

Effects of an Intrahospital Exercise Program Intervention for Children with Leukemia

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ABSTRACT

SAN JUAN, A. F., S. J. FLECK, C. CHAMORRO-VIÑA, J. L. MATÉ-MUÑOZ, S. MORAL, M. PÉREZ, C. CARDONA, M. F. DEL VALLE, M. HERNÁNDEZ, M. RAMÍREZ, L. MADERO, and A. LUCIA. Effects of an Intrahospital Exercise Program Intervention for Children with Leukemia. *Med. Sci. Sports Exerc.*, Vol. 39, No. 1, pp. 13–21, 2007. **Purpose:** The purpose was to investigate the effect of a 16-wk intrahospital supervised conditioning program including both resistance and aerobic training and a 20-wk detraining period on measures of aerobic fitness, muscular strength, functional mobility, ankle range of motion, and quality of life (QOL) in children receiving treatment for acute lymphoblastic leukemia (ALL). **Methods:** Seven children (four boys, three girls; age: 5.1 ± 1.2 yr, body mass: 24.0 ± 5.8 kg, height: 114.6 ± 7.7 cm) in the maintenance phase of treatment against ALL performed three sessions per week for 16 wk of resistance (one set of 8–15 repetitions of 11 exercises) and aerobic training (30 min at $> 70\%$ HRmax) followed by 20 wk of detraining where no structured exercise program was performed. Before training, after training, and after detraining, a treadmill test determining $\dot{V}O_{2\text{peak}}$ and ventilator threshold (VT), muscular strength (6RM), functional mobility (timed up and down stairs test, time up and go 3-m and 10-m tests), passive and dynamic ankle range of motion, and self-reported quality of living were determined. **Results:** After training, significant increases in $\dot{V}O_{2\text{peak}}$, VT, upper- and lower-body muscular strength, and all measures of functional mobility were shown ($P < 0.05$). Muscular strength was well maintained (significantly greater than before training and no significant decrease from after training) during detraining, whereas $\dot{V}O_{2\text{peak}}$, VT, and functional mobility (not significantly different from before training but no significant decrease from after training) were only partially retained. **Conclusion:** Young children in the maintenance phase of treatment against ALL can safely perform both aerobic and resistance training. Training results in significant increases in measures of aerobic fitness, strength, and functional mobility. During detraining, strength and functional mobility are well maintained, whereas $\dot{V}O_{2\text{peak}}$ and VT are partially maintained. **Key Words:** CANCER, QUALITY OF LIFE, RESISTANCE TRAINING, DETRAINING

Acute lymphoblastic leukemia (ALL) is the most common childhood malignancy, accounting for approximately 26% of all childhood cancers. The dramatic improvements in treatment over the last decades have translated into a 70% cure rate for children with standard risk disease (17). However, as survival rates have improved, there has been an increasing recognition of adverse short-, mid-, or long-term effects associated with treatment and cancer itself that impair the quality of life (QOL) and functional capacity of patients and survivors of childhood ALL. These adverse

effects include impaired neuropsychological functioning, gross and fine-motor disturbances, anthracycline-induced cardiotoxicity, sarcopenia and muscle weakness, osteopenia and osteoporosis, pain, paresthesias, reduced ankle range of motion, and decreased energy expenditure (17).

Structured, supervised exercise training has been shown to increase the functional capacity of adult cancer patients and survivors, with subsequent improvement in their QOL (16). However, considerably less interventional research has been performed on childhood cancer. One pioneer study has been performed by Marchese et al. (18) on children receiving maintenance therapy against ALL. They evaluated the effects of a 4-month intervention program combining physical therapy sessions and home-based exercises (aerobic training, stretching exercises) in children with ALL. Ankle dorsiflexion range of motion and knee-extension strength, both of which are important functions for normal gait, were significantly improved after the aforementioned intervention.

We are unaware, however, of a study specifically assessing the cardiopulmonary and neuromuscular effects

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of a supervised intrahospital conditioning program including both resistance and aerobic training in children with ALL. If appropriate training guidelines are followed (i.e., qualified instruction, competent supervision, and an appropriate progression of the volume and intensity of training), resistance training increases motor performance skills and enhances the physical capacity and muscle strength of healthy children, including prepubescents (24). Similarly, endurance or aerobic training can increase the $\dot{V}O_{2peak}$ of healthy children, including prepubescents (28). Thus, both strength and aerobic training could result in physiological adaptations that could improve the functional capacity and QOL in childhood survivors of ALL, and both training modalities should be included in a training program for childhood survivors of ALL.

Little information is available concerning the effect of a training-cessation period or a detraining period in healthy children. However, detraining in healthy children does result in loss of strength (9,24,31) and $\dot{V}O_{2peak}$ (11). No longitudinal investigation has assessed the magnitude of functional capacity loss of previously trained ALL patients after a period of detraining. Thus, it is unknown how fast detraining occurs and which of the common fitness indices (i.e., $\dot{V}O_{2peak}$, muscle strength, etc.) is (are) most affected by the detraining process in ALL patients. This is an important consideration because it is unrealistic to assume that previously sedentary children who enroll in a scientific study including supervised individualized training will continue with a structured training program after completing participation in the study. Additionally, information concerning the detraining process in ALL patients may provide guidance concerning how long a period of detraining can be before decrements in functional capacity occur, and therefore training should be resumed if terminated for a personnel or medical reason.

It was the purpose of the present study to determine whether a 16-wk intrahospital supervised conditioning program including both resistance and aerobic-type training would improve functional capacity (i.e., peak oxygen uptake ($\dot{V}O_{2peak}$), ventilatory threshold, etc.), dynamic muscular strength of the upper and lower extremities, muscle functional mobility, ankle range of motion, and QOL in children receiving treatment against ALL. We also analyzed the effects of a 20-wk detraining period on these same parameters. We hypothesized that this type of program would have a significant beneficial effect on the aforementioned variables. On the basis of recent research on adult cancer survivors (13) and what is known to occur in healthy adults (22) and children (9,11,24,31), we also hypothesized that these children would retain some of the training gains after the detraining period.

MATERIAL AND METHODS

Methodological Approach to the Problem

For this study we chose to assess the effects of an exercise program in children in the last phase of treatment

(the “maintenance phase” (8)) against ALL, because those undergoing the earlier, more aggressive phases of treatment frequently experience one or more complications (tumor recurrence, marked anemia, infections, etc.) that could considerably compromise adherence to the program. For the same reason, we did not study children who had undergone bone marrow transplantation, because in this subpopulation of children with ALL, treatment complications, side effects, and tumor recurrences are frequent, which would compromise training adherence. We chose to study children of a very young age (4–7 yr) because no study on exercise training and cancer had previously assessed children during this early, critical phase of life, during which sedentary and poor physical capacity can have deleterious health consequences later in life.

Dependent variables were 1) functional capacity: peak oxygen uptake ($\dot{V}O_{2peak}$) relative to body mass ($mL \cdot kg^{-1} \cdot min^{-1}$) during graded exercise until exhaustion and the ventilatory threshold (VT). 2) Dynamic muscle strength endurance as measured by six-repetition maximum (6RM) lifting ability of both the upper (seated bench press and seated lateral row) and lower body (leg press) using a standardized testing procedure (15). We chose to assess dynamic muscle strength endurance instead of maximal dynamic muscle strength or one-repetition maximum (1RM). The rationale for this decision was that although improvements in the ability to perform maximal strength tests are of interest for athletic populations, they would be of little practical relevance for children under treatment for ALL. In ALL patients, maximal strength is not a main determinant of their ability to perform physical activities of daily living, which are mostly submaximal-strength tasks (e.g. climbing stairs, sitting and rising from a chair, etc.). Additionally, determination of maximal strength or 1RM is not recommended in healthy children (1), and therefore it would not be advisable in children suffering from diseases such as ALL. 3) Functional mobility that reflects performance in functional tests that reflect children’s ability to perform important physical abilities of daily living such as normal gait (i.e., the timed up and go test (TUG)) or navigating stairs (the timed up and down stairs test (TUDS) (12)). 4) Range of motion (passive and active) of ankle dorsiflexion and 5) QOL measured with a specific questionnaire for children and their parents.

An intrahospital gymnasium designed to be used by children during treatment against ALL (Children’s Hospital Niño Jesus of Madrid, Department of Onco-Haematology and Bone Marrow Transplantation, Madrid, Spain) (17) was the site of all physical conditioning and dynamic strength and functional mobility tests performed. Among other equipment, the intrahospital gymnasium includes pediatric (specifically built for the body size of children) weight training machines (Strive Inc, Canonsburg, PA) and bicycle ergometers (Rhyno Magnetic H490, BH Fitness Proaction, Vitoria, Spain).

Although one original goal was to assess a control group of age- and gender-matched children receiving the same treatment against ALL, it was not possible to recruit such a

group because none of the parents contacted gave us their permission to perform several strength and functional tests on their children given that they were not going to enter any type of interventional training program despite being required to undergo a tedious (4- to 6-wk duration) familiarization period (as detailed below). This would have required nonhospitalized children who do not have to visit the hospital more than one or two times per month to visit the hospital on several occasions during a 4- to 6-wk period despite not enjoying the benefits of a supervised conditioning program. Thus, although a control group would have strengthened the experimental design, for ethical and logistic reasons it was not possible to test a control group. If the familiarization process had not been included in the study's design, the validity and reliability of our measurements would have been significantly affected. Despite the lack of a formal control group, the study does use a controlled design in that each child served as his/her own control to compare pre-, post-, and detraining results (see below).

Patients

Before entering the study, written informed consent was obtained from each participant's parents, and the study was approved by the local human investigations committee and review board. A preliminary screening for subject selection was performed in the medical database of the onc-hematology department at the Children's Hospital Universitario Niño Jesús (Madrid, Spain). A total of 26 medical records of children treated for ALL in the aforementioned hospital were examined. After the oncologist treating each patient provided consent, subjects were deemed eligible for the study if they met each of the following conditions: 1) undergoing the last phase of maintenance therapy against standard-medium risk ALL following the ALL-BFM 95 protocol, which does not require constant hospitalization (8); 2) time elapsed after start of treatment ranging between 18 and 24 months; 3) 4–7 yr of age and within Tanner's stage I of maturation status; 4) having no condition that could contraindicate vigorous physical activity, such as severe anemia (hemoglobin < 8 g·dL⁻¹), fever > 38°C, or severe cachexia (loss of >35% pre-morbid body mass), platelet count lower than 50 × 10⁹ μL⁻¹, neutrophil count lower than 0.5 × 10⁹ μL⁻¹, or anthracycline-induced cardiotoxicity (17); and 5) currently living with their parents in Madrid (Spain).

Seven children (four boys, three girls; age: 5.1 ± 1.2 (mean ± SD) yr, body mass: 24.0 ± 5.8 kg, height: 114.6 ± 7.7 cm) met all the above-mentioned eligibility criteria and were included in the study. Their clinical characteristics are shown in Table 1. The maintenance therapy they were receiving throughout the entire study duration (including both training and detraining periods) consisted of daily mercaptopurine (50 mg·m⁻²·d⁻¹) and weekly methotrexate (20 mg·m⁻²·wk⁻¹) (8).

Measurements at Pretraining, Posttraining, and Detraining

All children consumed their usual breakfast (cereal, milk, and fruit juice) 3 h before the test protocols described below. All children performed a graded exercise test on a treadmill (Technogym Run Race 1400HC; Gambettola, Italy) for the determination of $\dot{V}O_{2peak}$. Each child performed at least one familiarization session before the actual treadmill test. Treadmill speed began at 1.0 km·h⁻¹ (or 1.5 km·h⁻¹ for the oldest participants) with a grade of 5.0%, and both treadmill speed and inclination were increased (by 0.1 km·h⁻¹ and 0.5%, respectively) every 15 s. The tests were terminated on volitional fatigue of the children and/or when they showed loss of ability to maintain the required workload. During the test, children could not see their parents, but they were given verbal encouragement by the investigators. Gas-exchange data were measured breath-by-breath using open-circuit spirometry and specific pediatric face masks (\dot{V}_{max} 29C, Sensesmedics, Yorba Linda, CA). $\dot{V}O_{2peak}$ was recorded as the highest value obtained for any continuous 20-s period.

All exercise tests were performed under similar environmental conditions (20–24°C, 45–55% relative humidity) and at the same time of day (10:00 a.m. to 1:00 p.m.). Heart rate was continuously monitored during the tests from a 12-lead ECG (Quest Exercise Stress System, Burdick Inc., Milton, WI).

The $\dot{V}O_2$ (mL·kg⁻¹·min⁻¹) at the ventilatory threshold (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 (PetO₂) with no increase in the ventilatory equivalent of carbon dioxide ($\dot{V}_E/\dot{V}CO_2$) (13).

None of the subjects had ever participated in a weight training or conditioning program before the study. To minimize the influence of a possible learning effect (attributable to improvement of technique and coordination and/or diminishment of muscle inhibition) and to stabilize the initial test results, before the start of the study, all subjects underwent a familiarization period. The familiarization period consisted of two to three sessions per week of 60-min duration for 4–6 wk. 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 of the study. The body of each familiarization session consisted of two to three sets of one to three repetitions of the exercises (seated bench press, seated lateral row,

TABLE 1. Clinical characteristics of the children with acute lymphoblastic leukemia (ALL).

Subject	Sex	Age	Time (months) Elapsed Since Start of Treatment	Risk Factor
A	Boy	6 yr, 7 months	24	Medium
B	Boy	5 yr, 9 months	24	Standard
C	Boy	7 yr, 4 months	22	Medium
D	Girl	4 yr, 7 months	21	Standard
E	Girl	4 yr, 4 months	20	Standard
F	Boy	5 yr, 5 months	18	Medium
G	Girl	6 yr, 3 months	24	Standard

seated leg press) used to evaluate muscular strength and two to three repetitions of the tests used to evaluate functional mobility (TUDS, 3-m TUG (TUG 3 m), and 10-m TUG (TUG 10 m) tests). Test–retest assessments were preceded by a warm-up period including aerobic and stretching exercises (~10 min) and a specific warm-up that preceded each test for the test–retest assessment.

Very high intraclass correlation coefficients ($R \geq 0.974$; $P < 0.001$) between repeated tests were demonstrated for all the tests that are described below: $R = 0.995$ ($P < 0.001$) for seated bench press, $R = 0.997$ ($P < 0.001$) for leg press, $R = 0.977$ ($P < 0.001$) for seated lateral row, $R = 0.989$ ($P < 0.001$) for the TUDS test, and $R = 0.974$ and $R = 0.997$ ($P < 0.001$) for the TUG 3 m and TUG 10 m, respectively. Using the same tests and equipment in older children of both sexes ($N = 7$; mean age: 10 ± 1 yr) being treated in the same hospital against several types of cancer, we have obtained similar results indicative of high test–retest reliability ($R \geq 0.989$ and $P < 0.001$ for all tests combined). Thus, any potential learning effect on the results of the variables determined should be minimal.

Dynamic upper- and lower-body muscle strength endurance were measured using a seated bench, seated lateral row, and seated leg-press machine (Strive Inc, Canonsburg, PA), respectively. The 6RM value was measured in kilograms and is described as the maximum strength capacity to perform six repetitions until momentary muscular exhaustion. The testing protocol consisted of three warm-up sets at 50, 70, and 90% of the perceived 6RM separated by 1-min rest periods (15). A 2-min rest period followed the last warm-up set, after which a 6RM attempt was made at 100–105% of perceived 6RM depending on the effort needed to perform the last warm-up set at 90% of the perceived 6RM. If the first 6RM attempt was successful, the resistance was increased by 2.5–5%, and after 2 min of rest, another 6RM attempt was made. If the second 6RM attempt was successful, a second testing session was scheduled after 24 h of rest. If the first 6RM attempt was not successful, the resistance was decreased 2.5–5%, and after 2 min of rest, another 6RM attempt was made. If the second 6RM attempt was successful, the weight used was considered the 6RM. If the second 6RM 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.

To measure children's functional mobility, we used the TUG 3 m, TUG 10 m, and TUDS tests (12). Both types of tests have been shown reliable and valid in healthy children and also in children with various diseases or disabilities (12,18). The TUG 3 m and 10 m tests are measures of the time needed to stand up from a seated position in a chair, walk 3 or 10 m, turn around, return to the chair, and sit down. For the TUDS, the time it took to ascend and descend 12 stairs was measured (12). All the children used a hand railing in all the tests. The use of a railing while ascending and descending the stairs was allowed 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.

A goniometer was used to measure ankle dorsiflexion passive and active range of motion (ROM). Ankle dorsiflexion passive (passive DF-ROM) and active (active DF-ROM) range of motion was measured with the children sitting with the knee flexed to 90° and the foot in neutral alignment (25).

The QOL of the children was assessed using the child report form of the Child's Health and Illness Profile—Child Edition (CHIP-CE/CRF), which is a self-report health-status instrument for children <11 yr old (26) and also using parents' ratings of their children's QOL (27). The CHIP-CE/CRF includes five domains: satisfaction (with self and health), comfort (concerning emotional and physical symptoms and limitations), resilience (positive activities that promote health), risk avoidance (risky behaviors that influence future health), and achievement (social expectations in school and with peers). In our study, after obtaining permission from the authors and the corresponding institution (see Acknowledgments section), we used the Spanish version of the CHIP-CE, which has been shown to be valid in Spanish children <11 yr (26).

Training Intervention

Exercise program. All children followed a 16-wk training program, consisting of three weekly sessions with a duration ranging from 90 min (in the first few weeks of the program) to 120 min (by the end of the program). Each session started and ended with a low-intensity 15-min warm-up and cool-down period consisting of cycle ergometer pedaling at very light workloads and stretching exercises involving all major muscle groups. The core portion of the training session was divided into strength and aerobic exercises.

Strength training included 11 exercises engaging the major muscle groups (bench press, shoulder press, leg extension, leg curl, abdominal crunch, low-back extension, arm curl, elbow extension, seated row, and lateral pull-down). For each exercise, the children performed one set of 8–15 repetitions (total of approximately 20-s duration). Rest periods of 1–2 min separated the exercises. Stretching exercises of the muscles involved in the previous exercise were performed during the rest periods between exercises (2). The load was gradually increased as the strength of each child improved. Aerobic exercises consisted of pedaling a cycle ergometer, running, walking, and aerobic games involving large muscle groups (i.e., jumping exercises, ball games, group games, etc.). The duration and intensity of the aerobic training was gradually increased during the 16-wk period so that the subjects started with at least 10 min of aerobic exercises at 50% of age-predicted maximum heart rate (HRmax) and progressed to at least 30 min of continuous exercise at $\geq 70\%$ HRmax by the end of the 16-wk program. All children wore a portable heart rate monitor during the sessions to monitor their exercise intensity. Aerobic and

TABLE 2. Mean \pm SD values of performance during functional mobility and strength endurance tests at pretraining, posttraining, and detraining.

Type of Test	Pretraining	Posttraining	Detraining	P Value Pre- vs Posttraining	P Value Pre- vs Detraining	P Value Post- vs Detraining
Seated bench press (kg)	23.6 \pm 5.9	34.1 \pm 8.1	33.3 \pm 9.4	<0.01	<0.05	NS
Seated row (kg)	16.6 \pm 6.8	21.8 \pm 6.1	22.2 \pm 6.9	<0.05	<0.01	NS
Seated leg press (kg)	58.2 \pm 21.4	78.3 \pm 25.6	78.3 \pm 21.0	<0.05	<0.01	NS
Passive DF-ROM ($^{\circ}$)	27.9 \pm 6.2	24.0 \pm 4.3	20.7 \pm 6.8	NS	<0.01	NS
Active DF-ROM ($^{\circ}$)	20.6 \pm 7.4	18.4 \pm 7.5	17.9 \pm 9.1	NS	NS	NS
TUGS (s)	8.3 \pm 1.3	7.6 \pm 0.9	7.8 \pm 0.9	<0.01	NS	NS
TUG 3 m (s)	6.3 \pm 0.7	5.3 \pm 0.6	5.6 \pm 0.5	<0.01	NS	NS
TUG 10 m (s)	13.7 \pm 1.7	12.5 \pm 1.5	12.7 \pm 1.4	<0.05	NS	NS

Passive DF-ROM, passive dorsiflexion range of motion; active DF-ROM, active dorsiflexion range of motion; TUG, timed up and go test; TUGS, timed up and down stairs test; NS, not statistically significant ($P > 0.05$). See text for explanation of the tests.

group games were necessary to maintain and improve the children's adherence to the training program; that is, by making every session different, the children's compliance and retention of subjects were maintained. All sessions were supervised by exercise physiologists and qualified fitness instructors (one instructor for every two children). A pediatrician was also present at each of the training sessions.

Each child was evaluated by his or her oncologist every 2 wk during the training period. These examinations included a thorough physical evaluation and complete hematological and biochemical blood analysis. All the children and their parents were instructed to follow the children's usual nutritional habits throughout both the familiarization and training period. None of the children were taking any nutritional supplement during the entire duration of the project.

Data Analyses

Statistical analyses were performed with the Statistical Package for Social Sciences (SPSS) 11.5 software (SPSS Inc., Chicago, IL). As previously mentioned, it was not possible to use a true experimental design, that is, a randomized controlled trial with two groups of patients: a treatment (training) group and a nontraining (control) group. Thus, a quasiexperimental reversal design (i.e., lacking a control group (30)) was used. The use of this type of design in scientific research has grown considerably in recent years. The purpose of the research design used was to determine a baseline measurement, evaluate a treatment (e.g., exercise training), and evaluate a return to a no-treatment condition (e.g., detraining) in the same subjects (30). One practical advantage of this type of design is its applicability to real-world settings (in which random assignment is sometimes impossible) while still controlling internal validity as best as possible (30). This type of design particularly controls subject bias well because the same subjects are used at each testing time point. Additionally, given the small sample size (and thus to avoid having a statistical type I error), we used the nonparametric

Friedman test (instead of a repeated-measures ANOVA) to compare the mean values of all the variables measured at pretraining, posttraining, and detraining within subjects. The level of significance was set at 0.05. Results are expressed as means \pm SD.

RESULTS

Height and mass. Body mass at pretraining, posttraining, and detraining were 25.1 \pm 5.8, 25.8 \pm 5.9, and 28.0 \pm 6.4 kg, respectively. Height at pretraining, posttraining, and detraining were 114.6 \pm 7.7, 116.4 \pm 7.1, and 119.1 \pm 7.4. Both body mass and height were not significantly different between pretraining and posttraining or posttraining and detraining, but they were significantly different between pretraining and detraining. Pretraining values placed the boys and girls in the 70th \pm 0.54 and 97th \pm 2.53 percentiles for height and the 90th \pm 2.04 and 90th \pm 0.45 percentiles for body mass of healthy Spanish children (14).

Adherence to training and possible adverse effects. Adherence to training was above 85% in all subjects (i.e., >40 of 48 training sessions). None of the subjects missed more than two consecutive training sessions. No major adverse effects and no major health problems were noted in the subjects during the training and detraining period; hematological and biochemical blood parameters remained within normal limits, and children's physical examinations revealed no abnormality.

Performance during functional mobility and strength endurance tests. Performance in the TUGS, TUG 3 m, TUG 10 m, and strength endurance tests (i.e., seated bench press, seated row, seated leg press) significantly improved after training (Table 2). Of these measures, only the strength endurance tests remained significantly greater after detraining compared with pretraining and did not show a significant difference from posttraining after detraining, demonstrating maintenance of strength endurance measures during the detraining period. The TUGS, TUG 3 m, and TUG 10 m did not decrease significantly from posttraining to detraining, but they were no longer significantly different

TABLE 3. Mean \pm SD values of the main variables obtained during the treadmill tests at pretraining, posttraining, and detraining.

Variable	Pretraining	Posttraining	Detraining	P Value Pre- vs Posttraining	P Value Pre- vs Detraining	P Value Post- vs Detraining
$\dot{V}O_{2peak}$ (mL \cdot kg $^{-1}$ \cdot min $^{-1}$)	24.3 \pm 5.9	30.2 \pm 6.2	29.3 \pm 5.0	<0.05	NS	NS
$\dot{V}O_2$ (mL \cdot kg $^{-1}$ \cdot min $^{-1}$) at VT	15.8 \pm 3.3	20.7 \pm 2.9	19.5 \pm 2.8	<0.05	NS	NS

$\dot{V}O_{2peak}$, peak oxygen uptake; VT, ventilatory threshold; NS, not statistically significant ($P > 0.05$).

TABLE 4. Scores (mean ± SD) of the children's report of their health status: child report form of the Child Health and Illness Profile—Child Edition (CHIP-CE/CRF) (25).

Variable	Pretraining	Posttraining	Detraining	P Value Pre- vs Posttraining	P Value Pre- vs Detraining	P Value Post- vs Detraining
Resilience	29.3 ± 5.3	25.6 ± 4.5	23.3 ± 2.4	NS	NS	NS
Achievement	25.6 ± 5.7	25.0 ± 4.0	25.7 ± 2.3	NS	NS	NS
Satisfaction	37.0 ± 3.8	35.0 ± 7.9	35.9 ± 3.8	NS	NS	NS
Comfort	37.3 ± 11.1	41.0 ± 6.6	45.4 ± 5.0	NS	NS	NS
Risk avoidance	29.4 ± 7.4	30.6 ± 7.5	34.4 ± 2.8	NS	NS	NS

NS, not statistically significant ($P > 0.05$).

for pretraining after detraining, indicating only a partial maintenance during the detraining period. Passive DF-ROM and active DF-ROM were not significantly affected by training, and both showed no significant difference posttraining versus after detraining, whereas only passive DF-ROM showed a significant decrease after detraining compared with pretraining.

Treadmill tests. Mean values of $\dot{V}O_{2peak}$ ($\text{mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) and $\dot{V}O_{2peak}$ ($\text{mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) at VT improved significantly after training (Table 3). Both of these $\dot{V}O_{2peak}$ measures did not decrease from posttraining to detraining, but they were no longer significantly different from pretraining after detraining, indicating a partial maintenance during the detraining period.

QOL tests. No significant differences were found during the study period in the different variables measured by the CHIP-CE/CRF indicative of self-reported QOL of the children (Table 4) or in the parents' evaluations of their children's QOL (Table 5).

DISCUSSION

Our study shows for the first time that a midlength-duration (16 wk) intrahospital structured supervised training program combining cardiorespiratory and resistance exercises positively affects changes in maximal aerobic capacity ($\dot{V}O_{2peak}$), VT, dynamic muscle strength of the upper and lower extremities, and functional mobility (TUDS, TUG 3 m, TUG 10 m) in very young children (4–7 yr) receiving maintenance therapy against ALL. Additionally, many of these training-induced improvements do not significantly decrease after 20 wk of training cessation.

Given the uniqueness of our study population, it is difficult to directly compare our results with those of previous studies on children with (or survivors of) ALL or healthy children. The pretraining values of $\dot{V}O_{2peak}$ of our patients ($\sim 24 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) were clearly below the expected values for healthy age-matched controls, that is, approximately $45 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ in children of 6–8 yr (6). However, after completion of the training program,

$\dot{V}O_{2peak}$ values improved significantly from 54 to 67% of normal expected values. The $\dot{V}O_{2peak}$ of our patients were also below those of ALL survivors (i.e., children who have successfully completed treatment) <13 yr of age ($34 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) (7). Our findings indicate that the $\dot{V}O_{2peak}$ of young childhood survivors of ALL can significantly increase through participation in a supervised exercise training program. This is an important consideration for this population because $\dot{V}O_{2peak}$ is an excellent indicator of health status and an independent predictor of mortality in both healthy and unhealthy humans (21).

The VT values in our patients ($\sim 16 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) were also considerably lower than those usually reported in healthy children of 5–16 yr of age tested on a treadmill (usually ranging from 25 to $40 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) (20) and also lower than that of ALL survivors < 13 yr of age (i.e., $\sim 24 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) (7). This is an important finding because VT is a health indicator in diseased populations (20) and because improvements in VT result in attenuation of breathlessness and improved exercise capacity at submaximal levels and also contribute to the well-being of patients during their daily activities (20).

Similar to aerobic measures, strength endurance measures of both the upper and lower body did increase with training, but it is difficult to compare the present changes in strength with previous studies of children being treated for ALL. The pretraining strength values found in our children cannot be compared with those reported by Marchese et al. (12) in children with ALL (ages 4–15 yr) because both measuring instruments and evaluation tests differed between studies—that is, dynamometer and 1RM test in the previous study versus 6RM using specific weight training machines in the present study. Marchese et al. (18) did show an approximately 20% increase in knee-extension strength attributable to a 16-wk physical therapy intervention program combined with home-based exercises (aerobic training, stretching exercises), and this increase is higher than the present strength increases of approximately 14, 13, and 13% in the seated bench press, seated row, and seated leg press, respectively. We chose to assess dynamic muscle strength

TABLE 5. Scores (mean ± SD) of the children's parents evaluation of their child's quality of life: parent report form of the child report form of the Child Health and Illness Profile—Child Edition (CHIP-CE/CRF) (26).

Variable	Pretraining	Posttraining	Detraining	P Value Pre- vs Posttraining	P Value Pre- vs Detraining	P Value Post- vs Detraining
Resilience	71.9 ± 10.8	75.6 ± 7.3	73.4 ± 11.5	NS	NS	NS
Achievement	35.4 ± 5.2	37.3 ± 4.7	34.0 ± 4.9	NS	NS	NS
Satisfaction	44.4 ± 6.1	45.9 ± 3.2	42.7 ± 5.6	NS	NS	NS
Comfort	81.1 ± 15.6	88.1 ± 7.4	84.7 ± 15.3	NS	NS	NS
Risk avoidance	50.0 ± 2.2	55.4 ± 9.6	51.0 ± 10.1	NS	NS	NS

NS, not statistically significant ($P > 0.05$).

endurance (6RM) instead of maximal dynamic strength (1RM) to obtain results of practical relevance for children with ALL, in whom maximal strength is not a main determinant of their ability to perform physical activities of daily living, which are mostly submaximal-strength tasks (e.g. climbing stairs, sitting and rising from a chair, etc.). Thus, we feel that 6RM is as adequate as a maximal lifting test (1RM) for representing gains in muscle strength endurance that can be associated with improvements in the functional ability to perform daily living tasks.

We also found significant training-induced improvements in the TUDS, TUG 3 m, and TUG 10 m tests after the exercise program intervention, indicating a significant gain in muscle functional capacity and in tasks of daily living. This finding is of practical relevance because it indicates an increased ability to perform tasks of functional mobility.

Overall, the present results concerning physical training in children with ALL support a previous conclusion based on a literature review: there is no medical contraindication for children undergoing maintenance therapy against ALL to not engage in physical activities or exercise programs (17). The ability for young children being treated against ALL to participate in a physical training program is important for several reasons. First, a recent study showed that levels of moderate to vigorous weekly physical activity is significantly reduced in this subpopulation (3); this may result in decreased physical fitness because of a lack of normal physical activity. Additionally, the peak incidence of diagnosis for ALL is between 2 and 5 yr. Diagnosis is followed by approximately 30 months of treatment. The timing of diagnosis and the length of treatment coincide with a period of life when children are normally physically active and introduced to organized sports (e.g., soccer). Childhood activity patterns may track into adulthood (6), and thus there are possible long-term detrimental effects of ALL diagnosis on an individual's future physical activity patterns and health status, even if the primary therapy for ALL is successful. A structured physical training program may in part counteract the decreased physical activity patterns in children being treated for ALL, but it also may help develop a pattern of lifelong physical activity in this population.

During detraining, improvements in fitness measures attributable to training typically digress towards the untrained state. The present results indicate some loss of aerobic fitness, strength endurance, and mobility attributable to a 20-wk detraining period, but the majority of measures related to these characteristics were well maintained during detraining. The present results indicate that improvements in $\dot{V}O_{2peak}$ and VT are at least partially maintained (both variables did not significantly decrease from posttraining but were no longer greater than pretraining after detraining) during a 20-wk detraining period. Note that the maintenance in $\dot{V}O_{2peak}$ during detraining occurred in conjunction with a significant increase in body mass from pretraining to detraining. This finding is in contrast with previous data on healthy adults (21) and adult cancer survivors (13)

showing that the previous training-induced gains in $\dot{V}O_{2peak}$ are largely lost after a relatively short-term detraining period (~2 months). This contradiction between adult and child cancer survivors might be partially explained by previous decades of chronic deconditioning before the onset of the disease in adults that was not present in children, and by the fact that natural growth processes in children can result in increased aerobic fitness without training that may minimize losses during detraining.

Training-induced gains in strength performance were largely maintained (no significant decrease from posttraining during detraining, and still significantly greater than pretraining after detraining), whereas muscle functional mobility was partially maintained (no significant decrease from posttraining during detraining, but no longer significantly increased from pretraining after detraining) during the 20-wk detraining period. This partial maintenance of functional mobility is in overall agreement with previous research on healthy adults (22) and adult cancer survivors (13), showing that, at least compared with muscle oxidative capacity, muscular strength suffers a limited decrease after relatively short periods of detraining, which is attributable, at least partly, to some aspects of neuromuscular performance (i.e., motor unit recruitment) being well maintained during periods of detraining (22). Another factor that may explain the nonsignificant decrease in strength during detraining in our subjects is that in prepubescents, natural growth processes can result in increased strength, even without resistance training (10). Our data show much smaller changes in strength during detraining than previously shown in healthy children. For instance, Faigenbaum et al. (9) showed 28 and 19% decreases in leg-extension and bench press strength, respectively, after 8 wk of training cessation after a 20-wk weight training program in healthy children (mean age \approx 11 yr), whereas we reported only a -2% nonsignificant decrease in bench press ability, a small and nonsignificant increase in seated row ability of +1.8%, and a nonsignificant change (0%) in leg press ability attributable to detraining compared with posttraining. The reasons for better maintenance of strength in children being treated for ALL compared with healthy children is unclear, but it may be related to the additive effects of low pretraining fitness levels compared with healthy children, natural growth, and a longer time for recovery from ALL during detraining compared with pretraining.

Different from the measures of aerobic fitness, strength, and mobility, passive and active DF-ROM generally were not significantly affected by training and detraining. The only significant change in these measures was a significant decrease in passive DF-ROM from pretraining to detraining. This finding seems to be in disagreement with the data of Marchese et al. (18) showing improvements in active DF-ROM after a 16-wk physical therapy protocol. Our results might simply reflect a common phenomenon during normal development; that is, the median value of passive DF-ROM among healthy children decreases from 25° at 1 yr of age to 15° at 7 yr (29). As opposed to $\dot{V}O_{2peak}$ or muscle strength values, which were very low at pretraining,

all the children in our study had sufficient DF-ROM at baseline for sustaining normal activities of daily living, such as normal gait patterns (33).

Perhaps surprisingly, although significant increases in $\dot{V}O_{2peak}$, VT, strength endurance, and measures of mobility (TUDS, TUG 3 m, TUG 10 M) were observed with training, no significant improvements in the children's self-reported QOL or the parents' evaluation of the children's QOL after the training period were shown, although a trend towards improvement was observed in all the variables of the parents' test (e.g., 8% improvement after posttraining in the comfort score; Table 5). These findings are in agreement with those of Marchese et al. (18), who did not observe a significant improvement in the QOL of children of 4–18 yr of age receiving maintenance treatment against ALL, nor in their parents' QOL after a home-based 20-wk training program. As suggested by Marchese et al. (18), the lack of significant improvement in QOL might reflect a certain ceiling effect during the pretraining questionnaire, with the majority of children and parents minimizing their actual QOL problems, that is, reporting no problems with the items on the questionnaire (health status, satisfaction, etc.).

The potential value of a supervised intrahospital training program for children with ALL may be apparent by comparing the present results with those of a previous study. Marchese et al. (18) observed, in a group of children who were receiving treatment against ALL and who were of older age (4–18 yr) than our subjects (4–7 yr), that a 16-wk physical therapy intervention program combined with home-based exercises (aerobic training, stretching exercises) induced significant improvements in ankle dorsiflexion range of motion and knee-extension strength. However, no significant improvements in indirectly estimated aerobic capacity (i.e., 9-min run-walk test) or functional mobility (i.e., TUDS test) were observed. In contrast, our supervised training program including both aerobic and strength training did induce significant improvements in maximal ($\dot{V}O_{2peak}$) and submaximal aerobic capacity (VT), muscle strength endurance, and functional mobility (TUDS, TUG 3 m, TUG 10 M) of younger children with ALL. Our overall greater gains in measures of aerobic fitness, strength, and mobility measures may be related to the need for performing *individually* supervised training programs as the one used here (i.e., one

instructor for every two children) instead of home-based training. The need for an individually supervised program to bring about maximal fitness gains is supported by Mazzetti et al. (19), who showed that an individually supervised strength training program resulted in significantly greater gains in strength than a program involving instruction but in which the subjects had to perform the training on their own.

Overall, our findings are of significant clinical relevance because muscle weakness and subsequent impaired functional capacity and mobility are frequent complications of the treatment against childhood ALL (17). The significant improvement we found in variables indicative of cardiopulmonary and neuromusculoskeletal function with only 16 wk of training, and the general maintenance of these positive effects (especially muscle strength) during detraining, suggest the potential usefulness of including intrahospital supervised exercise programs in pediatric oncology departments. Future controlled studies should assess the effects of supervised exercise programs used earlier during treatment or among children with ALL who have undergone bone marrow transplantation as part of their treatment against ALL, because bone marrow transplantation is commonly associated with severe muscle weakness and physical deconditioning (e.g., because of aggressive treatment with corticosteroids after surgery (32)).

In summary, children at a very young age (4–7 yr) receiving the last phase of treatment against ALL can safely undergo an intrahospital structured, supervised conditioning program including both aerobic and resistance exercise training and experience positive physical benefits. The training results in significant improvements in measures of aerobic fitness, strength, and mobility, but it has no effect on self-reported QOL according to the children being treated for ALL or their parents' evaluations of their children's QOL. Measures of aerobic fitness, strength, and mobility are well maintained during a 20-wk detraining period after training in children being treated for ALL.

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REFERENCES

1. AMERICAN ACADEMY OF PEDIATRICS. Strength training, weight and power lifting and bodybuilding by children and adolescents. *Pediatrics* 86:801–803, 1990.
2. AMERICAN ACADEMY OF PEDIATRICS. Strength by children and adolescents. Committee on Sports Medicine and Fitness. *Pediatrics* 107:1470–1472, 2001.
3. AZNAR, S., A. L. WEBSTER, A. F. SAN JUAN, et al. Physical activity during treatment in children with leukemia; a pilot study. *Appl. Physiol. Nutr. Metab.* 31:407–413, 2006.
4. BARNES, H. V. Physical growth and development during puberty. *Med. Clin. North Am.* 59:1305–1317, 1975.
5. BAR-OR, O., and T. W. ROWLAND. *Pediatric Exercise Medicine: From Physiologic Principles to Health Care Application*. Champaign, IL: Human Kinetics, 2004, pp. 5–7.
6. CORBIN, C. B. The “untracking” of sedentary living: a call for action. *Pediatr. Exerc. Sci.* 13:347–356, 2001.
7. DE CARO, E., F. FIOREDDA, M. G. CALEVO, et al. Exercise capacity in apparently healthy survivors of cancer. *Arch. Dis. Child.* 91: 47–51, 2006.
8. DWORZAK, M. N., G. FROSCHL, D. PRINTZ, et al. Prognostic significance and modalities of flow cytometric minimal residual disease detection in childhood acute lymphoblastic leukemia. *Blood* 99:1952–1958, 2002.
9. FAIGENBAUM, A. D., W. L. WESTCOTT, L. J. MICHELI, A. R.

- OUTERBRIDGE, C. J. LONG, and R. L. LA ROSA-LOUD. The effects of strength training and detraining on children. *J. Strength Cond. Res.* 10:109–114, 1996.
10. FLECK, S. J., and W. KRAEMER. *Designing Resistance Training Programs*. 3rd ed. Champaign, IL: Human Kinetics, 2004, pp. 287–302.
 11. FOURNIER, M., J. RICCI, A. W. TAYLOR, R. J. FERGUSON, R. R. MONTPETIT, and B. R. CHATMAN. Skeletal muscle adaptation in adolescent boys: sprint and endurance training and detraining. *Med. Sci. Sports Exerc.* 14:453–456, 1982.
 12. GOCHA MARCHESE, V. G., L. A. CHIARELLO, and B. J. LANGE. Strength and functional mobility in children with acute lymphoblastic leukemia. *Med. Pediatr. Oncol.* 40:230–232, 2003.
 13. HERRERO, F., A. F. SAN JUAN, S. J. FLECK, C. FOSTER, and A. LUCIA. Effects of detraining on the functional capacity of previously trained breast cancer survivors. *Int. J. Sports Med.* In press.
 14. HERNANDEZ RODRIGUEZ, M. *Principios Basicos en Nutricion Infantil*. Madrid, Spain: Diaz de Santos, 1994, pp. 389–401.
 15. KRAEMER, W., and A. FRY. Strength testing development and evaluation of methodology. In: *Physiological Assessment of Human Fitness*, P. J. Mauch and C. Foster (Eds.). Champaign, IL: Human Kinetics, 1995, pp. 115–138.
 16. LUCIA, A., C. EARNEST, and M. PEREZ. Cancer-related fatigue: how can exercise physiology assist oncologists? *Lancet Oncol.* 4:616–625, 2003.
 17. LUCIA, A., M. RAMIREZ, A. F. SAN JUAN, S. J. FLECK, J. GARCIA-CASTRO, and L. MADERO. Intrahospital supervised exercise training: a complementary tool in the therapeutic armamentarium against childhood leukaemia. *Leukemia* 19:1334–1337, 2005.
 18. MARCHESE, V. G., L. A. CHIARELLO, and B. J. LANGE. Effects of physical therapy intervention for children with acute lymphoblastic leukemia. *Pediatr. Blood Cancer* 42:127–133, 2004.
 19. MAZZETTI, S. A., W. J. KRAEMER, J. S. VOLEK, et al. The influence of direct supervision of resistance training on strength performance. *Med. Sci. Sports Exerc.* 32:1175–1184, 2000.
 20. MEYER, T., A. LUCIA, C. P. EARNEST, and W. KINDERMANN. A conceptual framework for performance diagnosis and training prescription from submaximal parameters - theory and application. *Int. J. Sports Med.* 26(Suppl 1):S38–S48, 2005.
 21. MUJKA, I., and S. PADILLA. Cardiorespiratory and metabolic characteristics of detraining in humans. *Med. Sci. Sports Exerc.* 33:413–421, 2001.
 22. MUJKA, I., and S. PADILLA. Muscular characteristics of detraining in humans. *Med. Sci. Sports Exerc.* 33:1297–1303, 2001.
 23. MYERS, J., M. PRAKASH, V. FROELICHER, D. D. S. PARTINGTON, and J. E. ATWOOD. Exercise capacity and mortality among men referred for exercise testing. *N. Engl. J. Med.* 4:793–801, 2002.
 24. NATIONAL STRENGTH AND CONDITIONING ASSOCIATION. Youth resistance training: position statement paper and literature review. *J. Strength Cond. Res.* 18:62–76, 1996.
 25. NORKIN, C. C., and D. J. WHITE. *Measurement of Joint Motion: A Guide to Goniometry*. 3rd ed. Philadelphia, PA: FA Davis Company, 2003, pp. 256–259.
 26. RILEY, A. W., C. B. FORREST, G. W. REBOK, et al. The child report form of CHIP-Child Edition: reliability and validity. *Med. Care* 42:221–231, 2004.
 27. RILEY, A. W., C. B. FORREST, B. STARFIELD, G. W. REBOK, J. A. ROBERTSON, and B. F. GREEN. The parent report form of the CHIP-Child Edition: reliability and validity. *Med. Care* 42:210–220, 2004.
 28. ROWLAND, T. W. Aerobic response to endurance training in prepubescent children: a critical analysis. *Med. Sci. Sports Exerc.* 17:493–497, 1985.
 29. SUTHERLAND, D. H., R. A. OLSHEN, E. N. BIDEN, and M. WYATT. *The Development of Mature Walking*, London: Mac Keith, 1988, pp. 104–105.
 30. THOMAS, J. R., J. K. NELSON, and S. J. SILVERMAN. *Research Methods in Physical Activity*, 5th ed. Champaign, IL: Human Kinetics, 2005, pp. 335–343.
 31. TSOLAKIS, C. K., G. K. VAGENAS, and A. G. DESSYPRIS. Strength adaptations and hormonal responses to resistance training and detraining in preadolescent males. *J. Strength Cond. Res.* 18: 625–629, 2006.
 32. VAN BRUSSEL, M., T. TAKKEN, A. LUCIA, J. VAN DER NET, and P. J. HELDERS. Is physical fitness decreased in survivors of childhood leukemia? A systematic review. *Leukemia* 19:13–17, 2005.
 33. WRIGHT, M. J., S. E. HANNA, J. M. HALTONA, and R. D. BARR. Maintenance of ankle range of motion in children treated for acute lymphoblastic leukaemia. *Ped. Phys. Ther.* 15:146–152, 2003.