H-REFLEXES REDUCE FATIGUE OF EVOKED CONTRACTIONS AFTER SPINAL CORD INJURY

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Accepted 6 December 2013

ABSTRACT: *Introduction:* Neuromuscular electrical stimulation (NMES) over a muscle belly (mNMES) generates contractions predominantly through M-waves, while NMES over a nerve trunk (nNMES) can generate contractions through H-reflexes in people who are neurologically intact. We tested whether the differences between mNMES and nNMES are present in people with chronic motor-complete spinal cord injury and, if so, whether they influence contraction fatigue. *Methods:* Plantarflexion torque and soleus electromyography were recorded from 8 participants. Fatigue protocols were delivered using mNMES and nNMES on separate days. *Results:* nNMES generated contractions that fatigued less than mNMES. Torque decreased the least when nNMES generated contractions, at least partly through H-reflexes ($n = 4$ participants; 39% decrease), and torque decreased the most when contractions were generated through M-waves, regardless of NMES site (nNMES 71% decrease, $n = 4$; mNMES, 73% decrease, $n = 8$). *Conclusions:* nNMES generates contractions that fatigue less than mNMES, but only when H-reflexes contribute to the evoked contractions.
Muscle Nerve **50**: 224–234, 2014

Neuromuscular electrical stimulation (NMES) can generate contractions for people who have had a spinal cord injury (SCI).[1] Such contractions can reduce muscle and bone atrophy,[2] assist activities of daily living, and provide opportunities for exercise.[3] Unfortunately, rapid contraction fatigue limits the effectiveness of NMES for these applications.[4–6] Much of this fatigue is thought to be due to the nonphysiological way in which NMES recruits motor units (MUs).[5,7,8] We report experimental evidence in people with SCI to support the oft-cited idea[9–16] that the nonphysiological MU recruitment *order* is responsible for much of the fatigue that occurs during NMES.

During voluntary contractions, MUs are recruited by means of *central* pathways by descending commands from the brain and by means of reflex pathways from sensory receptors. Accordingly, MUs are recruited according to the Henneman size principle, with fatigue-resistant units recruited first.[17] In contrast, during NMES, MUs are typically recruited by means of a *peripheral* pathway, from the NMES site to the muscle, due to activation of motor axons beneath the stimulating electrodes. Recruitment through this peripheral pathway generates a motor- or M-wave in the electromyographic (EMG) signal,[8] and recruitment is random with respect to MU type.[15,16,18,19] The difference in recruitment order between voluntary and NMES-evoked contractions results in NMES recruiting relatively fewer fatigue-resistant MUs than voluntary contractions of similar amplitude, which is thought to be a main reason why NMES-evoked contractions fatigue rapidly.[5,7,8]

We have suggested that a way to reduce contraction fatigue during NMES is to maximize the electrically evoked sensory volley, thereby increasing synaptic drive to the motor pool[20–22] to recruit MUs according to the size principle.[11,23] During NMES, the discharge of MUs recruited through reflex, or central, pathways can be synchronous with each NMES pulse, in which case it is measured as a Hoffmann- or H-reflex in the EMG signal.[20,24] MUs recruited through central pathways can also discharge asynchronously from the NMES pulses[20,25,26]; however, whether such activity contributes to contractions during NMES in people with SCI is not known. In people who are neurologically intact, the extent to which contractions are generated through peripheral and central pathways depends on where NMES is delivered. For both the ankle plantar flexors[20] and knee extensors,[27] NMES over the muscle belly (mNMES) generated contractions predominantly through peripheral pathways (M-waves), while NMES over the nerve trunk (nNMES) generated contractions with robust contributions through central, predominantly H-reflex, pathways.

The experiments we report here build on this previous work.[20,27] Our first goal was to determine whether the differences in how mNMES and nNMES generate contractions in people who are neurologically intact are also present in people with chronic motor-complete SCI. The second goal

Abbreviations: AIS, American spinal injury association impairment scale; ANOVA, analysis of variance; EMG, electromyography; H-reflex, Hoffmann reflex; M-H, M-wave-H-reflex; M-wave, motor wave; M_{max}, maximal evocable M-wave; mNMES, NMES over the triceps surae muscle belly; MU, motor unit; NMES, neuromuscular electrical stimulation; nNMES, NMES over the tibial nerve trunk; PTT, peak twitch torque; rmANOVA, repeated measures ANOVA; SCI, spinal cord injury

Key words: electrical stimulation; M-wave; motor unit; recruitment; size principle

This work was supported by an Alberta Paraplegic Foundation PhD Studentship (A.J.B.), a University of Alberta PhD Dissertation Scholarship (A.J.B.), a University of Alberta PhD Recruitment Scholarship (M.J.W.), a Science without Boarders Scholarship - CNPq (M.J.W.) and the University of Alberta Centre for Neuroscience (Y.O.).

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Published online 12 December 2013 in Wiley Online Library (wileyonlinelibrary.com). DOI 10.1002/mus.24144

Table 1. Participant demographics.*

Code/ sex	Age	Years after SCI	Level of SCI	AIS*	Baclophen (mg/day)	H-reflex
1W	33	10	C 4–5	B	0	Yes
2M	58	5	C 6–7	B	0	Yes
3M	42	24	C 5–6	B	0	No
4M	29	11	C 5–7	B	80	Yes
5M	35	7	C 5	A	80	No
6M	45	4	T 4	A	40	No
7M	62	18	C 4–5	B	0	No
8M	25	3	C 5–6	B	80	Yes

American spinal injury association impairment scale.

was to determine whether contraction fatigue is reduced using nNMES compared with a more traditional approach using mNMES. We hypothesized: (1) that contractions evoked by mNMES would have smaller H-reflexes but more asynchronous MU activity compared with nNMES[20] and (2) that contraction fatigue, defined as a significant reduction in torque over repeated contractions,[28] would occur sooner (after fewer contractions in a fatigue protocol) and would be greater (less torque by the end of a fatigue protocol) during mNMES than nNMES. The ankle plantar flexors were studied, because these muscles are important for standing and walking, and there is interest in stimulating them in people with SCI.[1,29–31] Furthermore, we have demonstrated that there is a robust central contribution to contractions evoked by nNMES, but not by mNMES, of the plantar flexors in people who are neurologically intact.[20]

MATERIALS AND METHODS

Participants. Eleven participants with chronic (>2 years) motor-complete (American spinal injury association impairment scale A or B) SCI volunteered for this study after providing informed written consent (Table 1). None of the participants had experience with NMES of the plantar flexors. It was not possible to elicit a contraction during NMES in 3 of 11 participants. Thus, we report data from the 8 participants in whom we were able to generate contractions (Table 1). All participants took part in 2 sessions, each lasting ~2 h and separated by at least 5 days. A fatigue protocol delivered using mNMES or nNMES was tested in different sessions, the order of which was randomized for each participant. All procedures were performed on the right leg. Participants were secured comfortably in the chair of a Biodex dynamometer (System 3, Biodex Medical Systems, Shirley, New York) to measure isometric plantar flexion torque. The right foot was strapped to the Biodex footplate with the hip at ~110°, the knee at ~90°, and the ankle at ~90° with the lateral malleolus aligned with the axis of the dynamometer. With the knee at ~90°, the soleus muscle, the muscle from which we recorded, generates the majority of plantar flexion torque.[32,33] Muscle spasms were common when transferring participants in and out of the Biodex and when positioning the limb against the footplate but were relatively uncommon during NMES. This study was approved by the Health Research Ethics Board at the University of Alberta.

EMG. Surface EMG was recorded from soleus using adhesive gel electrodes (2.25 cm^2; Vermed Medical, Bellows Falls, Vermont) arranged in a bipolar configuration. The electrodes were placed parallel to the predicted path of the muscle fibers with ~1 cm interelectrode distance (Fig. 1). A reference electrode was placed over the tibia of the right leg. EMG signals were amplified 500–1,000 times and band-pass filtered (10–1,000 Hz; NeuroLog System; Digitimer, Welwyn Garden City, UK).

NMES. NMES was delivered using a constant-current stimulator (0.2 ms pulse duration; DS7AH Digitimer, Welwyn Garden City, UK), and current was measured using a current probe (mA 2000 Noncontact Milliammeter; Bell Technologies, Orlando, Florida). mNMES was delivered over the triceps surae through 2 flexible adhesive gel electrodes (7.5 × 13 cm; model CF7515, Axelgaard Manufacturing, Lystrup, Denmark) trimmed to fit (Fig. 1). The anode was placed over the gastrocnemii at the point of the largest circumference. The cathode was placed over soleus, just distal to the gastrocnemii. nNMES was delivered over the tibial nerve trunk through 2 flexible adhesive gel electrodes (3.2 cm round; model CF3200, Axelgaard Manufacturing, Lystrup, Denmark) placed on the skin of the popliteal fossa with an inter-electrode distance of ~1 cm (Fig. 1). If contractions of the

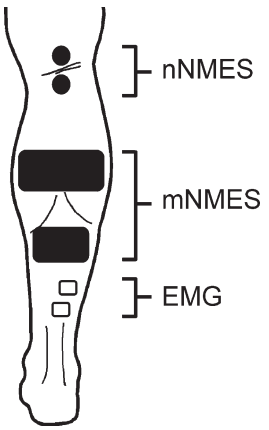

FIGURE 1. Schematic of the NMES and EMG sites on the right leg.

tibialis anterior or fibularis muscles were observed through visual inspection and palpation, the electrodes were re-positioned medially and, in the case of mNMES, were cut smaller to activate the triceps surae more selectively.

M-Wave-H-Reflex Recruitment Curve. At the beginning of each session, an M-wave-H-reflex (M-H) recruitment curve was constructed from soleus EMG responses to 50 pulses delivered by mNMES or nNMES. Stimulation pulses were delivered randomly every 8–10 s at current intensities ranging from below that which generated an M-wave or H-reflex to 1.5 times the current required to evoke the maximum evocable M-wave (M_{max}).

Peak Twitch Torque and M_{max}. After data were collected for the M-H recruitment curve, Peak twitch torque (PTT) was determined using single pulses delivered over the tibial nerve trunk (nNMES). Current intensity was increased every 8 to 10 s to ~1.5 times the current required to evoke M_{max}. This procedure was sufficient to generate maximal PTT and M_{max} in all participants. The number of pulses used for this assessment was always less than 10.

Setting NMES Intensity. To set the NMES intensity for the fatigue protocol, 2 s trains of 20 Hz NMES were delivered 20 s apart, while the intensity was adjusted until the peak torque was equivalent to the PTT for that participant. Approximately 5 NMES trains were required to set the NMES intensity for each session. Once this intensity was set, it was kept constant (i.e., was not changed) for the remainder of the fatigue protocol. In people with chronic SCI, PTT of the plantar flexors is equivalent to ~27% of the torque generated during maximal tetanic (40 Hz) NMES.[34] Thus, PTT provides a convenient sub-maximal normalization value. We chose to set the NMES intensity for the fatigue protocol at this sub-maximal value for 4 reasons: (1) NMES is often delivered at sub-maximal intensities for rehabilitation; (2) sub-maximal intensities minimize the risk of fracturing osteoporotic bones in people with chronic SCI[2]; (3) sub-maximal intensities minimize antidromic collisions in motor axons,[35] allowing for a contribution through central pathways; and (4) this contraction amplitude falls within the range (20–30% of maximum torque) required for walking.[36]

Fatigue Protocol. Five minutes after setting the NMES intensity, a fatigue protocol consisting of intermittent 20 Hz trains, 2-s on 2-s off for 5 min (75 contractions) was delivered. The 20 Hz frequency was chosen because: (1) it is the highest frequency that permits soleus H-reflex analysis uncontaminated by stimulation artifacts; (2) it minimizes muscle spasms compared with higher frequencies[37]; (3) it is within a recommended frequency range (18 to 25 Hz) for NMES of the lower limbs[6]; and (4) H-reflexes contribute to contractions at this frequency in people with SCI.[24]

Re-assessment of PTT and M_{max}. Five minutes after the fatigue protocol, PTT and M_{max} were reassessed by delivering 3 nNMES pulses at the supramaximal current intensity determined during the initial assessment.

Data Collection and Analyses. Data were sampled at 10 kHz using custom-written Labview software (National Instruments, Austin, Texas) and stored on a computer for subsequent analysis that was conducted using custom-written Matlab software (The Mathworks, Natick, Massachusetts). The amplitude of each M-wave and H-reflex was measured peak-to-peak and normalized to the single largest M-wave (i.e., M_{max}) recorded during the assessment of PTT, in which NMES was delivered using nNMES. To prevent overestimation of M-wave amplitude due to contamination of the EMG signal by the NMES artifact, all data were analyzed *post hoc* using a 2-step software-based signal processing procedure that removes the exponentially decaying tail of the stimulus artifact.[38] Asynchronous MU activity was quantified as described previously.[20]

H_{max}-to-M_{max} ratios (H_{max}/M_{max}) were calculated from the M-H recruitment curve data. M_{max} was calculated as the average of the 3 largest H-reflexes from a given M-H recruitment curve. PTT was measured as the mean peak torque generated by 3 supra-maximal nNMES pulses and was assessed at the beginning and end of each session. Torque generated during the fatigue protocol was normalized to each participant's PTT recorded at the beginning of each session.

The amplitudes of torque, M-waves, H-reflexes, and asynchronous MU activity during the fatigue protocols were averaged over each 2-s contraction (1 torque and 40 EMG measurements for each contraction). For each participant, torque, M-waves, H-reflexes, and asynchronous MU activity were averaged separately over 5 successive contractions (20-s intervals) to generate 15 data bins (i.e., bin 1 = mean of contractions 1 to 5, bin 2 = mean of contractions 6 to 10, etc.) for each fatigue protocol. Group means were calculated by pooling these mean data. Fatigue indices were calculated by dividing the mean torque of the final bin by the mean torque of the initial bin and multiplying by 100 (mean torque_{bin15} / mean $\text{torque}_{bin\ 1} \times 100$).

Statistical analyses were performed on group data using Statistica 8.0 software (StatSoft, Tulsa, Oklahoma). Shapiro-Wilk tests showed that all data

were distributed normally. Dependent (paired) *t*-tests were conducted to test for differences in PTTs and fatigue indices between NMES sites. Separate 2-factor repeated measures analysis of variance (rmANOVA) tests were conducted on PTT and M_{max} data that were collected before and after the fatigue protocol. Separate 2-factor rmANOVA tests were also conducted to determine the influence of NMES site (mNMES x nNMES) and Time (bin 1 to 15) on torque, H-reflexes and asynchronous MU activity during the 5 min fatigue protocol. To determine whether asynchronous MU activity developed during NMES, we calculated the root mean square of the baseline EMG before delivery of NMES, when no NMES-evoked asynchronous MU activity would be present, and included these data as a 16th level of *Time* in the rmANOVA test (4×16).

The spatial distribution of MUs recruited through peripheral pathways (i.e., M-waves) differs between mNMES and nNMES; superficial MUs are recruited preferentially during mNMES[39–42] but not nNMES.[42] Because superficial MUs contribute more to the surface EMG signal than deep MUs,[41,43] this difference in spatial distribution of recruited MUs between sites[42] makes it inappropriate to compare the amplitude of M-waves evoked between mNMES and nNMES as a measure of overall MU recruitment. Thus, comparisons of M-wave amplitude between NMES sites were not made. Instead, separate 1-factor rmANOVA tests were used to determine the influence of *Time* (bin 1 to 15) on M-wave amplitude. In addition, correlational analyses (Pearson product-moment correlations) were conducted to determine whether changes in M-wave amplitude correlated significantly with changes in torque during the fatigue protocol.

The analyses described above permitted comparisons based on where NMES was delivered (mNMES vs. nNMES), independent of *how* (with vs. without H-reflexes) contractions were generated. However, 4 of 8 participants generated contractions without any measureable activity through central pathways, regardless of NMES site. Therefore, to evaluate fatigue based on how contractions were generated, we divided our participants into 2 groups based on whether H-reflexes contributed to contractions during nNMES (Group 1; $n = 4$) or not (Group 2; $n = 4$) and used a 2-factor mixed between-within participants rmANOVA test (a split-pot rmANOVA) to test for differences in fatigue indices between NMES sites between and within groups. H-reflexes were considered to be present during nNMES if: (1) a consistent waveform was present at an H-reflex latency (between 25 and 50 ms); (2) the peak-to-peak measurement over this period was greater than 2% M_{max} during the M-H recruitment curve; and (3) the mean peak-to-peak measurement over this period during each 2 s contraction of the fatigue protocol was greater than 2% M_{max}. Significant main effects and interactions identified by the ANOVAs were tested *post hoc* using the Tukey honestly significant difference test when appropriate. An alpha level of 0.05 was used to evaluate statistical significance. All data are reported as mean ± standard error.

RESULTS

This section has been divided into 2 parts. The first provides comparisons based on *where* NMES was delivered (mNMES vs. nNMES), independent of *how* (with vs. without H-reflexes) contractions were generated. This analysis was conducted to test the hypotheses that: (1) contractions evoked by mNMES would have smaller H-reflexes but more asynchronous MU activity compared with nNMES; and (2) fatigue would occur sooner and would be greater during mNMES than nNMES. These hypotheses were based on the expectation that *how* contractions were generated would be markedly different between NMES sites in all participants.[27] Unexpectedly, however, only half of the participants generated contractions through central pathways (H-reflexes) during nNMES. As such, the second part of the Results section describes the results of analyses designed to compare fatigue based on how contractions were generated. Thus, data were compared between participants who generated contractions with (Group 1; $n = 4$) and without (Group 2; $n = 4$) H-reflexes during nNMES. There was no asynchronous MU activity generated during NMES at either site. Thus, these data are not presented.

Comparing Contractions Based on Where NMES Was Delivered (mNMES vs. nNMES). During data collection for the M-H recruitment curves, H-reflexes were evoked in 1 participant during mNMES ($H_{max}/M_{max} = 0.37$), while they were evoked in 4 of 8 participants during nNMES ($H_{max}/M_{max} = 0.38 \pm 0.18$).

Figure 2 shows mean torque (A), M-wave (B), and H-reflex (C) amplitudes during the mNMES and nNMES fatigue protocols. Each bin represents data averaged over 5 successive contractions for each participant and then averaged across the group. For torque, there was a significant interaction between *NMES site* and *Time* [$F_{(14,\ 98)} = 1.80$, $P = 0.04$, partial $\eta^2 = 0.20$, observed power = 0.89]. Torque generated over the first 5 contractions (bin 1) was not different between sites when compared as %PTT (rmANOVA) or when compared in absolute values (mNMES: 7.29 ± 1.42 Nm; nNMES: 6.93 ± 1.56 Nm) [$t_{(7)} = 1.02$; $P = 0.34$; d = 0.08]. After the first data bin (time 0 to 20 s), torque

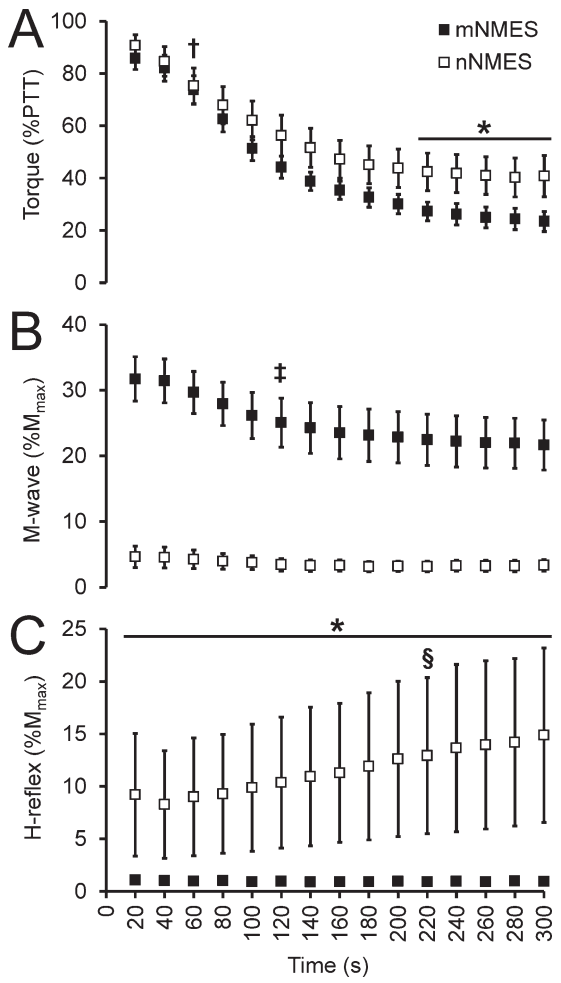

FIGURE 2. Mean torque (**A**), M-wave (**B**), and H-reflex (**C**) amplitudes recorded during the mNMES and nNMES fatigue protocols ($n = 8$). The asterisks (*) in all panels indicate a significant difference between mNMES and nNMES. The dagger (†) in panel A indicates the first significant decrease in torque from the initial 20 s bin for both mNMES and nNMES. The double dagger (‡) in panel B indicates the first significant decrease in M-waves from the initial 20 s bin for mNMES. The section mark (§) in panel C indicates the first significant increase in H-reflexes from the initial 20 s bin for nNMES. Error bars represent 1 standard error.

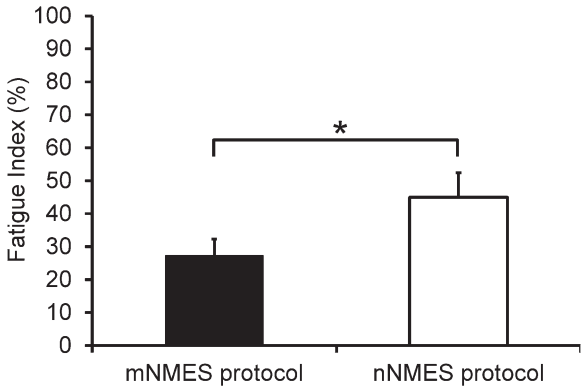

FIGURE 3. Fatigue indices for the mNMES and nNMES fatigue protocols for the group ($n = 8$). Error bars represent 1 standard error.

declined significantly (compared with bin 1;) starting between 41 and 60 s into the fatigue protocol (bin 1 > bins 3–15) for both sites. However, nNMES generated ~2 times more torque than mNMES during the last 1/3 of the fatigue protocol (bins 11 to 15;). By the end of the fatigue protocol (bin 15), torque had dropped by 73% (compared with bin 1) for mNMES and 55% for nNMES. Accordingly, Figure 3 shows that the fatigue index for the group ($n = 8$) was significantly smaller during mNMES than nNMES [$t_{(7)} = 2.36$; $P = 0.04$; d = 1.02]. The current used for the fatigue protocols was 162.6 ± 12.1 mA for mNMES and 46.0 ± 5.8 mA for nNMES.

During mNMES, there was a significant effect of *Time* on M-waves [$F_{(14,\ 98)} = 6.76$; $P < 0.01$, partial $\eta^2 = 0.49$, observed power = 0.99]. Compared with the first data bin (time 0 to 20 s), M-waves declined significantly starting between 101 to 120 s into the fatigue protocol (bin 1 > bins 6 to 15) during mNMES. During nNMES, there was no significant effect of *Time* on M-waves [$F_{(14,\ 98)} = 1.3$; $P = 0.22$, partial $\eta^2 = 0.15$, observed power = 0.78].

For H-reflexes (Fig. 2C) there was a significant interaction between *NMES site* and *Time* [$F_{(14,\ 98)} = 3.45$; $P < 0.01$; partial $\eta^2 = 0.33$, observed power = 0.98]. H-reflexes were significantly larger during nNMES than mNMES throughout the entire fatigue protocol (Fig. 2C), despite the fact that H-reflexes were evoked in only 4 of 8 participants. During nNMES, H-reflexes increased significantly starting between 201 and 220 s into the fatigue protocol compared with the first data bin (bin 1 < bins 11 to 15).

During the fatigue protocol, changes in torque were not correlated significantly with changes in M-wave amplitude during either mNMES (r = −0.07, $P = 0.87$; Fig. 4A) or nNMES (r = 0.14; $P = 0.74$; Fig. 4B). Thus there was no relationship between changes in torque and changes in M-wave amplitude.

Figure 5 shows mean PTT (A) and M_{max} (B) amplitudes, evoked by stimulation over the tibial nerve (i.e. nNMES) before and 5 minutes after the mNMES and nNMES fatigue protocols. For PTT, there was a significant main effect of *Time* [$F_{(1,\ 7)} = 8.85$, $P = 0.02$, partial $\eta^2 = 0.56$, observed power = 0.77]. PTT was ~25% smaller after the fatigue protocol compared with before, regardless of NMES site. There were no significant differences in M_{max} across all factors (Fig. 5B).

Comparing Fatigue Based on How Contractions Were Generated (with vs. without H-Reflexes). Unexpectedly, nNMES generated H-reflexes in only 4 of 8 participants. This was the case for the data collected for

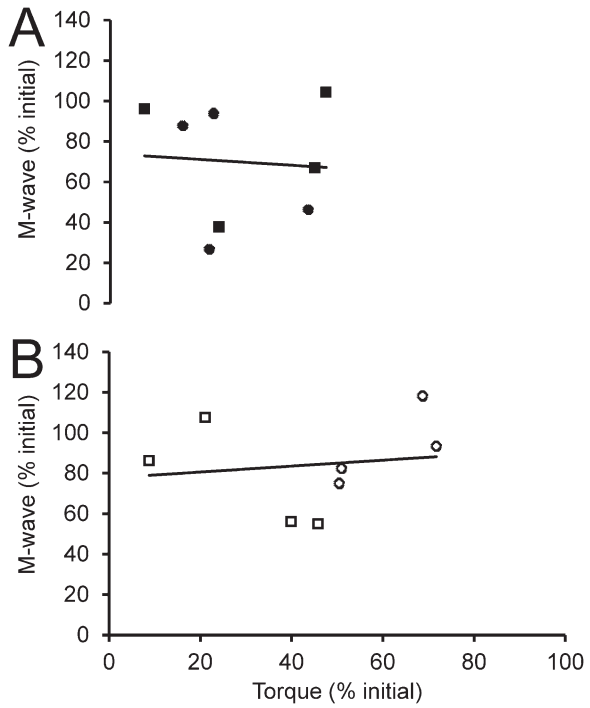

FIGURE 4. Torque plotted against M-wave amplitude (% of initial; bin 15 / bin 1 × 100) during the mNMES (**A**) and nNMES (**B**) fatigue protocols. Each symbol represents a different participant. Circles (● and ○) represent participants from Group 1, in whom contractions were generated by means of H-reflexes during nNMES, and squares (■ and □) represent participants from Group 2, in whom contractions were generated by means of M-waves only regardless of NMES site. Regression lines are displayed.

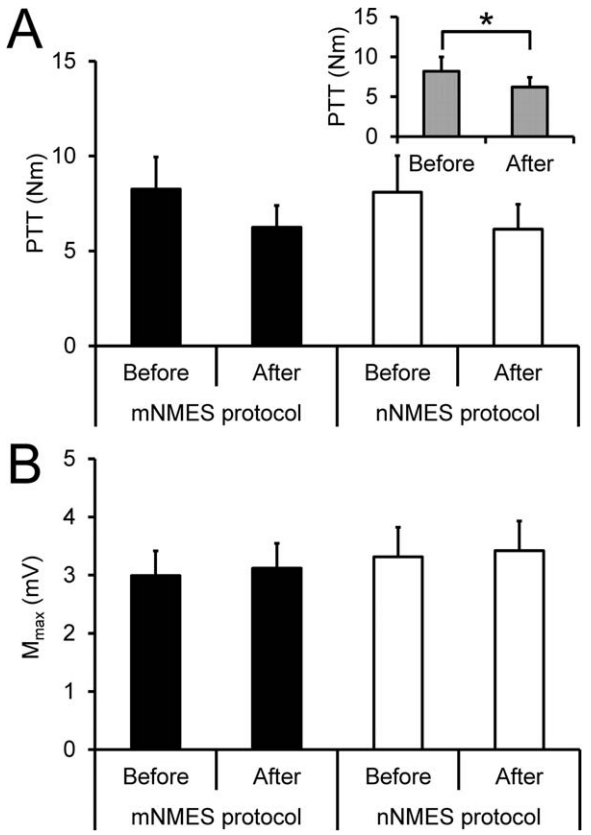

FIGURE 5. Mean PTT (**A**) and M_{max} (**B**) evoked by nNMES before and 5 min after the mNMES and nNMES fatigue protocols ($n = 8$). A significant main effect identified by the rmANOVA analysis is displayed within the inset in panel A. Error bars represent 1 standard error.

the recruitment curves (i.e. across the full range of NMES intensities) and during the fatigue protocols. Thus, to compare data based on how contractions developed during the fatigue protocol, we divided our participants into those who generated contractions through H-reflexes during nNMES (Group 1, n = 4) and those who did not (Group 2, n = 4). For the participants in Group 1, M-waves were 2.0 ± 1.4% M_{max} while H-reflexes were 22.1 ± 11.7% M_{max} when averaged across the entire nNMES fatigue protocol. For the participants in Group 2, M-waves were 5.1 ± 3.4% M_{max}, averaged across the nNMES fatigue protocol. For participants in Group 1, the current used for the fatigue protocols was 150.8 ± 20.3 mA for mNMES and 41.1 ± 7.7 mA for nNMES. For participants in Group 2, the current used for the fatigue protocols was 174.4 ± 13.3 mA for mNMES and 50.9 ± 9.0 mA for nNMES.

Figure 6 shows torque and EMG recorded from a participant assigned to Group 1. In this participant, H-reflexes contributed sporadically to contractions during mNMES (Fig. 6A), and contractions were generated exclusively through H-reflexes during nNMES with no measureable M-wave activity (Fig. 6B). During the initial 5 contractions, torque was similar (~15 Nm) between NMES sites. However, by the end of the fatigue protocols, mNMES generated ~6 Nm of torque, while nNMES generated ~10 Nm of torque. During mNMES, contractions were evoked through successive M-waves with robust H-reflexes appearing sporadically and then only during relatively few ($n = 9$) contractions. Of interest, only during the contractions in which torque spiked during mNMES (Fig. 6A) were robust H-reflexes evident in the EMG, providing anecdotal evidence for the contribution to torque made by MUs recruited as H-reflexes. The H-reflex shown in Figure 6A recorded during mNMES corresponds with the last NMES pulse of contraction 74. This was the only participant in whom H-reflexes were generated by mNMES and in whom contractions were generated exclusively through H-reflexes during nNMES (Fig. 6B). For the other 3 participants in Group 1, H-reflexes were accompanied by small M-waves during nNMES.

In contrast to the data shown in Figure 6, Figure 7 shows data recorded from a participant from Group 2 in whom, regardless of NMES site,

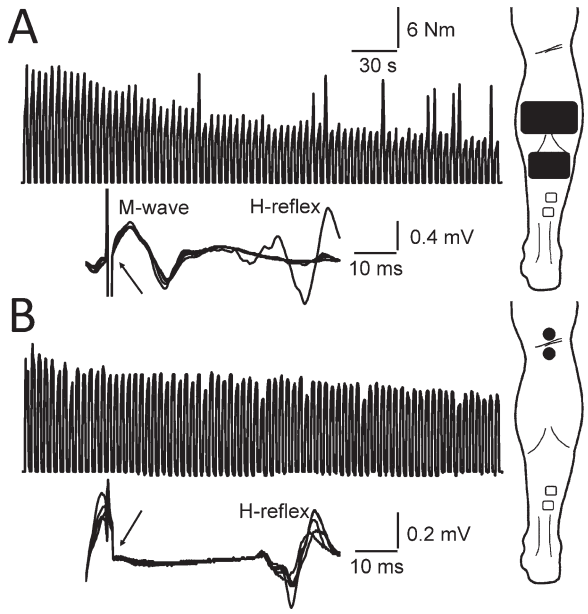

FIGURE 6. Torque and EMG evoked by mNMES (**A**) and nNMES (**B**) in a single participant who generated contractions with H-reflexes during nNMES (Group 1). In the top of each panel, the solid line represents torque during the 5 min, 2-s-on-2-s-off, fatigue protocol. The bottom of each panel shows EMG in response to the last NMES pulse of each of the last 5 contractions. The arrows point to where the tails of the preceding NMES artifact (A) or H-reflex (B) were removed. All torque data are shown on the same scale, as indicated in panel A.

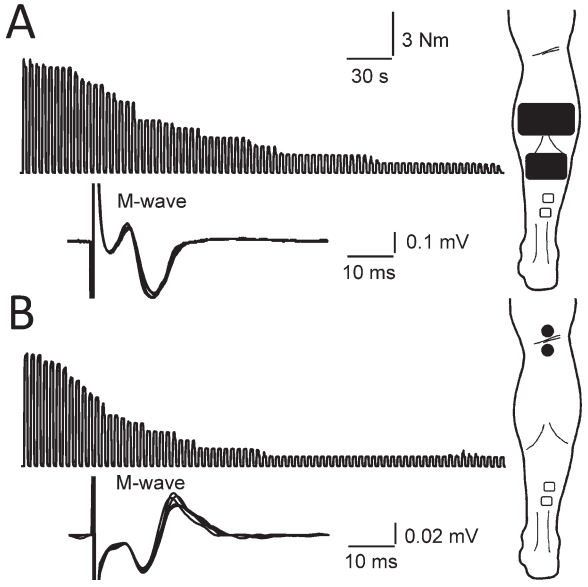

FIGURE 7. Torque and soleus EMG evoked by mNMES (**A**) and nNMES (**B**) in a single participant who generated contractions through successive M-waves only (Group 2). The organization of this figure is equivalent to that of Figure 6.

contractions were generated through successive M-waves with no measurable H-reflex. In this participant, torque was similar throughout both fatigue protocols and decreased from ~8 Nm at the beginning to ~1 Nm by the end.

To determine whether generating contractions through H-reflex pathways influenced the fatigue-resistance of evoked contractions, fatigue indices were compared between and within Groups 1 and 2. Figure 8 shows fatigue indices for both groups and NMES sites. There was a significant interaction between *NMES site* and *Group* [$F_{(1,6)} = 11.4$; $P < 0.01$, partial $\eta^2 = 0.65$, observed power = 0.81]. During mNMES, there was no difference in fatigue indices between groups ($P = 0.97$), both of which generated contractions mainly through successive M-waves. During nNMES, there was less fatigue when H-reflexes contributed to contractions, as the fatigue index was significantly larger ($P = 0.03$) for participants in Group 1, all of whom generated contractions through H-reflex pathways, than Group 2, all of whom generated contractions through successive M-waves only. Within Group 1, the fatigue index during mNMES (mainly M-waves) was significantly smaller than during nNMES (when H-reflexes contributed; $P < 0.01$). Within Group 2, there was no difference in fatigue index between NMES sites ($P = 0.96$), both of which generated contractions through M-waves only. When taking into consideration how contractions were generated, torque decreased the least when contractions were generated at least in part through H-reflexes (Group 1, $n = 4$, nNMES, ~39% decrease), and torque decreased the most when contractions were generated through M-waves, regardless of NMES site (Group 2, $n = 4$, nNMES, ~71% decrease; Groups 1 and 2, $n = 8$, mNMES, ~73% decrease).

DISCUSSION

These experiments were designed to compare the contributions made by central pathways to MU recruitment during mNMES and nNMES in people with chronic motor-complete SCI and to investigate whether fatigue can be reduced using nNMES, which can recruit MUs by means of H-reflexes compared with a more traditional approach using mNMES, which recruits MUs predominantly by means of M-waves. We tested 2 hypotheses: (1) contractions evoked by mNMES would have smaller H-reflexes but more asynchronous MU activity than nNMES, and (2) fatigue would occur sooner and would be greater during mNMES than nNMES. To test the second hypothesis, we compared torque based on where NMES was delivered (mNMES vs. nNMES), independent of how contractions were generated (with vs. without H-reflexes) based on the expectation that mNMES and nNMES would generate contractions through markedly different pathways in each participant.[27] However, nNMES generated contractions through H-reflex pathways in only 4 of 8 participants. As such, we divided our participants

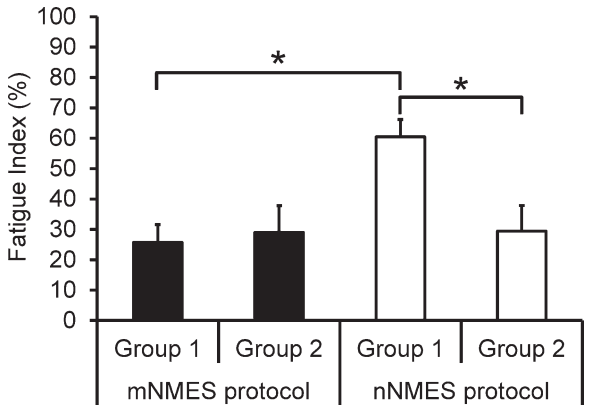

FIGURE 8. Fatigue indices for the mNMES and nNMES fatigue protocols for participants who generated contractions with (Group 1; $n = 4$) and without (Group 2; $n = 4$) H-reflexes during nNMES. Error bars represent 1 standard error.

into 2 groups based on whether H-reflexes contributed to contractions during nNMES (Group 1; $n = 4$) or not (Group 2; $n = 4$). This way of analyzing the data allowed us to compare fatigue based on how contractions were generated and tested more specifically whether contractions generated through H-reflex pathways were more fatigue-resistant than contractions generated through successive M-waves only.

Comparing Contractions Based on Where NMES Was Delivered. Consistent with our first hypothesis, the extent to which central pathways contributed to contractions differed between NMES sites. Among the 8 participants, H-reflexes were 10 to 15 times larger during nNMES than mNMES when averaged over the entire fatigue protocol. This shows that where NMES is delivered affects how contractions are generated in people with chronic SCI. We believe that the effect of NMES site reflects differences in how motor and sensory axons are recruited beneath the electrodes between sites. Muscle spindles are located preferentially deep in the triceps surae,[44] however, axonal recruitment during mNMES is preferentially superficial.[39,41,42,45,46] Thus, activation of sufficient Ia afferents to generate an H-reflex may occur only at high mNMES intensities at which H-reflexes would be blocked by antidromic collision in motor axons[47]; accordingly, mNMES generates few if any H-reflexes. In contrast, motor and sensory axons are bundled close together in the nerve trunk beneath the nNMES electrodes. Thus, compared with mNMES, nNMES likely recruits a greater proportion of Ia afferents before substantial antidromic collision develops, and we believe that this is why nNMES generates H-reflexes and mNMES, typically, does not.

The progressive decline in M-wave amplitude that often occurs when fatigue develops during NMES-evoked contractions[48] is thought to reflect failure of neuromuscular propagation.[49] Such failure can occur beneath the NMES electrodes,[50] at axonal branch points,[51,52] at the neuromuscular junction,[51] or at the sarcolemma.[53] The M-wave amplitude decreased significantly during the mNMES fatigue protocol, however, this decrease was not correlated significantly with decreases in torque (Fig. 4). Furthermore, M_{max} was not different before and after the fatigue protocols, while PTT decreased by ~25% regardless of NMES site (Fig. 5), consistent with a previous study of the chronically paralyzed plantar flexors.[48] These dissociations between the force-generating capacity of the muscle and M-wave amplitude indicates that the fatigue we observed is not due only to neuromuscular propagation failure. Thus, a primary contributor to the fatigue we observed is likely related to impaired excitation-contraction coupling. Accordingly, NMES approaches that preferentially recruit fatigue-resistant MUs that are relatively resistant to failure of excitation-contraction coupling, hold promise for reducing fatigue during NMES (see Significance below).

In contrast to the decline in M-waves during mNMES, M-waves were stable, and H-reflexes even increased during the nNMES fatigue protocols. The reason for the lack of change in M-waves during nNMES is unclear, yet there is a suggestion that changes in H-reflexes were not due to increased axonal recruitment at the nNMES site.[47] Instead, the enhanced H-reflexes reflect a change in the reflex gain, which may be due to potentiation of synaptic transmission[54] or increased excitability of spinal neurons.[55,56]

Unlike previous work conducted on plantar flexors in people who are neurologically intact,[20] there was no asynchronous MU activity during NMES in any of our chronic SCI participants. In our previous work,[20] NMES was delivered using relatively long pulse durations (1 ms) with brief periods of high frequencies (100 Hz) and/or with long on-times (7 to 8 s-on). Thus, the lack of asynchronous activity may be because the NMES parameters generated a smaller afferent volley than in our previous work[20]; this may have been insufficient for generating asynchronous activity.[57] Alternatively, asynchronous MU activity and the mechanisms that generate it may be less prevalent in people with chronic SCI than in people without. In line with this latter idea, it may be that previous recordings of asynchronous activity in neurologically intact participants[20] resulted from involuntary descending drive,[20,58] which would not be present in our participants with complete SCI.

Contrary to our second hypothesis, mNMES did not generate contractions that fatigued sooner

than nNMES; torque declined significantly starting 41–60 s into the fatigue protocol for both NMES sites. Consistent with our hypothesis, however, mNMES generated contractions that fatigued more than nNMES; mNMES generated significantly less torque than nNMES over the last 1/3 of fatigue protocols, and the fatigue index was significantly smaller for mNMES (27%) than nNMES (45%). This demonstrates that where NMES is delivered can influence the fatigue-resistance of evoked contractions. However, the differences in fatigue-resistance between NMES sites were due, in large part, to how the contractions were generated.

Comparing Fatigue Based on *How* Contractions Were Generated. The finding that H-reflexes contributed to evoked contractions in only 4 of 8 participants provided a unique opportunity to test more specifically the effect of H-reflexes on the fatigue-resistance of evoked contractions. Although nNMES generated contractions that fatigued the least for the group as a whole (n = 8), this difference was due to the 4 participants in whom H-reflexes contributed to contractions (Group 1; fatigue index = 61%), compared with the 4 participants in whom H-reflexes did not contribute (Group 2; fatigue index = 29%). This difference was not because participants in Group 1 had more fatigue-resistant plantar flexors than those in Group 2, because fatigue indices were not different between groups when mNMES generated contractions mainly by means of M-waves in both groups. Furthermore, within the participants in Group 1, the fatigue index for the nNMES site (when H-reflexes contributed to contractions) was significantly larger than that for the mNMES site (when contractions were generated mainly through M-waves). Together these data provide clear evidence that the differences in fatigue were not due to differences in muscle quality, but rather were due to how the contractions were generated and that H-reflexes reduced fatigue. Lastly, reductions in fatigue were not the result of nNMES activating other muscles innervated by the tibial nerve that generate plantar flexor torque (i.e., tibialis posterior, flexor digitorum longus, flexor hallicus longus), which may not be activated during mNMES, because there was no difference in fatigue index between NMES sites for participants in Group 2 (when contractions were generated exclusively through M-waves). Importantly, the effect size for these differences was large (partial $\eta^2 = 0.65$). Thus, despite the relatively small sample size (n = 4 for each group) for the split-pot rmANOVA analysis, these significant differences were identified with adequate power (> 0.8). Although this is not the first demonstration that robust H-reflexes can contribute to evoked contractions of muscle paralyzed by SCI,[24] this study demonstrates that generating contractions through this pathway reduces the fatigue of NMES-evoked plantar flexor contractions in people with chronic motor-complete SCI. Thus, these data provide experimental evidence to support the idea that MU recruitment *order*, as inferred by MU recruitment through central pathways, affects fatigue-resistance of NMES-evoked contractions in people with SCI.

Our finding that H-reflexes could be evoked in only 4 of 8 participants is inconsistent with 2 previous studies in which H-reflexes were evoked in 10 of 12[24] and 7 of 9[59] SCI participants. Although a long pulse duration (1 ms) is recommended for generating H-reflexes,[60,61] our use of a shorter pulse (0.2 ms) does not account for the complete lack of H-reflexes in 4 of 8 participants. Previous work has shown that H_{max} is unaffected by pulse duration,[60] and H-reflexes evoked by pulse durations of 0.2, 0.5, and 1 ms are not different during nNMES in people who are neurologically intact.[62] Regardless of pulse duration, the absence of soleus H-reflexes in people with chronic SCI who are free from lower motor neuron damage is surprising, given that inhibition of the H-reflex pathway is reduced after SCI. People with chronic SCI have reduced postactivation depression[63] and reduced Ia presynaptic[64] and reciprocal[65,66] inhibition of neural circuits that control the soleus muscle. Of note, 4 of 8 participants were taking baclofen ($GABA_B$ receptor agonist) to minimize muscle spasms[67]; this did not seem to influence the frequency of H-reflexes, because 2 participants who were taking baclofen generated contractions through H-reflexes, while 2 other participants who were not taking it did not (Table 1).

Significance. Muscle fatigue during NMES limits its effectiveness for clinical applications.[4–6] Although it has not been tested directly, such fatigue is thought to be due, in part, to the random order in which MUs are recruited during NMES.[9–16] We propose that the improvements observed in fatigue-resistance when contractions were generated through H-reflexes were the result of recruiting MUs in their physiological recruitment order, because fatigue-resistant MUs dominate the soleus H-reflex.[11,23] However, although the plantar flexors are relatively fatigue-resistant in the acute stages of SCI, fatigue-resistance in the chronic stages is poor, consistent with a transition toward fast-fatigable MUs.[37] Indeed, in people with chronic SCI, the soleus is made up predominantly of type II muscle fibers.[68] Given that the onset of fatigue did not differ between NMES sites, and

given the large extent to which torque declined by the end of the fatigue protocol during mNMES (~73%) and nNMES (~55%), contractions were likely generated predominantly by fatigable MUs, regardless of NMES site. That said, our finding that H-reflexes reduce fatigue indicates that, despite changes in MU type in people with chronic SCI, a more physiological recruitment order reduces fatigue of contractions for these people. We expect the fatigue-resistance of contractions evoked through H-reflexes to be even better in people in acute stages of SCI or in experienced NMES-users, as these people have more fatigue-resistant MUs than their sedentary counterparts.[69,70]

There are several practical issues to consider before taking this work from the laboratory to applications for rehabilitation. First, compared with contractions generated by M-waves, torque generated through H-reflexes is less consistent within[22] and between contractions.[22,27] Thus, it may prove difficult to adequately control contraction amplitude for fine motor tasks. Second, it is unclear whether H-reflexes will generate contractions of sufficient amplitude to restore functions such as standing and walking. It has been estimated that plantar flexor contractions of 20–30% of maximum torque are required for walking,[36] and contractions equivalent to ~27% of maximum torque[34] were evoked, at least in part, through H-reflexes in 4 participants. Whether contractions of sufficient amplitude can be generated by means of H-reflexes at higher NMES intensities, when H-reflexes are limited by antidromic collision in motor axons,[47] remains to be determined. Third, only half of our participants had H-reflexes during nNMES, thus nNMES may not be effective for reducing fatigue in everyone.

Summary. We report 4 novel findings: (1) Where NMES is delivered can affect how contractions are generated in people with chronic motor-complete SCI; mNMES generated contractions predominantly through M-waves, while nNMES generated contractions through H-reflexes in 4 of 8 participants. (2) Where NMES is delivered affects the fatigue-resistance of evoked contractions; nNMES generated contractions that fatigued less than mNMES. (3) Fatigue-resistance depends on how contractions are generated; contractions generated through H-reflexes fatigued less than those generated through M-waves. (4) Asynchronous MU activity did not contribute to evoked contractions. We conclude that nNMES generates contractions that are more fatigue-resistant than mNMES, but only when H-reflexes contribute. Generating contractions through H-reflex pathways may be advantageous for rehabilitation when fatigue limits the benefits of NMES-based programs.

The authors thank Mr. Alejandro Ley for his technical support.

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