ABSTRACT: It is essential to determine optimal parameters of stimulation to maintain muscle force during neuromuscular electrical stimulation (NMES). Protocols that increase in frequency and include doublets can prolong force output over time. However, stimulation intensity level could differentially affect muscle force output during variable-frequency NMES. We compared three intermittent stimulation patterns at maximal and submaximal intensities of stimulation of the median nerve: (1) a constant 20-Hz pattern; (2) 90 s at 20 Hz followed by a 90-s increase from 20 to 40 Hz; and (3) 90 s at 20 Hz followed by 90 s of doublets at 20 Hz. At submaximal intensities, the doublet pattern produced the highest overall force–time integral (FTI). At maximal intensities, the doublet pattern produced the lowest FTI and the increasing frequency pattern produced the least amount of fatigue. Thus, double-pulse stimulation was more effective during submaximal than maximal intensity NMES. These data demonstrate that intensity level must be taken into consideration when programming frequency patterns for NMES devices.

MAXIMAL VERSUS SUBMAXIMAL INTENSITY STIMULATION WITH VARIABLE PATTERNS

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Neuromuscular electrical stimulation (NMES) is a useful modality for facilitating movement in muscles affected by neurological impairment and paralysis. However, the use of NMES causes rapid fatigue in already weakened and denervated muscle, thereby limiting extended force production and the ability to successfully participate in strengthening and rehabilitative regimens. NMES systems involve stimulation over the skin of the muscle, devices implanted into the muscle, and nerve cuffs.

Although the effects of NMES have been studied during walking, far less is known about the use of NMES to restore hand function following neurological insult. Patients with spinal cord injury or stroke frequently lose grasp, pinch, and manipulation skills that are vital for independent living. Although previous work has examined variable patterns of stimulation and the fatigue effects of NMES in the upper extremity, the specific NMES parameters that are optimal for reducing motor deficits in the neurologically impaired hand remain unclear.

Various patterns of stimulation have been tested primarily using submaximal intensity stimulation over the muscle. Other studies have used maximal surface stimulation over the nerve in order to control for potential changes in motor unit recruitment. Most studies involving maximal stimulation during a fatigue task tested the use of doublets: one study found them to be effective, but the other two did not. Similar discrepancies have been found during submaximal stimulation protocols that incorporated doublets. Thus, it is unknown whether maximal stimulation produces the same effects on muscle force output over time as submaximal stimulation during the use of variable patterns of stimulation and whether this parameter should be taken into consideration when designing NMES programs.

Thus far, the most effective patterns of stimulation are those that change in the later stages of the fatigue task. Submaximal intermittent stimulation patterns that increased in frequency and included doublets in later stages of fatigue have enhanced force production compared to constant-frequency intermittent stimulation. Shields et al. found that,
during torque-feedback–controlled electrical stimulation, increasing frequency stimulation was selected at a higher rate than constant-frequency and doublet stimulation, suggesting that increasing frequencies of stimulation are more effective than introducing doublets later in the fatigue task.

The increase in stimulation frequency may function to override the effects of low-frequency fatigue (LFF).14 Binder-Macleod and Russ8 found that the degree of LFF was not different when fatigue was induced with trains regardless of whether they included doublets. However, LFF was less predominant when fatigue was induced with high than with low frequencies of stimulation.

The main purpose of this study was to test the effects of three variable stimulation patterns using maximal and submaximal intermittent stimulation of the median nerve. We expected that greater force–time integrals (FTIs) and less reduction in force from start to end would be present in response to variable-frequency than to constant-frequency stimulation, and that the increasing frequency pattern would be more effective at maintaining force output than the doublet pattern. We also hypothesized that the degree of LFF would be lowest for fatigue protocols that increased in stimulation frequency. Finally, we hypothesized that the FTIs, changes in force from start to end, and occurrence of LFF would not differ between maximal and submaximal intensities of stimulation.

METHODS

Participants. We studied 5 men and 5 women, aged 23.81 ± 2.71 years. All were healthy, with no physical limitation or medical history of neuromuscular or metabolic disorder. Each participant was oriented to the study protocol and signed consent forms prior to testing. All procedures were approved by our institutional review board.

Experimental Arrangement. All 10 subjects participated in six experimental sessions separated by at least 48 hours. Each session lasted 45 minutes on average. All experimental procedures were the same except for the type of fatigue task and intensity of stimulation (3 maximal and 3 submaximal). All participants tolerated the procedures well, and none withdrew from the study.

Participants sat in a high-back chair with their right forearm supinated and resting on a tabletop. The shoulder and upper arm were positioned parallel with the trunk, and the elbow was positioned at 90°. Hip, knee, and ankle joints were all maintained in a neutral 90° position. A custom-designed forearm apparatus made of thermoplastic material (North Coast Medical, Morgan Hill, California) immobilized the forearm and maintained it in supination. The forearm apparatus was attached to a sheet of laminated core-board bolted to the table. Straps secured the forearm at the wrist and forearm midpoint. The upper arm was secured with a strap positioned slightly medial to the elbow that attached to the chair. The hand was stabilized with therapeutic putty placed underneath, securing the dorsum; putty was placed on the volar surface as well, extending slightly below the metacarpal–phalangeal (MCP) joints to mid-palm. A thermoplastic plate was positioned on the putty over the digits, and a strap secured the interphalangeal (IP) and MCP joints in extension. The thumb was extended and abducted and positioned against the force transducer. The force transducer contact area spanned from the thumb tip to the center of the proximal phalanx of the thumb, an average of 5.00 ± 0.50 cm for all participants. The custom-designed force transducer device consisted of a mobile, rotating, height-adjustable horizontal arm made of two narrow aluminum surfaces with strain gauges that measured the evoked forces of thumb forces in the vertical (y) and horizontal (x) directions.

The resultant force, \( R = \sqrt{x^2 + y^2} \), was calculated, displayed on the computer monitor, and recorded using commercially available software (Spike2, version 5.14; Cambridge Electronics Design, Cambridge, UK). A stimulating electrode was placed over the median nerve at the wrist and secured with a Velcro band and tape after optimal placement was obtained. Electrical impulses of 50-μs pulse duration were delivered from a constant-current stimulator (Model DS7A; Digitimer, Ltd., Welwyn Garden City, UK) using custom-written scripts constructed through the Spike2 software. The electromyographic (EMG) signal was recorded through two adhesive pre-gelled Ag–AgCl bipolar surface electrodes 5 mm in diameter (Danlee, Syracuse, New York), with the active electrode over the thenar eminence slightly medial to the MCP joint and the reference electrode 1 cm more medial. A ground electrode was placed over the pisiform bone.

Experimental Protocol. All fatigue protocols used intermittent trains of 300 ms on time and 700 ms off time based on Burke’s experimental protocol.10 Three different 3-min fatigue tests were administered in random order, at maximal as well as submaximal stimulation levels, for a total of six sessions.
All sessions followed the same protocol and were identical except for the fatigue task.

Fatigue test 1 consisted of 20-Hz trains; test 2 consisted of stimulation that began at 20 Hz and, midway through the protocol, began gradually increasing in frequency from 20 Hz to 40 Hz such that 40 Hz was the terminal frequency reached at 180 s. In test 3, a doublet train similarly began at 20 Hz and, midway through the protocol, changed to a 20-Hz pattern of doublets that continued to the end of the train.

To find the best position for the stimulating electrode, single 1-Hz pulses were delivered at various stimulator placements over the median nerve, and the place where the largest M-wave amplitude and twitch force occurred was selected. For the maximal stimulation tests, the current was set approximately 10% higher than the intensity that elicited the maximum M-wave amplitude. For the submaximal stimulation tests, an intensity that elicited 70% of the force value obtained during a maximal 4-s, constant 20-Hz train was used. To obtain the 70% value, 1-s 20-Hz trains were administered, and the resultant force was monitored. On average, five trains were required to reach the appropriate value. At least 20 s elapsed between each 1-s train administered to prevent fatigue.

Five maximal or submaximal 1-Hz pulses were delivered before and after the fatigue test to monitor stability of the stimulating electrode from the beginning to the end of the experiment. This was followed by administration of a 4-s constant 20-Hz train to measure consistency of the experimental arrangement across test days. If the force of the 20-Hz train deviated by >10% between testing days, the thumb was repositioned and the experiment was restarted.

Next, three, 3-s MVCs were performed, followed by five random, constant-frequency, 4-s trains of 10, 20, 30, and 40 Hz and a 2-s train of 50 Hz. All trains were separated by 3 s and were repeated at the end of the fatigue task. The MVCs and the 4-s train data were used to obtain both voluntary and involuntary measures of fatigue following the fatigue protocols. The 4-s trains were also used to compare the presence of low-frequency fatigue across the four protocols. A schematic of the experimental protocol is shown in Figure 1.

Data Recording and Analysis. The force-output signal was amplified by 100 (Model 74030 Bridge 8 Amplifier System; World Precision Instruments, Sarasota, Florida), sampled at 1000 Hz and low-pass filtered at 1 kHz. EMG was amplified by 100, high-pass filtered above 8 Hz (Coulbourn Instruments, Allentown, Pennsylvania), sampled at 2000 Hz, and digitally converted (Micro 1401; Cambridge Electronics Design, Cambridge, UK). All data were recorded and analyzed using Spike2 software (v5.14, Cambridge Electronics Design, Cambridge, UK).

Statistical Analysis. Two-way repeated-measures analyses of variance (ANOVA) with stimulation intensity (maximal and submaximal) and pattern (20 Hz, 20–40 Hz and doublet) as the independent variables and Bonferroni’s post hoc analysis were used to compare pre- and post-fatigue MVCs, 4-s 20-Hz constant-stimulation trains, overall FTIs, and forces at 10-s intervals during all fatigue tasks.

MVCs and maximal M-wave amplitudes before and after fatigue were measured and compared with a $3 \times 2 \times 2$ repeated-measures ANOVA using pattern (20 Hz, 20–40 Hz, or doublet), intensity (maximal or submaximal), and time (pre- or post-fatigue stimulation pattern) with a post hoc Bonferroni correction. Pre-fatigue maximal vs. submaximal M-wave amplitudes were compared with a two-way repeated-measures ANOVA (factors: intensity and fatigue protocol) with a post hoc Bonferroni correction.

Maximum evoked forces from each of the five various frequency trains (10, 20, 30, 40, and 50 Hz) were compared across the three patterns (20 Hz, 20–40 Hz and doublet), the two stimulation intensities (maximal and submaximal), and the two time levels (pre- and post-fatigue) using a multivariate analysis of variance (MANOVA), with univariate ANOVAs and Bonferroni corrections for post hoc analysis.

An alpha level of 0.05 was used for all statistical comparisons, and significance was accepted at $P \leq 0.05$. All data are presented as mean ± standard deviation.

RESULTS

Maximal Voluntary Contractions and Day-to-Day Repeatability. There were no significant differences between the forces during the 4-s 20-Hz trains presented before each of the three fatigue tests administered with maximal (20 Hz, 19.22 ± 3.24 N; 20–40 Hz, 17.81 ± 3.05 N; doublet, 16.48 ± 2.23 N) or submaximal (20 Hz, 13.28 ± 1.42 N; 20–40 Hz, 14.10 ± 1.52 N; doublet, 14.25 ± 1.39 N) stimulation. As expected, a significant difference was present between intensities, with maximal intensities eliciting significantly higher forces than submaximal intensities.
There was no significant difference between average MVC forces collected before the maximal (20 Hz, 67.70 ± 8.66 N; 20–40 Hz, 71.00 ± 9.28 N; doublet, 71.67 ± 9.34 N) or submaximal (20 Hz, 67.72 ± 8.71 N; 20–40 Hz, 67.73 ± 9.93 N; doublet, 73.11 ± 10.79 N) fatigue tests.

Post-MVC forces were significantly lower following maximal (20 Hz, 63.77 ± 8.97 N; 20–40 Hz, 62.75 ± 6.94 N; doublet, 62.86 ± 8.04 N) and submaximal (20 Hz, 62.93 ± 7.96 N; 20–40 Hz, 60.50 ± 8.21 N; doublet, 66.80 ± 8.74 N) fatigue tests, with no statistical differences across protocols.

**Fatigue Test Forces.** Starting forces during the fatigue tests were measured at 10 s after the initiation of stimulation to allow time for the force to plateau from twitch potentiation. While the forces during maximal stimulation were higher than during submaximal stimulation, there were no significant differences between the starting forces across the three fatigue tests within each intensity level. Force loss at maximal intensities showed differences between patterns, with the 20–40-Hz pattern producing significantly lower force loss than the 20-Hz and doublet patterns. No significant differences in force loss were present between the three submaximal patterns. Figure 2 depicts the average forces for every 10 s of maximal and submaximal stimulation for all subjects and protocols.

The initiation of the doublet pattern at 90 s into the fatigue task immediately increased force output upon application during the maximal (29.64 ±
1.79% increase from preceding pulse) and submaximal (34.15 ± 3.00% increase) stimulation.

**Fatigue Test Force–Time Integrals.** FTIs showed significant overall differences across pattern and intensity level. The FTI for the 20–40-Hz pattern was significantly greater than for the doublet pattern during maximal intensity stimulation. There was no significant difference between the 20-Hz and the 20–40-Hz FTIs at this intensity. The FTI for the doublet pattern was significantly higher than either the 20-Hz or the 20–40-Hz pattern during submaximal stimulation (Fig. 3).

**Force–Frequency Distributions.** Average force data from the 10-, 20-, 30-, 40-, and 50-Hz trains for each pattern at both intensities are shown in Figure 4. Forces at the five different frequencies were similar across patterns. Maximal intensities produced higher average forces than submaximal intensities of stimulation. Percentage decreases in the five evoked forces at the various frequencies following fatigue are shown in Figure 5. There were no differences in relative force loss across intensity levels. There was a significant overall effect of frequency, with the 10-Hz trains producing significantly greater force loss than the other frequencies.

**M-Wave Amplitude.** Average M-wave amplitudes before and after fatigue for maximal and submaximal intensities are shown in Figure 6. There were no significant differences in values obtained before and after fatigue, validating consistency in electrode placement and stability. Additionally, no significant differences in maximum M-wave amplitudes were
present across all testing days. Submaximal M-wave amplitudes averaged approximately 72% of the maximal M-wave amplitude for all tests.

DISCUSSION

Maximal and submaximal stimulation intensities generated different results during evoked contractions with variable-frequency patterns. During submaximal intensities, the doublet pattern produced the highest average forces and the highest FTI; during maximal stimulation, the doublet pattern was the least effective at maintaining force output.

Submaximal nerve stimulation recruits motor units with fast-conducting axons before slow-conducting ones (in contrast to voluntary contraction) in animal models.9,15 However, in humans, motor unit recruitment has been found to be fast to slow41 or random39 in healthy muscle, and fatigue-resistant to fatigable (slow to fast) in paralyzed muscle.17 The types of motor units activated during submaximal stimulation in our study are unclear. During the 20-Hz protocol, forces during the fatigue test decreased by an average of 42% during maximal stimulation and 29% during submaximal stimulation, indicating that more fast-fatigable motor units may have been recruited during the maximal stimulation. Similarly, Godfrey et al.17 found that paralyzed muscle was more fatigable when using maximal rather than submaximal nerve stimulation.

Although doublets produce more force after fatigue than before,12,25,29 fatigue tasks using trains that included doublets have produced more,4,7,32 less,40 or the same42 force as constant-frequency stimulation. Scott and Binder-Macleod39 found that, during submaximal quadriceps muscle stimulation, constant-frequency trains that switched to trains that included doublets improved force output over time compared to constant-frequency stimulation. In the present study, FTI was enhanced with the use of doublets during submaximal but not maximal stimulation intensities.

Two pulses with short interspike intervals have the potential to increase available calcium.13 Further, Parmiggiani and Stein37 suggested that the rapid pulses of a doublet impart a forceful tightening of the series elastic element in fatigued muscle and therefore could cause the increase in force that occurred when the doublet trains began midway through the submaximal fatigue test in our study. At maximal intensities, a force increase was also present, but to a lesser extent. Submaximal stimulation may have enhanced the effect of the doublet due to the larger number of inactive motor units and greater slack in the muscle at the time of initiation.
Increasing Stimulation Frequency during Fatigue.
Bigland-Ritchie et al.² originally proposed that, during sustained evoked maximal contractions, stimulation frequencies should decrease (80 to 20 Hz) over time to prevent neuromuscular transmission failure (reduction in M-wave amplitude) associated with constant high-frequency (80-Hz) stimulation. Marsden et al.³⁴ later suggested that the slowing of motor unit firing rate during MVCs matched the slowing of contractile rate during fatigue and termed this “muscle wisdom.” More recently, however, Fuglevand and Keen¹⁶ found that, during submaximal evoked contractions, when frequencies were within the range of natural motor unit firing, a reduction in frequency (30 to 15 Hz) exacerbated force loss compared to constant 30-Hz stimulation.

Electrical stimulation in the low-frequency range can cause LFF, where greater force loss occurs during low compared to high frequencies of stimulation.¹⁴ LFF was equally present following all fatigue protocols in our study. Thus, to maintain absolute levels of force over time, stimulation frequencies should increase during fatigue. However, progressively increasing the stimulation frequency during the later stages of fatigue did not increase the overall force–time integral compared to intermittent, constant-frequency stimulation at maximal or submaximal intensities. This is consistent with our previous observations during continuous maximal stimulation of the median nerve for 3 min, in which the frequency was increased from 20 to 40 Hz from the start to the end of the fatigue task.²¹ However, the force loss during higher frequencies correlated with a reduction in M-wave amplitude during the continuous stimulation. In the present study, we used intermittent stimulation and the M-wave amplitudes were well maintained.

During the maximal intensity stimulation in this study, the least amount of force drop from the start to the end of the fatigue task occurred with the increasing frequency protocol, indicating that an increase in frequency was effective at preventing force loss during intermittent stimulation. Improvements in endurance time have also been observed during submaximal intermittent surface stimulation of the quadriceps muscle that increased in frequency in the muscle of able-bodied²⁶,²⁷ and paralyzed⁴¹ patients.

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REFERENCES
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