Published in final edited form as:

Muscle Nerve. 2006 July ; 34(1): 84–91. doi:10.1002/mus.20564.

PREDICTIVE MODEL OF MUSCLE FATIGUE AFTER SPINAL CORD INJURY IN HUMANS

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Abstract

The fatigability of paralyzed muscle limits its ability to deliver physiological loads to paralyzed extremities during repetitive electrical stimulation. The purposes of this study were to determine the reliability of measuring paralyzed muscle fatigue and to develop a model to predict the temporal changes in muscle fatigue that occur after spinal cord injury (SCI). Thirty-four subjects underwent soleus fatigue testing with a modified Burke electrical stimulation fatigue protocol. The between-day reliability of this protocol was high (intraclass correlation, 0.96). We fit the fatigue index (FI) data to a quadratic-linear segmental polynomial model. FI declined rapidly (0.3854 per year) for the first 1.7 years, and more slowly (0.01 per year) thereafter. The rapid decline of FI immediately after SCI implies that a “window of opportunity” exists for the clinician if the goal is to prevent these changes. Understanding the timing of change in muscle endurance properties (and, therefore, load-generating capacity) after SCI may assist clinicians when developing therapeutic interventions to maintain musculoskeletal integrity.

Keywords

electrical stimulation; muscle fibers; plasticity; reliability; spinal cord injury

Paralysis after spinal cord injury (SCI) deprives the musculoskeletal system of important stresses necessary to maintain the health of the paralyzed extremities.^{30,33} Without these normal stresses, muscle atrophy and severe osteoporosis develop rapidly.³⁰ Electrically induced muscle contractions are an integral part of contemporary methods designed to place physiological stresses on the paralyzed extremities.^{3,4,6,17,24} However, as muscle adapts after SCI it loses its fatigue resistance^{29,36} and becomes a less effective source for generating stress to the paralyzed extremities. Establishing the time course of muscle fatigability may aid rehabilitation practitioners when developing comprehensive rehabilitation plans to maintain musculoskeletal properties after SCI. To our knowledge, no previous study has developed a model based on longitudinal data to predict the temporal changes in muscle fatigue after SCI.

The chronically paralyzed soleus muscle transforms to highly fatigable fibers, while the acutely paralyzed muscle is fatigue resistant.^{29,36} Numerous studies have tried to determine

optimum stimulation parameters to attenuate this rapid fatigue in chronically paralyzed muscle.^{9,13,15,37} Rarely has the goal been to prevent the muscle from becoming highly fatigable by intervening early after SCI, before the fibers become fatigable. Accordingly, a window likely exists after SCI that represents a key period during which an intervention would need to be initiated in order to maintain the endurance properties of paralyzed muscle.

The most direct approach to quantifying muscle fatigue is to measure the torque generated at the beginning and end of a series of repetitive contractions. The quotient of these torques, the Burke fatigue index (FI), differs according to the type of motor unit being activated (being higher for slow and lower for fast motor units).⁷ In paralyzed muscle, electrical stimulation with a modified Burke fatigue protocol is also sensitive to the dominant fiber type of the muscle.²⁹ Modified Burke fatigue protocols, such as those that last a shorter time¹⁰ or that use a lower frequency,²⁹ are typically used to assess skeletal muscle fatigue in humans, but the reliability of these measures has not been established in individuals with SCI. Knowing the extent to which physiological measures (FI) are reliable is critical when striving to document temporal changes in muscle endurance after SCI.

The purposes of this study were: (1) to establish the between-day reliability of a modified Burke protocol in a subset of individuals after SCI, and (2) to predict the time course for muscle adaptations leading to fatigue after SCI.

MATERIALS AND METHODS

Subjects

Seven subjects (1 woman) participated in the reliability arm of this study. Time after SCI varied from 1 month to 12 years, and age varied between 17 and 63 years. Two subjects had cervical lesions and five had thoracic lesions. Six of the subjects had both legs assessed. Subjects in the reliability arm of the study returned 1 week after their first test session for a second, identical test session.

A second cohort of 34 individuals with complete cervical or thoracic SCI (5 women) participated in the temporal component of this study. Time after SCI varied from 3 weeks to 12 years. Mean age was 32.5 (± 7.2) years. Twelve subjects had cervical lesions and 22 had thoracic lesions. Twelve subjects attended only one testing session each. The remaining 22 subjects attended between two and six testing sessions (maximum duration between first and last session was 6 years). The study yielded 66 data points from the 34 subjects.

All subjects in both groups had complete SCI (ASIA-A: no motor or sensory function¹), confirmed by a neurological examination. Exclusion criteria were lower motor neuron lesion affecting the soleus, systemic illness, musculoskeletal injury to the paralyzed extremities, previous training with electrical stimulation, and lesions below T11. The University of Iowa Human Subjects Institutional Review Board approved the protocol. All subjects provided written informed consent. All subjects underwent the same experimental procedures using the same test apparatus.

Test Apparatus

We activated the soleus muscle by electrical stimulation of the tibial nerve using a custom-designed stimulator.²⁸ The stimulator had a range of 1–400 V and a constant current up to 200 mA. It was triggered by digital pulses from a data-acquisition board (Metabyte DAS 16F; Keithley Instruments, Cleveland, Ohio) housed in a microcomputer under customized software control. We stimulated the tibial nerve in the popliteal fossa with a double-pronged surface-stimulation electrode (placed so that the cathode was distal to the anode). The stimulating electrode was a single unit with dual probes, each measuring 0.5 cm in diameter

and 3 cm in length. The stimulation intensity was supramaximal (about 1.5 times the intensity required to produce a maximal compound muscle action potential, recorded by a surface EMG electrode).

Subjects sat in their wheelchairs and placed one foot on a force measurement device, as previously described.^{29,31,32} The knee and ankle were at 90°. In this position the soleus is considered the greatest contributor to plantarflexion torque, because the gastrocnemius operates at a mechanical disadvantage.²⁸ A soft ankle cuff with turnbuckle attachments secured the foot to the footplate, ensuring that the heel could not lift during plantarflexion contractions. Soft straps over the thigh and forefoot further secured the leg and foot to the torque measurement system. A force transducer beneath the footplate^{29,31,32} was aligned perpendicular to the first metatarsal head. We calculated torque as the product of the external moment arm and the perpendicular force measured from the transducer.

Stimulation Protocol

Two silver-silver chloride electrodes (8 mm in diameter, with an interelectrode distance of 20 mm) recorded the soleus compound muscle action potential (M-wave). The M-waves were displayed on an oscilloscope to verify supramaximal activation. Each electrode contained an on-site pre-amplifier with a gain of 35. A GCS 67 amplifier (Therapeutics Unlimited, Iowa City, Iowa) with adjustable gain from 500–10,000 in five discrete increments further amplified the signal. The amplifier utilized a high impedance circuit (greater than 15 megohms at 100 HZ), with a common mode rejection ratio of 87 dB at 60 HZ and a bandwidth of 40–4,000 HZ.

We established supramaximal stimulation intensity during several single twitches delivered at 1 HZ. The testing protocol (a 2-min modified Burke fatigue protocol) consisted of 125 stimulus trains (20 HZ) with an on/off time equal to 330 ms/670 ms. Plantarflexion torque was sampled on-line at 500 HZ by EasystLx software (Keithley Instruments) through a Das16 A-D converter.

Predictive Model and Statistical Analysis

We calculated the FI as the quotient of the torque of the final contraction and the torque of the first contraction (final torque/initial torque). cursory inspection of the data indicated that FI may have declined rapidly in the early phases after SCI, and then declined less rapidly thereafter. Several statistical models (such as exponential regression and high-order polynomial regression) offered ways to determine the rate of decline of FI. However, we adopted a quadratic-linear segmented polynomial model, a class of segmented polynomial models,^{2,11,27} because it could reveal the chronological time at which the rate of FI decline changed. We assumed that the response curve was a quadratic polynomial that transferred to a linear polynomial function at some point in time. The time point at which the two polynomials meet, the joint point, was labeled θ . The θ represented the critical time beyond which FI declined more slowly. We defined the model as follows, where Y_i is the fatigue index; X_i is time after SCI; $\beta_0, \beta_1, \beta_2, \epsilon_i, \gamma_0$, and γ_1 are mathematical constants (parameters); and θ is the critical time:

$$\begin{aligned} Y_i &= \beta_0 + \beta_1 X_i + \beta_2 X_i^2 + \epsilon_i & \text{if } X_i \leq \theta \\ Y_i &= \gamma_0 + \gamma_1 X_i + \epsilon_i & \text{if } X_i \geq \theta \end{aligned}$$

Based on two constraints:

$$\beta_0 + \beta_1\theta + \beta_2\theta^2 = \gamma_0 + \gamma_1\theta \quad (1)$$

$$\frac{\partial Y(X \leq \theta)}{\partial X} \bigg|_{X=\theta} = \left| \frac{\partial Y(X > \theta)}{\partial X} \right|_{X=\theta} \quad (2)$$

To simplify the model, we defined a variable T to identify when X was $\leq \theta$ or X was $> \theta$.

Let T=0 if $X \leq \theta$ and T=1 if $X > \theta$

The model becomes:

$$Y_i = \beta_0 + \beta_1 X_i + \beta_2 [X_i^2 + T(X_i - \theta)^2]$$

We also obtained:

$$\gamma_1 = \beta_1 + 2\beta_2\theta,$$

the slope for a linear trend after θ .

We utilized the R^2 value from a regression analysis of variance (ANOVA) to determine the significance of the model in predicting the FI over time. We calculated standard error for all parameter estimates in the regression analysis.

We also aggregated the data into four epochs (bins) according to the following: bin 1 was for time less than 0.5 years after injury; bin 2 was from 0.5 years to 2 years after injury; bin 3 was from 2 to 7 years; and bin 4 was from 7 to 12 years. We used a one-way ANOVA to test for significant changes in aggregated data. We calculated standard errors and 95% confidence intervals on all group mean data.

FI reliability data were entered into a repeated-measures ANOVA, the results of which were used to calculate intraclass correlations (ICCs) between the two sessions.²⁶

RESULTS

Reliability of the Modified Burke Protocol

The protocol yielded a notable torque decline in the six subjects with chronic SCI (mean FI was 0.22 ± 0.13 and 0.23 ± 0.10 for the two trials). In contrast, the subject with acute SCI (1 month) demonstrated good fatigue resistance (FI was 0.88). A scatterplot and the best fit linear regression equation are presented in Figure 1 for the repeated FI trials. The R^2 value and ICC between the two repeated sessions for all subjects was 0.98 and 0.96, respectively, indicating good between-day reliability of the modified Burke protocol. Based on these findings, we could confidently interpret change over time as meaningful change in physiology and not attributable to day-to-day variability.

Temporal Changes in FI

A representative example of the first and last contraction for an individual with complete SCI tested at 6 weeks after injury, 6 months after injury, 1 year after injury, and 1.5 years after injury is presented in Figure 2. The FIs (contraction 125/contraction 1) for this

individual were 0.78, 0.61, 0.52, and 0.32 at 6 weeks, 6 months, 1 year, and 1.5 years after SCI, respectively.

The mean FI was 0.80 ± 0.03 , 0.42 ± 0.034 , 0.27 ± 0.21 , and 0.23 ± 0.026 for time bins 1, 2, 3, and 4, respectively, after SCI (Fig. 3). The 95% confidence intervals for the group means were 0.06, 0.064, 0.05, and 0.05 for time bins 1, 2, 3, and 4, respectively. The mean FI for bins 2, 3, and 4 was significantly less than the FI for bin 1 ($P < 0.05$); FI for bin 3 was not significantly different from the FI for bin 4 (Fig. 3).

We present a scatterplot of the fatigue index for all subjects at various times after SCI in Figure 4. The rapid change in FI over the first 2 years is evident from visible inspection. Applying the quadratic-linear segmented polynomial model to the FI data yielded an R^2 value of 0.864. The corresponding P -value was <0.0001 (Table 1). In contrast, the R^2 values for simple first- and second-order regression lines were 0.545 and 0.702, respectively. These values support the nonlinear relationship for fatigue changes following SCI.

Estimates and standard errors for the model parameters appear in Table 2. Using these parameter estimates, the model became:

$$\begin{aligned}\hat{Y} &= 0.895 - 0.6676X + 0.1946X^2 - T(X - 1.721)^2 \\ T &= 0 \text{ if } X \leq 1.721 \\ \text{and } T &= 1 \text{ if } X > 1.721\end{aligned}$$

The critical time θ was therefore 1.721 years.

When $T = 0$, (i.e., when time $X \leq 1.721$ years), the FI declines according to the expression $Y/X = 0.3854X - 0.6676$ (Fig. 5). When $T = 1$ (i.e., when time $X > 1.721$ years), the FI declines more slowly according to the expression $Y/X = -0.01$. From time 0 to 1.721 years, the FI declined by 0.3854 per year (Fig. 5). After 1.721 years, this rate was reduced to less than a 0.01 per year change in the FI. Thus, the model indicates that nearly half of the drop in FI (from 0.89 to 0.41) occurs in the first year following SCI.

DISCUSSION

The first major finding of this study was that the between-day reliability of the modified Burke fatigue protocol was high ($ICC = 0.96$). Changes in FI values observed over time can therefore be expected to reflect adaptations occurring within the muscles, not day-to-day fluctuations in test conditions. The second major finding of this study was that the FI of the soleus muscle declined over the first year following injury, with the mathematical break point (elbow) occurring at 1.7 years following injury. This relationship was well represented by the quadratic-linear statistical model. Based on the quadratic-linear model used in this study, immediate postinjury FI was 0.893, and FI declined to 0.4181 within 1 year. The initial FI and subsequent decline within year 1 did not differ from previous findings.^{29,31,32,36} Accordingly, clinicians or other investigators may estimate the FI of the soleus by merely incorporating the time after SCI injury into this mathematical model.

Visually, it is apparent that most change in FI occurs over the first year following SCI. However, mathematically the critical time of 1.7 years indicates the break point at which we can confidently be assured that the FI slope has changed. The temporal changes presented are consistent with the limited work in this area from previous reports. Most previous reports, however, have not measured the temporal changes in a large cohort of subjects at various times following SCI. Instead, previous reports have looked at cellular changes at shorter durations following SCI. For example, Castro et al.⁸ found that fiber-type

composition and cross-sectional area (CSA), fiber type-specific succinate dehydrogenase (SDH) and alpha-glycerophosphate dehydrogenase (GPDH) activities, and myosin heavy chain proportion changed by 6 months after injury, but they did not quantify muscle fatigue. Gaviria and Ohanna¹² suggest a critical period of maximum atrophy and enzymatic conversion of paralyzed quadriceps around the 10th month after SCI, followed by long-term stabilization; however, temporal data to support this assertion was not included. The findings from this study represent a cohort of temporal measures regarding change in muscle fatigue from the early onset of SCI to several years following SCI.

One possible contributor to the decline of FI after SCI is selective atrophy of type I muscle fibers, which comprise ~80% of the human soleus before SCI.¹⁶ In the rat soleus, which contains >80% type I fibers,¹⁹ Lieber et al.^{19,20} found that paralyzed muscle develops fast and fatigable properties by 58 weeks after SCI. In contrast, the extensor digitorum longus (EDL) muscle, which contains only 5% slow fibers, underwent minimal changes. The authors concluded that type I fibers demonstrated selective atrophy after SCI.¹⁹ This mechanism may also be in operation in the paralyzed human model.

However, an equally plausible mechanism for the decline in FI after SCI is conversion of type I to type II fibers. This conversion has been observed in rat muscle¹⁸ and in human soleus muscle after SCI.^{8,22,29} Although the precise mechanism of these changes is unknown, it is clear that myosin heavy chain (MHC) expression as well as the entire enzyme system plays a role. After SCI the number of hybrid muscle fibers (coexpressing two MHC types) increases dramatically.^{25,38} The expression of various MHC isoforms gradually shifts toward a faster profile as time passes after SCI. The sequence and timing of this transformation have been quantified in rats,²⁵ but remain unclear in humans. In the later stages of the process, by 1 year after SCI, paralyzed human muscles show a preponderance of fast (type IIX) myosin.²¹

Other mechanisms may contribute to fatigue as a result of chronic disuse. Impairments in neuromuscular transmission during fatigue have been reported in individuals with chronic SCI.³⁹ We do not suspect that such alterations played a significant role in the FIs demonstrated by our subjects. Our previous studies utilizing the same fatigue protocol found that the torque–frequency curve shifted rightward after fatigue, implicating factors other than neuromuscular transmission failure as the primary cause of fatigue.³¹ Instead, we suggest that low-frequency fatigue may be the major determinant of fatigue induced by this modified Burke protocol.³² Low-frequency fatigue, in turn, is believed to relate to uncoupling of the excitation–contraction mechanism.^{5,23} Therefore, the time course of FI decline found in this study likely reflects the fact that chronic disuse alters the T-tubule voltage-gated receptors, ryanodine receptors, or sarcoplasmic reticulum enzymes all associated with excitation–contraction coupling impairment.^{5,23} Further examination of the molecular changes in chronically paralyzed muscle would delineate the precise mechanisms contributing to changes in muscle fatigability.

This study included two individuals with chronic paralysis who were over 50 years of age. Based on these two subjects, age did not appear to have a confounding influence on FI decrement across time. The FI of a 62-year-old subject in this study did not significantly differ from the FI of a 32-year-old subject with a similar duration of injury (5.3 years). Similarly, no FI difference existed between a 53- and a 27-year-old subject, both of whom were injured for 3.4 years. Likewise, previous studies support that fatigue properties of individual muscle fibers differ minimally as a function of age, but the elderly have fewer fast motor units than the young.¹⁴ Future studies, with larger samples of young and old subjects, are warranted to determine whether age and SCI duration provide divergent effects on muscle fatigue.

This study presents a novel use of a quadratic-linear model to estimate the rate and duration of FI decline after SCI. Although other statistical models exist as candidates to fit FI decline after SCI (such as an exponential model or a high-order polynomial model), we selected a quadratic-linear model for two main reasons. First, only a quadratic-linear model could estimate the critical time point at which FI decline becomes a linear function. Second, the R^2 value of quadratic-linear model was higher than these other models, indicating that this model is robust in predicting FI as a function of time following SCI.

An important reason for documenting the temporal changes in paralyzed muscle is to understand when opportunities to prevent musculoskeletal changes have passed after SCI. Understanding the timelines of muscle change after SCI may be a critical part of future comprehensive plans to develop rehabilitation strategies to prevent musculoskeletal deterioration after SCI for improved general health or in preparation for a cure. We are not suggesting that paralyzed muscle is not mutable after several years of paralysis with electrical stimulation intervention. However, we are suggesting that the time has come to consider maintaining the muscle contractile machinery after SCI rather than trying to build it up after it has deteriorated. Interestingly, the rate of change in muscle endurance appears to covary with the rate of bone loss and certain neural circuitry changes after SCI.³⁰

In conclusion, paralyzed soleus muscle became highly fatigable after SCI. The steepest decline in FI occurred over the first year, with a mathematical change in slope occurring by 1.7 years after SCI. After this point, minimal further declines were apparent. The rapid decline of FI immediately after SCI implies a window of opportunity for the use of electrical stimulation as an intervention to prevent the muscle changes. In patients with chronic SCI, whose muscles and bones have undergone significant transformation, it has long been uncertain as to whether electrical activation of muscle is a useful strategy to deliver stresses to the paralyzed extremities. Furthermore, it is unknown whether long-term use of electrical stimulation, if started immediately after SCI, could preserve muscle function and bone over the life span of an individual. However, we recently demonstrated that long-term electrical stimulation training introduced early after SCI can preserve musculoskeletal properties for up to 2 years following SCI.^{34,35} Timely rehabilitation interventions designed to maintain musculoskeletal integrity after SCI will likely play a role in the future treatment of those sustaining SCI.

Acknowledgments

This work was supported by an award (R01-HD 39445) from the National Center for Medical Rehabilitation Research (NIH) (to R.K.S.) and by the Christopher Reeve and Sam Schmidt Paralysis Foundations (to R.K.S.). S.D.J. received a scholarship from the Foundation for Physical Therapy, Inc.

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Abbreviations

ANOVA	analysis of variance
CSA	cross-sectional area
FI	fatigue index
GPDH	alpha-glycerophosphate dehydrogenase
ICC	intraclass correlation
MHC	myosin heavy chain
SCI	spinal cord injury
SDH	succinate dehydrogenase

FIGURE 1.

Between-day reliability of fatigue index for two sessions separated by 1 week. The subject with FI > 0.8 had an acute SCI (1 month). All other subjects had chronic SCI (>1 year). The line of identity (dotted) indicates perfect agreement between days.

FIGURE 2.

An example of a single subject's first (contraction 1; solid line) and last (contraction 125; dashed line) torque curve during a repetitive stimulation protocol delivered at 6 weeks (**A**), 6 months (**B**), 12 months (**C**), and 18 months (**D**) after spinal cord injury.

FIGURE 3.

Mean FI aggregated into four time bins. Bin 1 is less than 0.5 years ($n = 20$), bin 2 is 0.5–2 years ($n = 11$), bin 3 is 2–7 years ($n = 17$), and bin 4 is 7–12 years ($n = 18$) after spinal cord injury. Bins 2, 3, and 4 are significantly reduced from bin 1 ($P < 0.05$). Bin 3 is not significantly different from bin 4 ($P = 0.12$). Error bars are standard errors.

FIGURE 4.

FI versus time after SCI. The subjects with repeated assessments longitudinally are depicted in **A**. The best fit model and break point (1.72 years) are presented in **B**.

FIGURE 5.

Rate of FI decline before and after 1.72 years as determined by the quadratic-linear segmented polynomial model.

Table 1

Analysis of variance. $R^2 = 0.864$.

Source	DF	Sum of squares	Mean square	F value	P
Regression	4	18.2544	4.5636	118.72	<.0001
Residual	62	0.8074	0.0132		
Uncorrected total	66	19.0619			
Corrected total	65	5.5227			

DF, degrees of freedom.

Table 2

Model parameters, with estimates and standard errors.

Parameter	Estimate	Standard error
β_0	0.8950	0.0338
β_1	-0.6676	0.2103
β_2	0.1911	0.1174
θ	1.721	0.5023