Circuit Training and Protein Supplementation in Persons with Chronic Tetraplegia

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ABSTRACT

KRESSLER, J., P. A. BURNS, L. BETANCOURT, and M. S. NASH. Circuit Training and Protein Supplementation in Persons with Chronic Tetraplegia. *Med. Sci. Sports Exerc.*, Vol. 46, No. 7, pp. 1277–1284, 2014. Circuit resistance training (CRT) performed three times weekly for 40–45 min each session increases muscular strength and both aerobic and anaerobic capacity in untrained individuals with chronic paraplegia. Whether similar CRT is also effective for conditioning of persons with chronic tetraplegia is unknown. In addition, protein supplementation (PS) before and immediately postexercise has been shown to enhance exercise adaptations. **Purpose**: This study aimed to investigate whether a modified 40–45 min CRT program will improve fitness attributes in individuals with tetraplegia and whether these changes are enhanced by PS. **Methods**: Eleven individuals with chronic tetraplegia underwent 6 months of CRT performed three times per week. Six randomly assigned participants received PS (whey protein = 36–37 g) in split doses immediately before and after exercise sessions. Others consumed a matched protein dose 24 h postexercise. Measurements of one-repetition maximum (1-RM) strength for six different resistance exercises, arm peak oxygen consumption ($\dot{V}O_{2peak}$), and arm anaerobic power (Wingate) were obtained 3 months before (−3mo), at the beginning (0mo), 3 months into (3mo), and 6 months after (6mo) the beginning of CRT. **Results**: One-repetition maximum increased by 8%–11% ± 6%–12% for each successive 3-month period ($P \leq 0.001$–0.012), independent of PS group ($P = 0.105$). $\dot{V}O_{2peak}$ increased significantly from 0mo to 6mo with immediate PS (35% ± 29%, $P = 0.020$) but failed to reach significance for delayed PS (15% ± 8%, $P = 0.147$). Power drop changes during the Wingate test were also only significant for the immediate PS (median difference 40W, $P = 0.028$) and not for delayed (10W, $P = 0.500$). **Conclusion**: CRT effectively increased muscular strength, aerobic capacity, and anaerobic fatigue resistance in persons with chronic tetraplegia. The latter two conditioning benefits were further enhanced by timely PS.

Key Words: SPINAL CORD INJURY, CARDIORESPIRATORY FITNESS, ANAEROBIC POWER, RESISTANCE TRAINING

All-cause cardiovascular disease (CVD) has emerged as a leading cause of death in persons with spinal cord injury (SCI) and especially for those who survive for 30 or more years with their disability. It is widely reported that persons with SCI constitute the lowest end of the human fitness continuum and that a sedentary lifestyle and low levels of fitness contribute to an accelerated trajectory of both overall aging and early CVD for this population (28). In some cases, sedentary behavior after SCI represents a lifestyle choice but may otherwise involve recognized barriers to exercise participation that involve special needs for transportation, architectural access, adapted equipment, and professional support (6). Notwithstanding the cause, combating sedentariness and low fitness with physical activity (PA) has been recognized as an important goal by all major health authorities, including the U.S. Surgeon General, the American Heart Association, the Centers for Disease Control and Prevention, the American Diabetes Association, and the American College of Sports Medicine. These authorities recommend that persons of all ages should increase their habitual PA to a level appropriate to their capacities. This is particularly important for people with SCI, and as fitness deficiencies and well-being are improved by exercise conditioning (25,28,39), population-specific guidelines have been developed to improve PA and fitness in persons with SCI (15).

One of the anticipated barriers to exercise participation after SCI involves the level of functional impairment, which typically increases as the level of injury ascends. Nonambulatory people with chronic tetraplegia (TP) are therefore most at risk. Although general guidelines are available (15), specific information on exercise conditioning for persons with TP is sparse, leaving end users with SCI and their health care providers with limited information to guide sought-after conditioning benefits (17). Moreover, it is commonly

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recommended that people (including those with TP) engage in both aerobic and resistance training (15), yet little is known about interventions that combine resistance and endurance training. Only two investigations have used both aerobic endurance and resistance training in persons with TP (18,19). Although these investigations provided evidence for the general effectiveness of combined exercise training, they were delimited by extended time commitments (90–120 min per session) and/or for extensive inpatient care (18,19). These needs may impose new barriers to physical conditioning and prevent many from adopting these types of lifestyle modifying programs.

Circuit resistance training (CRT) has been shown to be an effective conditioning strategy for improving muscle strength and cardiorespiratory (CR) endurance in fit and unfit populations and has the advantage of requiring limited time (40–45 min) for conditioning sessions. We have previously reported in persons with paraplegia that 40–45 min of CRT performed three times weekly using adapted resistance training equipment is safe and effective for improving peak CR capacity (i.e., $\dot{V}O_{2\text{peak}}$), time to fatigue, peak and average anaerobic power output, and both isokinetic and isoinertial strength (32). This protocol has recently been incorporated into authoritative exercise recommendations for persons with SCI (34). Whether similar benefits of CRT can be obtained in persons with TP has not yet been investigated.

In addition, a popular strategy to maximize fitness gains is nutritional supplementation, particularly protein supplementation (PS). PS is commonly used to enhance muscle hypertrophy related fitness improvements (i.e., strength) by increasing muscle protein synthesis and decrease degradation (2). The timing of the protein intake seems critical in maximizing these effects (11), and failure to ingest amino acids soon after exhaustive exercise may represent a barrier to optimal muscle repair and growth (1). Conversely, various populations that ingest immediate ($\leq$2–3 h) postexercise PS benefit from increased strength gains and fatigue resistance when compared with controls (13). Importantly, these advantages appear not only in healthy individuals but also in persons with physical impairments due to frailty, ill health, or advanced age (12).

The purpose of this investigation was therefore to investigate whether CRT as modified for persons with TP can improve multiple attributes of fitness, and whether these enhancements are augmented by optimized PS. It was hypothesized that CRT will improve measures of muscular strength, CR fitness, and anaerobic capacity and that this effect would be improved by optimized timing of PS.

METHODS AND PROCEDURES

Design

The study was a randomized, double-blinded, placebo-controlled, parallel-group design in persons with chronic TP.

Subjects

Participants included 11 males and females aged 18–55 yr with cervical SCI (ASIA Impairment Scale [AIS] A-D, International Standards for Neurological Classification of SCI; ASIA/IMSOP, Revised 2002) at the C5–C8 levels for more than 1 yr (Table 1). All subjects had been physically inactive for at least 6 months before entry into the study. Signed informed consent was obtained from all subjects before the start of the study, which was approved by the University of Miami Medical Sciences Committee for the Protection of Human Subjects.

Exclusion Criteria

Subjects were excluded if they had had surgery within 6 months or pressure ulcer within 3 months of the beginning of the intervention, had upper limb pain that limited the completion of exercise, had recurrent acute infection or illness requiring hospitalization or IV antibiotics, is pregnant, had previous myocardial infarction or cardiac surgery, had a history of glucose-lowering and lipid-lowering drug therapy, had type I or type II diabetes (by World Health Organization criteria), or were taking medications including beta-adrenergic antagonists or maintenance alpha-adrenergic blockers.

TABLE 1. Subject characteristics.

Group	Age (yr)	Gender	Duration of Injury (yr)	Level of Injury	ASIA Impairment Scale	Height (m)	Weight (kg)	$\dot{V}O_{2\text{peak}}$ (mL·kg^{-1}·min^{-1})
DPS	31	Male	10	C5	A	1.85	99.5	5.3
DPS	46	Female	28	C5	C	1.68	64.0	8.6
DPS	24	Male	2	C5	A	1.72	84.1	4.6
DPS	36	Female	2	C6	C	1.63	90.0	6.9
DPS	50	Male	27	C5	A	1.80	75.0	9.3
Mean	37	NA	14	NA	NA	1.74	82.5	6.9
SD	11	NA	13	NA	NA	0.09	13.7	2.0
IPS	49	Male	5	C6–C7	D	1.75	70.5	20.6
IPS	30	Male	>2	C5–C6	D	1.85	108.0	13.5
IPS	44	Male	9	C6–C7	D	1.75	87.3	6.5
IPS	37	Male	>2	C8–C5	C	1.78	87.5	9.2
IPS	58	Male	>2	C6	A	1.77	70.0	7.6
IPS	32	Male	1	C6	A	1.70	71.8	9.5
Mean	42	NA	5	NA	NA	1.77	82.5	11.2
SD	11	NA	4	NA	NA	0.05	14.9	5.2

Control for Dietary Intake

Study participants were counseled to maintain their habitual diet and physical activity throughout the study.

Randomization and Intervention Assignment

Subjects were randomly assigned to either immediate protein supplement (IPS) or delayed protein supplement (DPS) groups. A 3-month "wash-in" control strategy to obtain data on "untreated" subjects was adopted in lieu of a control group.

Protocol

Subjects performed CRT three times weekly on nonconsecutive days for 26 wk. The previously described protocol of CRT for persons with paraplegia (32) was adapted for persons with TP with a spinal injury level as high as the C5. These include adjusting the order of the resistance maneuvers so that time in changing stations was minimized and resistance and endurance exercises in contiguous time blocks were performed. Each session lasted approximately 40–45 min and used resistance training (weight lifting) and endurance activities (reciprocal arm exercise, Vita-Glide; RehaMed International, Chelsfield, United Kingdom) with interposed periods of incomplete recovery (i.e., heart rate not falling to baseline). The following full-range bilateral resistance maneuvers were performed on an Equalizer 7000 multistation exercise system (Helm, Bozeman, MT): 1) wide grip latissimus pull-down and 2) dips, 3) pectoralis ("pec") deck, 4) preacher curls (elbow flexion), 5) lateral raise, and 6) horizontal rows. Each training session was preceded by a 2-min arm ergometry warm-up using the Vita-Glide reciprocating arm ergometer. The resistance and endurance activities for our past circuit training protocols were rapidly alternated without allowing time for rest. To minimize setup and transfer time needed in persons with TP, we instructed participants to perform all resistance activities and then all endurance activity in contiguous time blocks, with the order of exercise (i.e., resistance and endurance) alternated each training day. We also had an exercise technician assist with station setup and changes. Resistance exercises incorporated 10 repetitions of each maneuver (6-s movement; 3 s concentric [lifting] and 3 s eccentric [lowering]). Ten seconds of rest was allowed, and 10 additional repetitions were performed. Resistive loads for training during weeks 1 and 2 were 50% of the one-repetition maximum (1-RM) as calculated during initial isoinertial strength testing (for details, see Outcome Measures section). These loads were increased to 55% and 60% of the 1-RM during training weeks 3 and 4, respectively. The 1-RM for each maneuver was recomputed during the last training session every 4 wk to adjust for training effects. Endurance exercise was performed on Vita-Glide arm ergometer at a cadence of 50 rpm. Sessions began with 10 min of work (added to resistance maneuvers) and increased to 20 min of continuous activity. Work intensity was determined on a Polar® monitor using a 60% target for heart rate reserve determined by the equation of Karvonen. Resting and peak HR values that were needed to compute target HR from the Karvonen equation were obtained from the arm exercise tests (for details, see Outcome Measures section) and were recomputed at the midterm reassessment (month 3 of 6) to correct for training effects.

All exercise session were supervised by the same exercise technician who assisted with station setup and changes.

Missed training sessions were made up by extending the training period. In no case was an extension of >2 wk necessary.

Supplement Composition and Administration

Participants randomized to the IPS group consumed a blended drink containing 48 g of ion exchange and hydrolyzed chocolate or vanilla-flavored whey protein supplement (Gold Standard Natural 100% Whey, ON, Sunrise, FL or Metabolic Whey, MRM, Vista, CA) containing 36–37 g protein, <8 g CHO, and <4 g fat. The drink was administered in split doses immediately before and after each training session, which represents a timing schedule that best stimulates muscle anabolism in persons undergoing exercise training (35). Subjects assigned to the DPS group consumed the identical supplement and dose on days during which training was not performed.

Outcomes Measures

Participants were instructed to refrain from exercise, caffeine, and alcohol 24 h before all testing. $\dot{V}O_{2peak}$ was determined at wash-in (−3mo) baseline (0mo), midterm (3mo), and after training (6mo) via maximal continuous graded exercise test (GXT) on an arm crank ergometer (Monark Rehab Trainer 881E, Vansbro, Sweden). An initial workload of 0 W was increased by 5 W (C5–C6) or 10 W (C7–C8) every 2 min until volitional exhaustion was reached. To keep the total duration of the graded exercise test less than 20 min, the transitional workload was adjusted to 20 W for two subjects after training. Exercise termination points were consistent with the *Guidelines for Exercise Testing and Training* (7th Edition) of the American College of Sports Medicine. Expired gases were continuously analyzed by an open circuit indirect calorimetry system (Vmax229 with integrated EKG monitoring; Sensormedics, Inc., Conshohocken, PA). EKG rhythm was monitored throughout the test and provided resting and peak HR used for training targets.

The upper extremity dynamic strength for each of the described resistance maneuvers was assessed before the start of the program and every 4 wk thereafter. One-repetition maximum was calculated using the Mayhew regression equation as we have previously reported (30):

$$\text{1-RM} = \text{Wt}/(0.533 + 0.419\text{e} - 0.055 \times \text{reps}),$$

where Wt is the resistance used in the last set where more than three repetitions but less than eight repetitions were completed, and reps indicates the number of repetitions completed in the last set of testing.

The Wingate Anaerobic Test was used to assess anaerobic power. Subjects propelled a table-mounted cycle ergometer (Monark 834e; Monark Exercise AB, Vansbro, Sweden) for 30 s at maximal speed against a constant force, with flywheel velocity assessed by an infrared sensor (Optosensor 2000; Sports Medicine Industries, St. Cloud, MN). The constant resistance for each subject was set at 3.5% of body mass, as recommended (22).

Diet was analyzed from a 4-d (2 weekdays and 2 weekend days) self-reported food log for total daily caloric (Dcal) and protein (Dpro) intake with a nutritional software package (Food Processor II Windows v. 7.6; ESHA Research Inc., Salem, OR). Research staff provided training on how to complete a food log to participants.

Data Analysis

General statistical design. Hypothesis testing was conducted by a mixed-design ANOVA, with time points as the within-subjects factor and supplementation group as the between-subjects factor.

All data were screened for normality by inspection of Q-Q plots and the Kolmogorov–Smirnov test. For all ANOVA analysis, if sphericity did not hold, the Greenhouse–Geisser adjustment was used to evaluate main effects of the within-subjects variable and/or the interaction. Significant main effects were followed by least significant difference *post hoc* comparisons. Because of the small n within each PS group, the Friedman test (nonparametric) was used to confirm findings of the simple effect analysis at the level of PS group if significant interactions were identified during the omnibus test. Wilcoxon signed rank test was performed to confirm significant *post hoc* comparisons at each PS group level. Nonparametric tests were used because of their robustness regarding normality assumptions and the small sample size (38). Significance level for all analysis was set *a priori* at $P < 0.05$.

Data Transformation

Data for 1-RM were expressed as a percentage relative to baseline values for each exercise maneuver. Further, the assumption of normality/homogeneity did not hold for the $\dot{V}O_{2peak}$ and Dpro data, which were subsequently transformed by taking the natural logarithm ($\log_e x$).

Data from Wingate testing could not be transformed to meet the assumptions of ANOVA, and the effect of time for each PS group was therefore assessed by the Friedman test as described earlier. To assess the effect of supplementation on training (i.e., interaction with time), values were transformed to ranks.

Missing data. Missing values were assumed to be missing completely at random. For the Wingate data, missing values were substituted by the last value carried forward technique (backward for −3mo only). One value missing for the 1-RM was replaced by mean imputation from the values for other exercises at the same time point for that subject.

Exploratory analysis. Motor level of injury (MLI) and AIS scores were screened for potential baseline differences between the two supplementation groups using an independent-sample *t*-tests (confirmed by the Mann–Whitney test). The statistical significance of the ANOVA was double-checked using MLI, AIS scores, and change in Dcal or Dpro as covariates. To "fit" within the repeated-measures framework, covariates were transformed to *z*-scores. For this purpose, MLI and AIS scores were converted to interval scales. MLI was assigned a number equal to cervical levels, which were then averaged for left and right sides of the body. AIS scores were assigned full integers starting at one from A to D.

RESULTS

MLI/AIS

AIS scores did not differ significantly between PS groups. Average injury level was approximately one spinal segment lower (0.97 ± 0.86) for the IPS group ($z = -2.47$, $P = 0.013$).

Diet. The change in Dcal was not significant, $F(1,9) = 4.43$, $P = 0.065$, and not dependent on supplementation group, $F(1,9) = 0.47$, $P = 0.512$, $\eta_P^2 = 0.05$. However, the unweighted mean difference between −3 and 6 months was quite substantial 480 ± 760 kcal. No significant differences or interactions were identified for Dpro, with an unweighted mean difference between −3mo and 6mo of 30 ± 80 g.

Body weight. A significant interaction was observed for time and supplementation group, $F(3,27) = 9.76$, $P < 0.001$, $\eta_P^2 = 0.52$ (Fig. 1). Regression analysis revealed that changes in body mass were not associated with changes in Dcal and Dpro, $F(2,8) = 0.58$, $P = 0.584$, adjusted $R^2 = -0.093$ (even when split by group), and consequently, the addition of either as covariate did not significantly affect the analysis. The simple effect analysis revealed a significant effect of time, $F(3,15) = 6.38$, $P = 0.005$) for the IPS group with

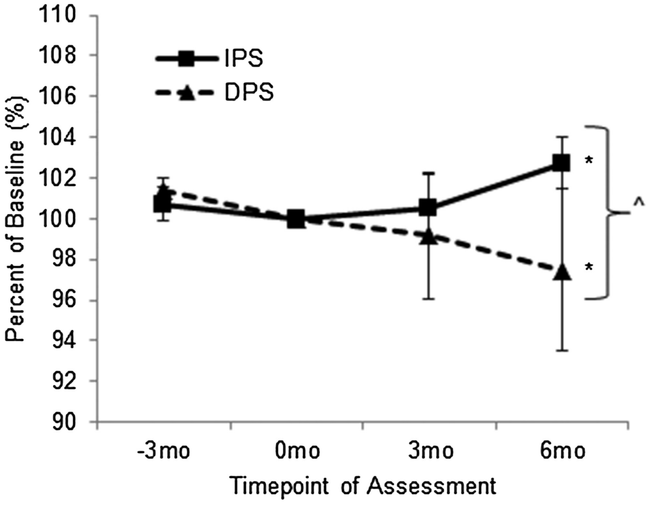

FIGURE 1—Body weight as a percent of baseline across time points. IPS, immediate protein supplementation; DPS, delayed protein supplementation. ^Significant interaction between group and time ($P < 0.05$). *Significant difference from baseline ($P < 0.05$).

the values at 6mo being 2.3 ± 1.3 kg higher than at 0mo ($P = 0.012$). The effect of time in the DPS group was also significant, $F(3,12) = 4.93$, $P = 0.019$, although the only significant decline in BW between individual time points (−3mo vs 6mo, −3.2 ± 1.9 kg, $P = 0.020$) could not be confirmed nonparametrically ($z = -1.83$, $P = 0.068$).

Strength. We observed a significant effect of time on the overall 1-RM (i.e., averaged across all resistance maneuvers, $F(3,27) = 32.15$, $P < 0.001$). The improvement ranged from 8%–11% ± 6%–12% ($P \leq 0.001$–0.012) among the individual assessment time point (Fig. 2). The effect was independent of supplementation group, $F(3,24) = 0.934$, $P = 0.105$, $\eta_P^2 = 0.11$, and was not significantly changed by any covariates.

Anaerobic Power

No significant effect was observed for time on peak power, or interaction of time and supplementation. Power drop changed significantly with time, $\chi^2(3, N = 11) = 8.51$, $P = 0.048$. Significant differences between individual time points were identified for 0mo (median = 70 W) versus 6mo (median = 40 W), $z = -2.134$, $P = 0.033$ (Fig. 3). The interaction was not significant for power drop, $F(3,27) = 2.33$, $P = 0.096$, $\eta_P^2 = 0.21$, but the considerable effect size prompted the simple effect analysis. The simple effect analysis revealed a significant effect of time (only) for the IPS group, $\chi^2(3, N = 6) = 13.84$, $P = 0.003$, with significantly lower drops than at 0mo (median = 100 W) for values at 3mo (median = 70 W, $P = 0.028$) and 6mo (median = 40 W, $P = 0.028$). No such effect was observed for the DPS, $\chi^2(3, N = 5) = 2.62$, $P = 0.455$.

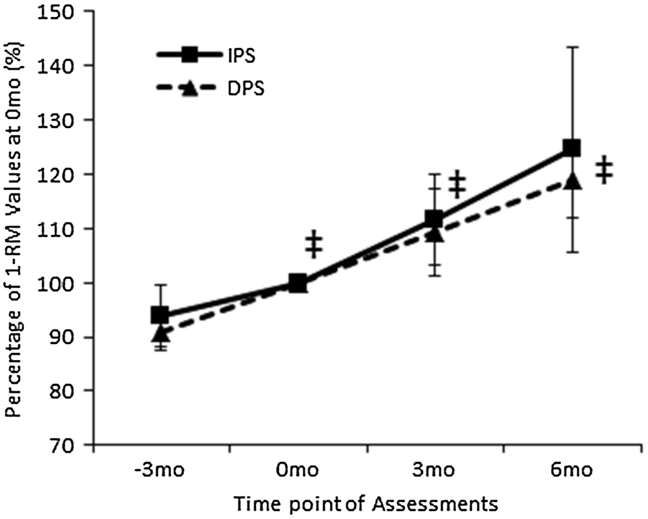

FIGURE 2—Combined 1-RM values for all exercises as a percent of baseline across time points. IPS, immediate protein supplementation; DPS, delayed protein supplementation. ‡Significant difference from previous time point ($P < 0.05$).

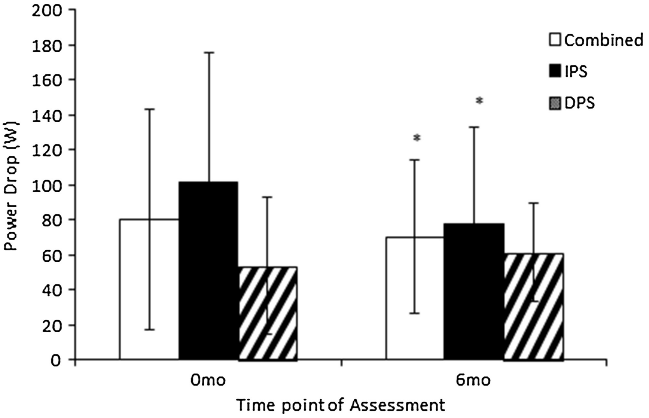

FIGURE 3—Power drop during Wingate arm anaerobic endurance testing at baseline and after training. IPS, immediate protein supplementation; DPS, delayed protein supplementation; *Significant difference from baseline ($P < 0.05$).

$\dot{V}O_{2peak}$

Despite ln transformation, the 3mo values for $\dot{V}O_{2peak}$ violated the homogeneity assumption and were thus excluded from statistical analysis. $\dot{V}O_{2peak}$ increased significantly with time, $F(2,18) = 9.75$, $P = 0.001$ (Fig. 4). This increase was not significantly affected by any of the covariates and resulted in a 26% ± 24% increase from 0mo to 6mo ($P = 0.006$). The interaction was not significant, $F(2,18) = 2.28$, $P = 0.131$, $\eta_P^2 = 0.20$, but the considerable effect size prompted the simple effect analysis. Similar to the analysis of power drop, the simple effect analysis showed a significant effect for time only in the IPS group $F(2,10) = 11.34$, $P = 0.003$ with 6mo values being 35% ± 29% higher than at 0mo ($P = 0.020$). The DPS group increased only 15% ± 8% over the same interval ($P = 0.147$).

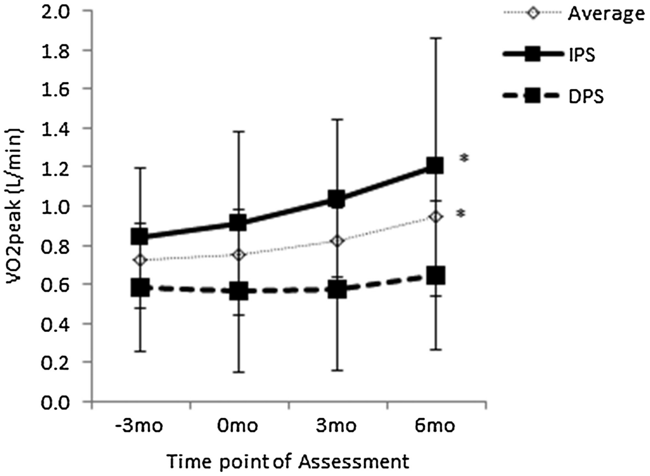

FIGURE 4—Peak oxygen uptake with incremental arm crank ergometry across time points. IPS, immediate protein supplementation; DPS, delayed protein supplementation; $\dot{V}O_{2peak}$, peak oxygen uptake. *Significant difference from baseline ($P < 0.05$).

DISCUSSION

The main finding of this investigation was that a 40- to 45-min CRT program could be effectively adapted for persons with TP and elicit improvements in key aspects of physical fitness, including strength, aerobic capacity, and anaerobic fatigue resistance. Furthermore, improvements in aerobic and anaerobic capacity were enhanced with immediate PS. These outcomes provide promising background for the development of low-cost yet efficient exercise training interventions.

Some but not all studies have reported an improved CR capacity after exercise conditioning of persons with TP. Two studies reported no improvement in CR capacity despite significant improvements in SCI cohorts with paraplegia after 6–8 wk of aerobic interval training 3–5 $\text{d}\cdot\text{wk}^{-1}$ (5,23). Another reported nonsignificant improvements after 1 yr of hand cycling at least once per week (40). Case studies reported increased $\dot{V}O_{2\text{peak}}$ in two out of three persons with TP after 8 wk of aerobic interval training or wheel chair propulsion on an indoor track 3 $\text{d}\cdot\text{wk}^{-1}$ (37,41). Significant improvements were reported in a series of studies by DiCarlo (8–10) as well as by others (14,26) using arm crank ergometry or wheelchair treadmill training for 5–10 wk 3–5 $\text{d}\cdot\text{wk}^{-1}$. None of these studies incorporated any form of resistance training. Only two studies have used a combined aerobic and resistance exercise training program for persons with TP (18,19). In an earlier study, Hjeltnes (19) reported significantly improved $\dot{V}O_{2\text{peak}}$ after 4–6 wk of daily interval arm cycling, strength training, and recreational activities (i.e., table tennis and archery) within an inpatient setting. However, the best evidence for the effects of combined endurance and resistance training comes from a clinical trial conducted by Hicks et al. (18). After 9 months of combined endurance and CRT for 90–120 min twice weekly, participants significantly improved their strength, submaximal aerobic power output, and quality of life (18). In general, previous interventions were delimited by either requirement for daily training and comprehensive inpatient care (19) and/or the need for extended time commitments to perform the training (18). For the latter study, this need imposed new barriers to participation resulting in a dropout rate approaching 50% (18). By contrast, the CRT program used in the current study required a much more limited time commitment (40–45 min), used standard exercise equipment adapted for use by persons in wheelchairs, and required minimal assistance. It was very well received by participants, and there were no dropouts during the training phase. We have previously published an adaptation of the circuit using elastic resistance bands (31), allowing easy translation for use by persons who do not have access to adapted equipment or wish to perform training at home.

We also investigated whether timely PS would enhance training outcomes. Contrary to our hypothesis, there was no discernible difference for PS timing on outcomes reflecting enhanced upper extremity musculoskeletal strength. In past studies, untrained, elderly, and recreationally trained men exhibit greater muscle strength and hypertrophy after resistance training with timely PS (7,11) (although this may not apply to highly trained athletes [20]). Others have shown that muscle protein synthesis in response to exercise is very sensitive to timing of protein intake, with consumption ideally occurring immediately before and shortly after the exercise stimulus (1,11). We therefore adopted a feeding strategy that provided PS both immediately before and after acute exercise for the IPS group but controlled for the additional nutritional load by complementary feeding in the DPS groups outside this recommended time window. It is unclear why this strategy failed to significantly enhance strength gains in the IPS compared with the DS group, although the unidentified effects of the disability status, the potential neural adaptations, or the lack of effect of PS *per se* provide possible explanations. It is also possible that the catabolic effects of the aerobic training component may have interfered with the hypertrophic responses (24).

Although PS did not differentially affect upper extremity strength, anaerobic fatigue resistance and aerobic capacity were both enhanced by IPS. This is evidenced by the fact that only the IPS group showed reduced fatigue resistance (i.e., power drop) significantly with training, whereas the change from baseline to 6 months was not significant in the DPS group. Likewise, only the IPS group showed significant increases in $\dot{V}O_{2\text{peak}}$. Particularly striking was the relative increase in $\dot{V}O_{2\text{peak}}$ for the IPS group, which was more than double that of the DPS group (35% vs 15%). The mechanism underlying this marked difference was not examined and remains subject to speculation. Unlike the well-established exercise conditioning adaptations experienced by the nondisabled population, central adaptation (i.e., an increase in stroke volume) in response to (conventional) exercise training is not among key factors that explain improved $\dot{V}O_{2\text{peak}}$ after training in individuals with TP, making peripheral factors the default justification (26). One such peripheral adaptation might be muscle hypertrophy, but this is unlikely given the nonsignificant results of strength testing. In addition, group differences remained evident when $\dot{V}O_{2\text{peak}}$ was normalized to body mass (31% ± 28% and 18% ± 8% increase for IPS and DPS, respectively) but should have been negated if muscle hypertrophy largely accounted for the differences observed between the groups. Alternatively, changes in oxygen extraction capacity related to mitochondrial density could offer an explanation. The BCAA leucine has recently been reported to increase mitochondrial mass in C2C12 myocytes (36), and several regulatory genes of mitochondrial biogenesis respond to leucine administration including SIRT1 and PGC1α (4,36). Both have been reported to be involved in AMPK-mediated mitochondrial biogenesis resulting in improved oxygen consumption and endurance (16,27). Given that AMPK phosphorylation is potentiated by muscle contraction (21), it is tempting to speculate that timely PS could increase AMPK activity, which in turn stimulates key regulators of mitochondrial biogenesis and increases oxidative capacity

The study findings revealed some unforeseen changes in body mass in response to training. Although the primary purpose of this study was to investigate effects of CRT on fitness outcomes, significant changes were observed in BW for both groups (increase with IPS and decrease with DPS), which were independent of changes in dietary caloric and protein intake. The reduction in BW for the DPS group in combination with increased strength and aerobic capacity could indicate that this loss was not from metabolically active and/or functional muscle tissue but rather from inactive tissue. Conversely, the increase in BW observed in the IPS group combined with the enhanced increase in $\dot{V}O_{2peak}$ in this group could be explained by an increase in metabolically active muscle mass. However, such an increase would be expected to enhance upper extremity strength, a finding not supported by the study outcomes. Without measures of body composition, these inferences remain speculative. Of note is that both females were randomized to the DPS group. Commonly, women experience smaller anabolic responses to strength training than men, which could have potentially skewed outcomes. The women showed decreases in body weight of −7% and −3%, respectively, compared with −3% to 1% for the men in the same group. The strength gain for the women was 13% and 30%, respectively, compared with 13%–20% for the men in their group.

Limitations

A 3-month wash-in was adopted as part of the study plan instead of a control group or crossover design. In our view, it is questionably ethical to instruct persons with SCI to remain sedentary for a study when most study findings and clinical recommendations indicate a need to become more active and conditioned. The alternative of a crossover design was deemed unfeasible. Expecting participants to intentionally relinquish their training gains during a (extensive) washout period in such a design would likely lead to excess dropout and frustration among participants randomized to receive the training first.

Beyond the wash-in, there was no control for a potential learning effect. Because there were no significant differences from −3mo to 0mo for either the Wingate or $\dot{V}O_{2peak}$ measures, it is reasonable to assume that any learning effect was minimal. The significant increase in strength from −3mo to 0mo, however, indicates that substantial learning took place. The possibility that further increases observed with training are related to a continued learning effect cannot be categorically excluded. Nevertheless, it would be unlikely that an un abated learning effect would persist over 6 months with 1-RM assessments being performed every 4 wk.

Further, we observed nonsignificant yet substantial differences in self-reported caloric and protein intake. However, variability was very large and no measure, including BW (likely the most sensitive measure to changes in diet), was significantly mediated by these changes. In light of challenges that are generally observed when attempting to change behaviors—such as dietary intake—it seems unlikely that consistent dietary changes having significant effects on any of the other outcome measures occurred.

Despite randomly assigning subjects to each group, the injury level for the IPS group was significantly lower than for the DPS group. This was predictably accompanied by greater overall strength in the IPS group. However, when baseline strength was entered as a covariate, it did not significantly influence training effects for any of the measurements. Others have also reported that the trainability of TP was not related to level of injury (33) or physical capacity (26).

Last, the small sample size within each group limits the generalizability of study findings. However, all but one statistically significant result (weight loss in DPS) were confirmed by nonparametric statistics (that are robust to outliers and nonnormality) at the preset significance level of $\alpha = 0.05$, and even for this difference, there remained a trend (body weight loss in DPS $z = -1.83$, $P = 0.068$). Also, study findings were in the direction of the hypothesized effect and consistent with well-established benefits of physical conditioning.

Implications and Future Directions

The current study shows clear improvements in several fitness measures with a relatively simple and time-effective CRT. Similar fitness improvements are associated with chronic disease prevention, greater function/independence, and improved quality of life (3,18,30). Because of their low fitness levels, TP are at elevated risk for developing CVD and accelerated disease progression. Other nonpharmacological interventions such as diet restrictions suffer from limited applicability in this population (29), making exercise intervention as a monotherapy or in combination with diet all the more attractive. Although there is currently no direct evidence for the benefits of long-term exercise training on chronic disease outcomes in persons with TP, the present protocol provides a promising basis for exercise training as a primary prevention tool.

CONCLUSION

In conclusion, 6 months of 40–45 min of CRT performed three times weekly by persons with TP resulted in marked improvements in strength, anaerobic fatigue resistance, and aerobic capacity. Gains in anaerobic fatigue resistance and aerobic capacity were further enhanced by timely PS.

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REFERENCES

1. Andersen LL, Tufekovic G, Zebis MK, et al. The effect of resistance training combined with timed ingestion of protein on muscle fiber size and muscle strength. *Metabolism*. 2005;54(2):151–6.

2. Borsheim E, Aarsland A, Wolfe RR. Effect of an amino acid, protein, and carbohydrate mixture on net muscle protein balance after resistance exercise. *Int J Sport Nutr Exerc Metab*. 2004;14(3):255–71.
3. Bostom AG, Toner MM, McArdle WD, Montelione T, Brown CD, Stein RA. Lipid and lipoprotein profiles relate to peak aerobic power in spinal cord injured men. *Med Sci Sports Exerc*. 1991;23(4):409–14.
4. Bruckbauer A, Zemel MB. Effects of dairy consumption on SIRT1 and mitochondrial biogenesis in adipocytes and muscle cells. *Nutr Metab (Lond)*. 2011;8(1):91.
5. Brurok B, Helgerud J, Karlsen T, Leivseth G, Hoff J. Effect of aerobic high-intensity hybrid training on stroke volume and peak oxygen consumption in men with spinal cord injury. *Am J Phys Med Rehabil*. 2011;90(5):407–14.
6. Cowan R, Nash M, Anderson K. Exercise participation barrier prevalence and association with exercise participation status in individuals with spinal cord injury. *Spinal Cord*. 2012;51(1):27–32.
7. Cribb PJ, Hayes A. Effects of supplement timing and resistance exercise on skeletal muscle hypertrophy. *Med Sci Sports Exerc*. 2006;38(11):1918–25.
8. DiCarlo SE, Supp MD, Taylor HC. Effect of arm ergometry training on physical work capacity of individuals with spinal cord injuries. *Phys Ther*. 1983;63(7):1104–7.
9. DiCarlo SE. Effect of arm ergometry training on wheelchair propulsion endurance of individuals with quadriplegia. *Phys Ther*. 1988;68(1):40–4.
10. DiCarlo SE. Improved cardiopulmonary status after a two-month program of graded arm exercise in a patient with C6 quadriplegia. A case report. *Phys Ther*. 1982;62(4):456–9.
11. Esmarck B, Andersen JL, Olsen S, Richter EA, Mizuno M, Kjaer M. Timing of postexercise protein intake is important for muscle hypertrophy with resistance training in elderly humans. *J Physiol*. 2001;535(Pt 1):301–11.
12. Evans WJ, Roubenoff R, Shevitz A. Exercise and the treatment of wasting: aging and human immunodeficiency virus infection. *Semin Oncol*. 1998;25(2 Suppl 6):112–22.
13. Evans WJ. Protein nutrition and resistance exercise. *Can J Appl Physiol*. 2001;26(suppl):S141–52.
14. Gass GC, Watson J, Camp EM, Court HJ, McPherson LM, Redhead P. The effects of physical training on high level spinal lesion patients. *Scand J Rehabil Med*. 1980;12(2):61–5.
15. Ginis KM, Hicks A, Latimer A, et al. The development of evidence-informed physical activity guidelines for adults with spinal cord injury. *Spinal Cord*. 2011;49(11):1088–96.
16. Hardie DG. AMP-activated protein kinase: an energy sensor that regulates all aspects of cell function. *Genes Dev*. 2011;25(18):1895–908.
17. Hicks A, Ginis KM, Pelletier C, Ditor D, Foulon B, Wolfe D. The effects of exercise training on physical capacity, strength, body composition and functional performance among adults with spinal cord injury: a systematic review. *Spinal Cord*. 2011;49(11):1103–27.
18. Hicks AL, Martin KA, Ditor DS, et al. Long-term exercise training in persons with spinal cord injury: effects on strength, arm ergometry performance and psychological well-being. *Spinal Cord*. 2003;41(1):34–43.
19. Hjeltnes N. Capacity for physical work and training after spinal injuries and strokes. *Scand J Soc Med Suppl*. 1982;29:245–51.
20. Hoffman JR, Ratamess NA, Tranchina CP, Rashti SL, Kang J, Faigenbaum AD. Effect of protein-supplement timing on strength, power, and body-composition changes in resistance-trained men. *Int J Sport Nutr Exerc Metab*. 2009;19(2):172–85.
21. Iwanaka N, Egawa T, Satoubu N, et al. Leucine modulates contraction- and insulin-stimulated glucose transport and upstream signaling events in rat skeletal muscle. *J Appl Physiol*. 2010;108(2):274–82.
22. Jacobs PL, Mahoney ET, Johnson B. Reliability of arm Wingate Anaerobic Testing in persons with complete paraplegia. *J Spinal Cord Med*. 2003;26(2):141–4.
23. Knutsson E, Lewenhaupt-Olsson E, Thorsen M. Physical work capacity and physical conditioning in paraplegic patients. *Paraplegia*. 1973;11(3):205–16.
24. Kraemer WJ, Patton JF, Gordon SE, et al. Compatibility of high-intensity strength and endurance training on hormonal and skeletal muscle adaptations. *J Appl Physiol*. 1995;78(3):976–89.
25. Martin Ginis KA, Arbour-Nicitopoulos KP, Latimer AE, et al. Leisure time physical activity in a population-based sample of people with spinal cord injury part II: activity types, intensities, and durations. *Arch Phys Med Rehabil*. 2010;91(5):729–33.
26. McLean KP, Skinner JS. Effect of body training position on outcomes of an aerobic training study on individuals with quadriplegia. *Arch Phys Med Rehabil*. 1995;76(2):139–50.
27. Narkar VA, Downes M, Yu RT, et al. AMPK and PPARdelta agonists are exercise mimetics. *Cell*. 2008;134(3):405–15.
28. Nash MS. Cardiovascular Fitness After Spinal Cord Injuries. In: Lin V, editor. *Spinal Cord Medicine*. New York (NY): Demos Medical Publications; 2002. p. 637–46.
29. Nash MS, Jacobs PL, Johnson BM, Field-Fote' E. Metabolic and cardiac responses to robotic-assisted locomotion in motor-complete tetraplegia: a case report. *J Spinal Cord Med*. 2004;27(1):78–82.
30. Nash MS, Jacobs PL, Mendez AJ, Goldberg RB. Circuit resistance training improves the atherogenic lipid profiles of persons with chronic paraplegia. *J Spinal Cord Med*. 2001;24(1):2–9.
31. Nash MS, Jacobs PL, Woods JM, Clark JE, Pray TA, Pumarejo AE. A comparison of 2 circuit exercise training techniques for eliciting matched metabolic responses in persons with paraplegia. *Arch Phys Med Rehabil*. 2002;83(2):201–9.
32. Nash MS, van de Ven I, van Elk N, Johnson BM. Effects of circuit resistance training on fitness attributes and upper-extremity pain in middle-aged men with paraplegia. *Arch Phys Med Rehabil*. 2007;88(1):70–5.
33. Needham-Shropshire BM, Broton JG, Cameron TL, Klose KJ. Improved motor function in tetraplegics following neuromuscular stimulation-assisted arm ergometry. *J Spinal Cord Med*. 1997;20(1):49–55.
34. Physical Fitness for Individuals With Spinal Cord Injury [Internet]. American Physical Therapy Association (APTA) and APTA Neurology Section [cited 2013 12/6]. Available from: http://www.apta.org/PFSP/.
35. Roy BD, Tarnopolsky MA, MacDougall JD, Fowles J, Yarasheski KE. Effect of glucose supplement timing on protein metabolism after resistance training. *J Appl Physiol*. 1997;82(6):1882–8.
36. Sun X, Zemel MB. Leucine modulation of mitochondrial mass and oxygen consumption in skeletal muscle cells and adipocytes. *Nutr Metab (Lond)*. 2009;6:26.
37. Tawashy AE, Eng JJ, Krassioukov AV, Miller WC, Sproule S. Aerobic exercise during early rehabilitation for cervical spinal cord injury. *Phys Ther*. 2010;90(3):427–37.
38. Tomkins CC. An introduction to non-parametric statistics for health scientists. *University of Alberta Health Sciences Journal*. 2006;3(1):20–6.
39. Valent L, Dallmeijer A, Houdijk H, Talsma E, van der Woude L. The effects of upper body exercise on the physical capacity of people with a spinal cord injury: a systematic review. *Clin Rehabil*. 2007;21(4):315–30.
40. Valent LJ, Dallmeijer AJ, Houdijk H, Slootman HJ, Post MW, van der Woude LH. Influence of hand cycling on physical capacity in the rehabilitation of persons with a spinal cord injury: a longitudinal cohort study. *Arch Phys Med Rehabil*. 2008;89(6):1016–22.
41. Whiting RB, Dreisinger TE, Dalton RB, Londeree BR. Improved Physical Fitness and Work capacity in quadraplegics by wheelchair exercise. *J Cardiac Rehab*. 1983;3:251–5.