Does increasing the number of channels during neuromuscular electrical stimulation reduce fatigability and produce larger contractions with less discomfort?

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Running Head: Multi-channel NMES: fatigability, torque, discomfort

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ABSTRACT:

Purpose: Neuromuscular electrical stimulation (NMES) recruits motor units (MUs) at unphysiologically high rates, leading to contraction fatigability. Rotating NMES pulses between multiple electrodes recruits different MUs from each site, reducing MU firing rates and fatigability. This study was designed to determine whether rotating pulses between an increasing number of stimulation channels (cathodes) reduces contraction fatigability and increases the ability to generate torque during NMES. A secondary outcome was perceived discomfort. **Methods:** Fifteen neurologically-intact volunteers completed 4 sessions. NMES was delivered over the quadriceps through 1 ($NMES_1$), 2 ($NMES_2$), 4 ($NMES_4$) or 8 ($NMES_8$) channels. Fatigability was assessed over 100 contractions (1s on/1s off) at an initial contraction amplitude that was 20% of a maximal voluntary contraction (MVC). Torque-frequency relationships were characterized over 6 frequencies from 20-120Hz. **Results:** $NMES_4$ and $NMES_8$ resulted in less decline in torque (42% and 41 %) and generated more torque over the 100 contractions than $NMES_1$ and $NMES_2$ (53% and 50% decline in torque). Increasing frequency from 20-120Hz increased torque by 7, 13, 21 and 24% MVC, for $NMES_1$, $NMES_2$, $NMES_4$ and $NMES_8$, respectively. Perceived discomfort was highest during $NMES_8$. **Conclusion:** $NMES_4$ and $NMES_8$ reduced contraction fatigability and generated larger contractions across a range of frequencies than $NMES_1$ and $NMES_2$. $NMES_8$ produced the most discomfort, likely due to small electrodes and high current density. During NMES, more is not better and rotating pulses between 4 channels may be optimal to reduce contraction fatigability and produce larger contractions with minimal discomfort compared to conventional NMES configurations.

KEYWORDS: functional electrical stimulation; neuromuscular electrical stimulation; sequential; motor unit; fatigability; evoked contractions; rehabilitation; muscle

DECLARATIONS:

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ABBREVIATIONS

SDSS - Spatially-distributed sequential stimulation

EMG – Electromyography

MU – Motor unit

MVC – Maximum voluntary contraction

NMES - Neuromuscular electrical stimulation

VAS – Visual analog scale

INTRODUCTION

Neuromuscular electrical stimulation (NMES) evokes contractions when pulses of current are applied through electrodes on the skin and it is used in diverse applications to enhance or maintain neuromuscular function (Sheffler and Chae 2007; Bickel et al. 2011). Long-term benefits of NMES-based programs after neurotrauma include reduced muscle atrophy and spasticity with increased muscle strength, bone mineral density and cardiovascular fitness (Bélanger et al. 2000; Davis et al. 2008; Griffin et al. 2009). For many applications the large knee-extensor muscles (quadriceps) are stimulated using a single channel comprising of two electrodes over the muscle belly, an “active” cathode and a “return” anode (Maffiuletti 2010; Bergquist et al. 2011). Due to the non-physiological way motor units (MUs) are recruited during this type of NMES, however, with superficial MUs discharging synchronously at high rates and in a non-physiological order, it can be difficult to produce contractions of sufficient amplitude and contractions fatigue rapidly (Barss et al. 2018). Contraction fatigability and the inability to produce sufficient torque limits the benefits of NMES programs by shortening the duration and intensity of NMES sessions (Kluger et al. 2013).

One way to reduce contraction fatigability during NMES is by rotating stimulation pulses between multiple electrodes. Rotating pulses between electrodes distributed over a muscle belly recruits MUs in different parts of the muscle sequentially, not synchronously, decreasing firing rates (Nguyen et al. 2011; Sayenko et al. 2014). This type of NMES has been given various names, the most descriptive of which may be spatially-distributed sequential stimulation (SDSS). SDSS reduces fatigability of contractions of tibialis anterior (Wiest et al. 2019) and the triceps surae (Nguyen et al. 2011) in neurologically intact participants and of the quadriceps in both neurologically intact participants (Bergquist et al. 2017; Laubacher et al. 2017) and those who

have experienced a spinal cord injury (Popović and Malešević 2009; Malešević et al. 2010; Nguyen et al. 2011; Laubacher et al. 2019). For SDSS approaches to work effectively, different pools of MUs must be recruited by each stimulation channel, with little if any overlap of MUs recruited by adjacent channels. Thus far the evidence suggests that to reduce contraction fatigability more NMES channels are better, however, little work has been done to determine how many channels are optimal.

The inability to produce sufficient torque during conventional NMES is another major barrier to its wide-spread use that SDSS may be able to address. During SDSS, when different MUs are recruited from each stimulation site, as the number of stimulation channels increases more MUs are recruited at lower frequencies to produce a given contraction amplitude. For example, to produce 20% of the torque produced during an MVC, conventional one-channel NMES delivered at 40 Hz might recruit 1000 MUs synchronously at 40 Hz, whereas to produce the same amount of torque four-channel SDSS delivered at 40 Hz might recruit 4000 MUs in 4 separate groups, each at 10 Hz. Thus, one limitation of conventional one-channel NMES is that it must be delivered at relatively high frequencies to produce sufficiently large contractions. The resulting high discharge rates place MUs at the high end of the curve that describes the relationship between torque and discharge frequency, leaving little if any room to increase torque with further increases in NMES frequency. As the number of stimulation channels increases, and MU firing rates decrease (see above), however, MUs shift progressively leftward on the torque-frequency curve, potentially leaving a much larger range over which NMES frequency can be used to modulate torque. Thus, as the number of NMES channels increases, there may be an opportunity to increase NMES frequency and generate larger contractions while keeping MU firing rates in their physiological range to minimize contraction fatigability. The relationship

between torque and NMES frequency when stimulating through multiple channels, however, has not been established.

Therefore, the primary purpose of this study was to determine the effect of rotating NMES pulses through an increasing number of NMES channels on contraction fatigability and the ability to generate torque across a range of frequencies. Given that discomfort plays a role in the clinical application of NMES (Fukuda et al. 2013) perceived discomfort was a secondary outcome measure. NMES was delivered over the quadriceps muscles through 1 ($NMES_1$), 2 ($NMES_2$), 4 ($NMES_4$) and 8 ($NMES_8$) channels and outcome measures were assessed over a series of intermittent isometric contractions of a fatigue protocol. We hypothesized that as the number of channels progressively increased, contraction fatigability would progressively decrease. Thus, we predicted that torque would decline the most during $NMES_1$ and would decline progressively less as the number of cathodes increased. We also hypothesized that increasing the number of channels would increase evoked torque across a range of stimulation frequencies. Thus, we predicted that when NMES frequency increased from 20-120 Hz torque would increase the least during $NMES_1$, with progressively greater increases in torque across the range of frequencies as the number of channels increased. The results of these experiments will help identify the optimal number of stimulation channels for NMES of the quadriceps muscles to generate large, fatigue-resistant, contractions with the least discomfort.

METHODS

Participants

Fifteen neurologically intact participants (5 women, 10 men; aged 28.5 ± 12.0 years, range 18-55 years) completed 4 sessions. A different type of NMES was tested in each session

and the order of sessions was randomised for each participant. Sessions lasted approximately 45 minutes and were separated by a minimum of 48 hours. Participants provided informed written consent and procedures were approved by the University of Alberta Research Ethics Board.

Torque

Isometric knee extension torque produced by the right leg was measured while participants sat in the chair of a Biodex dynamometer (System 3, Biodex Medical Systems, Shirley, New York, USA). The leg was secured to maintain a knee angle of ~100º and the fibular head was aligned with the axis of the dynamometer.

Neuromuscular Electrical Stimulation (NMES)

A constant current DS7AH stimulator (Digitimer, Welwyn Garden City, UK) was used to deliver one ms square wave pulses of current through self-adhesive electrodes (Large 2"x 4" and Small 2"x 2"; UltraStim; Axelgaard Manufacturin Co., Fallbrook, CA, USA) over the quadriceps. A custom-built system was used to distribute stimulus pulses to the appropriate electrode pairs. $NMES_1$, $NMES_2$, $NMES_4$, and $NMES_8$ were delivered through 1, 2, 4 or 8 active electrodes (cathodes), respectively, as shown in Figure 1A. These configurations are described below and were chosen based on the results of pilot studies designed to reduce fatigability by recruiting different MUs with each cathode.

For all configurations one large electrode was placed~2-4 cm from the proximal edge of the patella centered over the midline of the quadriceps and another~3-5 cm from the inguinal crease centered over the midline of the quadriceps. $NMES_1$: One large cathode was placed near the hip and one large anode was placed near the knee as described above. $NMES_2$: Same

configuration as for $NMES_1$ although the anode and the cathode alternated between electrodes 1 and 2 with every other pulse. $NMES_4$: Four large cathodes were placed in a rectangular pattern in the middle of the thigh (electrodes 1-4), between anodes (electrodes A and B). The proximal cathodes (1 and 3) were paired with the distal anode (A) and the distal cathodes (2 and 4) were paired with the proximal anode (B). Stimulus pulses were rotated sequentially through the numbered electrodes shown in Figure 1A. $NMES_8$: Due to space limitations on the thigh large electrodes could not be used, thus small cathodes were placed in a 2x4 array (1-8) between the anodes (A and B). Pulses were rotated sequentially through electrode pairs as shown in Figure 1A with proximal cathodes (1, 3, 5, and 7) being paired with the distal anode (A) and the distal cathodes (2, 4, 6, and 8) being paired with the proximal cathode (B). Skin was prepared using alcohol swabs before placement of the electrodes. Current was measured with a current probe from channel 1 during all trials (mA- 2000, F.W. Bell).

General Protocol

As shown in Figure 1B, each session began with maximal voluntary contractions (MVCs) followed by collection of data to generate the torque-frequency curves. Participants then completed the fatigue protocol followed by another MVC (details described below).

Maximal Voluntary Contractions (MVCs)

Participants performed isometric knee extension MVCs for 2-3s with verbal encouragement and visual feedback of torque provided throughout. Each participant performed 2 MVCs separated by a minimum of 1 minute with a 3rd MVC being completed if the first 2 varied by more than 10%. The MVC that elicited the most torque was used to normalize all

subsequent torque measurements. Another MVC was performed within one minute after the fatigue protocol. Torque recorded during MVCs was quantified as the average torque over a 0.3 s window centered on the peak.

Torque-Frequency Relationships

The relationship between torque and frequency was characterized for each NMES configuration. One second trains (n=2) of each type of NMES were delivered at 20, 40, 60, 80, 100, and 120 Hz at an intensity that generated 20% MVC at 40 Hz. Trains were separated by at least 5 seconds and the order of the 12 stimulation trains for each configuration was randomised for each participant. Peak torque was calculated over a 10 ms window centered around the peak and was normalized to each participants' MVC. Perceived discomfort was assessed during the first contraction of each frequency. Discomfort scores were provided verbally by the participant using a Visual Analogue Scale (VAS) with endpoints ranging from 0 (no pain) to 100 (worst pain imaginable).

Fatigue Protocol

For each fatigue protocol NMES was delivered at 40 Hz to evoke 100 contractions using a 1 second on, 1 second off duty cycle. Stimulus intensity was adjusted to generate contractions that produced 20% MVC torque at the beginning of the fatigue protocol. Two measures of contraction amplitude were used; Peak torque was calculated as described above (see *Torque-frequency Relationships*) and the torque-time integral (TTI) was calculated as the area under the torque versus time curve for each contraction. All data were averaged into bins representing 10 successive contractions, resulting in a total of 10 bins. Fatigability was assessed using five

outcome measures: 1) percent decline in mean torque from bin 1 to bin 10, 2) percent decline in TTI from bin 1 to bin 10, 3) mean torque across all 100 contractions, 4) mean TTI across all 100 contractions and, 5) percent decline in MVC torque from before to after the fatigue protocols. Discomfort scores were recorded (as described above) during the 5th, 50th and 100th contractions. Current (in mA) was also measured and current density was calculated based on electrode area.

Data Acquisition

Data were acquired using custom written LabVIEW software (National Instruments, Austin, Texas) sampled at 2000 Hz and stored for later analyses using MATLAB (The Mathworks, Natick, Massachusetts) custom-written software.

Statistical analyses

Statistical analyses were conducted on group data. To compare fatigability between NMES configurations, the five outcome measures were tested using separate 1 x 4 (NMES configuration; $NMES_1$, $NMES_2$, $NMES_4$, $NMES_8$) analyses of variance (ANOVAs). To compare torque across frequencies (20-120 Hz), a 4 (NMES configuration) x 6 (Frequency) rmANOVA was performed. Differences in perceived discomfort during the fatigue protocols were determined using a 3 (Time; beginning, middle, end) x 4 (NMES type) rmANOVA. Differences in perceived discomfort across frequencies (20-120 Hz) were determined using a 4 (NMES configuration) x 6 (Frequency) rmANOVA. To assess differences in current and current density separate 1 x 4 (NMES configuration) ANOVAs were performed. For all ANOVAs, significant interactions were followed by separate analyses for each factor followed by pairwise comparisons using a Bonferroni correction for multiple comparisons. A *p*-value of less than 0.05

was considered statistically significant. All data are reported as mean ± sd. For brevity, only significant results are presented in the Results section and values are included in either text or figures without duplication.

RESULTS

Single participant data

Torque recorded from a single participant during all contractions of each fatigue protocol are shown in Figure 2A and these data, binned over 10 successive contractions, are replotted in Panel B. Over the course of the fatigue protocol for this participant, torque declined by 44%, 46%, 38%, and 32% (from bin 1 to bin 10) during $NMES_1$, $NMES_2$, $NMES_4$, and $NMES_8$, respectively.

Group data

Contraction Fatigability

Figure 3A shows torque recorded during the fatigue protocols, binned and averaged across participants, for each NMES configuration. There were no significant differences in peak torque ($F_{(3, 42)} = 0.414$, $p = 0.744$) or TTI ($F_{(3, 42)} = 0.709$, $p = 0.522$) over the first ten contractions of the fatigue protocol (i.e. Bin 1) between any of the NMES configurations. The average initial peak torque and TTI was 18.9% MVC and 11.3% MVC·s, respectively. There was, however, a significant main effect of NMES configuration both for the percent decline in peak torque ($F_{(3, 42)} = 8.070$, $p < 0.001$) and TTI ($F_{(3, 42)} = 9.899$, $p < 0.001$). Both peak torque (Figure 3B) and TTI (Figure 3C) declined significantly more from bin 1 to bin 10 when using $NMES_1$ and $NMES_2$ compared to $NMES_4$ and $NMES_8$. There was also a significant main effect of NMES

configuration for average peak torque ($F_{(3, 42)} = 9.789$, $p < 0.001$) and TTI ($F_{(3, 42)} = 9.670$, $p < 0.001$). Consistent with percent decline data in panels B and C, there was significantly less mean torque across the entire fatigue protocol when using $NMES_1$ and $NMES_2$ compared to $NMES_4$ and $NMES_8$ (panel D). A similar result was obtained for the mean TTI across the fatigue protocol, with the exception that $NMES_8$ was not significantly different from $NMES_2$ (panel E). There were no significant differences in the amount that torque produced during MVCs declined from before to after the fatigue protocols between NMES configurations ($F_{(3,42)} = 0.205$, $p=0.892$; data not shown). The average decline in MVC torque across NMES configurations was 11±6 %.

Torque-Frequency Relationships

Mean torque averaged across participants when each NMES configuration was delivered across a range of frequencies is shown in Figure 4A. There was a significant interaction between NMES configuration and NMES frequency ($F_{(15, 210)} = 49.9$, $p<0.001$). To test for differences between NMES configurations at each frequency, separate one-way ANOVAs were run within each frequency and significant main effects of NMES configuration were identified at 20 Hz ($F_{(3, 42)} = 52.1$, $p<0.001$), 60 Hz ($F_{(3, 42)} = 24.1$, $p<0.001$), 80 Hz ($F_{(3, 42)} = 37.6$, $p<0.001$), 100 Hz ($F_{(3, 42)} = 35.3$, $p<0.001$) and 120 Hz ($F_{(3, 42)} =28.2$, $p<0.001$). All significant differences in pairwise comparisons for each frequency of NMES are shown in the lower portion of 4A. To summarise, $NMES_4$ and $NMES_8$ evoked more torque than $NMES_1$ and $NMES_2$ at all frequencies above 40 Hz ($p<0.05$), torque was only different between $NMES_4$ and $NMES_8$ at 100 Hz and 120 Hz ($p<0.05$) and torque was only different between $NMES_1$ and $NMES_2$ at 120 Hz ($p<0.05$).

To test for differences between frequencies within each NMES configuration, separate

one-way ANOVAs were run within each NMES configuration and these identified significant main effects of frequency for all configurations; $NMES_1$ ($F_{(5, 70)}$ = 75.9, p<0.001), $NMES_2$ ($F_{(5, 70)}$ = 141.3, p<0.001), $NMES_4$ ($F_{(5, 70)}$ = 249.3, p<0.001) and $NMES_8$ ($F_{(5, 70)}$ = 81.7, p<0.001), as shown in Figure 5A. For $NMES_1$ and $NMES_2$, torque reached a steady-state at 80 Hz, as torque produced at 80, 100 and 120 Hz was not significantly different (p>0.05). For $NMES_4$ and $NMES_8$, torque reached a steady-state at 100 Hz (p>0.05). The inset in Figure 4A shows the range over which torque increased as NMES frequency increased from 20-120 Hz for each configuration. There was a significant main effect of NMES configuration ($F_{(3,42)}$ = 67.347, p<0.001) and post-hoc tests showed that when NMES frequency increased from 20-120 Hz, torque increased the least during $NMES_1$ (7% MVC) , followed by $NMES_2$ (13% MVC), and torque increased the most during $NMES_4$ and $NMES_8$ (21 and 24% MVC, respectively), which were not different from each other (p=0.072).

Perceived discomfort

Current, current density and discomfort during the fatigue protocols

There were significant differences in current used during the fatigue protocols between NMES types ($F_{(3,42)}$ = 6.893, p=0.003) as shown in Figure 5A. Significantly more current was needed to generate the target 20% MVC contraction when using $NMES_1$ than $NMES_4$ (p=0.01) and $NMES_8$ (p=0.049). There were also significant differences in current density between NMES configurations ($F_{(3,42)}$ = 54.6, p<0.001). Current density was higher during $NMES_8$ than all other NMES configurations ($p \leq 0.001$) and was higher during $NMES_1$ than $NMES_4$ (p=0.001) as shown in Figure 5B.

There was no significant interaction between Time and NMES configuration for

discomfort during the fatigue protocols ($F_{(6, 84)}$ = 2.184, *p*=0.103) and no main effect of Time ($F_{(2,28)}$ = 2.128, *p*=0.138) although there was a significant main effect of NMES configuration ($F_{(3, 42)}$ = 9.916, *p*=0.001). Pooled across the fatigue protocol, $NMES_8$ (40.4±20.9) resulted in significantly greater ratings of perceived discomfort than the other configurations (*p*<0.001) as shown in Figure 5C.

Discomfort across frequencies

Mean perceived discomfort scores recorded when the different NMES configurations were delivered from 20-120 Hz are shown in Figure 4B. There was a significant interaction between NMES type and frequency ($F_{(15, 195)}$ = 49.9, *p*=0.002) and subsequent one-way ANOVAs conducted to test for differences between configurations at each frequency identified significant main effects of NMES configuration at 80 ($F_{(3, 39)}$ = 3.759, *p*=0.018), 100 ($F_{(3, 39)}$ = 4.291, *p*<0.010) and 120 Hz ($F_{(3, 39)}$ =5.704, *p*=0.002). As shown in the bottom portion of Figure 4B, there were no differences in discomfort between $NMES_1$, $NMES_2$ and $NMES_4$ at any frequency (*p*>0.05). However, there was significantly more discomfort during $NMES_8$ at 80 Hz and 100 Hz compared to the other configurations (*p*<0.05) and at 120 Hz, $NMES_8$ produced more discomfort than $NMES_1$, $NMES_2$ (*p*<0.05).

Four 1 x 6 (Frequency) ANOVAs were run to test for an effect of frequency within each NMES configuration and they indicated significant main effects of frequency for all configurations; $NMES_1$ ($F_{(5, 65)}$ = 4.661, *p*=0.001), $NMES_2$ ($F_{(5, 65)}$ = 4.402, *p*=0.002), $NMES_4$ ($F_{(5, 65)}$ = 12.587, *p*<0.001) and $NMES_8$ ($F_{(5, 65)}$ = 10.878, *p*<0.001). Post hoc analyses showed that discomfort was not significantly different between any two frequencies for $NMES_1$ and $NMES_2$ (*p*>0.05). For $NMES_4$, discomfort scores increased from 20 to 40 Hz and then reached a

steady state as there were no differences in discomfort between 40-120 Hz (p>0.05). During $NMES_8$, discomfort increased up to 80 Hz and then reached a steady state. (p>0.05).

DISCUSSION

This study was designed to investigate the effect of rotating NMES pulses between an increasing the number of stimulation channels (cathodes) on contraction fatigability, the relationship between torque and NMES frequency and discomfort. Although contraction fatigability did not decrease progressively as the number of cathodes increased, there was significantly less fatigability when using more cathodes ($NMES_4$ and $NMES_8$) than fewer cathodes ($NMES_1$ and $NMES_2$). Similarly, the amount of torque generated across a range of NMES frequencies did not increase progressively as the number of cathodes increased, however, the number of cathodes clearly influenced the relationship between torque and NMES frequency and in general more cathodes produced more torque, particularly at the higher NMES frequencies. Finally, $NMES_8$ caused the most discomfort, likely due to higher current density. These results help establish the relationship between number of NMES channels and these important outcome measures and suggest that delivering SDSS through 4 cathodes may be optimal for reducing contraction fatigability of the quadriceps and producing large contractions with minimal discomfort.

Fatigability

Contrary to our hypothesis, contraction fatigability did not decrease progressively as the number of channels increased. Instead, contraction fatigability decreased when stimulus pulses were rotated between 4 or 8 cathodes ($NMES_4$ and $NMES_8$), compared to delivering pulses

through a single fixed cathode ($NMES_1$) or alternating anode and cathode back and forth between two electrodes ($NMES_2$). These differences in fatigability were evidenced by less decline in torque and, on average, more torque over the 100 contractions of the fatigue protocols when using $NMES_4$ and $NMES_8$ versus $NMES_1$ and $NMES_2$. SDSS has been shown previously to reduce contraction fatigability for contractions of tibialis anterior (Wiest et al. 2019), triceps surae (Nguyen et al. 2011) and quadriceps (Bergquist et al. 2017; Laubacher et al. 2017; Popović and Malešević 2009; Malešević et al. 2010; Nguyen et al. 2011; Laubacher et al. 2019). The reduced fatigability is thought to be due to reduced MU firing rates, afforded by the recruitment of different pools of MUs from each spatially-distributed cathode (Nguyen et al. 2011; Sayenko et al. 2014). However, in the present study there was no improvement in fatigability when doubling the number of cathodes from 1 to 2 ($NMES_1$ to $NMES_2$) or from 4 to 8 ($NMES_4$ to $NMES_8$). This lack of improvement in fatigability contrasts with improvements gained when doubling the number of channels from 1 to 2 when stimulating tibialis anterior to dorsiflex the ankle(Lou et al. 2017), and may be accounted for by the electrode configurations used in the present study. The locations of the two electrodes used to deliver $NMES_1$ and $NMES_2$ were identical, the only difference being that anode and cathode were "fixed" during $NMES_1$, and were alternated between the two electrodes during $NMES_2$. Thus, the path for current flow was the same during both protocols, and despite alternating the cathode between electrodes, $NMES_2$ may have recruited the same MUs with each pulse, effectively rendering $NMES_1$ and $NMES_2$ equivalent in terms of MU discharge rates and contraction fatigability. Accordingly, approaches that alternate anode and cathode between the same two electrodes may not be effective to reduce contraction fatigability. Similarly, configurations for $NMES_4$ and $NMES_8$ occupied the same area on the thigh and, other than number of cathodes, the difference for $NMES_8$ was that the

electrodes were half the size as for the other configurations. Thus, during $NMES_8$ there was likely a high overlap of MUs recruited by adjacent cathodes, effectively making adjacent pairs a single electrode and thus $NMES_4$ and $NMES_8$ equivalent in terms of MU discharge rates and fatigability. Together the present results suggest that for reducing contraction fatigability of the quadriceps, alternating anode and cathode between the same electrodes is not sufficient to reduce contraction fatigability, instead, an SDSS approach may be best and presently we show that rotating pulses through 4 or 8 cathodes is equally effective and better than 1 or 2.

Torque-frequency relationships

Contrary to our hypothesis, increasing the number of cathodes did not progressively increase the amount of torque produced over a range of NMES frequencies, although the number of cathodes clearly influenced the relationship between torque and frequency. When NMES frequency increased from 10–120 Hz, torque increase 7, 13, 21 and 24% MVC using $NMES_1$, $NMES_2$, and $NMES_4$ and $NMES_8$ (which were not different), respectively. $NMES_4$ and $NMES_8$ evoked more torque than $NMES_1$ and $NMES_2$ at all frequencies above 40 Hz and further differences between configurations emerged at the highest NMES frequencies. $NMES_8$ produced more torque than $NMES_4$ at 100 and 120 Hz and $NMES_2$ generated more torque than $NMES_1$ at 120 Hz. Thus, at the highest frequency tested (120 Hz), torque increased progressively with the number of cathodes, consistent with our hypothesis. The differences that emerged between configurations at the highest frequencies suggest there are subtle differences how MUs are recruited between these configurations but they are not sufficient to measurably influence contraction fatigability.

We propose that the differences in torque-frequency relationships between configurations

are due to recruiting more MUs, at progressively lower rates, as number of channels increase. The lower firing rates place MUs progressively leftward on their torque-frequency curves. Thus, as the number of channels increase, there is a wider range over which increases in NMES frequency produce increases in torque. The ability of SDSS to reduce MU firing rates, while still being delivered at sufficiently "net" frequencies to produce large contractions, provides a unique opportunity to remove two of the main impediments to the widespread use of NMES, contraction fatigability and the inability to produce sufficiently large contractions.

Current and discomfort

Although significantly less current was required to evoke the target contractions of 20% MVC when rotating pulses between 4 or 8 cathodes ($NMES_4$ and $NMES_8$), than when stimulating through a single fixed cathode ($NMES_1$), the smaller electrode size necessitated when using 8 cathodes resulted in significantly higher current density than the other three configurations. This higher current density corresponded to the highest ratings of perceived discomfort for $NMES_8$ during the fatigue protocols and at the higher NMES frequencies used to generate the torque-frequency curves. These results are consistent with previous work indicating that higher current densities increase discomfort during NMES (Alon 1985; Patterson and Lockwood 1991; Maffiuletti 2010). Smaller electrodes were required during $NMES_8$ due to limitations in space over the quadriceps which poses a limitation moving forward with higher channel numbers and for smaller muscles as discomfort limits the use of NMES (Barss et al. 2018). Of note, however, is that SDSS through 4 cathodes has proven to reduce contraction fatigability for contractions of tibialis anterior, a muscle with markedly less surface area for stimulation (Wiest et al. 2019). Considering that fatigability was similar between $NMES_4$ and

$NMES_8$ but discomfort during $NMES_4$ was less than $NMES_8$ and was not different than $NMES_1$ and $NMES_2$, $NMES_4$ may provide most clinically meaningful balance between reducing both fatigability and discomfort.

Applications, limitations, and future directions

Rotating stimulus pulses between multiple channels over a muscle during NMES provides a readily translatable advancement to improve outcomes of NMES-based programs and reduce secondary complications that stem from inactivity. Despite the potential for further refinements (see below), four-channel SDSS, as described in this and other studies (Nguyen et al. 2011; Sayenko et al. 2014; Bergquist et al. 2017; Wiest et al. 2019), produces larger and more fatigue-resistant contractions than conventional NMES and could be relatively-easily incorporated into NMES-based programs. Indeed, 4-channel SDSS over the quadriceps enables individuals with a complete spinal cord injury to cycle 3x longer than when using conventional NMES (Barss TS, *unpublished observation*). Future research involving longitudinal training studies is needed to determine the extent to which SDSS improves relevant musculoskeletal and cardiovascular outcomes of NMES-based programs compared to conventional NMES approaches.

Although the electrode configurations used in the present study were based on pilot experiments designed to identify configurations that reduced contraction fatigability by minimizing MU overlap between adjacent electrodes, the configurations chosen may not be optimal. Accordingly, further exploration to identify optimal electrode number and configuration will be important to maximise the potential of SDSS. The optimal configuration will be the one that maximises MU recruitment (i.e. recruits the highest percentage of MUs in the target muscle)

and minimises overlap of MUs recruited by adjacent electrodes. Randomising the order of stimulation between channels, changing the placement of the anode, rotating anode-cathode pairs, and orienting channels to target separate MUs to decrease overlap all remain as potential strategies to reduce contraction fatigability, reduce discomfort and increase evoked torque.

SDSS offers a unique opportunity to maintain low MU discharge rates, by delivering stimulus pulses to each channel at relatively low frequencies ("net" frequency / number of channels), while still generating large contractions, as the forces generated by separate pools of MUs recruited by each channel sum at the tendon at the net frequency of stimulation. For example, discomfort issues aside, delivering $NMES_8$ at 120 Hz would take advantage of the opportunity to generate large contractions, due to the high "net" frequency, while still maintaining MU firing rates within their physiological range with pulses delivered at 15 Hz to each channel. Indeed, had each type of NMES been delivered at a net frequency of 120 Hz for the fatigue protocols in the present study there may have been a markedly greater effect of channel number on fatigability. Future research is needed to identify the optimal frequency for SDSS that provides a compromise between the high frequencies needed to generate large contractions and the low frequencies that minimise fatigability. It may be that different frequencies are optimal for different applications or even at different times within a given setting. The high net frequencies that are feasible during SDSS, while still minimizing contraction fatigability, may also have the added benefit of sending a relatively large neuromodulatory signal to the central nervous system, by the stimulation of sensory axons, which may promote beneficial neuroplasticity within central nervous system.

Conclusions

Rotating NMES pulses between an increasing number of cathodes over the quadriceps muscles did not progressively reduce contraction fatigability or increase the ability to generate torque across a range of frequencies. Rotating pulses between 4 or 8 cathodes did, however, reduce contraction fatigability and generate more torque across frequencies than when using 1 or 2 cathodes. Delivering NMES through 8 cathodes required smaller electrodes than for the other configurations which increased current density and perceived discomfort. Thus, during NMES, more stimulation channels are not necessarily better, and rotating pulses between 4 cathodes may be optimal to minimize contraction fatigability and generate large contractions with minimal discomfort.

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Figure legends

Figure 1. Electrode placements and experimental protocol. Panel **(A)** shows the placement of electrodes over the quadriceps where letters represent anodes and numbers represent cathodes. Stimulus pulses were delivered to cathodes sequentially in the numerical order represented on the diagram. During $NMES_2$, the cathode (and anode) alternated between positions 1 and 2 with each pulse. During $NMES_4$, proximal cathodes (1, 3) were paired with anode A and distal cathodes (2, 4) were paired with anode B. Similarly, during $NMES_8$, proximal cathodes (1, 3, 5, 7) were paired with anode A and distal cathodes (2, 4, 6, 8) were paired with anode B. Panel **(B)** shows the timeline of the protocol used for each experiment divided into PRE, FATIGUE and POST phases. Torque recorded during the first 10 (Bin 1) and last 10 (Bin 10) contractions of a fatigue protocol are shown for a representative participant in Panel **(C)**.

Figure 2. Data recorded one participant during the fatigue protocols. Panel **(A)** shows torque recorded during all 100 contractions of each fatigue protocol. These data are also shown in Panel **(B)** where the mean torque during each contraction was averaged over 10 successive contractions to form 10 bins for each NMES configuration.

Figure 3. Group data recorded during the fatigue protocols and associated measures of contraction fatigability. Panel **(A)** shows torque recorded during the fatigue protocols using each configuration, binned and averaged across participants. Percent change in mean torque and the torque-time integral (TTI) from the first 10 contractions (bin 1) to the last 10 contractions (bin 10) of the fatigue protocols, are shown in panel **(B)** and panel **(C)**, respectively. Average torque **(D)** and TTI (**E**) calculated over the 10 bins. Significant differences are indicated by the

pound symbols (#). Open circles represent data from individual participants. Data are presented as mean ± SD.

Figure 4. Group data showing torque-frequency and discomfort-frequency relationships for each NMES configuration. Panel **(A)** shows torque produced when each NMES configuration was delivered at frequencies from 20 Hz to 120 Hz. The dagger symbol (†) indicates the frequency at which torque produced by $NNMES_4$ and $NMES_8$ was not different than torque that each produced at 120 Hz. Double daggers (‡) indicate the frequency at which torque produced by $NMES_1$ and $NMES_2$ was not different than that each produced at 120 Hz. Comparisons between configurations at each a frequency are shown below the x axis below their corresponding frequency. In these graphs the pound symbol (#) denotes significant differences as indicated and asterisks (*) denote a significant difference from all other configurations. The inset in the top left corner shows the increase in torque produced by each configuration when NMES frequency increased from 20-120 Hz. Panel **(B)** shows perceived discomfort assessed at each frequency using a Visual Analogue Scale (VAS). Double daggers († †) indicate the frequency at which VAS scores for $NMES_8$ were not different than scores at 120 Hz and the four daggers (‡‡) indicate the frequency at which VAS scores for $NMES_4$ were not different than scores that at 120 Hz. Comparisons between configurations at each a frequency are shown below the x axis in the same format as for Panel A. In both panels data are presented as mean ± SD.

Figure 5. Group data showing current, current density and perceived discomfort during the fatigue protocols. Panel **(A)** shows the mean current and Panel **(B)** shows the current density used to generate the contractions for the fatigue protocols using each NMES configuration. VAS

scores in Panel **(C)** represent the pooled mean of scores from the 5th, 50th and 95th contractions of the fatigue protocols for each participant. Pound symbols (#) denote significant differences as indicated and asterisks (*) denote significant differences from all other configurations. Open circles represent data from individual participants. Data are presented as mean ± SD.