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Mitigation of excessive fatigue associated with functional electrical stimulation

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Abstract

Objective.—Restoration of motor function in paralyzed limbs using functional electrical stimulation (FES) is undermined by rapid fatigue associated with artificial stimulation. Typically, single electrodes are used to activate muscles with FES. However, due to the highly distributed branching of muscle nerves, a single electrode may not be able to activate the entire array of motor axons supplying a muscle. Therefore, stimulating muscle with multiple electrodes might enable access to a larger volume of muscle and thereby reduce fatigue.

Approach.—Accordingly, we compared the endurance times that ankle dorsiflexion could be sustained at 20% maximum voluntary force using feedback controlled stimulation (25 Hz) of human tibialis anterior (TA) using one or four percutaneous intramuscular electrodes. In addition, we measured endurance times in response to direct stimulation of the nerve supplying TA and during voluntary contraction. In all sessions involving electrical stimulation, an anesthetic nerve block proximal to the site of stimulation was used to isolate the effects of stimulation and alleviate discomfort.

Main results.—Endurance time associated with stimuli delivered by a single intramuscular electrode (84 ± 19 s) was significantly smaller than that elicited by four intramuscular electrodes (232 ± 123 s). Moreover, endurance time in response to nerve stimulation (787 ± 201 s) was not significantly different that that produced during voluntary contraction (896 ± 272 s).

Significance.—Therefore, excessive fatigue associated with FES is probably due to the inability of conventional FES systems to enlist the full complement of motor axons innervating muscle and can be mitigated using multiple electrodes or nerve-based electrodes.

Keywords

functional electrical stimulation; fatigue; paralysis; skeletal muscle; spinal cord injury

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Introduction

Functional electrical stimulation (FES) is a rehabilitative technology that serves to restore motor function in paralyzed individuals. FES takes advantage of the retained excitability of motor axons that innervate most paretic skeletal muscles. This enables induction of muscle contraction through artificial electrical stimulation delivered by surface electrodes, intramuscular electrodes, or by electrodes that encircle peripheral nerves supplying muscles. The utility of FES, however, is undermined because of the rapid muscle fatigue that occurs during FES (Bhadra and Peckham 1997, Mizrahi 1997, Kesar *et al* 2008, Doucet *et al* 2012, Guiraud *et al* 2014, Ibitoye *et al* 2016, Barss *et al* 2018). While a component of this accelerated fatigue is due to peripheral adaptations that occur in chronically paralyzed muscle (Grimby *et al* 1976, Martin *et al* 1992, Stein *et al* 1992, Shields 1995, Butler and Thomas 2003, Thomas *et al* 2003), FES-induced contractions also fatigue rapidly in able-bodied subjects (Naess and Storm-Mathisen 1955, Binder-Macleod and Snyder-Mackler 1993, Karu *et al* 1995).

One reason proposed to account for rapid fatigue with FES is that the normal recruitment order of motor units, from weakest and most fatigue resistant toward the strongest and most fatigable, is disrupted. This is thought to occur because extracellular stimulation favors activation of the larger diameter axons (Blair and Erlanger 1933, McNeal 1976, Rattay 1986, Fang and Mortimer 1991, Grill and Mortimer 1995) that innervate strong, fatigable motor units (Wuerker *et al* 1965, Jami and Petit 1975, Zajac and Faden 1985). In addition, everything else being equal, axons closest to the stimulating electrode are those most readily activated by electrical stimulation (Mortimer 1981, Grill and Mortimer 1995). Because axons of varying diameters appear to be intermingled within motor nerves and muscle, there would be no particular spatial bias favoring activation of one type of motor unit over another (Thomas *et al* 2002). As a consequence, investigators have suggested that electrical stimulation tends either to invert the normal recruitment order (Parker *et al* 1986, Kubiak *et al* 1987, Sinacore *et al* 1990, Trimble and Enoka 1991, Binder-Macleod and Snyder-Mackler 1993, Yoshida and Horch 1993, Heyters *et al* 1994, Mizrahi 1997, McDonnall *et al* 2004, Navarro *et al* 2005, Sheffler and Chae 2007, Malešević *et al* 2010) or to activate motor units in a relatively random way (Knaflitz *et al* 1990, Binder-Macleod *et al* 1995, Feiereisen *et al* 1997, Bickel *et al* 2011, Barss *et al* 2018). It should be noted, however, that some studies have shown little disruption in normal recruitment order with electrical stimulation (Thomas *et al* 2002, Farina *et al* 2004).

A second reason often cited as a possible cause for rapid fatigue with FES is related to the synchronized discharge of motor units induced by peripheral electrical stimulation (Binder-Macleod and Snyder-Mackler 1993, Karu *et al* 1995, Mizrahi 1997, Chou *et al* 2008, Popović and Malešević 2009, Malešević *et al* 2010, Rohm *et al* 2013, Sayenko *et al* 2014, Downey *et al* 2015, Lou *et al* 2017, Barss *et al* 2018, Zheng and Hu 2018). Such synchronization can lead to marked fluctuations in evoked force, which in turn, can itself provoke fatigue because of the additional work required by the contractile apparatus repeatedly shortening against series elastic elements in muscle (Garland *et al* 1988, Sandercock 2006). To minimize force fluctuations (which also compromises force control),

stimulus frequencies can be increased. Yet excessively high stimulus frequencies can also promote rapid fatigue (Naess and Storm-Mathisen 1955, Jones *et al* 1979, Metzger and Fitts 1986, Jones 1996, McDonnall *et al* 2004). Therefore, some FES investigators have turned to asynchronous stimulation (Lind and Petrofsky 1978, Yoshida and Horch 1993, Wise *et al* 2001, McDonnall *et al* 2004, Malešević *et al* 2010, Nguyen *et al* 2011, Maneski *et al* 2013, Sayenko *et al* 2014, Downey *et al* 2015, Bergquist *et al* 2016, 2017, Laubacher *et al* 2017, Lou *et al* 2017), an approach originally described by Rack and Westbury (1969), wherein different sets of motor units are activated sequentially at relatively low rates using multiple electrodes. Such asynchronous (or interleaved stimulation) can produce reasonably smooth muscle force despite low stimulus rates delivered to each set of motor units that, on their own, would cause markedly unfused contractions (Rack and Westbury 1969, Wise *et al* 2001, Sandercock 2006).

What is puzzling, however, is that the advantage of asynchronous over synchronous stimulation practically disappears for stimulus rates above ~10 Hz (Rack and Westbury 1969, Sandercock 2006). And while those studies involved cat soleus, the average contraction time of cat soleus (76 ms, Nelson (1969)) is briefer (and hence, the fusion frequency higher) than that found in many lower limb muscles of humans (e.g. 81 ms for tibialis anterior, Marsh *et al* (1981), 87 ms for quadriceps, Bergstrom and Hultman (1990), 104 ms for triceps surae, Marsden and Meadows (1970)). Yet, many interleaved FES protocols involve frequencies ⩾10 Hz (Malešević *et al* 2010, Nguyen *et al* 2011, Maneski *et al* 2013, Sayenko *et al* 2014, Bergquist *et al* 2016, 2017, Lou *et al* 2017). Indeed, we have recently shown that there was no difference in the degree of fatigue induced with interleaved versus synchronous stimulation when delivered to two different locations in a muscle using stimulus frequencies >15 Hz at each electrode (Buckmire *et al* 2018). Therefore, it seems possible that the documented improvement in fatigue resistance using interleaved stimulation compared to single site stimulation (Malešević *et al* 2010, Nguyen *et al* 2011, Sayenko *et al* 2014, Downey *et al* 2015, Bergquist *et al* 2016, Laubacher *et al* 2017, Lou *et al* 2017) was not primarily because of the asynchronous activation per se. Rather, given the widespread distribution of motor nerve branches within human muscle (Amirali *et al* 2007, Mu and Sanders 2010, Won *et al* 2011, Yu *et al* 2016), multi-site stimulation may simply enable access to more of the muscle fibers within a muscle (Buckmire *et al* 2018).

To test this possibility, here we compared the duration that submaximal isometric contractions of human tibialis anterior could be sustained when feedback-controlled electrical stimulation was delivered through a single intramuscular electrode to that delivered synchronously through multiple electrodes. In addition, in separate sessions we also measured contraction duration evoked by direct stimulation of the peripheral nerve proximal to its entry into tibialis anterior (i.e. at a site where motor axons are spatially constrained) and during voluntary contractions.

We found that multi-electrode stimulation markedly extended the endurance time of submaximal contractions over single-electrode stimulation. Moreover, the duration of contractions induced by electrical stimulation delivered directly to the peripheral nerve was no different, and in some cases longer, than that achieved during voluntary contractions. These findings indicate that the rapid fatigue associated with conventional FES is unlikely to

be primarily caused by synchronized discharge or disrupted recruitment order of motor units but rather because only a fraction of the motor units can be readily enlisted using single electrodes placed in or over muscle.

Methods

Subjects and muscle

Five healthy human subjects (one female, four male), ages 20 to 58 were included in this study in accordance with human subjects guidelines and approved by the University of Arizona institutional review board. Each subject participated in four experimental sessions (separated by ⩾2 d) involving sustained isometric contraction of the tibialis anterior muscle. The tibialis anterior (TA) was selected for this study because it is readily accessible for intramuscular stimulation and it generates the preponderance of the dorsiflexion torque at the ankle. In addition, the nerve supplying the TA (deep peroneal neve) is reasonably accessible for stimulation while the major nerve (common peroneal nerve) giving rise to the deep peroneal nerve can be anesthetically blocked several centimeters proximal to the deep peroneal nerve, thereby isolating the TA for study.

Force and EMG measurements

Subjects were seated in a dental chair with their knee extended and their right foot secured to a custom-built footplate instrumented with a transducer to measure isometric force during dorsiflexion. The footplate rotated freely about an axis aligned approximately co-linear with the talocrural joint axis of the ankle. Once the foot was secured with Velcro straps, the footplate was rotated such that it held the ankle in a plantar-flexed position. An isometric force transducer (Grass FT-10, Warwick, RI, USA using custom-built heavy-duty springs inserted into the housing of the transducer) was then attached to the distal end of the footplate (22.5 cm from the axis of rotation of the footplate) that resisted ankle dorsiflexion. The knee was held in an extended position with a wide strap that ran over the anterior surface of the distal thigh and was tightened and secured to the chair. Bipolar surface electrodes (4 mm diameter, ~5 cm inter-electrode separation) were placed on the skin over the TA and over the triceps surae to record electromyographic (EMG) activity. EMG signals were amplified (×1000, band-pass filtered 30 to 1000 Hz., Grass Technologies Product Group, Astro-Med Inc.; West Warwick Rhode Island). Force and EMG signals were digitally sampled (1000 and 4000 samples s^{-1}, respectively) by a computer-controlled data acquisition system (Power 1401, Spike2, Cambridge Electronic Design, Cambridge England).

Electrical stimulation

Current-regulated stimuli (0.25 ms duration, rectangular, monophasic, cathodic pulses) were delivered to the TA or deep peroneal nerve through percutaneous tungsten microelectrodes (250 μm shaft diameter, 1–5 μm tip diameter, 2–4 mm of insulation removed from the tip, 30 mm total length, Frederick Haer, Bowdoin Maine, USA) using a programmable multi-channel stimulator (STG4008 MultiChannel Systems, Reutlinger, Germany). Surface electrodes (Covidien/Kendall, Pediatric cloth ECG Hydrogel Electrodes H59P, Medtronic, Dublin, Ireland) placed over the tibia or the lateral malleolus of the fibula served as common

return electrodes for electrical stimulation. Current pulses delivered by the stimulator were digitally sampled (12 kHz) by measuring the voltage drop across an in-series resistance (~150 Ω).

Anesthetic block

Strong electrical stimulation can be painful. Such painful stimuli can trigger spinal reflexes and descending activity that interferes with measures of force from the target muscle. Furthermore, some subjects may not tolerate the high stimulus intensities delivered over prolonged periods needed for tests of muscle endurance. Therefore, we used an anesthetic block of the common peroneal nerve supplying the TA to largely eliminate sensory feedback associated with the stimulation and to fully paralyze the TA.

Under ultrasound guidance, 10–15 ml of 1.5% Mepivacaine was administered to the peri-neural space surrounding the common peroneal nerve at a site ~8–10 cm proximal to the head of the fibula. Complete anesthetic block was confirmed by the subject's inability to voluntarily generate detectable dorsiflexion force. This occurred within ~20 min of the injection in all cases but one. In that one case where a complete nerve block was not achieved, the experimental session was terminated and the subject returned on a different day during which the nerve block was successful. As a precaution, prior to the nerve block, an intravenous line was placed into a peripheral vein in the upper extremity to administer fluids or medications in the unlikely event of anesthetic toxicity. No such events occurred in any of the subjects tested. Following experiments involving the nerve block, subjects wore a plastic ankle cast to prevent foot drop for a period of about 4–5 h until the paralysis resolved.

Procedure

Subjects participated in four experimental sessions in random order, one session involving sustained voluntary contraction of the TA and three sessions involving sustained stimulation of the TA with a nerve block present. For sessions using electrical stimulation, in one session a single intramuscular electrode was used to deliver stimuli, in a second session four intramuscular electrodes distributed throughout TA and each controlled by a separate stimulus channel were used to deliver stimuli, and in a third session stimuli were delivered by a single electrode placed adjacent to the deep peroneal nerve just distal to the fibular head.

In each session, subjects first performed three brief (~2 s duration) maximum voluntary contractions (MVC) of ankle dorsiflexion with about 60 s between trials. The largest force exerted among the three trials was deemed the MVC force. For the voluntary fatigue task, subjects observed a target force of 20% MVC displayed on a computer screen and matched that force by isometric dorsiflexion of the ankle. To keep subjects motivated, subjects were verbally encouraged throughout the contraction to sustain the target force for as long as possible (e.g. Fuglevand and Keen (2003)). The task was terminated when the force continuously remained below the target force for a period of 5–10 s.

For sessions involving intramuscular stimulation, sterilized microelectrodes were inserted through alcohol cleansed skin and into the TA following induction of paralysis by the nerve

block. For experiments involving a single intramuscular electrode, the initial electrode placement was at a proximal site ~1/3 of the length of the muscle and ~2 cm lateral to the tibial ridge. This site was selected based on nerve dissection (Watt *et al* 2013) and surface EMG-array studies (Barbero *et al* 2012) indicating that this site approximates the location where major branches of the deep peroneal nerve typically penetrate the TA. For experiments involving four electrodes, one electrode was inserted at this proximal site, two electrodes were placed at ~50% of the length of the TA with one located ~1 cm lateral to the tibial ridge and the other ~3 cm lateral to the ridge, and the fourth electrode was inserted at a distal site ~2/3 of the length of muscle and inserted into the midline of the TA.

Each electrode was initially inserted to a depth of about 5–8 mm below the skin. Brief (1 s) trains of stimuli (5 mA, 25 Hz) were delivered and the evoked force recorded. The electrode was then advanced in ~2 mm steps to a maximum depth of ~30 mm with stimulation repeated at each step. Electrode depth was estimated at each stimulation site by measuring the length of the electrode extending above the skin surface. The insertion site was marked with ink and then the electrode was removed and reinserted at sites ~1–2 cm proximal, distal, medial, and lateral to the original insertion site and the process repeated. Following this survey, the electrode was then reinserted at the site that evoked the largest force in response to the stimulus train. Stimulation was repeated at this site to confirm similar levels of evoked force as detected originally. If needed, small adjustments to the electrode depth were made to ensure robust force responses were evoked. In cases involving four electrodes, this process was repeated for each electrode. The time needed to place all four electrodes was usually about 1 h. Because of concerns that the anesthetic might begin to wear off, we did not carry out additional procedures to assess the degree of independence of each electrode by stimulating each electrode separately and in various combinations with other electrodes and measuring the degree of force summation.

For sessions involving nerve stimulation, a single tungsten microelectrode was inserted at an oblique angle to the skin immediately distal to the head of the fibula in order to approach the deep peroneal nerve. The electrode position was manually adjusted until strong dorsiflexion forces were elicited in response to 1 s trains of 1 mA pulses delivered at 25 Hz. We often also observed toe extension during stimulation of the nerve indicating activation of extensor hallucis longus and extensor digitorum longus. This was largely unavoidable because axons to those muscles are also carried in the deep peroneal nerve.

Once electrodes were in place, single stimulus pulses were delivered to each electrode separately and the associated twitch forces were recorded with amplitude incremented in 1 mA steps from 1 mA to 32 mA and with a 2 s delay between pulses. The associated current—twitch force relationships were evaluated immediately to identify the operating range of currents for each electrode for the upcoming fatigue task.

Prior to the fatigue test, a few 1 s trains of stimuli (25 Hz) were delivered to identify the stimulus pulse amplitudes needed initially to elicit the 20% MVC target force. For the case involving four electrodes, stimulus amplitudes were identified separately for each electrode that evoked ~5% MVC force (assuming that the forces would sum near linearly). A custom-

designed Matlab (Mathworks, Natick MA) program was then used to provide on-line feedback control of stimulus pulse amplitude during the fatigue task.

The inputs to the program included the target force (20% MVC), the starting current levels (based on those identified with 1 s trains), the upper current levels (based on the current—twitch force relationship), the force exerted by the subject sampled in real time, and a gain factor. Force was sampled in parallel by two data acquisition systems: one dedicated exclusively for feedback control (120 samples s^{-1}, USB 6001, National Instruments, Austin, TX) and one for general data acquisition and storage that was used for off-line analyses (1000 samples s^{-1}, CED Spike2). The gain factor in this simple proportional feedback system was used to transform the detected error between target and a six-point (50 ms) moving average of the actual force into a current adjustment scaled to the operating range of the electrode. We used a nominal gain value of 0.25 indicating that 25% of the full current range would be added to the ongoing current in the case of an error representing 100% of the full force range. In brief tests before the fatigue run, if overt force oscillations developed, we reduced the magnitude of the gain. If, on the other hand, evoked force was slow to approach the target, we increased the gain. For the majority of cases tested, however, a gain of 0.25 worked reasonably well.

The commanded adjustments in current amplitude were then dispatched every ~240 ms to the MultiChannel Systems stimulator that delivered continuous 25 Hz (0.25 ms pulse duration) stimuli to the electrode(s). A stimulus frequency of 25 Hz was selected because it evokes fused force responses and is within the upper range of motor unit firing rates of TA recorded during voluntary contractions (Connelly *et al* 1999, De Luca and Hostage 2010). In the case of multielectrode stimulation, the timing of the pulses were offset by 1 ms across electrodes to help prevent summation of otherwise subthreshold electric fields (i.e. ‘subliminal fringe’) at sites relatively distant from the electrodes (Mortimer 1981, Branner *et al* 2001). For example, we found in some experiments that precisely synchronized stimulation (i.e. without the 1 ms delay) could lead to overt plantar flexion that was not evoked by any electrode alone when stimulating using maximal intensities. Feedback-controlled stimulation was maintained until the evoked force was clearly below the target force by at least 10% for ~5–10 s despite escalating current intensities.

Data analysis

For each fatigue trial, we used a custom-written program (Spike2) to measure the endurance time as the duration from when the force initially came within 10% of the target force until the time when force fell 10% below the target for more than 5 s. A one-way repeated-measures analysis of variance (ANOVA) was performed to determine whether endurance time varied significantly with different fatigue protocols. Mann–Whitney rank sum post-hoc test was used to evaluate differences in endurance times between fatigue protocols with Bonferroni correction for multiple comparisons. The level of statistical significance was set at $P < 0.05$ and data are reported as means ± one standard deviation (SD).

Results

Current—twitch force relation

Figure 1 shows example twitch force responses to escalating current-amplitude stimuli delivered during separate trials to each of four intramuscular electrodes placed in different locations in TA in one subject during a single session. In this example, a small twitch was detected for the lowest current delivered (1 mA) on electrodes 1, 2, and 4, while 3 mA of current was needed to elicit a detectable twitch on electrode 3. Peak twitch forces of 17.4, 17.1, 17.4, and 15.7 N were attained at 31, 32, 29, and 30 mA for electrodes 1–4, respectively. The difference in peak forces between the electrode that evoked the largest twitch and that which evoked the smallest was 9.8%.

Across all subjects and all cases involving one or four intramuscular electrodes, the average threshold current for evoking a detectable twitch response was 1.6 ± 1.0 mA while the average current associated with peak twitch force was 27.4 ± 5.7 mA (range 9–32 mA). For the case of four intramuscular electrodes, the average percent difference across electrodes evoking the largest and smallest peak forces was 25.6% ± 18.1% (range 9.8%–51.6%). During nerve stimulation we did not get clear measures of the threshold currents due to the large increments (1 mA) used for the current—twitch force assessment. In all subjects during nerve stimulation, 1 mA (the smallest value tested) always evoked a strong twitch (>50% of the peak twitch force) while the current associated with peak twitch force was ⩽5 mA.

Intermediate plateaus

While twitch forces tended to progressively increase with current above threshold up to the current associated with peak force, there were often intermediate plateaus wherein evoked force saturated across a range of increasing currents. Such plateaus are highlighted with red horizontal lines in the examples shown in figure 1. Force responses to stimuli delivered by electrode 1, for example, saturated across a nearly three-fold increase in stimulus intensities (from 5–14 mA). We quantified the prevalence of such intermediate plateaus using a method we described previously (Buckmire *et al* 2018). Namely, we calculated the percentage change in force associated with each 1 mA increment in current for all of the current—twitch force sequences involving intramuscular electrodes. We then identified the number of cases for which the change in force fell below 5% for two or more consecutive steps in current and which was then followed by increases in force above 5%. For all 25 intramuscular electrode sequences tested (20 from 4-electrode experiments, five from 1-electrode experiments), 80% exhibited one or more intermediate plateaus. The average span of currents over which twitches saturated during these intermediate plateaus was 4.7 ± 3.4 mA (range 2–14 mA).

Fatigue

The target force for all fatigue trials was set at 20% of the MVC obtained in each session. Across all sessions and subjects, the average MVC force was 218.8 ± 32.2 N (49.2 ± 7.2 N • m of torque). There was little variation in MVC force across sessions for individual subjects (average coefficient of variation =5.6% ± 3.9%). Figure 2 shows example force responses

obtained in a single subject during sustained voluntary effort (figure 2(A)), stimulation of the TA with a single intramuscular electrode (figure 2(B)), stimulation of the TA with four intramuscular electrodes (figure 2(C)), and stimulation of the deep peroneal nerve supplying TA (figure 2(D)). The TA surface EMG is shown in figure 2(A), whereas the feedback controlled stimulus currents are shown in figures 2(B)–(D). For clarity, only one of the four stimulus-current signals is shown in figure 2(C). All four panels in figure 2 are depicted using the same time base so their durations can be directly compared.

During the voluntary contraction (figure 2(A)), EMG activity progressively increased reflecting increased motor unit recruitment and rate coding needed to compensate for diminishing force capacities of the active muscle fibers. Eventually, however, the increased drive to the muscle was insufficient to maintain the target force and the contraction was halted. Across all five subjects, the average value of the rectified TA EMG signal measured over the last 10 s of the trial was 71.6% ± 34.5% (range 47.8%–132.1%) larger than that measured over the initial 10 s. The endurance time for the voluntary contraction shown in figure 2(A) was 740 s. In the session involving stimulation with a single intramuscular electrode (figure 2(B)), ~10 mA of current was needed at the outset to achieve the target force. The stimulus current then increased rapidly up to its assigned upper limit of 24 mA under feedback control in order to maintain the target force. Despite the increasing current, force decayed slowly over much of the trial and stimulation was halted when the force was <90% of the target level. The endurance time for this trial was 80 s. When four intramuscular electrodes were used to deliver stimuli (figure 2(C)), force was maintained five times longer (endurance time 448 s) compared to stimulation with a single electrode. At the outset, the evoked force overshot the target but with feedback control, the stimulus intensities delivered to the four electrodes were rapidly adjusted and the evoked force was then stably maintained at the target force. Stimulus current then increased almost linearly over much of the trial except near the end when current amplitude rapidly accelerated in an attempt to maintain the target force in the face of weakening output of the active muscle fibers. Despite this increase in stimulus intensity, additional force was not generated and the trial was halted when force dropped below 90% of the target even though current had not reached the upper limit on any of the four stimulus channels.

The most remarkable trial was that associated with nerve stimulation (figure 2(D)). In this case, the endurance time (993 s) far surpassed (by 34%) that of the voluntary contraction (figure 2(A)). The stimulus currents involved were much lower than that used for intramuscular stimulation and the amplitude only gradually increased over much of the trial except a sharp escalation near the end. In one other subject, endurance time of nerve stimulation exceeded that of the voluntary contraction by 42%. As can be seen in figure 2(D), force fluctuations were evident throughout the trial but grew in intensity during the latter two-thirds of the trial. These force fluctuations were seen in all subjects and were dominated by a 4.2 Hz oscillation. It was only discovered later that these oscillations were due to an inadvertent lengthening of every 5th interpulse interval (occurring at cycle period of ~240 ms), presumably due to buffering delays in the computer-stimulator interface. As such, the average stimulus rate was ~22 Hz rather than 25 Hz for all subjects.

The mean (SD) endurance times for the five subjects across the four fatigue tasks is shown in figure 3. ANOVA indicated a significant effect of fatigue task on endurance time ($P < 0.001$). Post hoc analysis indicated no significant difference ($P = 0.46$) in the mean endurance times between voluntary (896 ± 272 s) and nerve stimulation tasks (787 ± 201 s). The mean endurance time associated with stimuli delivered by a single intramuscular electrode (84 ± 19 s) was significantly ($P < 0.01$) smaller than that elicited by four intramuscular electrodes (232 ± 123 s). All other between-task comparisons were significant ($P < 0.01$).

Discussion

Here we have shown that the rapid fatigue associated with electrical stimulation of muscle can be partially mitigated by increasing the number of intramuscular electrodes used to activate muscle. Furthermore, stimulating the nerve proximal to where it enters muscle produced a target force that could be sustained as long as, and in some cases longer, than that produced during voluntary contraction. We conclude, therefore, that the excessive fatigue associated with FES must primarily be due to the inability of conventional FES systems to enlist the full complement of motor units within muscle. Moreover, these results indicate that neither altered motor unit recruitment order nor synchronized motor unit activity can account for much of the fatigue seen with FES as both of these factors presumably were in play in the present experiments.

A likely explanation as to why a single stimulating electrode (as has been the convention in many FES systems) is unable to activate all the motor units in a muscle is because of the widely distributed arrangement of nerve branches within muscle. A long-held view is that nerves typically enter muscle at a single location to innervate muscle fibers along a constrained central region referred to as the innervation zone (Coërs and Telerman-Toppet 1977, Lee *et al* 2012, Behringer *et al* 2014, Jahanmiri-Nezhad *et al* 2015). Yet, many anatomical studies have clearly shown extensive and complex ramification of nerve branches prior to entry into (Sunderland and Hughes 1946) and throughout large expanses of skeletal muscle (Amirali *et al* 2007, Mu and Sanders 2010, Won *et al* 2011, Yu *et al* 2016). Because of the steep decay in the electric field with distance from a stimulating electrode (McIntyre and Grill 2002, Rattay 2004), it may be challenging in practice to deliver sufficient current to excite all of the widely dispersed nerve branches, particularly in large muscles such as the tibialis anterior. As such, using more electrodes situated in different regions of a muscle should enable electrical access to a larger subset of the nerve branches. In support of this idea, we have recently shown that the maximum force that could be evoked using intramuscular electrodes was always greater when using multiple compared to a single electrode (Buckmire *et al* 2018).

Indeed, the prevalence of intermediate plateaus in evoked force responses to increasing stimulus intensities observed here (figure 1) and previously (Crago *et al* 1980, Cameron *et al* 1998, Buckmire *et al* 2018) probably reflects the presence of widely separated nerve branches within muscle. Namely, the initial increase in force with increased stimulus intensity likely arises due to progressive activation of more motor axons contained within nerve branches in the vicinity of the electrode. Eventually, however, most motor axons in

such nearby branches might be recruited and thereafter, no additional force would be elicited over a range of increased stimulus strengths (Cameron *et al* 1998). At some point, however, sufficient current could be delivered such that other distant nerve branches begin to be activated, leading to an additional rise in evoked forces with increasing current. In the present experiment, there was no way to be sure that additional intermediate plateaus might have been detected had we delivered currents higher than the 32 mA maximum allowed by our stimulator.

It is possible that secondary increases in evoked force after a plateau might have been due to activation of neigh-boring synergist muscles, such as extensor hallucis longus or extensor digitorum longus, both of which contribute to ankle dorsiflexion. Yet, we only rarely detected toe extension during intramuscular stimulation of tibialis anterior, which would have been indicative of activating those synergists. Furthermore, such intermediate plateaus were observed in response to intramuscular stimulation of cat hindlimb muscle when no muscles, other than the target muscle, were attached to the force transducer (Crago *et al* 1980, Cameron *et al* 1998).

In the context of fatigue resistance, the ability to engage more motor units with multiple electrodes is beneficial. A larger reserve of motor units that can be called upon (by increasing stimulus strength) as force declines in earlier activated motor units will enable a given target force to be maintained for a longer duration. Indeed, when we stimulated the deep peroneal nerve (at a site where most of the motor axons supplying tibialis anterior are bundled together), no evidence of excessive fatigue was found. Moreover, in two of the five subjects tested, the duration over which the target force could be sustained with such nerve stimulation exceeded that associated with voluntary effort. Although some previous studies have shown that the extent of fatigue to be similar during sustained maximum voluntary contractions and maximal nerve stimulation (Merton 1954, Bigland-Ritchie *et al* 1979, Jones *et al* 1979, Marsden *et al* 1983), we are unaware of previous cases for which fatigue resistance of electrically evoked contractions surpassed that of voluntary effort.

While caution against over-interpretation of these two cases is certainly warranted, some consideration as to why such supra-endurance arose in these cases seems worthwhile. First, it is possible that the two subjects simply did not exert themselves fully to sustain the voluntary contraction for as long as possible. Indeed, those two subjects had the briefest endurance times associated with the voluntary contraction (see figure 3). Yet, both subjects showed substantial increases in TA EMG during the voluntary fatigue task indicative of increasing exertion. Indeed, the subject who showed the greatest increase in endurance time with nerve stimulation compared to voluntary contraction also exhibited the greatest increase (>100%) in TA EMG during the voluntary task.

Thus, if taken at face value, it is then important to ask why such supra-endurance has not been observed previously. Perhaps one reason is that few other studies have used feedback control during electrical stimulation to determine the duration over which a given target force can be maintained. Rather, most fatigue studies involving electrical stimulation measure the change in force in response to a fixed stimulus intensity applied over a set duration (e.g. Yoshida and Horch (1993), Thomas *et al* (2002), Lou *et al* (2017) and

Buckmire *et al* (2018)). Because it is difficult to 'clamp' the intensity of voluntary drive during fatiguing contractions, it is not possible to directly compare such electrically evoked contractions to that produced voluntarily. On the other hand, voluntary contractions naturally lend themselves to visual feedback control of a displayed target force and as such, can be compared to that produced by electrical stimulation under force-feedback control, as was done here. It should be said that under open-loop stimulation involving fixed stimulus intensities, the same set of motor units would be activated throughout a stimulation bout. In this case, the tendency of extracellular stimulation to favor activation of higher threshold, fatigable motor units would indeed contribute to more rapid loss in force than that associated with activation of motor units that mimics that which occurs naturally.

A second possible reason for the absence of such observations previously is that few such studies have used anesthetic nerve blocks as we used here to isolate the effects of electrical stimulation. Intense electrical stimulation delivered to muscle not only activates motor axons but also engages an array of sensory axons including nociceptors. The associated sensory signals can provoke spinal reflexes and perhaps even descending inputs leading to unregulated contraction of agonists and antagonists, which in turn contaminates the force signals meant to detect the effect of electrical stimulation alone (Lagerquist *et al* 2009). Furthermore, subjects may not readily tolerate the pain associated with prolonged intense stimulation and investigators may avoid imposing such discomfort on human volunteers.

An additional possible reason relates to the fortuitous selection of the TA as the target muscle in the present study. The deep peroneal nerve supplying the TA arises as one of two main branches (the other being the superficial peroneal nerve) of the common peroneal nerve. From this bifurcation point, there typically is about a one centimeter span of the deep peroneal nerve before it gives rise to the first of multiple branches destined for the TA along ~20 cm of length of the nerve (Sunderland and Hughes 1946). This span of the nerve was targeted for stimulation in the present experiments. What is advantageous about this site is that it also carries axons supplying the two other ankle dorsiflexors, extensor hallucis longus and extensor digitorum longus. Therefore, stimulation at this site engaged all of the ankle dorsiflexors (as evidenced by toe extension as well as ankle dorsiflexion during nerve stimulation), just as would likely occur during voluntary dorsiflexion. Consequently, the total muscle mass involved in voluntary and nerve stimulation experiments was reasonably similar.

It should be noted, however, that the branching patterns of the peroneal nerves are highly variable across human cadaver specimens (Sunderland and Hughes 1946, Aigner *et al* 2004). For example, in six of 20 specimens, the first branch to the TA arose from the common peroneal nerve above its bifurcation to the deep and superficial nerves (Sunderland and Hughes 1946). Therefore, a portion of the TA would not have been activated with nerve stimulation in the present study in subjects with such a branching arrangement. In addition, the superficial peroneal nerve runs almost adjacent to the deep peroneal nerve in the region targeted for stimulation such that the distance between the centers of the two nerves may be as small as 5 mm (Aigner *et al* 2004). It is possible, therefore, that with increasing stimulus intensity during the fatigue task, some portion of the superficial peroneal nerve supplying the peroneus muscles, may have been activated. Indeed, in some subjects, we visually

observed contraction of the peroneus muscles during the later stages of the fatigue protocol involving nerve stimulation. Because the peroneus muscles contribute to ankle plantarflexion, their activation would tend to curtail dorsiflexion endurance time. Therefore, these two factors (possibility of not activating all nerve branches to TA and possibility of activating antagonists), may have limited the measured endurance time in response to nerve stimulation in some of the subjects.

The results of the nerve stimulation experiments also bear on fundamental questions related to the contribution of the central nervous system (CNS) to voluntary muscle fatigue. The observation that endurance time in some cases was longer with electrical stimulation than during voluntary contraction strongly suggests some degree of failure of the CNS to fully engage muscle during prolonged activity in those cases. There is a significant body of work that supports this contention and numerous mechanisms have been proposed to account for such fatigue-related impairment of CNS drive (see reviews by Gandevia (2001) and Taylor *et al* (2016)).

Finally, based on the findings of the present study, it would seem appropriate to consider using multiple stimulating electrodes (particularly for large muscles), and where possible, to stimulate the peripheral nerves supplying muscle for FES applications in paralyzed individuals. Of course, this must be weighed against the increased complexity of the control system and associated hardware, and added surgical challenges for implanted systems (Memberg *et al* 2014). For therapeutic interventions involving surface electrodes, using more than one active electrode would also seem beneficial. Indeed, the efficacy of interleaved stimulation among multiple surface electrodes suggests this to be the case (Malešević *et al* 2010, Nguyen *et al* 2011, Maneski *et al* 2013, Sayenko *et al* 2014, Downey *et al* 2015, Bergquist *et al* 2016, 2017, Laubacher *et al* 2017, Lou *et al* 2017). The results reported here and previously (Buckmire *et al* 2018) indicate that the improved fatigue resistance associated with interleaved stimulation is most likely related to the use of multiple electrodes (providing access to a greater volume of muscle) rather than the asynchronous activation induced by the interleaved protocol. Additional studies will need to be performed to determine the degree of improved fatigue resistance using multiple electrodes or nerve stimulation for a variety of tasks including intermittent contractions and different target forces. Likewise, it will be especially important to evaluate the degree of improved fatigue resistance in individuals with spinal cord injuries given the changes in fiber type composition and atrophy that often occur with paralysis. Nevertheless, we expect such an approach to increase both the strength and endurance of electrically evoked contractions and thereby enhance the capability of FES to restore movement in paralyzed individuals.

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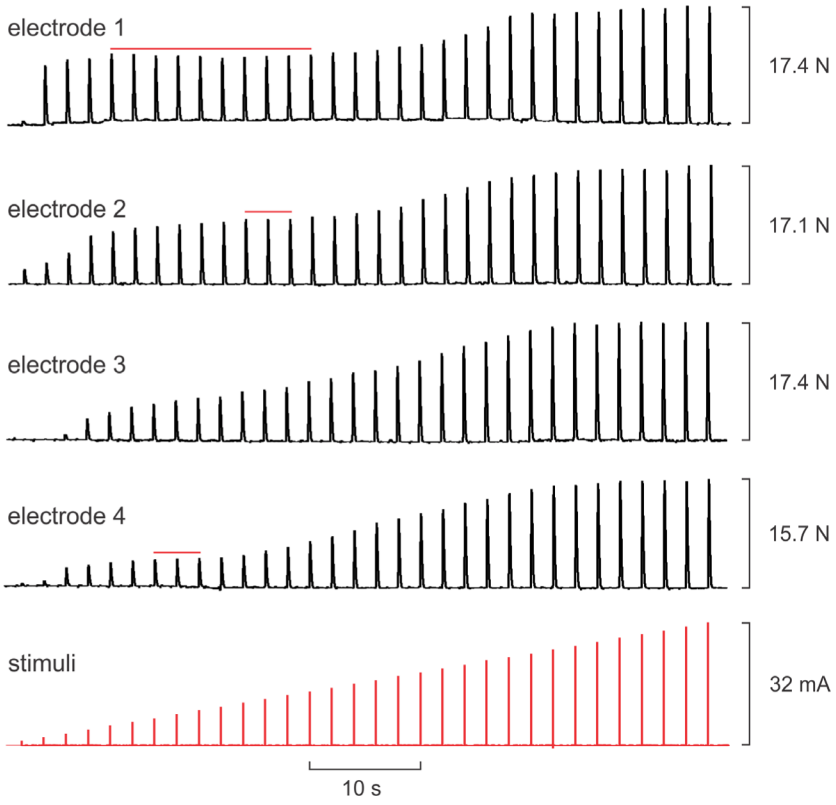

Figure 1.

Example dorsiflexion twitch force responses (upper four traces) to increasing stimulus current pulses (bottom trace) delivered through four intramuscular electrodes placed in different locations within tibialis anterior in one subject. Stimulation through each electrode was performed in separate trials but traces have been aligned for compact display. Red horizontal lines indicate intermediate plateaus wherein force saturated across a range of increasing stimulus intensities.

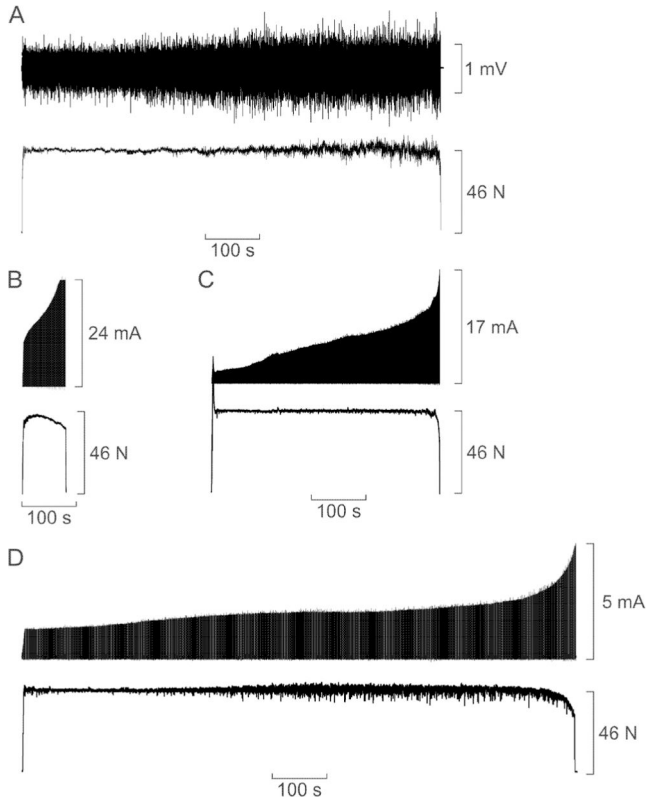

Figure 2.

Example force responses (bottom traces) recorded in a single subject during four sessions involving (A) voluntary contraction, (B) intramuscular stimulation of the tibialis anterior (TA) with a single electrode, (C) intramuscular stimulation of the TA with four electrodes, (D) stimulation of deep peroneal nerve. In (A), the top trace shows the surface EMG signal recorded from the TA. In (B)–(D), the top trace indicates the feedback controlled stimulus current delivered to the electrodes. In (C), only one of the four stimulus current signals is depicted for clarity. All four stimulus current signals associated with the trial shown in (C) increased exactly in parallel but the absolute values were different.

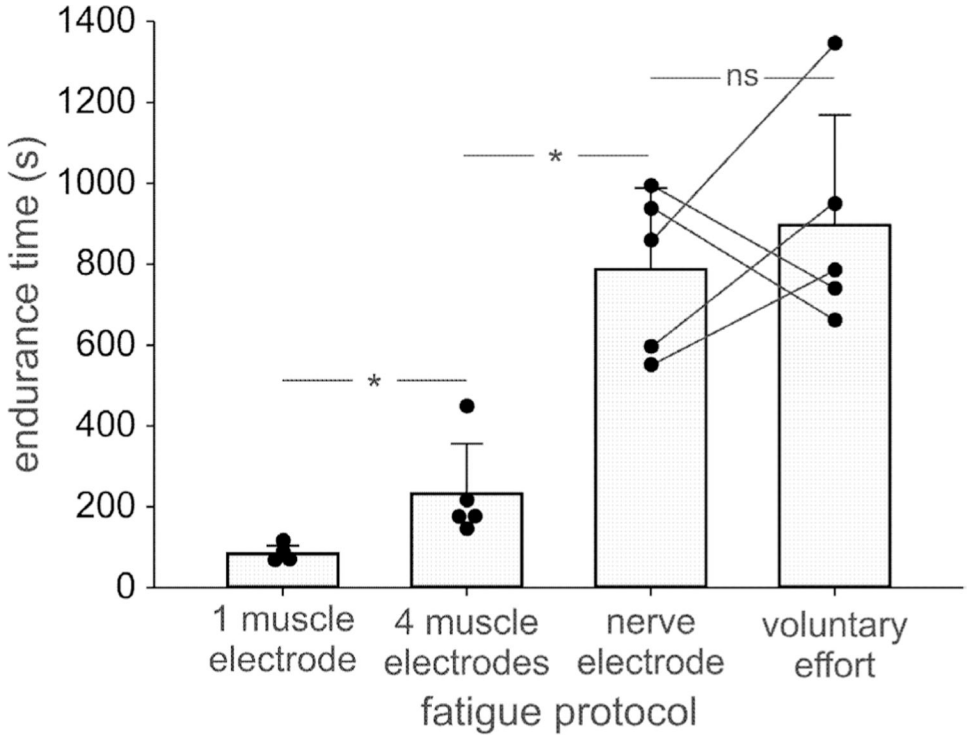

Figure 3.

Mean (SD) and individual values (dots) of endurance times of ankle dorsiflexion at a 20% MVC force target in response to feedback controlled stimulation of tibialis anterior with one or four intramuscular electrodes, feedback controlled stimulation of the deep peroneal nerve, or during voluntary contraction. ns—non-significant difference ($P = 0.46$). *—significant difference ($P < 0.01$).