

ORIGINAL ARTICLE

A Randomized Controlled Trial on the Effects of Cycling With and Without Electrical Stimulation on Cardiorespiratory and Vascular Health in Children With Spinal Cord Injury

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ABSTRACT. Johnston TE, Smith BT, Mulcahey MJ, Betz RR, Lauer RT. A randomized controlled trial on the effects of cycling with and without electrical stimulation on cardiorespiratory and vascular health in children with spinal cord injury. *Arch Phys Med Rehabil* 2009;90:1379-88.

Objective: To examine the cardiorespiratory/vascular effects of cycling with and without functional electrical stimulation (FES) in children with spinal cord injury (SCI).

Design: Randomized controlled trial.

Setting: Pediatric referral hospital.

Participants: Children with SCI (N=30), ages 5 to 13 years, with injury levels from C4 to T11, and American Spinal Injury Association grades A, B, or C.

Interventions: Children were randomly assigned to 1 of 3 groups: FES leg cycling exercise, passive leg cycling, or non-cycling control group receiving electrical stimulation therapy. After receiving instruction on the use of the equipment, children exercised for 1 hour 3 times per week for 6 months at home with parental supervision.

Main Outcome Measures: Oxygen uptake ($\dot{V}O_2$) during an incremental arm ergometry test, resting heart rate, forced vital capacity, and a fasting lipid profile.

Results: There were no differences ($P > .05$) between groups after 6 months of exercise when comparing pre- and postvalues. However, there were differences between groups for some variables when examining percent change. The FES cycling group showed an improvement ($P = .035$) in $\dot{V}O_2$ ($16.2\% \pm 25.0\%$) as compared with the passive cycling group ($-28.7\% \pm 29.1\%$). For lipid levels, the electrical stimulation-only group showed declines ($P = .032$) in cholesterol levels ($-17.1\% \pm 8.5\%$) as compared with the FES cycling group ($4.4\% \pm 20.4\%$).

Conclusions: Cycling with FES led to gains in $\dot{V}O_2$, whereas electrical stimulation alone led to improvements in cholesterol.

Key Words: Pediatrics; Rehabilitation; Spinal cord injuries.
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AEROBIC FITNESS IS DEFINED as the capacity to perform endurance activities that mainly depend on aerobic metabolism.¹ One component of aerobic fitness is $\dot{V}O_2$ max (mL/kg/min). High $\dot{V}O_2$ max values reflect good function of the cardiorespiratory system, making it possible to accomplish submaximal tasks with less fatigue.¹ For adults with SCI, $\dot{V}O_2$ peak during upper-extremity ergometry is 5% to 59% less than age- and sex-matched peers without disability during lower-extremity exercise.² This decrease is partially caused by decreased lean body mass that occurs post-SCI, with greater loss with higher levels of injury and complete SCI. With less lean tissue, there is less muscle available to participate in exercise that would maximally stress the cardiorespiratory system to obtain sufficient benefits.³ Despite the fact that daily energy expenditure is reduced with decreased muscle mass,⁴ 1 out of 4 young people with SCI does not have the level of fitness required to perform essential activities of daily living.⁵ These activities are compromised, in part, by an insufficient circulatory response (decreased blood pressure and increased resting heart rate) because of vascular atrophy, impaired work capacity, and increased $\dot{V}O_2$ peak in response to submaximal work.⁶

After an acute SCI, muscle atrophy occurs quickly, with decreases in average lower-extremity muscle cross-sectional area of up to 45% reported 6 weeks post-SCI.⁷ These values then decrease approximately 3.2% per decade post-SCI as compared with 1% per decade in the general male population. In addition to impacting energy expenditure, decreased muscle mass increases the risk of cardiovascular disease.⁸ Other factors such as increased adiposity, hyperlipidemia, and decreased physical activity contribute to this increased risk⁸ and the risk of metabolic syndrome and diabetes.^{4,8} In fact, cardiovascular disease is now the leading cause of mortality in persons with chronic SCI, with an earlier onset⁹ and increased prevalence than in the general population.¹⁰

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List of Abbreviations

FES	functional electrical stimulation
FVC	forced vital capacity
HDL	high-density lipoprotein
LDL	low-density lipoprotein
rpm	revolutions per minute
SCI	spinal cord injury
$\dot{V}O_2$	oxygen uptake
$\dot{V}O_2$ max	maximum oxygen consumption
$\dot{V}O_2$ peak	peak oxygen uptake

Aerobic exercise may be used to reduce these risk factors and improve life expectancy.¹¹ One method, lower-extremity FES cycling, has been proposed as an ideal means to address long-term complications of SCI because it is an exercise that can target the larger lower-extremity muscles.³ Numerous studies¹²⁻²⁴ have examined the effects of FES cycling on the cardiovascular and respiratory systems of adults with SCI. Studies involving cycling training 2 to 3 days per week for 12 to 16 weeks have shown increases in VO_2peak ,^{19,25} cardiac output,^{19,26} stroke volume,²⁶ and pulmonary ventilation during FES cycling.¹⁹ Faghri et al²⁶ reported that heart rate and blood pressure during submaximal cycling decreased, whereas stroke volume and cardiac output increased, suggesting an improvement in central cardiovascular fitness. Hooker et al²² examined respiratory change after a program of FES cycling of 24 sessions over 19 weeks, showing improvement in VO_2peak , indicating that gains can be obtained with a less intense program. In addition, FES cycling has led to improved circulatory responses to ischemia and the reversal of cardiac atrophy in people with tetraplegia.⁶ These studies show that improvements in cardiorespiratory fitness can be obtained by adults with SCI after a program of FES cycling.

FES cycling may have an impact on the exercise capacity of the upper body. Suggested mechanisms include improvements in venous return and decreased blood pooling, which may then increase the upper-body exercise capacity.^{3,16} Both peripheral muscular effects and central cardiovascular effects have been reported after a program of FES cycling.²⁶ Other reports suggest that the effects of FES cycling are more peripheral; however, they acknowledge that higher power outputs may have an impact on the cardiorespiratory system.¹⁹

FVC is reduced in adults with SCI, with greater deficits with higher injury levels.²⁷ After a program of upper-extremity exercise, adults with SCI showed increases in FVC and ventilatory endurance. These changes were possibly caused by improvements in strength and endurance of the diaphragm, abdominals, and more directly on the accessory muscles of inspiration. The impact of lower-extremity exercise on FVC post-SCI is not known. However, FVC has been shown to increase in healthy children after a running program with the theory that the activity could lead to increased strength and endurance of the respiratory muscles and changes in the structure of the respiratory system.²⁸

Despite the focus on FES cycling with adults with SCI, this technique has not been studied in children with SCI. For children with SCI, cardiorespiratory deficits are contributed to respiratory complications, which occur in up to 33% of persons with pediatric-onset SCI²⁹ and respiratory illness accounts for 22% of the deaths in persons with SCI.³⁰ If FES cycling leads to similar improvements in children with SCI as seen with adults, the potential exists to improve cardiorespiratory health at an early age. The purpose of this study, therefore, was to examine the effects of leg cycling exercise both with and without electrical stimulation to determine whether the same cardiorespiratory changes that were reported in the adult population can be achieved in the pediatric population. It was hypothesized that the FES cycling group would have the greatest cardiorespiratory and vascular improvements.

METHODS

Subjects and Exercise Protocol

A controlled, randomized study with a pre-post within-subjects repeated-measures design was conducted. Children were recruited through a hospital-based pediatric SCI clinic. By using

block randomization, children were randomly assigned to 1 of 3 groups: FES leg cycling exercise, passive leg cycling, and a noncycling control group receiving electrical stimulation therapy. The groups were balanced as to the amount of time they received the specific therapy.

Parents and children signed an institutional review board-approved informed consent and assent forms, respectively. Inclusion criteria were 12 months postinjury; cervical or thoracic level SCI with an American Spinal Injury Association grade A, B, or C classification (if C, nonambulatory or only able to walk with long leg braces); age 5 to 13 years; and innervated lower-extremity muscles. Exclusion criteria included chronic steroid treatment, history of seizures, cardiac disease, ventilator dependency, severe spasticity in the legs, lower-limb stress fractures, lower-extremity fractures of unknown origin, uncontrolled autonomic dysreflexia, heterotopic ossification, and hip dislocation. Children were also excluded if they had participated in activities involving electrical stimulation or activity-based therapy within the past 3 months.

Children exercised at home with parental assistance for 1 hour 3 times per week for 6 months. Parents received instruction on the use of the equipment from the same investigator. The FES cycling group cycled at a target cadence of 50rpm by using an RT300-P FES cycle^a while seated in their wheelchairs (fig 1). The cycle provided 10 minutes of a passive warm-up, 40 minutes of FES cycling, and 10 minutes of a passive cool down. FES to the quadriceps, hamstring, and gluteal muscles was delivered by using the largest surface electrodes^b appropriate for the child's leg. Stimulation frequency was fixed at 33Hz, and pulse duration was set at 150, 200, 250, or 300 μs . The current amplitude increased automatically up to a maximum of 140mA to generate sufficient force to maintain the cadence. This maximum was decreased for the smaller children based on individual muscle response. At higher stimulation levels, the quadriceps and hamstring muscles were often activated simultaneously by the quadriceps and/or the hamstrings electrodes, likely because of the small muscle size of these children. This cocontraction would cause the cycling cadence



Fig 1. Child with paraplegia on the FES cycle.

to decrease. The resistance cycled against started at 1Nm and was increased in increments of 0.14Nm once the child could cycle for an entire session at the current resistance level. If the children's cycling cadence dropped below 35rpm for greater than 30 seconds, the muscles were determined to be fatigued and the cycle would go into the passive cool down mode.

The passive cycling group used the RT100^a motorized cycle, which passively moved the legs for the entire hour at 50 rpm with children seated in their wheelchairs. The RT300 and RT100 only differ in that the RT300 provides FES, whereas the RT100 does not. Children in the electrical stimulation therapy group used a portable, 2-channel surface stimulation unit^c to bilaterally create strong muscle contractions of the hamstrings, quadriceps, and gluteal muscles. Each muscle was stimulated for 20 minutes with a duty cycle of 5:15 seconds for a total of 1 hour. Subjects exercised in the supine position, working against zero resistance. Parents were instructed to increase the stimulation level delivered if the muscle response decreased during the session.

For children performing either cycling exercise, adjustments were made to accommodate each child's size and wheelchair configuration. For example, crank arm length was shortened to accommodate smaller legs, and the calf support could be manipulated to prevent it from hitting the wheelchair. The cycle's height was raised with a custom-made wooden platform so the children's feet would reach the pedals. The goal was to position the child to obtain a position of approximately 30° to 40° less than full knee extension during the extension phase of the revolution.

Before exercising, all children participated in lower-extremity muscle passive range of motion exercises. Children were permitted to continue their previously established therapeutic activities, such as standing and walking with braces, but were not permitted to participate in nonstudy-related lower-extremity repetitive motion tasks or electrically stimulated exercise. It was decided not to alter the prestudy exercise routine because declines from baseline values might have occurred if these activities were stopped.

Children were permitted to miss up to 12 sessions over the 6-month period. If a greater number of sessions were missed, parents were instructed to add 1 extra session per week to make up for the missed sessions. Parents logged each session performed on a weekly log sheet that was sent to the investigators on a monthly basis. In addition, telephone calls were made to the parents every 2 weeks to receive information on how the child was doing and if the required number of sessions was being completed.

Data Collection

Data were collected before and after 6 months of at-home exercise. Heart rate and $\dot{V}O_2$ (mL/kg/min) were measured during an incremental upper-extremity ergometry test³¹ by using a breath-by-breath technique with a SensorMedics VMax29 metabolic cart.^d The measurement error for this test with children is unknown. An upper-extremity test was chosen instead of a lower-extremity FES cycling test because all subjects were not trained with FES cycle. During the upper-extremity ergometry test, subjects wore a small airtight facemask^e over the mouth and nose that held the flow sensor that measured the volume of oxygen per kilogram of body weight. Before each test, the flow sensor and the gas analyzer were calibrated according to the manufacturer's guidelines. $\dot{V}O_2$ was measured under 4 consecutive conditions: (1) sitting quietly for 5 minutes (baseline), (2) upper-extremity cycling at 10W at a self-selected cadence for 1 minute (warm-up), (3) upper-extremity cycling at 10W with increases of 10W every minute until self-determined fatigue,

and (4) sitting quietly for 3 minutes (recovery). Each subject's heart rate was monitored during the test, but setting a heart rate criterion based on adult recommendations for an exercise test was not practical because growing children can reach an exercising heart rate between 195 and 210bpm.³² Oxygen saturation was monitored during the test to ensure that it did not drop below 95%. Children were instructed to terminate the test if they were not feeling well, such as feeling dizzy or nauseous or experiencing pain; however, no child experienced these reactions to the test. On occasion, the mask was removed during the recovery phase because of a child feeling short of breath or hot while wearing the mask. After the test, the resting heart rate was averaged from baseline data, and $\dot{V}O_{2peak}$ (mL/kg/min) was calculated by determining the highest 15-second average value.

FVC was assessed by using the same metabolic cart that was used for upper-extremity ergometry testing by taking the best of 3 trials. With the nose closed by a soft nose clip, children were asked to breathe normally for at least 3 breaths through a mouthpiece and then were instructed to take as deep of a breath in as possible and blast the air out as fast and long as possible (goal=6s). FVC was recorded as a percentage of the norm based on age and height.^{33,34}

Finally, cholesterol, HDLs, LDLs, and triglycerides levels were obtained by a fasting lipid profile with children fasting at least 10 hours before the test. The measurement error has been reported to be 18.2mg/dL for triglycerides, 6.1mg/dL for cholesterol, 2.3mg/dL for HDL levels, and 7.4mg/dL for LDL levels in a sample of 19 children.³⁵

The same investigator, who was not blinded to group, performed all testing with the children, except the blood draw and blood histochemical analysis. The blood was collected and analyzed by blinded personnel.

Data Analysis

Two-way analyses of variance were used to compare all data across time (baseline and 6mo) and group. One-tailed paired *t* tests were used to examine any differences within groups over time. To allow for comparisons with published results for children with typical development, average percent change in $\dot{V}O_2$, and average change in values for the lipids were also analyzed.

RESULTS

Subjects

Thirty children with C4 to T11 SCI, ages 5 to 13 years (table 1), participated in the study. In total, 58 children were screened for possible participation (fig 2). Of the children who participated in the study, only 1 (passive cycling group) was involved in regular upper-extremity strengthening activities. Four children were participating in other recreation activities (hand cycling, 1 FES cycling, 1 electrical stimulation) and wheelchair basketball (1 electrical stimulation, 1 passive cycling). These activities were not new to the children during the study.

Adherence values (percentage) were calculated with and without the allowance for up to 12 missed sessions over the 6 months. With the allowance, adherence rates were $95.2\% \pm 18.1\%$, $107.2\% \pm 16.2\%$, and $105.5\% \pm 19.6\%$ for the FES cycling, passive cycling, and electrical stimulation groups, respectively. Without the allowance, this corresponded to $81.6\% \pm 15.5\%$, $91.9\% \pm 13.9\%$, and $89.6\% \pm 17.4\%$, respectively. The maximal resistances obtained by the FES cycling subjects ranged from 1.28 to 2.25Nm. Using these resistance levels and a cadence of 35 to 50rpm, the range of power outputs was 3.67 to 13.1W.

Table 1: Subject Demographics

Group	Age	Sex	Level of Injury	ASIA Grade	Years Postinjury	Cause of Injury	Height (cm)	Weight (kg)
FES	7	F	T4	A	5	MVC	119	27.5
FES	7	M	T1	A	5	MVC	120.5	20.2
FES	7	M	C4	B	6	Transverse myelitis	122	23.1
FES	8	M	C8	B	6	MVC	122.5	26.8
FES	8	M	T5	B	8	Atresia	120	19.7
FES	9	F	C7	A	5	MVC	130	23.7
FES	11	M	T1	A	5	MVC	138.5	27.5
FES	12	F	T11	A	2	MVC	160.5	57.8
FES	12	F	T1	A	1	MVC	156.5	89.4
FES	13	F	T10	C*	3	MVC	156	66
PC	5	F	C7	A	4	MVC	116.5	24
PC	7	F	T8	B	7	Ischemia	120	24.1
PC	7	M	T3	A	3	MVC	118.5	19.7
PC	7	M	T7	C†	1	MVC	118.5	17.7
PC	8	F	C5	A	7	MVC	122	23.3
PC	8	M	T1	A	5	MVC	134.7	37
PC	8	M	C7	A	6	MVC	121.5	24.6
PC	11	F	C8	B	7	MVC	139	41.6
PC	11	M	C7	A	8	MVC	144.5	29.1
PC	12	F	T4	A	1	MVC	149	38
ES	6	F	T7	A	1	MVC	118	20.7
ES	11	F	T5	A	7	MVC	146	45
ES	11	M	T11	B	7	Chemotherapy	156	49.1
ES	12	F	C7	A	2	MVC	161.5	54.8
ES	12	M	T7	A	8	MVC	161.3	72.6
ES	12	M	C7	A	12	Birth	146	33.9
ES	12	M	T5	A	2	MVC	167	75.4
ES	12	M	C7	A	10	MVC	153	37.7
ES	13	M	T4	A	7	MVC	171.4	70.2
ES	13	M	T5	A	1	Transverse myelitis	165.5	67.6

Abbreviations: ES, electrical stimulation; F, female; M, male; MVC, motor vehicle collision; PC, passive cycling.

*Hip flexion grade 2 only. No other lower-extremity movement.

†Anal contraction only. No lower-extremity movement.

Baseline Measures

There were significant differences between groups in baseline height, weight, and age. In addition, the groups were unbalanced in terms of injury levels, with the greatest number of subjects with tetraplegia in the passive cycling group. However, there were no differences between groups for any of the baseline measures (VO_2 peak, resting heart rate, FVC, lipid values).

Oxygen Uptake (mL/kg/min) and Resting Heart Rate

There were no differences between groups over time for VO_2 peak when comparing baseline and 6-month values (fig 3). However, when examining average percent change, there were significant differences between groups with Bonferroni post hoc testing showing that the FES cycling group had a significant change ($16.2\% \pm 25\%$) as compared with the passive cycling group ($-28.7\% \pm 42\%$). In examining baseline and 6-month values within each group, the changes did not reach statistical significance. In addition, resting heart rate did not change when comparing the groups over time (fig 4), and 1-tailed paired t tests showed no changes within each group. Table 2 displays each subject's individual data for VO_2 and resting heart rate.

Forced Vital Capacity

There were no differences between groups over time for FVC when comparing baseline and 6-month values (fig 5).

One-tailed paired t tests also showed no changes within each group. Table 2 displays each subject's individual data.

Lipids

There were no differences between groups over time for any of the lipids when comparing baseline and 6-month values (table 3). One-tailed paired t tests also showed no changes within each group. When examining average change in lipid values, there were significant differences between groups for cholesterol and HDL levels. Bonferroni post hoc testing showed that the electrical stimulation group had a decrease in cholesterol as compared with the FES cycling group.

DISCUSSION

In this study, 30 children with SCI exercised at home for 6 months with an FES cycle or passive cycle or they used noncycling electrical stimulation therapy. The results showed a greater percent change in VO_2 peak for the FES cycling group and a greater percent decrease in cholesterol levels for the electrical stimulation group. Therefore, our hypothesis was partially supported because the FES cycling group showed greater respiratory changes but not greater cardiovascular changes.

Compliance with the exercise protocol was between 80% and 92% for the 3 groups, suggesting that the exercise protocols were integrated successfully into the family routine. The

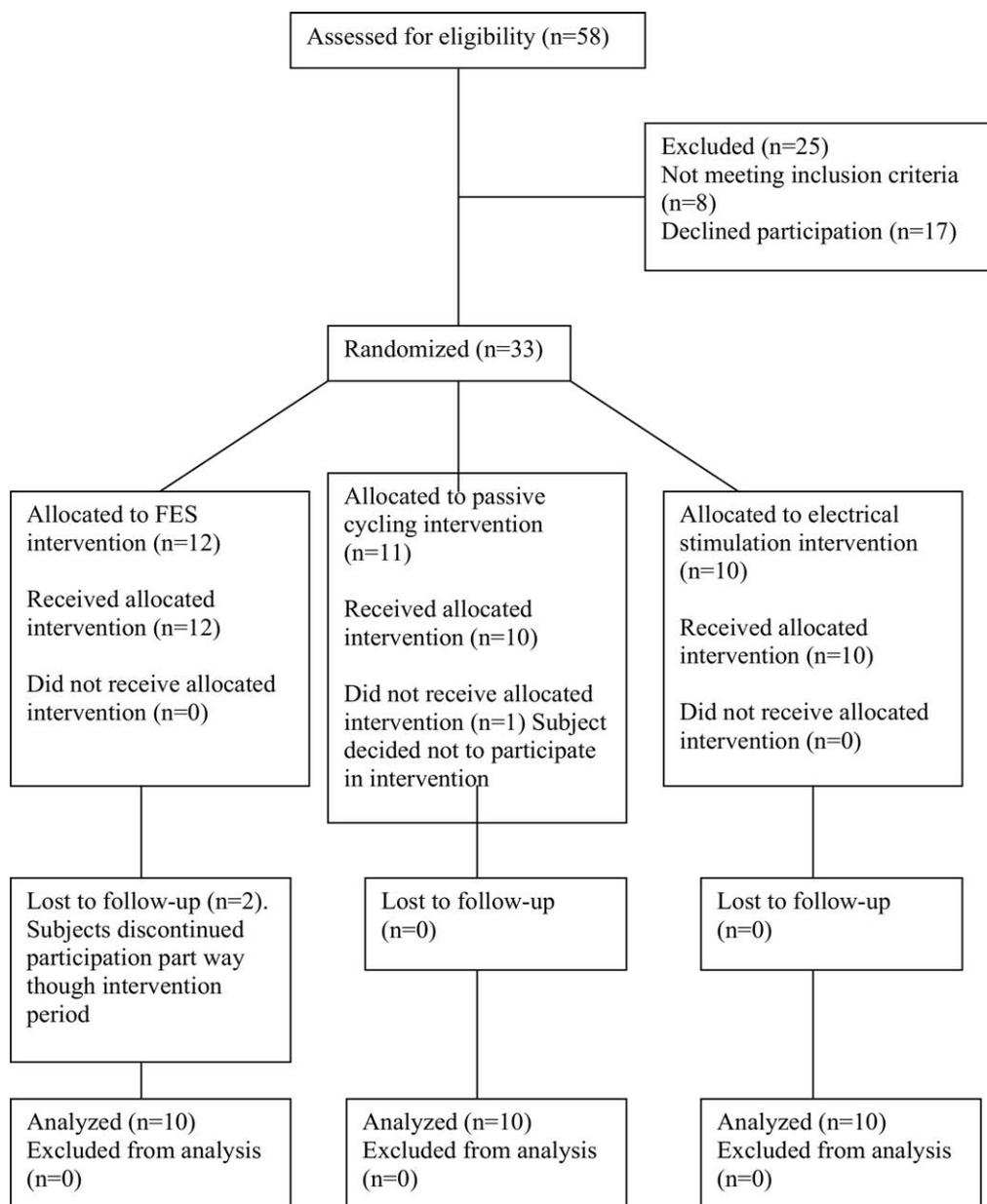


Fig 2. Flowchart diagram for the study.

adherence rate for the FES cycling group was likely less than the other groups because of the added time for setup, occasional computer malfunctions, and the need for greater parental supervision to advance resistance. Only 1 child (12y) complained of occasional discomfort with the FES; however, she did not miss sessions because of this issue. During the study, medications taken by the children were primarily for spasticity and bladder management. These medications remained stable throughout the study, other than occasional antibiotics because of urinary tract infections.

The FES cycling group showed improvements in $\dot{V}O_{2peak}$ with values improving from 9.9 ± 5.4 to 12.7 ± 7.6 mL/kg/min. A decline was observed in the passive cycling group, and a minimal increase was seen in the electrical stimulation group. To interpret these findings, it is important to understand how

children with typical development respond to exercise because children respond differently than do adults. One study examining $\dot{V}O_{2max}$ changes after a 12-week aerobic exercise program for 10- to 12-year-old children with typical development showed average $\dot{V}O_{2max}$ increases of 6.5% ($P < .05$).³⁶ In our study, children in the FES cycling group showed average increases of 16.2%, suggesting that they experienced a clinically significant improvement in this measure. The percent decrease in $\dot{V}O_2$ of 28.7% for the passive cycling group was surprising. Children in the electrical stimulation group showed no overall change (2.5% increase). Overall, these results suggest that both types of exercise involving electrical stimulation helped to improve or maintain $\dot{V}O_2$, whereas the passive exercise did not, indicating that active muscle contractions may be important. These active contractions may have impacted the

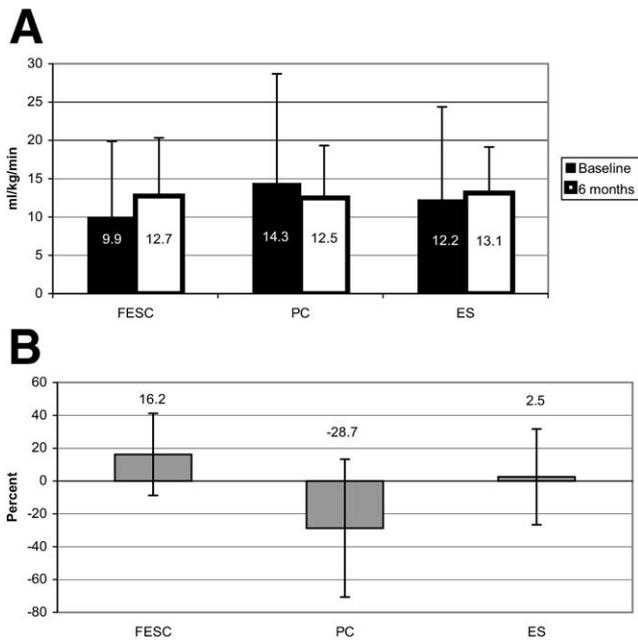


Fig 3. (A) $\dot{V}O_2$ values and (B) average percent change in $\dot{V}O_2$ per group. There were no differences between groups in uptake values over time ($P=.588$, power=.133); however, the FESC group showed a significant increase in average percent change as compared with the passive cycling group ($P=.033$, power=.651) with Bonferroni post hoc testing showing that the FESC group had a greater positive percent change than did the passive cycling group ($P=.035$) (FESC vs ES, $P=1.00$; PC vs ES, $P=.185$). In examining baseline and 6-month values within each group, the changes did not reach statistical significance (FESC, $P=.056$; PC, $P=.095$; ES, $P=.23$). Abbreviations: ES, electrical stimulation; FESC, functional electrical stimulation cycling; PC, passive cycling.

central cardiorespiratory system through improvements in venous return and decreased blood pooling.³ One possible limitation to these findings is that the impact of the upper-extremity exercise participation during the study for 5 (1 FES cycling, 2 passive cycling, 2 electrical stimulation) of the 30 children cannot be determined. However, the children were participating in these activities regularly before enrolling in the study.

In children³¹ and adults with SCI,³⁷ exercise responses vary based on level of injury, with people with tetraplegia showing the smallest changes in $\dot{V}O_2$ values with exercise because of alterations in the sympathetic nervous system and differences in lean body mass. These factors may have impacted the results by decreasing the average change per group. Each group included children with tetraplegia and children with paraplegia (3, 5, and 3 children with tetraplegia in the FES cycling, passive cycling, and electrical stimulation groups, respectively). When re-examining the data based on level of injury, the average changes in $\dot{V}O_2$ were $-12.1\% \pm 22.8\%$ for subjects with tetraplegia ($n=9$), $41.2\% \pm 78\%$ for subjects with T1 to T5 paraplegia ($n=10$), and $-5.2\% \pm 35.5\%$ for subjects with T7 to T11 paraplegia ($n=7$). Therefore, the largest change was seen in the group with T1 to T5 paraplegia. When only examining the children in the FES cycling group, the average changes in $\dot{V}O_2$ were $-7\% \pm 9.9\%$ for subjects with tetraplegia ($n=2$), $52.8 \pm 69.3\%$ for subjects with T1 to T5 paraplegia ($n=4$), and $-32.4\% \pm 35.0\%$ for subjects with T7 to T11 paraplegia ($n=2$). These results suggest that lean body mass may have had an impact on the results because greater improvements were seen in the children with

paraplegia. This finding must be viewed cautiously because of the small sample size of the FES cycling group.

Adults with SCI have shown improvements in $\dot{V}O_{2peak}$ after upper-extremity³⁸ and lower-extremity FES cycling³⁹ exercise. A systematic review of $\dot{V}O_{2peak}$ after a 3 or more times per week upper-extremity exercise program showed average increases of $17.6\% \pm 11.2\%$ over a period of 4 to 32 weeks.³⁸ Our finding of an increase of 16.2% for subjects in the FES cycling groups was comparable with their results. In an FES cycling study for adults with SCI,³⁹ statistically significant improvements were found in $\dot{V}O_{2peak}$ during FES cycling after a minimum of twenty-four 30-minute sessions performed twice per week.

Resting heart rate decreased approximately 5 beats/min on average for all groups. It is difficult to discern the exercise effect because of the natural decline in resting heart rate that occurs as children become older.³² A 2- to 3-beats/min decrease of over a 6-month period of time occurs in children with typical development⁴⁰; however, it is unknown if the similar decrease occurs in children with SCI. In addition, adults with SCI show variability in their resting heart rate⁴¹; therefore, resting heart rate may not be a good indicator of fitness levels. Variability in resting heart rate has not been reported for children with SCI.

FVC did not change over time for children in any group. The baseline average FVC value for subjects in this study was $66.9\% \pm 24.7\%$ (range, 22%–124%) of predicted based on children with typical development. Therefore, as a group, these children have low values. In a study with prepubescent children with typical development,²⁸ FVC (in liters) increased by 7% ($P<.05$) after an 8-week running program, indicating that exercise can increase FVC. However, in that study, it was unknown if this training increased lung volume or if the increase was because of improvements in the expiratory muscles.²⁸ For adults with SCI, 1 study showed that a 30-minute, 3-times-per-week, 6-week upper-extremity aerobic program could increase FVC. This change may have been because of increased strength and the endurance of accessory muscles that were impacted directly or indirectly by the exercise.²⁷

Perhaps the children in our study did not reach sufficient exercise intensity to realize significant changes in FVC, resting heart rate, and lipid levels. Resistance was increased for the FES cycling group to increase overall power output; however, the resistance may not have allowed subjects to reach power output levels necessary to realize further gains. To reach higher resistances, the cadence of 50rpm would likely have to be decreased. Fornusek and Davis⁴² showed a higher average

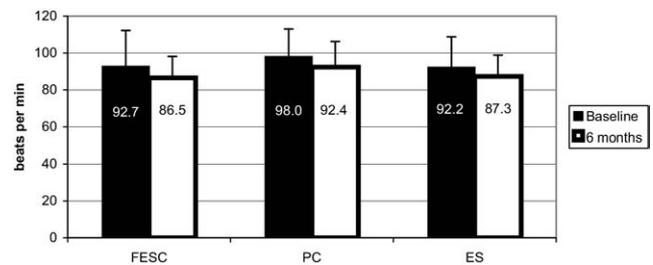


Fig 4. Resting heart rate values per group. There were no changes in resting heart rate over time for any group ($P=.991$, power=.051). One-tailed paired t tests also showed no changes within each group (FESC, $P=.12$; PC, $P=.16$; ES, $P=.18$). The slight decline noted may be because of children being 6 months older. Abbreviations: ES, electrical stimulation; FESC, functional electrical stimulation cycling; PC, passive cycling.

Table 2: Individual Data and Percent Change for the Upper-Extremity Ergometry Test (Vo₂peak, resting heart rate, peak heart rate, and maximal power) and the FVC Test

Group	Age	Sex	Vo ₂ peak (mL/kg/min)			Resting HR (beats/min)			HR Peak (beats/min)			Max Power Output (W)			FVC (% Predicted)		
			Pre	Post	% Δ	Pre	Post	% Δ	Pre	Post	% Δ	Pre	Post	% Δ	Pre	Post	% Δ
FES	7	F	6.2	15.7	153.2	105	96	-8.6	185	173	-6.5	30	40	33.3			NT
FES	7	M	12.1	11.4	-5.8	76	89	17.1	110	112	1.8	20	20	0.0	61	52	-14.8
FES	7	M		NT			NT			NT			NT		36	50	38.9
FES	8	M	8.6	7.4	-14.0	88	90	2.3	134	112	-16.4	20	10	-50.0	54	55	1.9
FES	8	M		NT		122	89	-27.0	170	137	-19.4	20	20	0.0	90	99	10.0
FES	9	F	6.0	6.0	0.0	111	94	-15.3	132	116	-12.1	10	10	0.0	36	35	-2.8
FES	11	M	7.7	10.4	35.1	66	61	-7.6	100	103	3.0	30	30	0.0	55	59	7.3
FES	12	F	17.0	26.7	57.1	101	84	-16.8	170	180	5.9	180	100	-44.4	124	111	-10.5
FES	12	F	3.5	4.5	28.6	97	99	2.1	100	110	10.0	40	50	25.0	71	63	-11.3
FES	13	F	18.4	19.8	7.6	68	77	13.2	159	172	8.2	130	115	-11.5	115	119	3.5
PC	5	F	9.9	8.8	-11.1	108	82	-24.1	143	130	-9.1	10	10	0.0	50	56	12.0
PC	7	F	25.4	25.7	1.2	101	86	-14.9	200	191	-4.5	60	70	16.7	115	96	-16.5
PC	7	M		NT		101	99	-2.0	136	141	3.7	20	20	0.0	54	67	24.1
PC	7	M	19.7	15.3	-22.3	95	122	28.4	146	82	-43.8	30	30	0.0	49	60	22.4
PC	8	F		NT		82	85	3.7		NT			NT		22	20	-9.1
PC	8	M	14.0	7.4	-47.1	130	102	-21.5	160	165	3.1	20	30	50.0	75	60	-20.0
PC	8	M	14.4	9.0	-37.5	99	104	5.1	129	129	0.0	20	10	-50.0	53	49	-7.5
PC	11	F	7.0	4.0	-42.9	77	81	5.2	110	128	16.4	20	40	100.0	58	69	19.0
PC	11	M	13.6	17.1	25.7	85	79	-7.1	127	142	11.8	40	30	-25.0	46	46	0.0
PC	12	F	10.7	12.6	17.8	101	84	-16.8	168	138	-17.9	20	20	0.0	66	69	4.5
ES	6	F	33.8	13.1	-61.2	91	103	13.2	194	175	-9.8	30	30	0.0	81	41	-49.4
ES	11	F	9.1	9.7	6.6	87	93	6.9	181	190	5.0	40	70	75.0	70	73	4.3
ES	11	M	20.5	18.3	-10.7	80	86	7.5	163	165	1.2	80	80	0.0	81	84	3.7
ES	12	F	4.5	3.3	-26.7	107	96	-10.3	132	128	-3.0	20	20	0.0	32	35	9.4
ES	12	M	18.8	17.3	-8.0	78	87	11.5	168	189	12.5	100	100	0.0	84	85	1.2
ES	12	M	7.0	5.8	-17.1	125	103	-17.6	139	127	-8.6	10	20	100.0	60	55	-8.3
ES	12	M	4.7	14.5	208.5	99	77	-22.2	195	163	-16.4	100	130	30.0	83	83	0.0
ES	12	M	14.8	17.0	14.9	76	69	-9.2	105	143	36.2	30	50	66.7	56	55	-1.8
ES	13	M	20.0	21.0	5.0	104	94	-9.6	205	174	-15.1	115	100	-13.0	87	84	-3.4
ES	13	M	10.3	11.3	9.7	68	75	10.3	170	154	-9.4	70	80	14.3	76	6	-92.1

Abbreviations: ES, electrical stimulation; F, female; HR, heart rate; M, male; NT, not tested; PC, passive cycling; % Δ, percent change.

power output in adults with SCI when cycling with FES at 30rpm as compared with 50rpm. Another option would be to perform upper- and lower-extremity exercise simultaneously. Hooker et al¹⁹ reported an increase of 23% in Vo₂ after a combined lower-extremity FES and arm-crank ergometry program for adults with SCI. This type of combined exercise has not been tested in children with SCI. Future research should examine these and other methods to increase exercise intensity

in children with SCI to determine if greater cardiorespiratory improvements can be realized. Additionally, future studies should include a rating of perceived exertion to determine the intensity as related to each of the children because children will vary in their levels of fitness.

No significant changes in lipid levels were seen between groups over time. However, it is important to consider how lipids typically respond to exercise for children in general to better interpret our results. A meta-analysis⁴³ of lipid profiles after aerobic exercise in typically developing children (5–19y) reported changes only with triglyceride levels (average change 12%). In this meta-analysis, the confidence intervals for lipid changes were found to be -22.8 to 0.8mg/dL for triglycerides, -4.4 to 3.3mg/dL for cholesterol, -4.8 to 1.9mg/dL for HDL, and -4.3 to 6.7mg/dL for LDL levels.⁴³ Using these confidence intervals, the FES cycling group had a small increase in cholesterol levels, the passive cycling group had a decrease in cholesterol levels (a positive change) but also a decrease in HDL levels (a negative change), and the electrical stimulation group had decreases in cholesterol, HDL, and LDL (positive change) levels. Therefore, the findings were mixed. In adults with SCI, arm-cranking exercise training has been associated with positive changes in HDL levels but not in total cholesterol or triglyceride levels.⁴⁴ Another study⁴⁵ reported that adults with SCI with greater physical capacity had better lipid profiles, thus suggesting that physical activity can have an impact.

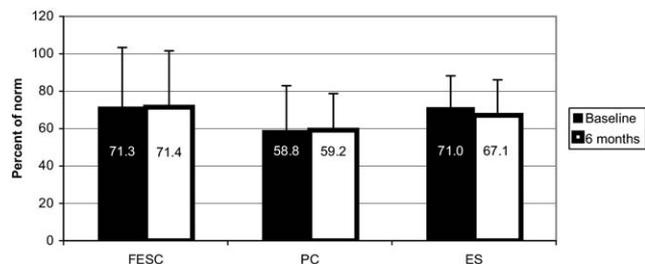


Fig 5. FVC per group. There were no differences between groups over time for FVC when comparing baseline and 6-month values ($P=.637$, power=.098). One-tailed paired t tests also showed no changes within each group (FESC, $P=.50$; PC, $P=.45$; ES, $P=.10$). Abbreviations: ES, electrical stimulation; FESC, functional electrical stimulation cycling; PC, passive cycling.

Table 3: Baseline and 6-Month Lipid Values (in mg/dL)

Group	Age	Sex	Triglycerides			Cholesterol			HDL			LDL		
			Pre	Post	% Δ	Pre	Post	% Δ	Pre	Post	% Δ	Pre	Post	% Δ
FES	7	F	96	103	7.3	188	231	22.9	36	40	11.1	133	171	28.6
FES	7	M	59	63	6.8	144	124	-13.9	36	37	2.8	97	75	-22.7
FES	7	M	56	44	-21.4	140	158	12.9	49	60	22.4	80	90	12.5
FES	8	M	52	38	-26.9	143	128	-10.5	48	46	-4.2	85	75	-11.8
FES	8	M	67	52	-22.4	126	130	3.2	37	37	0.0	76	83	9.2
FES	9	F	45	48	6.7	143	147	2.8	38	36	-5.3	96	102	6.3
FES	11	M	136	77	-43.4	188	169	-10.1	31	31	0.0	130	123	-5.4
FES	12	F	111	50	-55.0	164	165	0.6	37	53	43.2	105	103	-1.9
FES	12	F	150	144	-4.0	210	211	0.5	25	26	4.0	155	157	1.3
FES	13	F	66	152	130.3	114	141	23.7	36	37	2.8	65	74	13.8
FES group averages			83.8±37.3	77.1±41.9	-6.7±40.6	156±30.1	160.4±35.8	4.4±20.4	37.3±7.1	40.3±10.1	3.0±5.9	102.2±28.8	105.3±34.7	3.1±15.8
PC	5	F	77	69	-10.4	164	172	4.9	43	44	2.3	106	115	8.5
PC	7	F	29	44	51.7	149	156	4.7	55	48	-12.7	89	100	12.4
PC	7	M	219	155	-29.2	181	182	0.6	30	26	-13.3	108	125	15.7
PC	7	M	139	118	-15.1	80	74	-7.5	33	23	-30.3	20	28	40.0
PC	8	F	56	42	-25.0	152	140	-7.9	40	41	2.5	101	91	-9.9
PC	8	M	72	69	-4.2	202	215	6.4	57	55	-3.5	131	147	12.2
PC	8	M	87	78	-10.3	102	101	-1.0	36	33	-8.3	49	53	8.2
PC	11	F	227	126	-44.5	204	154	-24.5	33	24	-27.3	126	105	-16.7
PC	11	M	75	75	0.0	219	181	-17.4	65	53	-18.5	139	113	-18.7
PC	12	F	48	40	-16.7	124	112	-9.7	44	36	-18.2	71	69	-2.8
PC group averages			102.9±69.5	81.6±39.1	-21.3±34.7	157.7±45.7	148.7±42.8	-9.0±20.4	47±18.5	43.5±22.8	-3.5±6.8	90.6±39.8	89.4±38.4	-1.2±14.8
ES	6	F	35	63	80.0	205	173	-15.6	57	41	-28.1	141	120	-14.9
ES	11	F	100	50	-50.0	140	129	-7.9	50	44	-12.0	70	75	7.1
ES	11	M	60	74	23.3	138	132	-4.3	36	34	-5.6	90	84	-6.7
ES	12	F	101	77	-23.8	260	240	-7.7	39	43	10.3	201	182	-9.5
ES	12	M	342	258	-24.6	237	218	-8.0	39	37	-5.1	130	130	0.0
ES	12	M	65	55	-15.4	175	152	-13.1	35	32	-8.6	127	109	-14.2
ES	12	M	23	99	330.4	123	98	-20.3	43	32	-25.6	76	47	-38.2
ES	12	M	56	45	-19.6	225	220	-2.2	36	39	8.3	178	172	-3.4
ES	13	M	148	97	-34.5	115	102	-11.3	24	20	-16.7	62	63	1.6
ES	13	M	97	76	-21.6	155	138	-11.0	46	50	8.7	90	73	-18.9
ES group averages			102.7±91.7	89.4±62.0	-13.3±45.2	177.3±51.3	160.2±50.6	-17.1±8.5	40.5±9.1	37.2±8.3	-3.3±6.5	116.5±47.1	105.5±45.7	-11±11.3

NOTE. There were no differences between groups over time for any of the lipids (triglycerides, $P=.929$, power=.061; cholesterol, $P=.733$, power=.097; HDL, $P=.705$, power=.103; and LDL, $P=.847$, power=.075). One-tailed paired t tests also showed no changes within each group. When examining average change in lipid values, there were differences between groups for cholesterol ($P=.032$, power=.656) and HDL levels ($P=.05$, power=.579). Bonferroni post hoc testing showed that the ES group had a decrease in cholesterol as compared with the FES cycling group.

Abbreviations: ES, electrical stimulation; F, female; HR, heart rate; M, male; NT, not tested; PC, passive cycling; % Δ, percent change.

One limitation of our study is that diet was not controlled, and diet is a key factor in cholesterol levels. Future research should include a component focusing on nutrition to determine its influence on lipid values in these children.

Study Limitations

There are several limitations of this study. First, a control group not receiving any intervention was not included in the randomized controlled trial; therefore, the results may have been influenced by the developmental stage and growth of the subjects. Because of this, normative values for children without disability and data from adults with SCI after exercise programs were used to assist in the understanding of the results. The physical development of children with SCI for the measures tested is not known and warrants further investigation. A second limitation is that we did not have a data-logging system on the cycling or electrical stimulation equipment, so we relied on the parents for providing the majority of the information on program adherence through biweekly telephone calls and handwritten logs. The parents were very motivated to participate in this study because of the potential benefits to their children, so we believe that overall the parents were accurate in their reports of adherence.

CONCLUSIONS

For the cardiorespiratory and vascular measures studied, only children in the FES cycling group showed significant differences in percent increase in $\dot{V}O_{2peak}$ as compared with children in the passive cycling and electrical stimulation groups. No differences were found with resting heart rate and FVC among groups. The electrical stimulation group showed a significant difference in cholesterol levels as compared with the FES cycling and passive cycling groups. These findings suggest that an important respiratory change was observed for children in the FES cycling group. However, the lack of an effect on the other variables suggests that an increased intensity of exercise may be needed. Passive cycling and electrical stimulated exercise alone led to no or minimal positive changes in the cardiorespiratory or vascular measures studied.

References

- Leger L. Aerobic performance. In: Docherty D, editor. *Measurement in pediatric exercise science*. Champaign: Human Kinetics, 1996. p 183-223.
- Haisma JA, van der Woude LH, Stam HJ, Bergen MP, Sluis TA, Bussmann JB. Physical capacity in wheelchair-dependent persons with a spinal cord injury: a critical review of the literature. *Spinal Cord* 2006;44:642-52.
- Hettinga DM, Andrews BJ. Oxygen consumption during functional electrical stimulation-assisted exercise in persons with spinal cord injury: implications for fitness and health. *Sports Med* 2008;38:825-38.
- Myers J, Lee M, Kiratli J. Cardiovascular disease in spinal cord injury: an overview of prevalence, risk, evaluation, and management. *Am J Phys Med Rehabil* 2007;86:142-52.
- Nash MS. Exercise as a health-promoting activity following spinal cord injury. *J Neurol Phys Ther* 2005;29:87-103, 106.
- Jacobs PL, Nash MS. Modes, benefits, and risks of voluntary and electrically induced exercise in persons with spinal cord injury. *J Spinal Cord Med* 2001;24:10-8.
- Castro MJ, Apple DF Jr, Staron RS, Campos GE, Dudley GA. Influence of complete spinal cord injury on skeletal muscle within 6 mo of injury. *J Appl Physiol* 1999;86:350-8.
- Bauman WA, Spungen AM. Coronary heart disease in individuals with spinal cord injury: assessment of risk factors. *Spinal Cord* 2008;46:466-76.
- Whiteneck GG, Charlifue SW, Frankel HL, et al. Mortality, morbidity, and psychosocial outcomes of persons spinal cord injured more than 20 years ago. *Paraplegia* 1992;30:617-30.
- Bauman WA, Kahn NN, Grimm DR, Spungen AM. Risk factors for atherogenesis and cardiovascular autonomic function in persons with spinal cord injury. *Spinal Cord* 1999;37:601-16.
- Dallmeijer AJ, van der Woude LH. Health related functional status in men with spinal cord injury: relationship with lesion level and endurance capacity. *Spinal Cord* 2001;39:577-83.
- Davis GM, Servedio FJ, Glaser RM, Gupta SC, Suryaprasad AG. Cardiovascular responses to arm cranking and FNS-induced leg exercise in paraplegics. *J Appl Physiol* 1990;69:671-7.
- Raymond J, Davis GM, van der PM. Cardiovascular responses during submaximal electrical stimulation-induced leg cycling in individuals with paraplegia. *Clin Physiol Funct Imaging* 2002;22:92-8.
- Raymond J, Davis GM, Der Plas MN, Groeller H, Simcox S. Carotid baroreflex control of heart rate and blood pressure during ES leg cycling in paraplegics. *J Appl Physiol* 2000;88:957-65.
- Raymond J, Davis GM, Bryant G, Clarke J. Cardiovascular responses to an orthostatic challenge and electrical-stimulation-induced leg muscle contractions in individuals with paraplegia. *Eur J Appl Physiol Occup Physiol* 1999;80:205-12.
- Raymond J, Davis GM, Climstein M, Sutton JR. Cardiorespiratory responses to arm cranking and electrical stimulation leg cycling in people with paraplegia. *Med Sci Sports Exerc* 1999;31:822-8.
- Raymond J, Davis GM, Fahey A, Climstein M, Sutton JR. Oxygen uptake and heart rate responses during arm vs combined arm/electrically stimulated leg exercise in people with paraplegia. *Spinal Cord* 1997;35:680-5.
- Hooker SP, Figoni SF, Glaser RM, Rodgers MM, Ezenwa BN, Faghri PD. Physiologic responses to prolonged electrically stimulated leg-cycle exercise in the spinal cord injured. *Arch Phys Med Rehabil* 1990;71:863-9.
- Hooker SP, Figoni SF, Rodgers MM, et al. Physiologic effects of electrical stimulation leg cycle exercise training in spinal cord injured persons. *Arch Phys Med Rehabil* 1992;73:470-6.
- Hooker SP, Figoni SF, Rodgers MM, et al. Metabolic and hemodynamic responses to concurrent voluntary arm crank and electrical stimulation leg cycle exercise in quadriplegics. *J Rehabil Res Dev* 1992;29:1-11.
- Hooker SP, Greenwood JD, Hatae DT, Husson RP, Matthiesen TL, Waters AR. Oxygen uptake and heart rate relationship in persons with spinal cord injury. *Med Sci Sports Exerc* 1993;25:1115-9.
- Hooker SP, Scremin AM, Mutton DL, Kunkel CF, Cagle G. Peak and submaximal physiologic responses following electrical stimulation leg cycle ergometer training. *J Rehabil Res Dev* 1995;32:361-6.
- Petrofsky JS. Blood pressure and heart rate response to isometric exercise: the effect of spinal cord injury in humans. *Eur J Appl Physiol* 2001;85:521-6.
- Petrofsky JS, Phillips CA. The use of functional electrical stimulation for rehabilitation of spinal cord injured patients. *Cent Nerv Syst Trauma* 1984;1:57-74.
- Ragnarsson KT. Physiologic effects of functional electrical stimulation-induced exercises in spinal cord-injured individuals. *Clin Orthop Relat Res* 1988;Aug(233):53-63.
- Faghri PD, Glaser RM, Figoni SF. Functional electrical stimulation leg cycle ergometer exercise: training effects on cardiorespiratory responses of spinal cord injured subjects at rest and during submaximal exercise. *Arch Phys Med Rehabil* 1992;73:1085-93.
- Silva AC, Neder JA, Chiurciu MV, et al. Effect of aerobic training on ventilatory muscle endurance of spinal cord injured men. *Spinal Cord* 1998;36:240-5.

28. Nourry C, Deruelle F, Guinhouya C, et al. High-intensity intermittent running training improves pulmonary function and alters exercise breathing pattern in children. *Eur J Appl Physiol* 2005; 94:415-23.
29. Vogel LC, Krajci KA, Anderson CJ. Adults with pediatric-onset spinal cord injuries: part 3: impact of medical complications. *J Spinal Cord Med* 2002;25:297-305.
30. Weaver FM, Smith B, Evans CT, et al. Outcomes of outpatient visits for acute respiratory illness in veterans with spinal cord injuries and disorders. *Am J Phys Med Rehabil* 2006;85: 718-26.
31. Johnston TE, Smith BT, Betz RR, Lauer RT. Exercise testing using upper extremity ergometry in pediatric spinal cord injury. *Pediatr Phys Ther* 2008;20:146-51.
32. Bar-Or O, Rowland TW. Physiologic and perceptual responses to exercise in the healthy child. *Pediatric exercise medicine*. Champaign; Human Kinetics, 2004. p 3-59.
33. Zapletal A. Lung function in children and adolescents. Methods, reference values. In: Zapletal A, Samanek M, Paul T, editors. *Progress in respiration research*. Basel: Karger; 1987. p 114-218.
34. Polgar G, Promadhat V. *Pulmonary function testing in children: techniques and standards*. Philadelphia: Saunders; 1971.
35. Tolfrey K, Jones AM, Campbell IG. Lipid-lipoproteins in children: an exercise dose-response study. *Med Sci Sports Exerc* 2004;36:418-27.
36. Rowland TW, Boyajian A. Aerobic response to endurance exercise training in children. *Pediatrics* 1995;96:654-8.
37. Burkett LN, Chisum J, Stone W, Fernhall B. Exercise capacity of untrained spinal cord injured individuals and the relationship of peak oxygen uptake to level of injury. *Paraplegia* 1990;28:512-21.
38. Valent L, Dallmeijer A, Houdijk H, Talsma E, van der WL. The effects of upper body exercise on the physical capacity of people with a spinal cord injury: a systematic review. *Clin Rehabil* 2007;21:315-30.
39. Barstow TJ, Scremin AM, Mutton DL, Kunkel CF, Cagle TG, Whipp BJ. Changes in gas exchange kinetics with training in patients with spinal cord injury. *Med Sci Sports Exerc* 1996;28: 1221-8.
40. Malina RM, Bouchard C. *Growth, maturation, and physical activity*. Champaign: Human Kinetics; 1991.
41. Stewart MW, Melton-Rogers SL, Morrison S, Fighi SF. The measurement properties of fitness measures and health status for persons with spinal cord injuries. *Arch Phys Med Rehabil* 2000; 81:394-400.
42. Fornusek C, Davis GM. Maximizing muscle force via low-cadence functional electrical stimulation cycling. *J Rehabil Med* 2004;36:232-7.
43. Kelley GA, Kelley KS. Aerobic exercise and lipids and lipoproteins in children and adolescents: a meta-analysis of randomized controlled trials. *Atherosclerosis* 2007;191:447-53.
44. El Sayed MS, Younesian A. Lipid profiles are influenced by arm cranking exercise and training in individuals with spinal cord injury. *Spinal Cord* 2005;43:299-305.
45. de Groot S, Dallmeijer AJ, Post MW, Angenot EL, van der Woude LH. The longitudinal relationship between lipid profile and physical capacity in persons with a recent spinal cord injury. *Spinal Cord* 2008;46:344-51.

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