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Fatigue modulates synchronous but not asynchronous soleus activation during stimulation of paralyzed muscle

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HIGHLIGHTS

- The soleus muscle H-reflex is larger after fatigue induced by supra-maximal repetitive stimulation.
- "Asynchronous" EMG bursts, consistent with fluctuations in muscle force, were not prevalent during supra-maximal stimulation.
- Supra-maximal stimulation, administered at physiologic frequencies (e.g. 15 Hz), is a useful strategy to administer fixed levels of physiologic stress (force) to paralyzed tissues.

ABSTRACT

Objective: Electrical stimulation over a motor nerve yields muscle force via a combination of direct and reflex-mediated activation. We determined the influence of fatigue on reflex-mediated responses induced during supra-maximal electrical stimulation in humans with complete paralysis.
Methods: We analyzed soleus electromyographic (EMG) activity during repetitive stimulation (15 Hz, 125 contractions) in 22 individuals with complete paralysis. The bout of stimulation caused significant soleus muscle fatigue (53.1% torque decline).
Results: Before fatigue, EMG at all latencies after the M-wave was less than 1% of the maximal M-wave amplitude (% MaxM). After fatigue there was a fourfold ($p < 0.05$) increase in EMG at the H-reflex latency; however, the overall magnitude remained low (<2% change in % MaxM). There was no increase in "asynchronous" EMG ~ 1 s after the stimulus train.
Conclusions: Fatigue enhanced the activation to the paralyzed soleus muscle, but primarily at the H-reflex latency. The overall influence of this reflex modulation was small. Soleus EMG was not elevated during fatigue at latencies consistent with asynchronous activation.
Significance: These findings support synchronous reflex responses increase while random asynchronous reflex activation does not change during repetitive supra-maximal stimulation, offering a clinical strategy to consistently dose stress to paralyzed tissues.
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1. Introduction

After spinal cord injury (SCI), electrical stimulation of paralyzed muscle is frequently used as a therapeutic intervention to precisely dose physiological stress to paralyzed tissues. Previous reports support that supra-maximal activation of muscle regulates muscle molecular transcription factors (Adams et al., 2011; Kunkel et al., 2011), muscle physiological properties (Shields and Dudley-Javoroski, 2006; Shields et al., 2006), and bone density (Dudley-Javoroski et al., 2012; Shields and Dudley-Javoroski, 2006) in humans with complete SCI. In this study, we examine if repetitive supra-maximal electrical stimulation and the associated muscle fatigue modulates synchronous and asynchronous reflex responses in human paralyzed muscle.

Electrical stimulation of skeletal muscle may yield a muscular force via a combination of peripheral and central mechanisms (Bergquist et al., 2011b; Collins, 2007). An electrophysiological analysis of skeletal muscle allows experimenters to delineate the various contributions to muscle activity. The muscle M-wave results from a direct activation of the motor nerve, yielding a wave of depolarization over the muscle sarcolemmal membrane (Lieber, 2002). Antidromic propagation of the stimulus can also elicit sporadic "backfiring" in the motor axon, yielding an F-wave (Kimura, 2001; Zappia et al., 1993). At low electrical stimulation intensities, activation of large peripheral sensory afferent fibers

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elicits H-reflexes (Pierrot-Deseilligny and Mazevet, 2000; Schieppati, 1987). Both axon mediated muscle activation (M-wave, F-wave) and reflex-mediated activation (H-reflex) contribute to skeletal muscle activity and may impact force generation during electrical stimulation of paralyzed muscle (Collins, 2007; Klakowicz et al., 2006). The H-reflex contribution to muscle force can be diminished via increased stimulation frequency (post-activation depression (Crone and Nielsen, 1989; Kohn et al., 1997; Shields et al., 2011)) or via increased stimulus intensity (antidromic collisions (Gottlieb and Agarwal, 1976)). Single supra-maximal stimulation of paralyzed muscle should eliminate the synchronous reflex responses (H-reflex), but the effect of repetitive stimulation (fatigue) is uncertain.

Recent studies suggest that other "asynchronous" EMG events may contribute to muscle force (Bergquist et al., 2011a; Lagerquist et al., 2009; Merletti et al., 2011; Nickolls et al., 2004). These asynchronous EMG events do not occur at the typical latencies of the F-wave or H-reflex. Nickolls and colleagues reported that a burst of 100 Hz stimulation augmented subsequent force during 25 Hz stimulation, which they called "extra contractions" that persisted >1 s after the last stimulus pulse of a train (Nickolls et al., 2004). Bergquist and colleagues described the "asynchronous" EMG activity occurring between the M-wave and H-reflex latencies during sub-maximal stimulation (Bergquist et al., 2011a). In the present study, the EMG activity following a 1 s rest between stimulation trains was analyzed to understand potential contributions of asynchronous EMG activity before and after fatigue.

The underlying mechanism and relative importance of asynchronous activation in the production and modulation of muscle force in human and animal models remains unclear (Bergquist et al., 2011a,b; Frigon et al., 2011). These mechanisms are methodologically challenging to explore in human subjects with intact nervous systems: volitional descending co-contraction may interfere with the precise interpretation of reflex or innate motor neuron activation (persistent inward currents) (Dean and Collins, 2009).

In this study, we examine individuals with complete paralysis from SCI. Sensory loss and the absence of descending voluntary drive in this population eliminate the influence of voluntary contractions during electrical stimulation of paralyzed muscle. However, stimulation intensity and the sensory signaling from muscle fatigue may both modulate circuitry and subsequent muscle activation levels. Several studies support that muscle fatigue activates group III and IV free nerve endings in skeletal muscle (Kaufman et al., 1983; Rotto and Kaufman, 1988; Sinoway et al., 1993) and that activation of these afferent fibers modulates complex spinal reflex responses (Schmit et al., 2002; Wu et al., 2006). We designed these experiments to address whether two sources of sensory information, supra-maximal stimulation and metabolic signaling from muscle fatigue, modulate muscle activation (synchronous: H-reflex/F-wave; asynchronous: after cessation of stimulation).

The purpose of this study is to investigate whether muscle activity from synchronous or asynchronous sources is modulated during supra-maximal electrical stimulation and muscle fatigue in humans with complete paralysis. We expect that synchronous reflex-mediated contributions to muscle force will systematically increase while asynchronous activation is minimally modulated. These findings will assist clinicians when dosing physiological stress to paralyzed tissues through electrical stimulation.

2. Methods

Twenty-two individuals with SCI participated in the study (Table 1). The protocol was approved by the University of Iowa Human Subjects Institutional Review Board. All subjects provided written informed consent before participating. Inclusion criteria were motor-and sensory-complete SCI (American Spinal Injury Association Impairment Score (AIS) – A) (Association, 2002) above T12, passive ankle dorsiflexion to neutral, and passive knee flexion to at least 90 degrees in a seated position. Exclusion criteria were lower motor neuron injury below T12, lower extremity trauma, pressure ulcers, or peripheral/systemic infection. We have previously demonstrated that repetitive supra-maximal soleus contractions can be safely performed in this population. This protocol induces an increase in several peripheral changes in muscle properties including increased relaxation time, decreased rate of relaxation, and long duration low frequency fatigue (Shields and Dudley-Javoroski, 2006).

2.1. Mechanical recordings

Subjects remained in their wheelchairs during the test procedure. One randomly-selected ankle was stabilized in a system which measured isometric plantar flexion torque, as described previously (Shields, 1995; Shields and Dudley-Javoroski, 2006). The knee was positioned at ninety degrees of flexion and the ankle was in neutral joint position. With this configuration, the soleus muscle produces most of the plantar flexion torque (Sale et al., 1982). The foot was positioned on a rigid footplate instrumented with a force transducing load cell (Genisco AWU-250) placed directly underneath the metatarsal heads. The single-axis force transducer had a range of ±5 V with linearity, hysteresis, repeatability and accuracy of 1.10%, 1.22%, 0.43% and 1.31% full scale, respectively (Shields, 1995). The foot was secured to the footplate via an ankle cuff with turnbuckles that directed force through the heel and into the footplate. A strap was secured tightly over the distal femur. This fastening system prevented upward movement of the heel during activation of the ankle plantar flexor muscles, helping to ensure that muscle contractions were isometric. We employed isometric contraction conditions because muscle length change introduces nonlinearity to the relationship between soleus stimulus input and torque output (Frigon et al., 2011). In addition, the influence of muscle length on M-waves is minimized during isometric contractions (Chang and Shields, 2002). Plantar flexor torque was calculated from the system in the manner previously described (Shields and Dudley-Javoroski, 2006). All force data were sampled at 1 kHz.

2.2. Electrical stimulation and EMG recordings

A probe over the tibial nerve in the popliteal fossa delivered electrical impulses to the plantar flexor muscles. The constant current electrical stimulator had a range of 0 to 200 mA at 400 V. It was triggered by digital pulses from a data-acquisition board (Metrabyte DAS 16F, Keithley Instruments Inc., Cleveland, OH, USA) housed in a microcomputer under custom software control.

Surface EMG signals were recorded with a bipolar silver–silver chloride electrode with 0.8 cm diameter and 2 cm fixed inter electrode distance (Therapeutics Unlimited, Iowa City, IA). The recording electrode was positioned over the soleus muscle parallel to its fibers, approximately 2 cm medial to the midline of the calf and distal to the medial head of the gastrocnemius. A ground electrode was placed over the anterior surface of the distal tibia. EMG signals were on-site pre-amplified by a factor of 35, followed by mainframe differential amplification. The EMG amplifiers (Therapeutics Unlimited, Iowa City, IA) had an input impedance of 15 MΩ at 100 Hz, a frequency response of 15–1000 Hz, a common mode rejection ratio of 87 dB at 60 Hz, and a gain range of 1000–20,000 times. EMG signals were monitored on an oscilloscope. Data were stored for later offline analysis with DataPac 2k2 software