Spinal Cord (1998) 36, 463–469

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Muscle atrophy is prevented in patients with acute spinal cord injury using functional electrical stimulation

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Severe muscle atrophy occurs rapidly following traumatic spinal cord injury (SCI). Previous research shows that neuromuscular or 'functional' electrical stimulation (FES), particularly FES-cycle ergometry (FES-CE) can cause muscle hypertrophy in individuals with chronic SCI (>1 year post-injury). However, the modest degree of hypertrophy in these already atrophied muscles has lessened earlier hopes that FES therapy would reduce secondary impairments of SCI. It is not known whether FES treatments are effective when used to prevent, rather than reverse, muscle atrophy in individuals with acute SCI. This study explored whether unloaded isometric FES contractions (FES-IC) or FES-CE decreased subsequent muscle atrophy in individual with acute SCI (<3 months post-injury). Twenty-six subjects, 14–15 weeks post-traumatic SCI, were assigned to control, FES-IC, or FES-CE against progessively increasing resistance. Subjects were involved in the study for 3 or 6 months. Total body lean body mass (TB-LBM), lower limb lean body mass (LL-LBM), and gluteal lean body mass (G-LBM) were determined before the study, and at 3 and 6 months using dual energy X-ray absorptiometry (DEXA). Controls lost an average of 6.1%, 10.1%, 12.4%, after 3 months and 9.5%, 21.4%, 26.8% after 6 months in TB-LBM, LL-LBM and G-LBM respectively. Subjects in the FES-IC group consistently lost less lean body mass than controls, however, only 6 month G-LBM loss was significantly attenuated in this group relative to the controls. In the FES-CE group, LL-LBM and G-LBM loss were prevented at both 3 and 6 months, and TB-LBM loss was prevented at 6 months. In addition, FES-CE significantly increased G-LBM and LL-LBM after 6 months of training relative to pre-training levels. Within the control group, there was no significant relationship between LL-LBM loss (3 and 6 months) and the number of days between injury and baseline measurement. In summary, this study shows that FES-CE, but not FES-IC, training prevents muscle atrophy in acute SCI after 3 months of training, and causes significant hypertrophy after 6 months. The magnitude of differences in regionalized LBM between controls and FES-CE subject raises hopes that such treatment may indeed be beneficial in preventing secondary impairments of SCI if employed before extensive post-injury atrophy occurs.

Keywords: spinal cord injury; muscle atrophy; functional electrical stimulation; isometric contraction; body composition

Introduction

Musculoskeletal atrophy is a serious complication of traumatic spinal cord injury (SCI) which contributes to the development of secondary impairements in spinal cord injured individuals. Pressure sores,[1,2] fractures[3–5] and deep venous thrombosis[6] are all thought to be at least partially related to musculoskeletal atrophy and disuse in these individuals. In animal models of disuse such as spaceflight,[7,8] spinal transection[9] and hindlimb suspension[10], muscle atrophy occurs at an extremely high rate within the first several months[7–10] after which, the rate of atrophy slows. Although data in humans is sparse, similarly high rates of acute atrophy have been reported following simulated hypogravity[11,12] and SCI.[13] The cellular mechanism associated with the development of disuse atrophy and the functional stimuli, which cause disuse atrophy, are not completely understood. It appears that atrophy results from a combination of decreased muscle protein expression and increased activity of intramuscular Ca^{2+} activated proteases that can be reversed if the muscles produce tension as occurs with stretch.[14–16] Without tension-producing activity, there are indications of muscle fiber disorganization within a period of days.[17]

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It has been hoped that the re-institution of forceful muscle contractions utilizing functional electrical stimulation (FES) training would counteract musculoskeletal atrophy in individuals with SCI, and thus decrease the likelihood of costly secondary impairments. Despite evidence that muscle atrophy appears to achieve a steady state within the first year of SCI,[18] clinical investigations using FES have focused primarily on individuals with chronic paralysis (>1 year post-injury), who have already experienced extensive musculoskeletal atrophy. These reports suggest that the use of portable handheld stimulators to reproduce muscular contractions is relatively ineffective in reversing disuse atrophy in lower limb musculature of individuals with chronic SCI.[19] In contrast, the use of FES-cycle ergometry (FES-CE), which produces more forceful contractions against some external load, can result in moderate increases in thigh girth[20,21] and muscle mass as measured by CT scan[22] in subjects with chronic SCI. However, the magnitude of these improvements relative to the degree of atrophy in chronically injured individuals has led clinicians to question whether the cost of FES-CE is worth the benefit it provides.

There has been far greater success in counteracting disuse atrophy when therapeutic interventions are employed during the course of rapid atrophy rather than after atrophy has occurred. FES resistance training has been successfully used to prevent disuse atrophy caused by immobilization[23–25] and weightlessness[26] in neurologically intact humans. In individuals with acute SCI, non-loaded FES contractions employed during the first year post-injury attenuated but did not prevent muscle atrophy and strength loss in the muscles of the hand and wrist.[27,28] However, no study has examined the affect of regular forceful muscular contractions against progressive resistance, as employed by FES-CE, in acute SCI. Thus, the aims of this study were first, to quantify the extent of lower limb muscle atrophy which occurs during a 6 month period beginning 4–15 weeks after complete SCI; and second, to determine whether FES-CE (loaded) or non-loaded FES-induced muscle contractions using portable electrical stimulators are capable of preventing disuse atrophy when employed during this time period.

Method

Subjects

The subjects were recruited from the acute Spinal Cord Injury inpatient rehabilitation unit at The Ohio State University. All subjects were within 15 weeks of incurring a traumatic motor complete (Frankel A or B) thoracic or cervical SCI. The subjects described in this manuscript were involved in either a 3 month or 6 month FES training study designed to characterize the effect of FES on musculoskeletal changes after acute SCI. As the demographics of the subject populations were almost identical between the 3 and 6 month studies (Table 1) and the training parameters were identical, the data from both studies has been combined for this report.

Subjects were randomly assigned into the FES-CE group, FES-isometric group (FES-IC) or a control group receiving no FES training. Subjects assigned to either FES-CE or FES-IC began their training program as soon as their medical condition was stable and/or they were no longer in spinal shock (60.5 ± 22.5 days after injury). Three subjects (one in each group) began the program more than 14 weeks after SCI with all other subjects beginning the study within 12 weeks of injury. Mild to moderate spasticity (not quantified) was noticeable in all patients at initiation of study. The duration of spinal shock was not quantified and similarly, the number of subjects excluded because of persistent spinal shock was not recorded. All FES-CE exercise sessions were conducted in a monitored setting. FES-IC sesssions were also conducted in a monitored setting for the first 4 or more weeks after which time the participants were given an electrode garment and stimulators and continued training at home.

Experimental electrical stimulation treatments

Subjects assigned to the FES-CE group rode an ERGYS 1 computerized functional electrical stimulation cycle ergometer (Therapeutic Alliance, Inc., Fairborn OH) for 30 min, three times per week. This system delivers between 0 and 140 mAmp of monophasic rectangular waveform with pulse duration of 375 μsec at 60 Hz through a closed-loop feedback

Table 1 Subject demographics

	Control		*FES-IC*		*FES-CE*	
Time	*0–3*	*0–6*	*0–3*	*0–6*	*0–3*	*0–6*
Age (years)	27.7 ± 6.8	26.6 ± 5.5	25.8 ± 4.7	25.0 ± 4.2	28.2 ± 6.6	27.8 ± 7.3
Sex (% male)	78	80	67.5	80	78	71
Height (cm)	177.3	179.8	181.4	182.9	175.8	178.6
Weight (kg)	77.4	79.3	80.0	80.8	63.8	64.5
% Tetraplegic	11	20	37.5	40	56	57
Weeks post-injury	8.4 ± 3.5	10.5 ± 5.3	8.3 ± 3.2	10.2 ± 4.8	9.2 ± 3.3	8.2 ± 3.1
n	9	5	8	5	9	7

system. Subjects wore a FES cycling garment (Bioflex Inc., Columbus OH) which contained electrodes over the hip extensors, knee extensors and knee flexors. The use of this garment assured that electrode placement remained the same throughout the duration of the study. Electrodes received asynchronous stimulation through leads from the cycle ergometer that maintained a pedaling rate between 35 and 50 rpm. Failure (fatigue) occurred when the subjects were not capable of maintaining a 35 rpm pedaling frequency against the assigned load. After failure, subjects performed a brief cool down and rest period; then resumed cycling until the total accumulated run time reached 30 min. All subjects started the protocol against no load. The cycling load increased by 6 watt increments when subjects completed three successive 30 min training sessions at 50 rpm.

The FES-IC group stimulated the same three muscle groups with a biphasic waveform at an intensity of 100 mAmp, a pulse duration of 500 μsec and a firing rate of 35 Hz for 1 h, five times per week using a 1 : 1 duty cycle (15 s on : 15 s off). Stimulation was performed while the subject was supine. Subjects wore the same garment as the FES-CE group which was connected to leads from a Focus EMPI portable two-channel stimulator (St. Paul, MN).

Quantification of lean body mass

Lean body mass (LBM) was measured at 0, 3 and 6 months of training using a Lunar DPX dual energy X-ray absorptiometry (Madison, WI). Extended research analysis using standard software packages provided by Lunar Radiation Corporation was used to measure leg and total body regions. Gluteal measurements were obtained from the region of the body between the L_4-L_5 juncture and the lesser trochanter. These boundaries were set manually by a single investigator. Coefficients of variation were 1.8%, 1.9% and 2.1% for six repeated measurements of total body, leg and gluteal scans respectively. The Lunar DPX was calibrated daily with a standard phantom. The mean percent change in LBM was calculated from measurements made before and after 3 and 6 months of participation for each group.

Table 2 Baseline body composition

	Gender	*SCI level*	*Lean body mass (KG)* *TB*	*LL*	*Gluteal*
Control					
1	M	T_{12}	62.2	25.5	12.4
2	F	T_{12}	38.3	12.2	8.7
3	F	T_4	33.9	10.9	5.7
4	M	T_{12}	41.2	15.3	7.7
5	M	T_{12}	44.5	13.5	6.2
6	M	T_4	57.9	18.4	9.6
7	M	T_7	69.7	23.4	13.3
8	M	C_5	45.3	12.1	11.0
9	M	T_7	58.5	19.7	9.5
X $\pm$ SEM			50.2 $\pm$ 4.1	16.8 $\pm$ 1.8	9.3 $\pm$ 0.9
FES-IC					
1	M	T_{10}	53.8	18.3	13.0
2	M	T_8	42.5	12.4	8.2
3	M	C_7	43.2	12.6	11.6
4	M	$C_{6\text{-}7}$	50.8	16.8	11.3
5	F	C_5	56.3	17.5	–
6	F	T_4	47.5	14.1	8.1
7	F	T_7	63.7	21.7	10.8
8	M	C_4	43.2	12.6	12.3
X $\pm$ SEM			50.1 $\pm$ 2.7	15.8 $\pm$ 1,2	10.8 $\pm$ 0.7
FES-CE					
1	M	T_3	48.2	15.3	12.7
2	M	$C_{6\text{-}7}$	44.2	13.7	10.6
3	M	C_7	39.4	13.5	12.7
4	M	T_4	42.4	14.7	11.9
5	F	C_5	43.8	13.9	11.3
6	F	C_5	35.8	10.9	8.8
7	M	T_{10}	50.0	17.8	10.6
8	M	C_4	49.5	17.6	11.3
9	M	T_7	47.9	14.4	9.6
X $\pm$ SEM			44.6 $\pm$ 1.6	14.6 $\pm$ 0.7	11.1 $\pm$ 0.4

These values were compared to determine differences between groups at each time point.

Statistics

Statistical significance between group means in regional lean body mass were determined by a repeated measures analysis of variance with *post hoc* Student-Newman-Keuls tests ($P<0.05$). Relationships between different measurements were determined by linear regression of individual data points.

Results

All subjects were able to preform the FES-CE or FES-IC training program without musculoskeletal complications. Two subjects had cycling sessions cut short due to lightheadedness during the initial stages of training. This symptom, however, was rare and occurred only during the first 2 months of training. Two subjects in the FES-CE group and one subject in the FES-IC group were treated for deep venous thrombosis during the first 3 weeks of their training program. One of these subjects (FES-CE group) missed four training sessions. Training was continued without interruption in the other two subjects. Two FES-IC and three control subjects developed pressure sores during the course of the study. The development of these pressure sores was unrelated to participation in the study. Plastic surgery was required to repair these sores in two control subjects, however neither of the two subjects in the FES-IC group were forced to miss training sessions.

Overall compliance in the FES-CE group was 80%. Missed sessions were most commonly due to illness or lack of transportation. Compliance was not monitored in the FES-IC group. Average weekly power output with FES-CE was 2.2 ± 1.1 watts at 3 months with all subjects obtaining a power output of at least 11 watts (range $11-35$) at the end of 6 months of training.

At baseline, there was no significant difference in body composition at the total body, lower limb or gluteal in subjects in any of the three treatment groups (Table 2). Values for tetraplegics were not noticeably different from paraplegics in any of the study groups at baseline.

Subjects in the control group lost an average of $6.1\pm1.6\%$, $10.1\pm3.1\%$ and $12.4\pm2.7\%$ (mean and standard error) in TB-LBM, LL-LBM and G-LBM respectively during the first 3 months; and $9.5\pm3.4\%$, $21.4\pm5.6\%$ and $26.8\pm4.4\%$, by the 6 month time point (Figures 1 and 2). FES-CE training prevented atrophy in all regions after 3 and 6 months when compared to the control group ($P<0.05$), and in LL-LBM after 6 months when compared to the FES-IC group ($P<0.05$). The lean body mass increased in the FES-CE group at all regions studies (Figures 1 and 2). These values were significantly higher than baseline for LL-LBM ($9.3\pm3.9\%$) and G-LBM ($7.7\pm2.9\%$) after 6 months of cycling ($P<0.05$). Average values for the FES-IC group fell between the control and FES-CE values at all sites, but were not significantly different from controls with the exception of 6 month G-LBM ($P<0.05$) (Figure 2). Body composition changes across time in the controls or in response to treatment intervention was not affected by level of SCI (Figure 2; data for TB and LL-LBM not shown).

As the length of time between SCI and intervention could impact on the efficacy of FES in preventing muscle atrophy, we were interested to see if there were any correlations between regionalized rates of atrophy and the amount of time from injury to baseline scan. Among control subjects, there was no significant linear

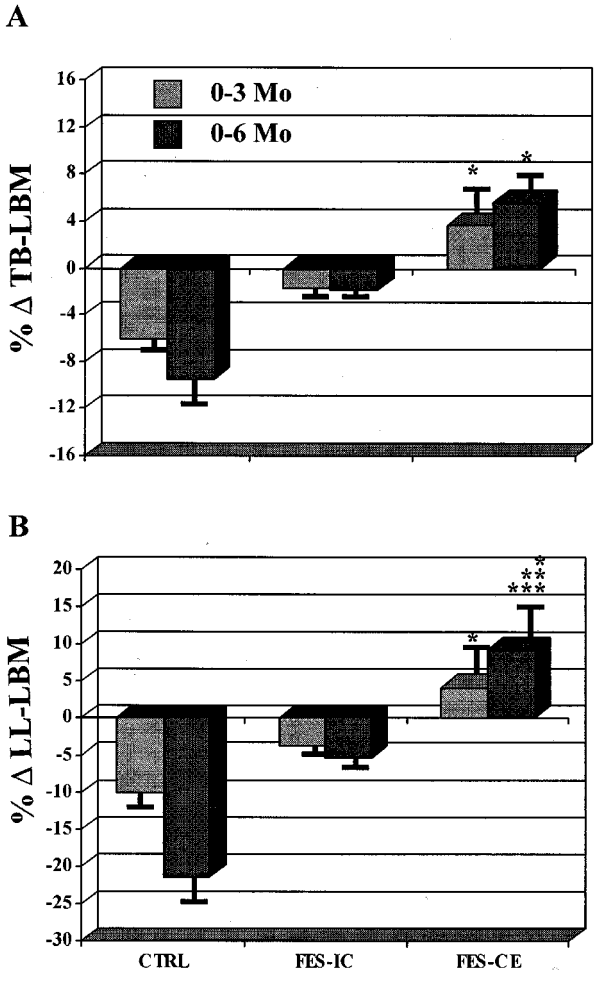

Figure 1 Percent change (mean ± SE) in total body lean body mass (**a**) and lower limb lean body mass (**b**) in comparison to baseline following spinal cord injury (CTRL) and in response to functional electrical stimulation isometric contractions (FES-IC) and FES cycle ergometry (FES-CE); *reflects a significant reduction ($P<0.05$) in LBM loss in comparison to CTRL; **reflects a significant reduction ($P<0.05$) in LBM loss compared to FES-IC; ***reflects a significant increase ($P<0.05$) in LBM in comparison to baseline

relationship between these values for G-LBM ($r=0.19$), LL-LBM ($r=0.49$) or TB-LBM ($r=0.19$) at 3 months. Similarly, no significant relationships were found in either the FES-IC or FES-CE groups.

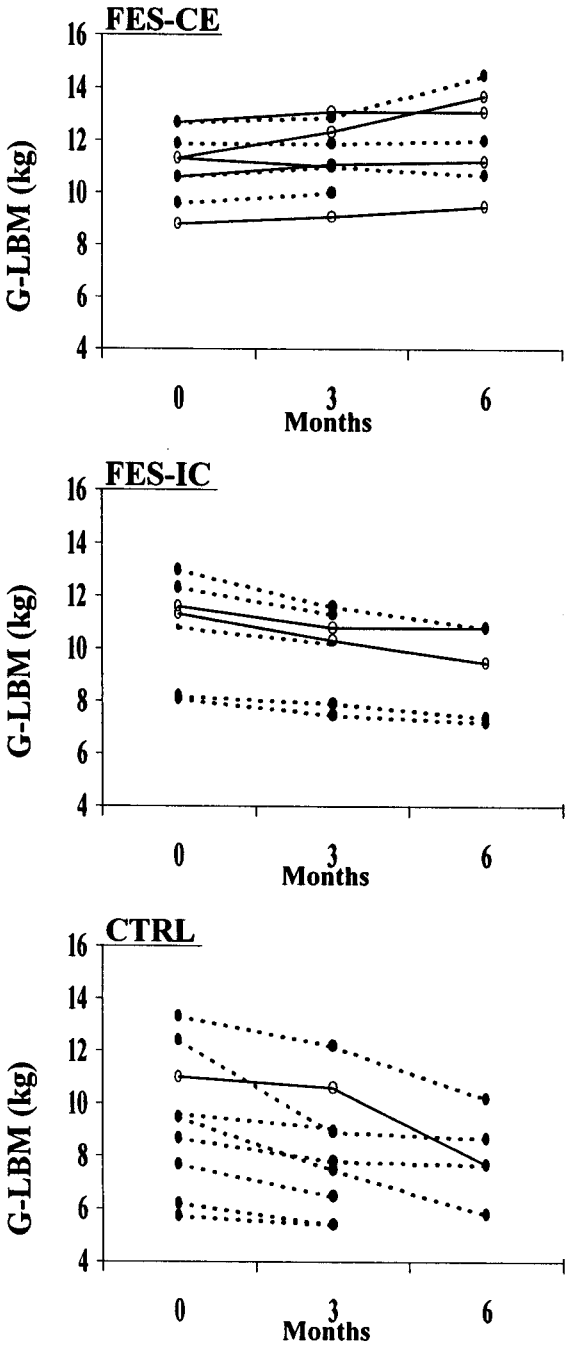

Figure 2 Change (mean ± SE) in gluteal lean body mass (G-LBM) in comparison to baseline for individual subjects. Dotted lines reflect paraplegic subjects and solid lines reflect tetraplegic subjects

Discussion

There is considerable debate as to the clinical benefits of FES in the treatment of SCI. Claims that FES-induced muscle contraction can decrease the prevalence of pressure sores are based on the suggestion that seating pressures can be decreased by increased lower limb muscle mass, combined with improved peripheral blood flow in these regions.[13,29] It has been hoped that FES could reverse neurogenic osteopenia by re-instituting forceful muscular contractions, which would in turn prevent bone fractures. Unfortunately, the modest improvements in muscle mass and force production following FES training in individuals with chronic SCI have fallen well short of values expected of able-bodied muscles, and have thus diminished hopes that FES is capable of these benefits.

Studies in animals[7–10] and humans[13] indicate that the most rapid rate of muscle atrophy occurs immediately following the removal of 'normal' neuromuscular activity. Round *et al*[18] reported that muscle fiber cross-sectional area in nine individuals paralyzed for greater than 11 months was significantly lower than able-bodied controls. However, the time after injury, which ranged from 11 months to 9 years, did not affect fiber size in the spinal cord injured group, suggesting that muscle mass had reached a new 'steady state' within the first year post-SCI. In studies on the effect of prolonged microgravity[26] or immobilization,[23–25] muscular atrophy can be prevented or attenuated if FES is initiated early, prior to the development of extensive atrophy and degeneration. However, when FES is employed after prolonged disuse, it is relatively ineffective in reversing disuse atrophy.[30]

Thus, it is not surprising that previous studies conducted in chronically paralyzed individuals have shown only moderate improvement in muscle mass. The present study showed that FES-CE could prevent disuse atrophy when training is initiated during the acute phase of muscle atrophy resulting from SCI. In fact, each of the subjects involved in the FES-CE training showed slight increases in regionalized lower limb muscle mass during a period when controls lost an average of 21–27% in the same region. These findings are in agreement with previous studies where early initiation of FES resistance training can almost completely prevent the development of disuse atrophy in individuals with intact neurologic systems experiencing microgravity[26] or joint immobilization.[23–25]

This study did not account for the decreases in regional LBM that occurred during the 4–15 weeks between injury and baseline measurements. The rate and duration of muscle atrophy following SCI in humans is not known. A recent study has shown that thigh girth decreases up to 50% within 3 weeks of SCI[13] suggesting that atrophy is virtually complete within the first month after SCI. Animal studies also show that muscle fiber cross-sectional area can

decrease by up to 45% in some rat muscles after 28 days of hindlimb suspension.[9] However, our findings indicate that significant atrophy continues well into the ninth month post-SCI in individuals receiving no treatment. In addition, we found no relationship between the time post-injury and the rate of muscle atrophy in control subjects, which suggests that atrophy rates are variable in this population. Regardless of the time course of atrophy following SCI, we acknowledge the likelihood that the individuals in the present study experienced significant decreases in regional LBM prior to the initiation of FES training. However, this does not lessen the significance of our finding that FES-CE prevented further decreases and in fact increased lean body mass in all subjects.

Assuming that atrophy was occuring rapidly after SCI, we attempted to begin FES training as quickly as possible following SCI. Several factors prevented the individuals in this study from initiating treatment earlier in their recovery. Spinal shock was present for periods of up to several weeks following injury in most subjects. During spinal shock, the musculature is unresponsive to stimulus parameters used by conventional FES equipment, preventing any treatment. Patients were also delayed by bouts of postural hypotension following prolonged bed rest (particularly tetraplegics), pain, and time constraints with their inpatient therapy schedules. Finally, one patient missed several FES-CE sessions due to a deep venous thrombosis that occurred during the second week of cycling. It should be noted that one tetraplegic subject in a halo was able to receive FES-CE training with the aid of restraining belts and a slightly increased seat angle. Based on the current literature and our findings, we postulate that the earlier FES-CE can be initiated following SCI, the more muscle atrophy can be prevented. However, such early FES training should be conducted in a clinical setting and under direct supervision of a physician.

Individuals in the FES-IC group consistently lost less regionalized LBM than the control group; however, this difference reached significance only in the 6 month G-LBM measurement. These findings corroborate the findings of Martin *et al*[19] who found that reinstitution of neuromuscular activity without external resistance is not sufficient to achieve significant muscle hypertrophy or strengthening in paralyzed limb musculature. However, other investigators have shown that protocols similar to that employed in the FES-IC group attenuates, but did not prevent muscle atrophy[28] and muscle weakening[27] in wrist extensors in individuals with acute paralysis. The differences between these studies may be due to inherent differences in the muscle examined or differences in the stimulation parameters.[31]

It is possible that the degree of variability in the control group concealed a potential difference between the FES-IC group and controls. There appeared to be no consistency in the rate of extent of atrophy in the control group, and decreases in 3 and 6 month regionalized LBM were unrelated to time post-SCI. However, the fact that FES-CE did prevent regionalized LBM loss indicates that unloaded FES is ineffective in preventing acute muscle atrophy following SCI. A lack of muscle hypertrophy does not imply that FES-IC training had no effect on these muscles. Chronic low-frequency electrical stimulation (against no resistance) of fast twitch rabbit muscle induces a rapid atrophic response while causing a dramatic shift in contractile and biochemical properties.[32] The resulting muscle is smaller, well perfused and extremely fatigue resistant. It is possible that the FES-IC training employed in this study had similar effects, while not inducing significant hypertrophy.

In conclusion, the results of this study indicate that regionalized LBM decreases significantly for up to 9 months following traumatic spinal cord injury and the rates of LBM loss are variable in this population. FES-CE that induces muscular contractions against progressive resistance not only prevents the loss of LBM, but causes moderate increases in LBM during this period. FES contractions against no resistance do not appear to alter rates of LBM loss with the exception of attenuating gluteal LBM loss after 6 months of training.

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