program has the potential to enhance children’s physical capacity and overall health and fitness status (9).

In our study, we did not find a training-induced improvement in pulmonary function and QoL. Discrepancy exists among previous RCTs in the field, with two studies showing significant training-induced increases in pulmonary function after resistance or aerobic exercise (31,33) and three studies reporting no such effect (12,15,24). Overall, it seems that long-term exercise interventions (i.e., several years) are necessary to overcome or at least attenuate the declining effect that CF has on pulmonary function (31). Further, clear
evidence is still lacking from RCTs on the effects of specific muscle respiratory training on the pulmonary function of children with CF (28). Previous research has shown significant improvements in the QoL of children with CF after interventions with a duration ≥6 months (12) or 2 (15) and 3 yr (31). Thus, although clinically relevant physiological gains in some parameters can be obtained after only 8 wk, longer exercise interventions are probably needed to elicit significant increases in the QoL of children with CF.

We believe there are several strengths in our design. For reaching the methodological fulfilments to support strong medical evidence, an exercise training intervention should meet four or more of the following criteria: randomization, intent-to-treat analysis, concurrent comparison group, adherence reported and equaling to at least 70% of the intervention prescription, less than 20% of participants lost to follow-up, documented reliability/validity of the exposure assessment and of the outcome, and blinded measurement (30). All the aforementioned criteria were met in our study. We believe that other methodological strengths and novelties of our design include the fact that we assessed the participants of both groups after a detraining period, as well as ensuring that, before baseline assessment, all participants were familiarized with the different tests for outcome measurements. A familiarization period to eliminate learning effects and assess the reliability of pretraining tests is necessary to accurately determine the effects solely attributable to training of muscular strength (11). Otherwise, potential increases in muscle strength could be artificially inflated. We believe another strength of our study stems from the fact that we performed an intrahospital training study. Previous research on another disease, childhood cancer, has shown the benefits of intrahospital individually supervised training programs combining aerobic and resistance exercises on the patients’ functional capacity versus home-based interventions (see Wolin et al. (38) for a review). Training interventions in diseased children are most successful when performed within the treating hospital, in part, to overcome the safety concerns expressed by some parents (38). On the other hand, there are limitations in our design. First, our population sample is limited, although we think this is partly overcome (and justifiable) by the fact that interventions were individually supervised and that each child was trained individually to minimize infection risk. Our findings on body composition are also limited by the fact that we used estimation equations for muscle and fat mass determination, and this method might not be sensitive enough to detect small changes in muscle mass (<2% here). It is likely that the use of more advanced and accurate techniques to assess body composition such as underwater weighing, air displacement plethysmography, or dual-energy x-ray absorptiometry may help to better elucidate the effect of the intervention on these patients. Besides the fact that we did not measure muscle mass, a potential weakness of our intervention arises from the lack of significant training-induced gains in secondary outcomes. Finally, children performed the aerobic training program on a cycle ergometer (because of the logistics of our intrahospital gymnasium, which is not yet equipped with treadmills), whereas HR values at the VT (which was used for aerobic training intensity determination) and \( VO_2\text{peak} \) were assessed during treadmill testing in our intrahospital exercise physiology laboratory. Treadmill training might have resulted in more appropriate training intensity prescription and higher training-induced \( VO_2\text{peak} \) gains. Despite this potential weakness, our training program did result in an improvement in \( VO_2\text{peak} \) in all of the 10 participants of the intervention group.

In summary, a short-term (8 wk) combined circuit weight and aerobic training program performed in a hospital setting induces significant benefits in the cardiorespiratory fitness and muscle strength of children with CF of moderate severity and stable clinical condition. Training-induced gains in cardiorespiratory fitness are lost relatively quickly (4 wk) after training cessation, whereas strength gains are maintained. Our data suggest that combining both supervised aerobic and resistance training in a hospital setting is a suitable option for exercise prescription in children with CF.

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REFERENCES