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Using Customized Rate-Coding and Recruitment Strategies to Maintain Forces During Repetitive Activation of Human Muscles

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Abstract

Background and Purpose—During functional electrical stimulation (FES), clinicians typically increase stimulation intensity to offset fatigue and maintain functional levels of force production. However, recent studies have suggested that increasing the stimulation frequency is an effective strategy for overcoming fatigue during FES. The purpose of this study was to compare the effectiveness of 5 stimulation strategies on maintaining forces during repetitive isometric muscle activation.

Subjects and Methods—The right quadriceps femoris muscles of 12 subjects with no history of lower-extremity orthopedic, neurological, or vascular problems were tested. The 5 stimulation strategies were: progressively increasing the frequency, progressively increasing the intensity, and 3 combination protocols that first increased the intensity and then increased the frequency. The only difference among the 3 combination protocols was the starting frequency used in each protocol (20, 30, or 40 Hz). For all protocols, the stimulation frequency or intensity was increased progressively every time the peak force declined more than 10% from a targeted force level. The specific step increases in frequency or intensity were customized for each subject. A *contraction* was defined as successful when its peak force exceeded 90% of the targeted force level.

Results—The results showed that progressively increasing only the frequency produced 59% more successful contractions than progressively increasing only the intensity. In addition, the combination stimulation protocol that began with 30-Hz trains produced the most successful contractions (mean=1,205 contractions; 35%–74% more than the other 4 protocols tested).

Discussion and Conclusions—The results suggest that increasing the stimulation intensity and then the frequency is the best strategy to maintain muscle performance and could help clinicians design optimal stimulation protocols to use for each patient during FES.

For individuals with central nervous system (CNS) lesions, if the lower motoneuron pathways remain intact, skeletal muscles still can be activated electrically. This use of electrical stimulation to activate paralyzed muscles to produce functional movements is termed "functional electrical stimulation" (FES).[1] During FES, muscle forces can be controlled by

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varying the electrical stimulation frequency (rate coding) and intensity (recruitment). In addition, during FES, skeletal muscles are required to generate precise forces that overcome external loads to repetitively produce a desired movement. For example, during the use of FES for the treatment of foot drop, dorsiflexor muscles must be repetitively activated to produce sufficient ankle dorsiflexion torques to overcome the weight of the foot and shoe and produce enough dorsiflexion excursions to provide ground clearance during the swing phase of gait. Thus, the maintenance of desired muscle forces is an essential prerequisite for successful task performance during FES. However, rapid muscle fatigue and imprecise force control during FES limit its widespread use as a clinical intervention.

The CNS controls skeletal muscle force output by varying both the firing rate (rate coding) and the number of activated motor units (recruitment).[2–5] By calculating the cumulative forces at both minimal and maximal motor unit firing rates for cat limb muscles, Botterman and colleagues[5] demonstrated that when all of the motor units were recruited at their minimum firing rate, the cumulative force output was approximately 10% to 25% of the total tension produced when the motor units were activated at their maximum firing rate. They concluded that rate coding provided a more important contribution than recruitment to muscle force production.[5] Analogous to the 2 mechanisms of rate coding and recruitment used by the CNS for skeletal muscle force control, stimulation frequency and intensity are the 2 parameters that can be modulated to control muscle force during FES. However, unlike physiological activation, the modulation of both frequency and intensity is not used for the control of muscle force in current FES systems. Most FES systems use a constant stimulation frequency (~30 Hz) and only increase the stimulation intensity to maintain muscle force output and overcome fatigue during repetitive activation.[6–11] Volitional and electrically elicited contractions also differ in the order of motor unit recruitment. Motor units are recruited in order from small to large units during volitional contractions.[12] In contrast, during FES using surface electrodes, some studies[13–15] suggested that the largest and the most fatigable motor units are recruited first, whereas other studies[16–18] suggested that a less orderly recruitment of motor units is produced.

Some studies have investigated the effects of modulating stimulation frequency and intensity on muscle performance. A study on animal muscles showed that a simultaneous modulation of both stimulation pulse duration and frequency could improve isometric torque generation compared with modulating either the pulse duration or frequency alone.[19] In a subject with paralysis, Graupe and colleagues[20] showed that a stochastic modulation of inter-pulse intervals decreased the rate of quadriceps femoris muscle fatigue compared with stimulation with constant frequency trains. Thrasher and colleagues,[21] however, showed that a random modulation of frequency, amplitude, and pulse duration by ±15% of their mean values every 100 milliseconds did not affect the rate of fatigue during isometric contractions of the tibialis anterior and quadriceps femoris muscles of subjects with spinal cord injuries.

A recent study of individuals without impairments or disabilities showed that, for the same initial peak force, progressively increasing the stimulation frequency every 16 contractions during repetitive stimulation resulted in better isometric performance than either progressively increasing the intensity or maintaining a constant frequency or intensity.[7] Interestingly, although previous studies have shown the significant contribution of rate coding in skeletal muscle force production during both voluntary[3,5] and electrically elicited[7] contractions, no study has systemically investigated how increasing both stimulation frequency and intensity can be used to overcome muscle fatigue and maintain a targeted force level during repetitive electrical stimulation. Thus, the purpose of this study was to compare the effectiveness of customized stimulation strategies involving progressively increasing stimulation frequencies and intensities on the maintenance of right quadriceps femoris muscle forces in subjects without impairments or disabilities during repetitive activation.

Materials and Methods

Subjects

Twelve subjects (8 female, 4 male), ranging in age from 21 to 31 years (mean = 23.25m SD = 2.70), with no history of lower-extremity orthopedic, neurological, or vascular problems voluntarily participated in this study. Sample size estimation, which was based on the results from a preliminary study (unpublished observations), showed that 12 subjects were needed for analysis of variance (ANOVA) to achieve a power level of 0.80 (α<.05). Subjects were recruited from the general population of students at the University of Delaware. Each subject was informed about the nature of the research, the procedures, and the potential risks involved and signed an informed consent form approved by the Human Subjects Review Board of University of Delaware.

Experimental Setup

Subjects were seated on a Kin-Com III 500–11 computer-controlled dynamometer[*] with their hips flexed to approximately 85 degrees and their knees flexed to 90 degrees. Each subject's trunk, waist, and thigh were stabilized using inelastic straps with Velcro closures.[†] The axis of the dynamometer was aligned with the axis of the subject's knee joint. A force transducer was placed at the anterior aspect of the tibia, with the lower edge of the transducer pad positioned 2.5 cm proximal to the lateral malleolus. Force recorded by the transducer was a measure of knee extension torque produced by the right quadriceps femoris muscles in response to electrical stimulation.

A Grass electrical stimulator (model S8800[‡]) and an SIU8T stimulus isolation unit[‡] were used to deliver voltage-regulated electrical stimulation to the quadriceps femoris muscles. A personal computer equipped with a PCI-6Q24FDAQ board, a PCI6602 counter-timer board, and custom-written LabVIEW software (version 6.0[§]) was used to control the timing of all pulses during testing. Although stimulation intensity can be modulated by varying either pulse amplitude or duration, pulse duration modulation was chosen in the present study because it can be more precisely controlled and requires less charge per stimulus pulse compared with stimulation amplitude modulation.[22] A custom-made pulse-duration control switch was connected in series with the Grass stimulator to enable the modulation of pulse duration from the computer. Two 7.6- × 12.7-cm, self-adhesive electrodes (Versa-Stim[‖]) were used for electrical stimulation. The electrode connected to the anode of the stimulator was placed over the motor point of the rectus femoris muscle and the vastus lateralis muscle belly; the cathode was placed over the motor point of the vastus medialis muscle and the distal portion of the rectus femoris muscle belly.[23]

Experimental Procedure

Each subject participated in 6 testing sessions. Sessions were separated by a minimum of 48 hours. Subjects were asked to refrain from strenuous exercise for 24 hours before each testing session.

Session 1—The purposes of the first session were to determine each subject's maximal voluntary isometric contraction (MVIC) and to obtain the force-frequency and force-intensity relationships of the quadriceps femoris muscles. The force-frequency and force-intensity

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[†]Velcro USA Inc, PO Box 5218, 406 Brown Ave, Manchester, NH 03103.
[‡]Grass Technologies, Astro-Med Inc, 600 E Greenwich Ave, West Warwick, RI 02893.
[§]National Instruments, 11500 N Mopac Expwy, Austin, TX 78759.
[‖]ConMed Corp, 525 French Rd, Utica, NY 13502.

relationships were obtained to determine the specific increments in frequency and intensity (ie, modulation steps) to be used during each of the 5 stimulation protocols (see Appendix for details). The MVICs were determined using the burst superimposition technique.[24] The burst superimposition technique used an 11-pulse (600-microsecond pulse duration, 135 V), 100-Hz train to stimulate the muscles while subjects performed a maximum voluntary contraction of their quadriceps femoris muscle. The MVIC was accepted if the volitional force was ≥95% of the "superimposed" tetanic force.[24] If any subject could not perform a successful MVIC within 3 attempts, they were not tested on that day and were rescheduled for another testing session. However, all subjects reached the 95% criterion during their first session.

After a subject's MVIC was successfully determined, he or she rested for 5 minutes. Next, stimulation amplitude was set for the first testing session. Quadriceps femoris muscles were first potentiated by delivering twenty 12-pulse (600-microsecond pulse duration), 14-Hz trains every 5 seconds (240 total pulses) with the stimulation amplitude set initially to produce approximately 15% of the subject's MVIC. We used a standardized protocol to potentiate the muscles at the start of each testing session to control for varying levels of potentiation across subjects and across testing sessions.[25] Previous work in our laboratory showed that, when using stimulation frequencies of 14 Hz or higher, the total number of pulses delivered to the muscle was the primary factor in potentiation development and approximately 200 pulses were needed to potentiate the human quadriceps femoris muscles.[25] Next, a series of 60-Hz (600-microsecond pulse duration), 300-millisecond-long trains was used to set the stimulation amplitude. The stimulation amplitude was gradually increased until the muscle force responses reached 20% of the subject's MVIC. The amplitude then was held constant throughout the remainder of the first session.

Immediately after setting the stimulation amplitude, a testing protocol containing sixty 300-millisecond-long trains was delivered to the quadriceps femoris muscles to examine the force responses to different stimulation frequencies and intensities. The testing trains included the 30 combinations of 6 different frequencies (10, 12.5, 20, 30, 40, and 60 Hz) and 5 different pulse durations (100, 200, 300, 400, and 600 microseconds). The 30 trains were delivered in a random order at a rate of 1 train every 10 seconds to avoid fatigue and then immediately repeated in a reverse order for a total of 60 trains. The force responses to the testing train with the same stimulation frequency and intensity combination were averaged and analyzed to obtain each subject's force-frequency and force-intensity relationships.

Sessions 2 to 6—The purpose of the second to sixth sessions was to compare the effects of 5 different stimulation strategies on isometric muscle force maintenance during repetitive activation. Each session involved one stimulation protocol, and each of the stimulation trains used in these sessions was 300 milliseconds long. At the beginning of each session, twenty 12-pulse (600-microsecond pulse duration), 14-Hz trains, with the stimulation amplitude set initially to produce approximately 35% of each subject's MVIC, were delivered to the quadriceps femoris muscles every 5 seconds to potentiate the muscles. Next, a series of 60-Hz (600-microsecond pulse duration), 300-millisecond-long trains was used to set the stimulation amplitude. The stimulation amplitude was gradually increased until the muscle force responses reached 50% of the subject's MVIC. Once the amplitude was set, it was held constant throughout the remainder of the session. Each stimulation protocol consisted of a starting frequency and pulse duration (intensity) combination that produced an initial peak force equal to 20% of the subject's MVIC. Immediately after determining the starting frequency and pulse duration, a stimulation protocol was tested.

The order of the 5 stimulation protocols was randomized for each subject. Stimulation trains within each protocol were delivered to the muscles at a rate of one train every 1.2 seconds, and the stimulation frequency or pulse duration was increased progressively every time the peak forces declined by more than 10% from the targeted force level (ie, less than 18% of the MVIC force) due to muscle fatigue. Stimulation was stopped if it failed to maintain muscle peak forces at or above 18% of subject's MVIC while both the stimulation frequency and pulse duration were at their upper limits (60 Hz and 600 microseconds, respectively). A novel calculation method, using the force-frequency and force-intensity relationships, was used to determine the required increments in stimulation frequency and pulse duration to maintain the peak forces at 20% of the subject's MVIC during repetitive activation (see Appendix for details).

The five fatiguing protocols were:

1. Frequency-modulation-only protocol: The pulse duration was fixed at 600 microseconds throughout the protocol, and the starting frequency was set so that the first train of the protocol produced a peak force equal to 20% of a subject's MVIC. Stimulation frequency was increased stepwise until a frequency of 60 Hz was reached.

2–4. Combination-modulation protocols: The starting frequency was 20, 30, or 40 Hz. For each protocol, the starting pulse durations were set so that the first train of the protocol produced a peak force equal to 20% of a subject's MVIC. The pulse duration was increased stepwise first. After the pulse duration reached 600 microseconds, the frequency was increased stepwise until it reached 60 Hz.

5. Intensity-modulation-only protocol: The frequency was fixed at 60 Hz throughout the protocol, and the starting pulse duration was set so that the first train of the protocol produced a peak force equal to 20% of a subject's MVIC. Pulse duration was increased stepwise until it reached 600 microseconds.

Preliminary Study

A preliminary study (results presented in Fig. 1) was conducted to investigate the effectiveness of progressively increasing pulse duration followed by progressively increasing stimulation frequency versus progressively increasing stimulation frequency followed by progressively increasing pulse duration (modulation order) on muscle force maintenance during repetitive electrical stimulation for 3 subjects without impairments or disabilities. Six stimulation protocols were tested. Three of the combination-modulation protocols progressively increased pulse duration first and then progressively increased stimulation frequency (initial frequencies: 20, 30, and 40 Hz). The other 3 combination protocols progressively increased stimulation frequency first and then progressively increased pulse duration (initial frequencies: 20, 30, and 40 Hz). The stimulation frequency or pulse duration was adjusted so that the initial peak forces produced by each of the 6 protocols were equal to 20% of a subject's MVIC. Brief stimulation trains (300 milliseconds long) were delivered to the muscles at a rate of one train every second to fatigue the muscle. The stimulation frequency or pulse duration was increased every time the peak force declined 10% from the initial targeted force level (20% of a subject's MVIC).

The results from our preliminary study showed that, on average, the combination protocols that first increased the pulse duration and then increased the frequency produced more successful contractions than the combination protocols that first increased the stimulation frequency and then increased the pulse duration for the starting frequencies of 20 and 30 Hz (Fig. 1). The 2 protocols that used a starting frequency of 40 Hz showed little difference in performance. Thus, it appears that stimulation protocols that progressively increase stimulation pulse duration followed by progressively increasing the frequency are a better approach for muscle force maintenance during repetitive activation. We, therefore, used stimulation strategies that progressively increased the pulse duration followed by progressively increasing the frequency in the current study.

Data Management and Analysis

The primary dependent variable in the current study was the number of successful contractions. A contraction was defined as successful when its peak force was equal to or exceeded 90% of the targeted force level (ie, 18 % of a subject's MVIC). Peak forces were calculated using the customized LabVIEW program. The numbers of successful contractions produced by the different stimulation protocols were compared using a one-way ANOVA for repeated measures (SPSS version 14.0[#]) to determine the best stimulation strategy for muscle force maintenance during repetitive activation. Tukey *post hoc* tests were performed if a significant main effect was observed. In addition, the number of successful contractions produced by the intensity-modulation-only protocol and the intensity-modulation portions of the 3 combination-modulation protocols were compared using a one-way ANOVA for repeated measures. Tukey *post hoc* tests were performed if a significant main effect was observed. Similar comparisons were made for the frequency-modulation portions of the protocols. Statistical significance was accepted at $P \leq .05$.

Results

The peak force responses during the 40-Hz combination-modulation protocol for one typical subject are shown in Fig. 2. The first stimulation train (stimulation frequency of 40 Hz and pulse duration of 120 microseconds) produced a peak force of 119 N (20% of a subject's MVIC). The peak forces gradually declined due to muscle fatigue from repetitive activation. Each time the peak forces declined below 18% of a subject's MVIC, the stimulation intensity or frequency was increased and produced peak forces close to the initial force level (119 N). These results show that the frequency and intensity modulation step calculation successfully predicted the required frequencies and pulse durations for peak force maintenance during repetitive activation. Similar results were observed for all subjects. Four testing sessions for 4 different subjects, including three 30-Hz and one 20-Hz combination-modulation protocols, were terminated before the stimulation frequency or intensity reached the highest value due to muscle soreness and discomfort from long testing durations (more than 1,000 contractions).

The total number of modulation steps for the 5 fatiguing protocols tested in the current study ranged from 10 (frequency-modulation protocol) to 14 (20- and 30-Hz combination-modulation protocols). For the 3 combination-modulation protocols, the intensity-modulation steps ranged from 9 (20-Hz combination-modulation protocol) to 12 (30- and 40-Hz combination-modulation protocols); the frequency-modulation steps ranged from 1 to 5.

The average number of successful contractions produced by each of the 5 stimulation protocols ranged from 317 contractions (intensity-modulation-only protocol) to 1,205 contractions (30-Hz combination-modulation protocol). A significant main effect was observed when comparing the total numbers of successful contractions produced by the 5 stimulation protocols ($F=7.80$, $P<.05$) (Fig. 3). *Post hoc* tests showed that the 30-Hz combination-modulation protocol produced significantly more successful contractions than the frequency-modulation-only, 20-Hz combination-modulation, 40-Hz combination-modulation, and intensity-modulation-only protocols (35%, 43%, 47%, and 74% more, respectively) (all $P<.05$). In addition, the intensity-modulation-only protocol produced less successful contractions than each of the other stimulation protocols (all $P<.05$). Comparing the effectiveness of progressively increasing stimulation frequency versus pulse duration, we found that the number of successful contractions produced by the frequency-modulation-only protocol (confidence interval [CI]=530.64–1,039.19) was significantly greater than the number of contractions produced by the intensity-modulation-only protocol (CI=180.81–455.02) ($P<.05$).

[#]SPSS Inc, 233 S Wacker Dr, Chicago, IL 60606.

A significant difference (F=10.26, *P*<.05) was observed when comparing the numbers of successful contractions produced by the intensity-modulation portion of the stimulation protocols tested (Fig. 3). The frequency-modulation-only protocol did not have an intensity-modulation portion and was excluded from this comparison. *Post hoc* tests showed that the intensity-modulation portion of the 20-Hz combination-modulation protocol produced the fewest successful contractions (CI=84.60–172.73) compared with each of the other protocols tested (all *P*<.01). In addition, the number of successful contractions produced by the intensity-modulation portion of the 30-Hz combination-modulation protocol (CI=471.34–869.33) was significantly greater than that of the intensity-modulation only protocol (CI=180.81–455.02) (*P*<.05).

A significant difference (F=8.22, *P*<.05) was observed when comparing the numbers of successful contractions produced by the frequency-modulation portion of the stimulation protocols tested. *Post hoc* tests showed that the 40-Hz combination-modulation protocol produced the fewest number of successful contractions (CI=87.10–230.90) compared with any of the other stimulation protocols tested (all *P*<.05).

Discussion

The current study was the first to report the use of stimulation strategies with customized frequency and intensity modulation for maintaining a targeted isometric force level during repetitive activation of human quadriceps femoris muscles. The major finding of this study was that the combination strategy that began at 30 Hz and first progressively increased the pulse duration and then progressively increased the frequency produced more successful contractions than any of the other stimulation strategies tested. Furthermore, the second best stimulation strategy for maintaining isometric muscle force was fixing the stimulation intensity at the maximum level and progressively increasing only frequency (frequency-modulation-only protocol). Interestingly, the stimulation strategy that fixed the stimulation frequency at the maximum level and progressively increased only intensity (intensity-modulation-only protocol) produced the fewest successful contractions.

We hypothesize 4 different physiological mechanisms that could contribute to the findings of the current study: (1) the force generated by each muscle fiber, (2) the number of pulses delivered during each of the protocols, (3) the extent of low-frequency fatigue (LFF) produced, and (4) the available range for frequency modulation.

The first physiological mechanism—force generation by each muscle fiber—can be used to explain the differences in performance between the frequency-modulation-only and intensity-modulation-only protocols. During the intensity-modulation-only protocol, the frequency was maintained at 60 Hz, and the lowest intensity was used initially (pulse duration at 143.58 microseconds). Thus, a smaller fraction of the motor unit pool was recruited initially. Whenever the muscles failed to generate the targeted peak forces, the pulse duration was progressively increased to recruit more motor units. Motor units that were recruited earlier in the protocol continued to be activated throughout the protocol. Thus, motor units that were recruited early were activated for a longer period of time compared with the motor units that were recruited later in the protocol.

In contrast, during the frequency-modulation-only protocol, the pulse duration was maintained at 600 microseconds throughout the protocol. Thus, because all of the protocols used the same pulse amplitude and had a maximum pulse duration of 600 microseconds, the maximum number of motor units that was recruited within each of the protocols was recruited throughout the frequency-modulation-only protocol.

This allowed the sharing of force generation among a greater number of muscle fibers throughout the protocol. The amount of adenosine triphosphate (ATP) utilized by actin-myosin adenosine triphosphatase (ATPase) is proportional to the force generated by each fiber.[26,27] Thus, greater ATP utilization by the actin-myosin ATPase per muscle fiber occurred during the intensity-modulation-only protocol compared with during the frequency-modulation-only protocol.

We, therefore, believe that the frequency-modulation-only protocol produced less fatigue in the recruited motor unit population because of greater motor unit recruitment at the commencement of the protocol, resulting in lower ATP consumption per active muscle fiber by actin-myosin ATPase and consequently improving muscle performance, as evidenced by a greater number of successful contractions. The contribution of greater motor unit recruitment at the commencement of the protocol also could help explain the generally better muscle performance observed during the combination-modulation protocols in which intensity was increased first followed by increasing frequency than the combination-modulation protocols in which frequency was increased first followed by increasing intensity in our preliminary study.

The second physiological mechanism—the number of stimulation pulses—also may have contributed to the large difference between the frequency-modulation-only and intensity-modulation-only protocols. During the intensity-modulation-only protocol, when all of the motor units were always activated at a high frequency of 60 Hz, a greater number of stimulation pulses were delivered to the muscle compared with during the frequency-modulation-only protocol, in which stimulation frequency was progressively increased from a low frequency (~13 Hz). The Ca^{2+} ATPase and Na^{+}-K^{+} ATPase reactions in response to each action potential contribute to ATP utilization during muscle force generation.[28–31] Because relatively fewer pulses were delivered during the frequency-modulation-only protocol compared with the intensity-modulation-only protocol, less ATP was utilized by the Ca^{2+} ATPase and Na^{+}-K^{+} ATPase during the frequency-modulation-only protocol.[31,32] Muscle fatigue is related to metabolic demand.[33–35] In addition, previous studies[16,36,37] showed that higher stimulation frequencies contribute to more rapid muscle fatigue. Thus, the frequency-modulation-only protocol might be less fatiguing than the intensity-modulation-only protocol because it delivers fewer pulses to the muscles. Taken together, compared with the intensity-modulation-only protocols, the frequency-modulation-only protocol appeared to be less fatiguing due to less metabolic demand per recruited muscle fiber by greater motor unit recruitment at the commencement of the protocol and by delivering fewer stimulation pulses, which resulted in better performance during repetitive activation.

The third physiological mechanism—LFF—may help to explain the differences in performance among the 3 combination-modulation protocols. Our results showed that the initial stimulation frequency and intensity combination had a significant effect on the number of successful contractions produced. First described by Edwards and colleagues in 1977,[38] LFF is characterized by a preferential loss of force at low stimulation frequencies and a slow recovery over the course of hours or even days (for a review, see Jones[39]). The mechanism that causes LFF still is not clear, but both metabolite build-up and the impairment in Ca^{2+} release from the sarcoplasmic reticulum have been shown to play a role in the development of LFF.[40,41] Low-frequency fatigue has been suggested to cause a shift in the normalized force-frequency relationship toward higher frequencies.[42,43] Because the majority of the shift in the force-frequency relationship due to LFF occurred at frequencies lower than 30 Hz, the loss in the force responses at 20 Hz would be greater than at 30 Hz. Thus, muscle peak forces would be more difficult to maintain at a targeted level during repetitive activation using 20-Hz stimulation trains. Thus, a faster increment in pulse duration was needed to maintain muscle peak force at the targeted level during the 20-Hz combination-modulation protocol, resulting in fewer successful contractions produced compared with the 30-Hz combination-modulation protocol.

We, therefore, believe the findings that fewer successful contractions produced by the intensity-modulation portion of the 20-Hz combination-modulation protocol and the overall better performance by the 30-Hz versus the 20-Hz combination-modulation protocols were primarily due to the greater LFF produced by repetitive stimulation at 20 Hz compared with 30 Hz. However, we unfortunately did not measure the extent of LFF in the current study and, therefore, could not test for differences in the extent of LFF among the protocols.

Finally, the fourth physiological mechanism—the available range for frequency modulation—also can be used to explain the differences in performance among the 3 combination-modulation protocols. Previous studies of human quadriceps femoris muscles have shown a sigmoidal relationship between stimulation frequency and muscle force production, with a steep rising portion generally observed between 5 and 40 Hz and with near-maximal forces produced at approximately 60 Hz.[16,43] In the present study, we decided a priori that the maximum stimulation frequency used was 60 Hz. Compared with the 20- and 30-Hz combination-modulation protocols, the 40-Hz combination-modulation protocol had far less capacity to modulate frequency to affect an increase in the force generated. Thus, this limited capacity of the 40-Hz combination-modulation protocol to increase force could explain the fewer successful contractions produced during the frequency-modulation portion of the 40-Hz combination-modulation protocol. Thus, we believe that 30 Hz was the best initial frequency for quadriceps femoris muscle activation because it avoided LFF during the intensity-modulation portion of the protocol and retained a large capacity to increase force during the frequency-modulation portion of the protocol.

This is the first study on human muscles that systematically investigated stimulation strategies involving increase of both the frequency and intensity based on customized modulation steps and real-time feedback of muscle forces. To our knowledge, only a few previous studies have investigated modulation of frequency and intensity on animal muscles to maintain muscle forces[19] or have tested the effects of a random modulation (both increase and decrease) of frequency and intensity on muscle fatigue during electrical stimulation.[21]

Two studies from our laboratory examined the effect on skeletal muscle performance of modulating from a lower frequency to a higher frequency during repetitive electrical stimulation for subjects without impairments or disabilities[44] and subjects with spinal cord injuries.[45] A more recent study[7] compared the effects of progressively increasing the frequency, progressively increasing the intensity, or not changing the stimulation frequency or intensity during repetitive isometric contractions of human quadriceps femoris muscles. However, there were important differences in methodology between the current study and our previous studies. The current study compared the effects of progressively increasing both frequency and intensity on force maintenance during repetitive electrical stimulation. In contrast, Kesar et al[7] compared the effects of progressively increasing either frequency alone or intensity alone on the force produced, and Kebaetse and colleagues[44,45] only modulated stimulation frequency and only increased from a lower frequency to a higher frequency. In the current study, by progressively increasing the stimulation frequency and intensity based on real-time feedback of muscle forces, muscle peak forces were maintained at a targeted level repetitively, which is similar to functional movements such as walking, in which muscles need to generate targeted forces repetitively. In contrast, previous studies either modulated the stimulation frequency or intensity every 16 contractions regardless of the peak force generated[7] or modulated stimulation frequency using only one step and did not try to maintain the muscle's performance in the protocol.[44,45] Another recent study[46] showed the enhancement of paralyzed human ankle muscle performance by the use of feedback-controlled stimulation strategies. However, unlike the current study, which investigated effects of modulating both frequency and intensity, only frequency modulation was tested by Shields and colleagues.[46]

During voluntary contractions, the CNS uses both recruitment and rate coding to modulate muscle forces. When the recruitment is completed at submaximal force levels, higher forces are achieved by using progressively higher activation rates of previously recruited motor units.[4,47] Interestingly, our preliminary study comparing stimulation frequency and intensity modulation order found that a similar motor unit activation strategy was needed to improve muscle peak force maintenance during repetitive electrical stimulation. Our results showed that progressively increasing stimulation frequency after reaching the maximum recruitment (600-microsecond pulse duration) (ie, progressively increasing pulse duration intensity followed by progressively increasing stimulation frequency) produced more successful contractions than progressively increasing the intensity after reaching the maximum frequency (60 Hz) (ie, progressively increasing stimulation frequency followed by progressively increasing pulse duration intensity). Current FES systems use a constant frequency (20–40 Hz) and only increase stimulation intensity to maintain muscle force output to overcome fatigue during repetitive activation.[6–11] Our findings suggest that, to improve muscle performance during repetitive activation of human skeletal muscle, such as during FES, both frequency and intensity modulation should be used and the modulation should start with progressively increasing intensity as seen in the current approach. After the stimulation intensity reaches the maximum level, progressively increasing frequency could allow the muscle to maintain a targeted force output for a longer period of time.

The current study served as a preliminary work that investigated the effectiveness of using 2 physiological mechanisms—rate coding and recruitment—for skeletal muscle force maintenance during repetitive electrical stimulation. Future studies are needed to confirm the usefulness of the current findings to other muscle groups and paralyzed muscles in patient populations for FES applications.

Conclusion

The current study was the first to investigate the effectiveness of motor unit rate coding and recruitment, and the combination of the 2 physiological mechanisms, on skeletal muscle force maintenance during repetitive electrical stimulation. Our findings suggest that, to maximize a muscle’s performance during repetitive activation of muscles using electrical stimulation, it would be useful to first determine the pre- and post-fatigue force-frequency relationships of the target muscles and select a starting stimulation frequency that avoids the LFF and provides sufficient capacity to increase force when the frequency is increased. Next, the best stimulation strategy would be progressively increasing the stimulation intensity first, then progressively increasing the stimulation frequency after the intensity reaches the maximum. The appropriate increments in the stimulation frequency and intensity are customized for each individual and could be determined by using each person’s force-frequency and force-intensity relationships. The findings of the current study could help provide general guidelines for improving skeletal muscle performance during repetitive electrical stimulation and help design optimal stimulation protocols for the application of FES. It appears that an optimal trade-off among the extent of LFF, force generated by each muscle fiber, number of stimulation pulses delivered, and the available range for frequency modulation can explain the success of the 30-Hz combination-modulation protocol.

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Appendix

Modulation Step Calculation

The modulation steps for both stimulation frequency and intensity were identified for each subject based on their force-frequency and force-intensity relationships. Here we use the force-intensity relationship as an example for describing the intensity modulation step calculation methods. First, an exponential equation,

$$\begin{aligned} &F = A\left(1 - e^{-(\mathrm{PD}-\mathrm{PD}_0)/\tau}\right) \\ &\qquad \text{for PD} \geq \mathrm{PD}_0 \\ &F = 0 \text{for PD} < \mathrm{PD}_0, \end{aligned}$$

was used to fit each of the force-intensity relationship curves, where parameter *A* is the scaling factor for the force (*F*), *PD* represents the duration of the stimulation pulse (in microseconds), PD_0 represents the threshold pulse duration (in microseconds) above which we predict there is a measurable force, and τ is the time constant controlling the rise of the force with increasing pulse duration. Because muscles cannot generate a negative force, *F* will be equal to zero when $PD \leq PD_0$.

A recent study from our laboratory[a] comparing the parameter values across a wide range of frequencies and between nonfatigue and fatigue conditions found that the value for both PD_0 and τ were consistent across frequencies and between non-fatigue and fatigue conditions and that only parameter *A*, the scaling factor, changed with changes in stimulation frequency or muscle fatigue. These results indicated that the shape and the threshold of the force-intensity relationship curve stayed the same, and the relationship was scaled according to the stimulation frequency and physiological conditions. The consistency in the shape and threshold of the force-intensity relationship curve across stimulation frequencies and conditions enabled us to predict the required stimulation intensity for a targeted force level. Five steps were needed to determine each modulation step (Fig. 4):

Step 1: The force-intensity relationship curve (black curve) obtained during the first session was fitted with the exponential equation shown above, and the parameter values for A, PD_0, and τ for the force-intensity relationship curve were determined.

Step 2: The starting pulse duration was identified by locating the pulse duration that produced 20% of the subject's maximal voluntary isometric contraction (MVIC) (black point). The stimulation trains were delivered at a rate of one train per second; therefore, muscle peak force output gradually declined due to muscle fatigue.

Step 3: We decided a priori that the stimulation intensity would be increased when the peak force dropped below 18% of the subject's MVIC (blue point).

Step 4: When the peak force dropped to 18% of the subject's MVIC, a new curve that represented the relationship between force output and stimulation intensity at that point of time then could be identified. Based on our previous study, only parameter A changed with fatigue. Thus, when all other parameter values were known, the new A value for the new force-intensity relationship curve (blue curve) that passes through the 18% MVIC data point then could be determined.

Step 5: By locating the pulse duration that produced 20% of the MVIC from the new force-intensity relationship curve, the next intensity step was determined.

These steps were repeated until the pulse duration reached 600 microseconds (Fig. 5). To enable peak forces to reach 20% of the subject's MVIC, the last predicted intensity step might exceed 600 microseconds. In that case, we used 600 microseconds for the last modulation step because pulse duration at 600 microseconds could still produce peak forces above 18% of the subject's MVIC. After the stimulation intensity reached the highest value (600 microseconds), stimulation was stopped when peak forces twice dropped below 18% of the subject's MVIC.

Unlike the force-intensity relationship, the force-frequency relationship changed with muscle fatigue. A rightward shift of the normalized force-frequency curve usually was observed after muscle fatigue, and the major shift of the curve occurred at frequencies below 30 Hz (for examples, see Binder-Macleod and colleagues[42,43]). In the current study, the timing for increasing stimulation frequency and intensity occurred only when minimal fatigue was present (muscle peak forces dropped from 20% to 18% of the subjects' MVICs); therefore, only a minor shift in the force-frequency relationship would occur at the early stage of each of the stimulation protocols. In addition, stimulation frequency was progressively increased after the frequency reached 30 Hz or higher, and the shift in the normalized force-frequency relationship was minimal and could be ignored. Thus, we believe that both the minimal shift in the force-frequency relationship at the early stage of the protocol and the progressive increase in frequency with each modulation step could overcome the gradual shift in the force-frequency relationship with fatigue and that the change in the force-frequency relationship with fatigue should have little effect on the accuracy of frequency modulation step prediction when using our calculation method described above. For simplicity, we used the same methods to calculate frequency modulation steps in the current study.

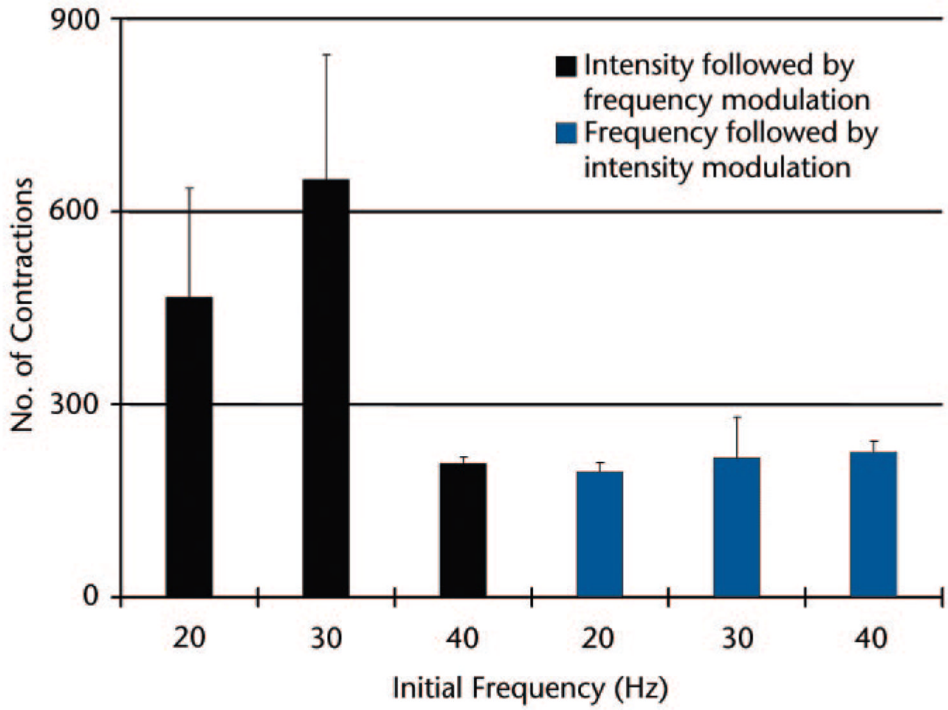

Figure 1.
Number of contractions (mean ± SE) produced by each of the 6 stimulation protocols in our preliminary study (N=3). In general, stimulation strategies that progressively increased stimulation intensity followed by progressively increasing stimulation frequency (black bars) produced more contractions than the strategies that progressively increased stimulation frequency followed by progressively increasing stimulation intensity (blue bars).

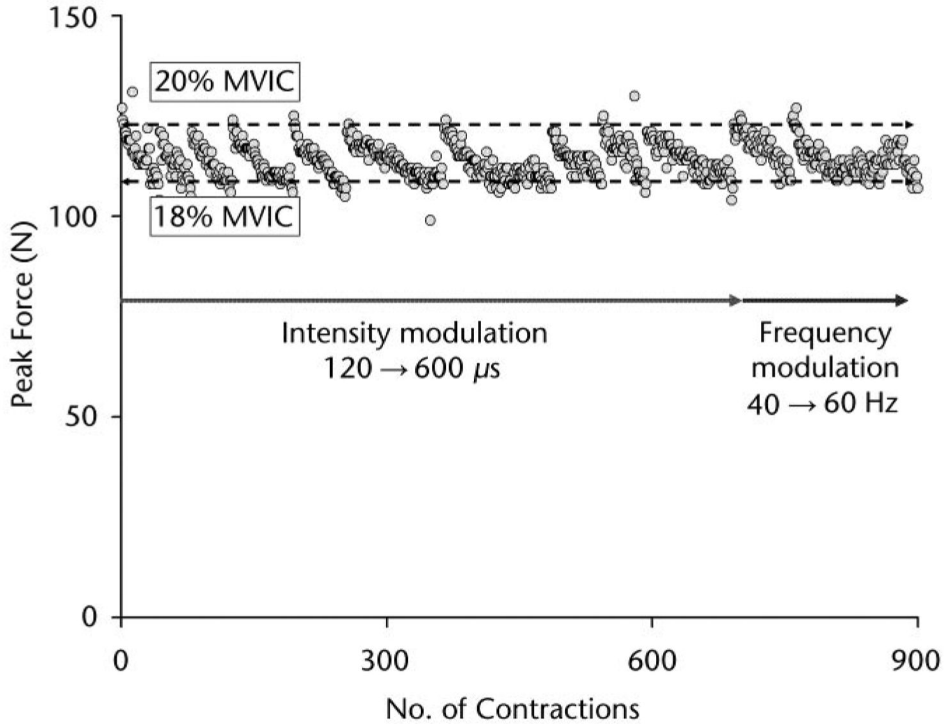

Figure 2.
Peak force responses to each train of the 40-Hz combination-modulation protocol for a typical subject. Each circle represents a peak force for one contraction. The initial peak force produced by the starting frequency (40 Hz) and pulse duration (120 μs) was equal to 20% of the subject's maximal voluntary isometric contraction (MVIC). Stimulation trains were delivered at a rate of one train every 1.2 seconds. First, pulse duration was increased every time the peak forces twice declined below 18% of the subject's MVIC. After the pulse duration reached 600 microseconds, the frequency was increased. Stimulation was stopped when the peak force could not be maintained above 18% of the subject's MVIC using the 60-Hz trains with pulse duration at 600 microseconds.

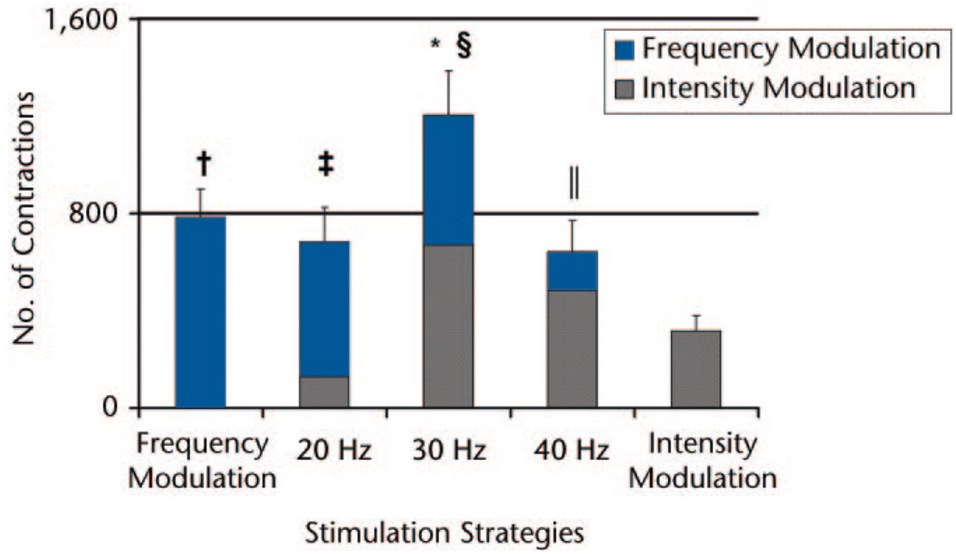

Figure 3.

The total number of successful contractions produced by both the intensity-modulation and frequency-modulation portions of each of the 5 fatiguing protocols. Asterisk (*) indicates that the 30-Hz combination-modulation protocol produced the most successful contractions compared with each of the other protocols. Dagger (†) indicates that the frequency-modulation-only protocol produced significantly more successful contractions than the intensity-modulation-only protocol. Double dagger (‡) indicates that the intensity-modulation portion of the 20-Hz combination-modulation protocol produced the fewest number of successful contractions compared with the intensity-modulation portions of the other stimulation protocols. Section mark (§) indicates that the intensity-modulation portion of the 30-Hz combination-modulation protocol produced significantly more successful contractions than the intensity-modulation-only protocol. Parallel sign (‖) indicates that the frequency-modulation portion of the 40-Hz combination-modulation protocol produced the fewest number of successful contractions compared with the frequency-modulation portions of the other stimulation protocols. Statistical significance was accepted at $P \leq .05$.

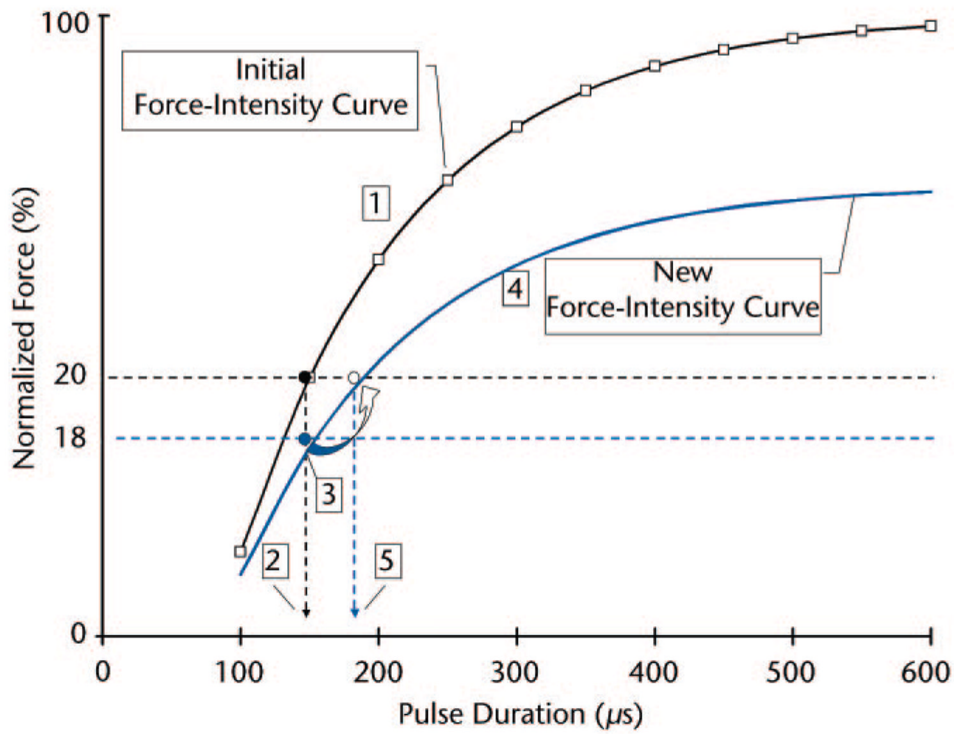

Figure 4.

Example for the determination of stimulation intensity modulation steps based on the force-intensity relationship curve for a typical subject. Stimulation frequency modulation steps were determined based on the same method. The force-intensity relationship curve (black curve) obtained in the first session was fitted with the equation shown in the Appendix, and the parameter values for A, PD_0, and τ were then determined for the subject. The starting pulse duration was determined by locating the pulse duration that produced 20% of the subject's maximal voluntary isometric contraction (MVIC) (black point). When the peak force dropped to 18% of the subject's MVIC (blue point), a new curve (blue curve) representing the new relationship between force output and stimulation intensity then could be determined by calculating the new A value (the results of a previous study[a] showed that only the A value changes with fatigue). By locating the pulse duration that produces 20% of the MVIC from the new force-intensity relationship curve, the next intensity modulation step was determined. Not drawn to scale. See Appendix for details.

[a]Chou LW, Binder-Macleod SA. The effects of stimulation frequency and fatigue on the force-intensity relationship for human skeletal muscle.

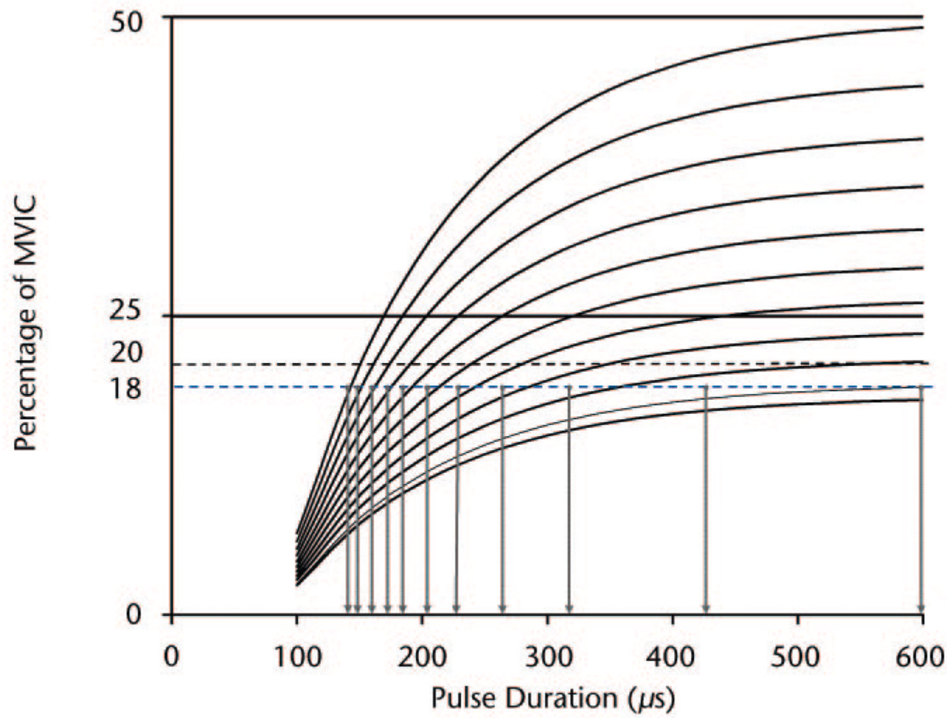

Figure 5.
Family of calculated force-intensity relationship curves plotted using a 60-Hz train for a typical subject. Each curve represents the force-intensity relationship as the muscle is progressively fatigued. The force-intensity relationship shifted down with fatigue. As shown by the arrows, the intensity modulation steps were determined by locating the intersection between the force-intensity curves and the dashed line representing 20% of maximal voluntary isometric contraction (MVIC).