Use of a Mathematical Model to Identify Optimal Activation Patterns for Skeletal Muscle During Cardiomyoplasty

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Abstract

In cardiomyoplasty the latissimus dorsi muscle is electrical stimulated in synchrony with the heartbeat to enhance ventricular function. Current clinical stimulation protocols use 6-pulse trains with pulses within the train equally spaced by 33.3 ms (CFTs). Recent studies, however, have shown that variable-frequency trains (VFTs), which take advantage of the catchlike property of skeletal muscle, can produce more force than traditionally used CFTs. The purpose of this study was to systematically explore the effects of the number and distribution of pulses within the train on muscle contractile output. With the aid of a mathematical model that we developed, a new stimulation pattern was identified that produced the greatest impulse per pulse for fatigued muscles. Experiments were conducted to compare muscle contractile performance by the new stimulation pattern (DFTs) with the traditionally used CFTs and with previously studied VFTs. The 6-pulse DFTs produced a 49% augmentation over the traditionally used 6-pulse CFT and a 23% augmentation over the 6-pulse VFT. DFTs thus show potential for improving muscle contractile performance in assisting cardiac function. This study illustrates the potential for using mathematical models to predict skeletal muscle forces and help to identify the optimal pattern of activation for each patient.

Key words: variable-frequency train, doublet stimulation, functional electrical stimulation, force optimization.

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Cardiomyoplasty is an alternative surgical procedure for patients in end-stage heart failure, but who are not heart transplant candidates. In this treatment, the latissimus dorsi muscle (LDM) is wrapped around the heart's ventricles and stimulation is synchronized with the heartbeat. The practical use of this procedure has been limited due to a number of factors, including the rapid muscle fatigue that develops during repetitive electrical activation [8, 9]. Studies have shown that the stimulation frequency affects both the forces produced [1] and the rate of muscle fatigue [2]. Thus, it is important to use the stimulation pattern that produces the best cardiac assistance.

Current cardiomyoplasty stimulators use 6 uniformly spaced pulses in a 30 Hz train (167-ms train duration) [10]. Such trains are termed constant-frequency trains (CFTs) (for example, see Fig. 1). The 30-Hz stimulation frequency is similar to that of physiological nerve discharges [10]. In addition, a study by Lucas et. al. showed that trains with frequencies higher than 30 Hz were more fatiguing to the LDM [18], suggesting stimulation frequency at 30 Hz is preferable.

More recently it has also been shown that the pattern of the pulses within a train can markedly affect force production and fatigue [3, 7]. Variable-frequency trains (VFTs), which contain one or two brief (~5 ms), initial, interpulse intervals (i.e., an initial doublet or triplet) followed by pulses equally spaced, produce greater impulses (force-time integral) than comparable CFTs [6, 7] under fatigued condition. However, the specific pattern of activation that maximizes the force varies from person to person [15] and, even for the same individual, depends on the physiological conditions of the muscle, such as the level of fatigue [6]. In addition, fatigue is a complex multi-factorial phenomenon and differs from subject to subject [19]. To systematically identify the optimal pattern for each patient experimentally would require numerous tests. One way to assist the search for the optimal pattern is to use mathematical models that can predict forces under a range of physiological conditions.

Materials and Methods

Mathematical model

Our laboratory has recently developed a 2-step model that successfully predicts force response to a wide range of stimulation patterns under various physiological conditions [12]. A major limitation of this model is that separate sets of parameter values were needed to predict the forces produced by CFTs and VFTs. This limitation prevents this model from being used to predict the optimal stimulation pattern when no restrictions are placed on the stimulation pattern. As one of the simplest mathematical representations of muscle force, our 2-step model overlooked many physiological details, such as the nonlinear summation of Ca^{2+} transients in single muscle fibers when stimulated with two closely spaced pulses [13]. The above limitation is probably a result of ignoring the nonlinear summation because the variable-frequency trains contain doublets (closely spaced pulses). We recently modified our two-step mathematical model by adding a factor that takes into account the nonlinear summation of Ca^{2+} transients in single muscle fibers when stimulated with two closely spaced pulses [Ding, J, AS Wexler, SA Binder-Macleod. Development of a mathematical model that predicts optimal activation patterns. Submitted to *J. Appl. Physiol.* August, 1999.]. Our new model consists of two differential equations:

$$\frac{dC_N}{dt} = \frac{1}{\tau_c}\sum_{i=1}^{n} R_i \exp\left(-\frac{t-t_i}{\tau_c}\right) - \frac{C_N}{\tau_c} \qquad (1)$$

with $R_i = 1 + (R_0 - 1)\exp\left(-\frac{t_i - t_{i-1}}{c}\right)$ and

$$\frac{dF}{dt} = A\frac{C_N}{1+C_N} - \frac{F}{\tau_1 + \tau_2 \frac{C_N}{1+C_N}} \ . \qquad (2)$$

The definition of each symbol used in the above equations is detailed in Table 1. Briefly, Equation 1 represents the dynamics of the rate-limiting step leading to the formation of Ca^{2+}-troponin complex (C_N, unitless), in which R_i (unitless) accounts for the nonlinear summation of Ca^{2+} transient in single muscle fibers when stimulated with two closely spaced pulses [13] and it decays with interpulse interval (t_i-t_{i-1}). Equation 2 represents the development of mechanical force (F, Newton), which is driven by force-producing cross-bridges, modelled by a Michaelis-Menten term $C_N/(1+C_N)$.

This new model is governed by only 5 free parameters R_0, A, τ_c, τ_1, and τ_2 (Table 1). Previous studies showed a fixed value of 20 ms for τ_c was sufficient for human quadriceps muscles under different physiological conditions [12], thus only four parameters need to be identified for each muscle. When the model was used to predict the activation pattern that produced the greatest impulse (the area under the force-time response curve) for human quadriceps femoris muscles that were fatigued, a stimulation pattern with doublets throughout the train was identified as the optimal pattern for the majority of subjects [Ding, J, AS Wexler, SA Binder-Macleod. Development of a mathematical model that predicts optimal activation patterns. Submitted to *J. Appl. Physiol.* August, 1999.]. This pattern, denoted as a DFT (Fig. 1), has rarely been tested before.

The purpose of this study was to test the prediction from our mathematical model that DFTs can optimize muscle performance. Experiments were conducted to test 167 ms duration CFTs, VFTs and DFTs. The 167ms was chosen for the train duration because it is the one currently used in clinical cardiomyoplasty.

Human subjects

Twelve healthy subjects, ranging in age 19-35 were recruited for this study. Each subject was informed of the procedures and signed a consent form that was approved by the University of Delaware Human Subjects Review Board before experimentation. All experiments were conducted on human quadriceps femoris muscles.

Experimental setup

The experimental setup was similar to that described previously [5]. Briefly, subjects were seated on a force dynamometer with their hips flexed to approximately 75° and their knees flexed to 90°. Two stimulating electrode pads were placed over the quadriceps muscle. The force transducer was positioned against the anterior aspect of the leg, proximal to the lateral malleolus. The stimulus intensity was set to elicit a force equal to 20% of the subject's maximum voluntary isometric contraction when stimulated with a 6 pulse, 100 pps train. Force data were collected directly from the force dynamometer into a personal computer via an analog-to-digital converter board digitized at a rate of 200 Hz.

Experimental protocols

Isometric muscle performance was tested using CFTs, VFTs and DFTs under non-fatigue and fatigue conditions. All stimulation trains were of 167 ms duration. The testing trains included 6 CFTs (containing 2 to 12 pulses), 5 VFTs (containing 4 to 12 pulses), and 5 DFTs (containing 4 to 12 pulses) (see Figure 1 for details). The doublets in VFTs and DFTs were always 5 ms. The order of the above 16 testing trains was randomized and the same randomized sequence was used for all subjects.

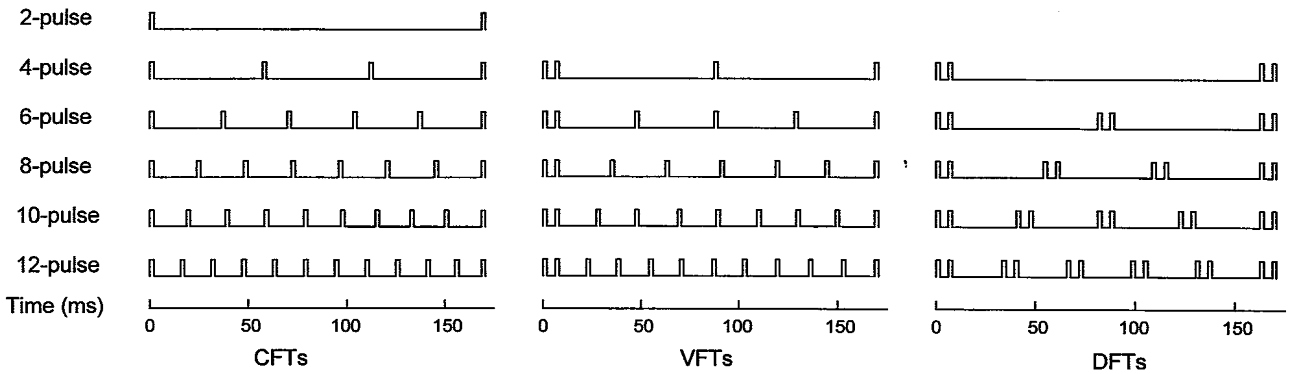

Figure 1. Schematic representation of the three types of trains used in this study. All trains were of 167 ms in duration. The left panel contains CFTs with number of pulse ranging from 2 to 12. The middle panel contains VFT with an initial brief interpulse interval of 5 ms followed by equally spaced pulses and number of pulse ranging from 4 to 12. The right panel contains DFTs with doublets of 5 ms separated by constant interpulse intervals and number of pulse ranging from 4 to 12.

The non-fatigue protocol consisted of the 16 testing trains and its reverse order for a total of 32 trains. Trains were delivered once every 10 s to avoid muscle fatigue. The subjects were then given 5 minute rest before the fatigue test (see Figure 2).

To produce fatigue, a 6 pulse CFT with 33.3 ms IPIs (CFT33.3) was delivered to the muscle at a rate of 1 train per 667 ms (90 times per minute) for a total of 100 contractions. Fatigue testing commenced 667 ms following the last fatigue producing train. Trains continued to be delivered at the rate of 1 train every 667 ms. The 16 testing trains were delivered, with each preceded by three fatigue-producing stimulations (6 pulse CFT with IPI of 33.3 ms). This procedure was used to control for prior activation history of the muscle and to ensure a stable level of fatigue throughout the fatigue testing. Thus, the fatigue protocol consisted of the 100 fatigue-producing trains and 16 testing trains with 48 intervening fatigue-producing trains, for a total of 164 trains.

Table 1. Definition of symbols used in the mathematical model.

Symbol	Unit	Definition
C_N	---	normalized amount of Ca^{2+}-troponin complex
F	N	mechanical force
t_i	ms	time of the i^{th} stimulation
n	---	total number of stimulus in the train before time t
τ_c	ms	time constant controlling the rise and decay of C_N
R_0	---	mathematical term characterizing the magnitude of enhancement in C_N from the following stimuli
A	N/ms	scaling factor
τ_1	ms	time constant of force decline at the absence of strongly bound cross-bridges
τ_2	ms	time constant of force decline due to the extra friction between actin and myosin resulting from the presence of cross-bridges.

Data management

For the non-fatigue data, the two occurrences of each CFT, VFT, and DFT were averaged to minimize the effects of previous activation history on the muscle's responses to each train type. For the force responses to each testing train, impulse (area under the curve) and impulse per pulse were calculated.

Because there were no data for 2-pulse VFTs and DFTs, the 2-pulse CFT data were excluded from comparisons. The same statistical analysis was done for data collected under both non-fatigue and fatigue conditions. First, within subject, one-way, analyses of variance

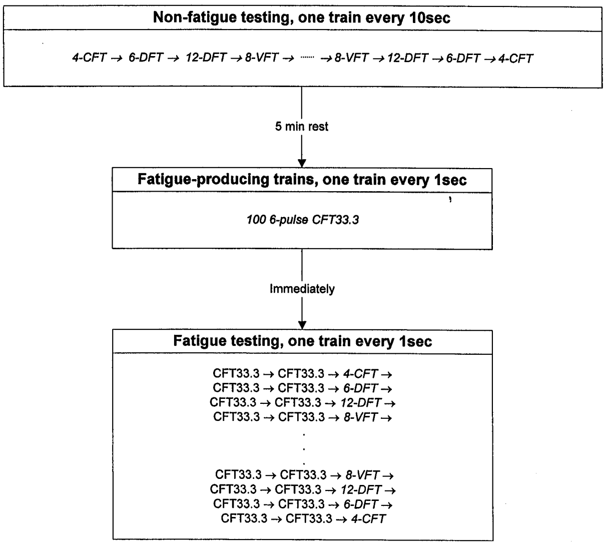

Figure 2. Schematic representation of the experimental protocols used in this study (see text for detail). The number before the train type designates the number of pulses in that train (e.g., 4-CFT means a 4 pulse CFT).

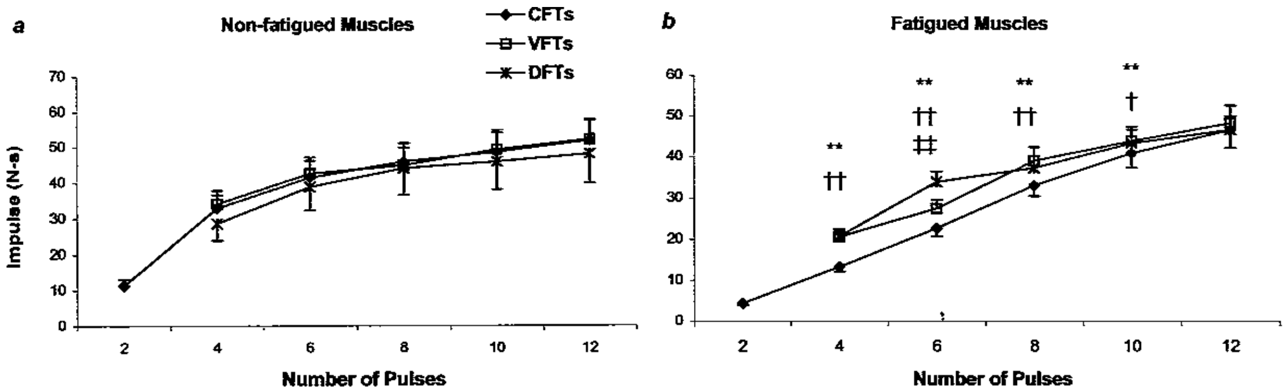

Figure 3. Impulses produced by N pulse CFTs, VFTs and DFTs for muscles under non-fatigued (a) and fatigued (b) conditions. Data were averaged across 11 subjects. Paired t-test was used to compare the impulses of between CFT and VFT (**: $p < 0.01$), CFT and DFT (†: $p < 0.05$; ††: $p < 0.01$), and VFT and DFT (‡‡: $p < 0.05$) at each number of pulses.

(ANOVAs) were used to compare the impulses produced by each of the three train types for trains having the same number of pulses (e.g., to compare the 4-pulse CFTs, VFTs and DFTs). Second, one-way ANOVAs were used to compare the impulses per pulse for trains of the same type and containing different numbers of pulses within each fatigue condition (e.g., VFTs with 4, 6, 8, 10, and 12 pulses). Finally, the pattern that produced the greatest impulse per pulse for each train type was identified and compared across train type using paired t-tests. Statistical significance was accepted for $P \leq 0.05$.

Results

As anticipated, for both conditions, all three train-types showed a positive relationship between the number of pulses and the impulse produced (Fig. 3). Under fatigue, the relationship was steepest and significant differences were observed among CFTs, VFTs and DFTs containing the same number of pulses. Generally, the VFTs and DFTs produced significantly greater impulses than the CFTs for muscles after repetitive activation (Fig. 3*b*). Compared with the 6 pulse CFTs (i.e., the train traditionally used during cardiomyoplasty), the 6 pulse VFTs and DFTs produced a similar amount of impulse for non-fatigued muscles (Fig. 4*a*). In contrast, for fatigued muscles the 6-pulse DFTs produced 23% greater impulses than the 6-pulse VFT and 49% greater impulses than the 6-pulse CFTs (Fig. 4*b*).

In the non-fatigue condition, the 4 pulse CFT produced the greatest impulse per pulse for all CFTs tested and the impulse per pulse significantly declined for CFTs containing more than 4 pulses. Similarly, the 4 pulse VFTs and 4 pulse DFTs produced significantly greater impulse per pulse than other VFTs and DFTs, respectively. However, no significant difference was seen among the 4 pulse CFTs, VFTs and DFTs (Fig. 5*a*).

In contrast, when muscles were fatigued, the 8 pulse CFTs produced the greatest impulse per pulse and the 4, 6 and 12 pulse CFTs produced significantly less impulse per pulse. For VFTs, the 4 pulse VFTs produced the greatest impulse per pulse and the 6, 10 and 12 pulse VFTs produced significantly less impulse per pulse. For DFTs, the 6 pulse DFTs produced the greatest impulse per pulse and all other DFTs produced significantly less impulse per (Fig. 5*b*). The 6 pulse DFT produced 9%

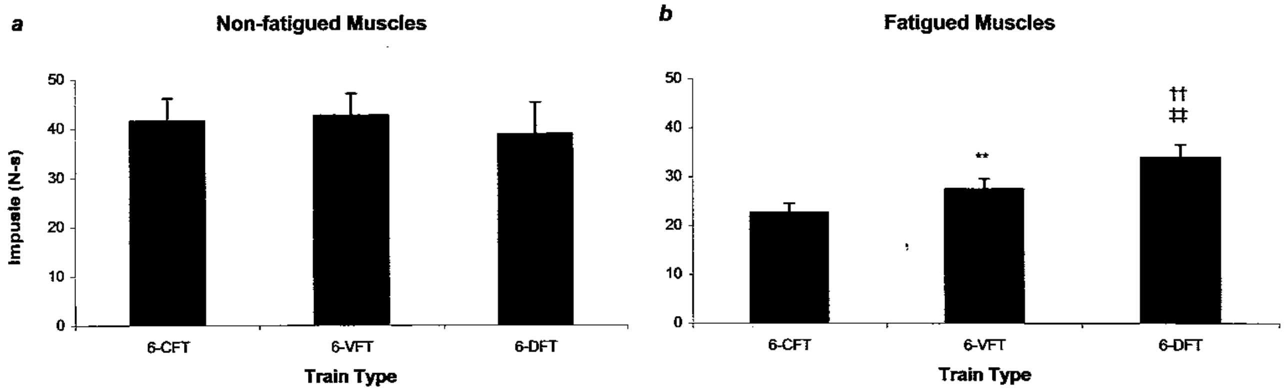

Figure 4. Impulses produced by 6 pulse CFT, VFT and DFT under non-fatigued (a) and fatigued (b) conditions. Data were averaged across 11 subjects. Paired t-test was used to compare the impulse of between CFT and VFT (**: $p < 0.01$), CFT and DFT (††: $p < 0.01$), and VFT and DFT (‡‡: $p < 0.05$).

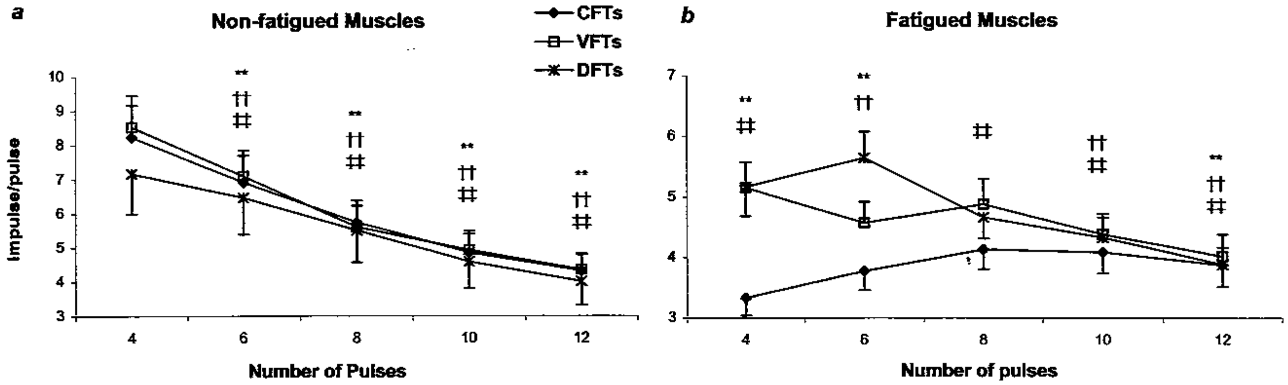

*Figure 5. Averaged impulse per pulse produced by N pulse CFTs, VFTs and DFTs for muscles under non-fatigued (*a*) and fatigued (*b*) conditions (n = 11). **: p < 0.01 between the best CFT and the other CFTs; ††: p < 0.01 between the best VFT and the other VFTs; ‡‡: p < 0.01 between the best DFT and the other DFTs.*

and 22% greater impulse per pulse than the 4-pusle VFT and the 8 pulse CFT (Fig. 6*a*). In addition, comparisons of the impulses produced by these three trains showed that the 6 pulse DFT produced 2% more impulse than the 8 pulse CFT and 64% more impulse than the 4 pulse VFT when the muscles were fatigued (Fig. 6*b*).

Discussion

In this study we investigated how the number and distribution of pulses within the stimulation train affected muscle performance for trains with a 167 ms duration. Our results showed that the impulse increased when more pulses were added into the stimulation trains (Fig. 3). However, previous studies have shown that the greater the number of pulses and the higher the frequency of the train, the greater the rate of fatigue [2]. Because fatigue must be minimized during cardiomyoplasty, the impulse per pulse was chosen as the relevant performance measure. Using this measure to identify the optimal train, our model suggested a new activation pattern, the DFT, as the optimal for activating fatigued muscles.

Though the DFT has rarely been studied experimentally [15, 20], its firing pattern has been observed in human motoneurones during voluntary contractions of skeletal muscles [16]. It is suggested that the origin of this pattern is not the additional discharge due to the after-depolarization, but either the intrinsic properties of the motoneurones or descending synaptic drive or both. Our results showed that for non-fatigued muscles, DFTs were comparable to CFTs and VFTs. In contrast, when muscles were fatigued, DFTs produced significantly more impulse per pulse than any CFT and more or equivalent impulse per pulse than any VFT (Fig. 5*b*). In particular, we found that when the muscles had been repetitive activated (i.e., fatigued), as would occur during clinical cardiomyoplasty, the 6 pulse DFT not only produced greater impulse per pulse than the other DFTs tested, it also produced the greatest impulse per pulse for all of the trains tested.

Recently VFTs have been shown to produce greater forces than traditionally used CFTs. Investigators have taken different approaches to identify optimal VFTs, such as building the train one pulse at a time [15, 23] or systematically varying the initial interpulse intervals of the train [4, 6]. These studies all showed that trains with an initial doublet or triplet of 5~10 ms produced the greatest forces. George and colleagues showed that adding a 10 ms triplet in the beginning of the train could

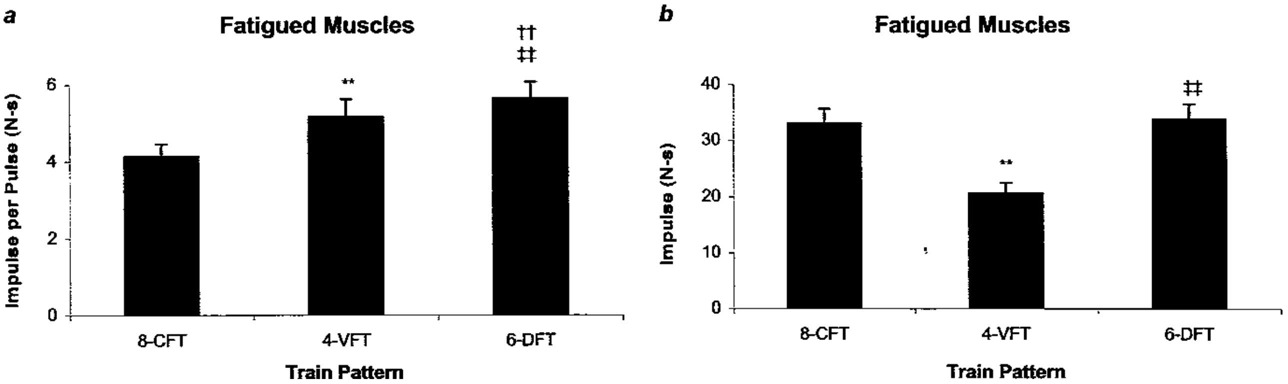

*Figure 6. Comparison of impulse per pulse (*a*) and impulse (*b*) among the train types for fatigued muscles. Data were averaged across 11 subjects. Paired t-test was used to compare the optimum between CFT and VFT (**: p < 0.01), CFT and DFT (††: p< 0.01), and VFT and DFT (‡‡: p < 0.01).*

enhance LDM performance [14]. Studies in our laboratory showed that adding doublets, triplets or quadruplets to the beginning of a train produced a similar augmentation compared with CFTs for human quadriceps muscles [5]. Though the VFTs in previous studies held promise for improving muscle performance, our results showed greater improvement by DFTs than VFTs compared with the traditionally used CFTs.

Similar to VFTs, DFTs also has doublets within the train, suggesting they might share the same mechanisms in augmenting forces over the CFTs for fatigued muscles. Two mechanisms have been proposed: increased Ca^{2+} transient [13] and increased stiffness [21] by the second pulse in the doublet. The impaired E-C coupling [23] and decreased muscle stiffness [11] with fatigued muscle could make the improvement by the doublet on force production more effective. In addition, unlike VFTs that have the doublet only in the beginning of the train, DFTs have doublets throughout the train. The positive effect of the doublet would be enhanced each time with the reappearance of the doublet.

In conclusion, consistent with our model's prediction, the 6 pulse DFT was the most efficient stimulation pattern for fatigued muscle. This demonstrates the predictive power of the mathematical model and the model's potential for helping to identify the optimal activation pattern in patient using cardiomyoplasty.

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