Variable-frequency train stimulation of canine latissimus dorsi muscle during shortening contractions

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George, David T., Stuart A. Binder-Macleod, Thomas N. Delosso, and William P. Santamore. Variable-frequency train stimulation of canine latissimus dorsi muscle during shortening contractions. J. Appl. Physiol. 83(3): 994–1001, 1997.—In cardiomyoplasty, the latissimus dorsi muscle (LDM) is wrapped around the heart ventricles and electrically activated with a constant-frequency train (CFT). This study tested the hypotheses that increased mechanical performance from the LDM could be achieved by activating the muscle with variable-frequency trains (VFTs) of shorter duration or containing fewer stimulus pulses than the CFT now used. The mechanical performance of the canine LDM (n = 7) during shortening contractions was measured while the muscle was stimulated with 5- and 6-pulse CFTs (of duration 132 and 165 ms, respectively) and 5- and 6-pulse VFTs (of duration 104 and 143 ms, respectively) that were designed to take advantage of the catchlike property of skeletal muscle. Measurements were made from fresh and fatigued muscles. For the fresh muscles, the VFTs elicited significantly greater peak power than did the 6-pulse CFT. When the muscles were fatigued, VFT stimulation significantly improved both the peak and mean power produced compared with stimulation by CFTs. These results show that stimulation of the LDM with shorter duration VFTs is potentially useful for application in cardiomyoplasty.

DYNAMIC CARDIOMYOPLASTY is a new surgical treatment for chronic heart failure in which the latissimus dorsi muscle (LDM) is wrapped around the heart ventricles and stimulated with a burst of electrical impulses to contract in synchrony with the heart (9). This procedure may provide an optional therapy for heart failure patients who are refractory to medical therapy or who are not heart transplant candidates. When skeletal muscle contraction is elicited through artificial electrical stimulation, the pattern of the electrical stimuli influences the strength and time course of muscle contraction. It is advantageous to have the muscle contract rapidly and strongly to provide maximum cardiac assistance. After active contraction, relaxation is important to allow adequate diastolic ventricular filling. Adequate ventricular filling is so important that in ~50% of cardiomyoplasty patients the LDM is stimulated on every other heart beat (14).

In current clinical practice, the LDM is electrically activated with a pattern of uniformly spaced electrical pulses [constant-frequency train (CFT)], consisting of 6 monophasic pulses, each 210 µs in duration, with an intraburst frequency of 30 pulses/s (10). While a 30-pulse/s CFT may be a reasonable choice, trains of nonuniformly spaced nerve impulses have been recorded during volitional contractions in a variety of muscles in both animals and humans (1, 15). The use of variable-frequency trains (VFTs) that take advantage of the “catchlike” property of skeletal muscle has been shown to augment force and reduce fatigue compared with CFTs during isometric (2–4, 7, 18, 24, 26) and nonisometric contractions (5). The catchlike property of skeletal muscle is the tension enhancement seen when an initial brief interpulse interval or burst of pulses is added to the beginning of a subtetanic train of pulses (4, 7, 8).

In addition to being affected by the pattern of electrical stimulation, the rate of fatigue of repeatedly stimulated skeletal muscle is partly determined by the number of pulses within the stimulus pattern (3, 17, 20). In the current practice of skeletal muscle cardiac assist, the LDM is converted into a fatigue-resistant phenotype through chronic electrical stimulation. Unfortunately, this conversion process decreases muscle strength, speed, and power, thereby diminishing potential cardiac assist (22, 25). If a stimulus pattern(s) could be identified that used fewer stimulus pulses, but yet elicited similar or enhanced muscle contractile performance, decreased muscle fatigue is possible. The use of an improved stimulus train may obviate the need for conversion of the muscle to a fully fatigue-resistant phenotype and reduce the decline in muscle performance presently noted.

This study investigated the application of VFT stimulation in a manner relevant to skeletal muscle cardiac assist. The hypotheses that increased mechanical performance from the canine LDM could be achieved by using VFT stimulation and that the train duration and number of stimulus pulses could be reduced without a commensurate decrease in muscle mechanical performance were tested. To test these hypotheses, the canine LDM was stimulated with the cardiomyoplasty-standard CFT (a 6-pulse, 30-Hz burst) and with VFTs. Because skeletal muscle must shorten to displace blood during cardiac assist, the effects of CFT and VFT stimulation were measured while the muscle shortened against a fixed load.

MATERIALS AND METHODS

Large-chest hounds (n = 7, weight 20–30 kg) were used in this study. All animals were cared for in accordance with the National Institutes of Health (NIH) Guide for the Care and
Use of Laboratory Animals [DHHS Publication No. (NIH) 85-23, Revised 1985, Office of Science and Health Reports, Bethesda, MD 20892].

Nerve-Cuff Placement

The dogs were anesthetized with intravenous pentobarbital sodium (25 mg/kg) and were intubated. Ventilation was maintained by using an Ohio ventilator, and anesthesia was maintained with halothane (0.5–1.0%) and oxygen by using a proportioner anesthesia machine. Under sterile conditions, the proximal LDM was exposed via a transverse axillary skin incision. A bipolar nerve-cuff electrode (model 4080, Medtronic, Minneapolis, MN) was placed around the thoracodorsal nerve. The electrode terminals were then tunneled underneath the skin and externalized at the base of the neck. The skin incision was sutured closed in layers. Immediately after surgery, the dogs were given antibiotics (Rocephin, 1 g iv). Additional antibiotics were given as needed (Rocephin, 0.5 g im).

Muscle Performance Studies

Studies were conducted 1–2 wk after nerve-cuff placement. The dogs were anesthetized with pentobarbital sodium (25 mg/kg iv); additional pentobarbital sodium was administered as needed. Isometric and shortening performances of the in vivo canine latissimus dorsi muscle were evaluated by using the system shown in Fig. 1 (11).

The dog was placed on a surgical table and surrounded with cloth-padded cinder blocks to prevent motion of the trunk during LDM contraction. The forepaw was connected to the chain and sprocket of the mechanical testing system by a leather strap secured with Velcro. The dog was positioned so that during LDM contraction the paw moved along the line of the chain and sprocket (Fig. 1). The sprocket was attached to an axle supported by bearings to allow it to rotate freely. One end of the axle was coupled to a 10-turn potentiometer that was coupled to a voltage divider to give an analog signal proportional to displacement. Developed tension through the chain was measured by using an in-line force transducer made in our laboratory from four strain gauges bonded to an aluminum C to form a Wheatstone bridge. Analog gain, excitation voltage, and signal conditioning for the Wheatstone bridge were provided by a physiological recorder (model VR-12, Electronics for Medicine, PPG Biomedical, Pittsburgh, PA). At the end of the chain was a platform that held weights for the muscle to lift during stimulation. The platform rested on a laboratory jack. Muscle preload (resting tension) was adjusted by manipulating the height of the laboratory jack, and afterload was determined by the weights. For isometric contractions, the weight placed on the platform was greater than the peak isometric force of the muscle.

The muscle testing system is based on earlier setups reported in the literature in which the LDM performance was measured indirectly at the paw (25). This indirect mechanical testing system is noninvasive and allows serial measurements of muscle performance without injury to muscle or dog. The cuff electrode was connected to a pulse stimulator (model S88, Grass Instruments, Quincy, MA). A microcomputer (Macintosh Iicx, Apple Computer, Cupertino, CA) equipped with a multifunction input/output card (MacAdios II, GW Instruments, Somerville, MA) was used to trigger the pulse stimulator. The duration (210 µs) and voltage of each pulse were set by the pulse stimulator. The voltage used was ~10% greater than necessary to produce maximum isometric twitch force from the muscle. Force, potentiometer, and stimulus signals were sampled at 500 Hz and stored on the hard disk of a second microcomputer.

Experimental Protocol

Mechanical loading of the muscle. For each dog, the optimal preload was found by monitoring the isometric-force responses of the muscle to stimulation with 100-pulse trains lasting 500 ms while the muscle was placed at a variety of resting tensions. The preload that produced the greatest developed force was used for the remainder of the experiment. Throughout the experiment the preload before and after each contraction was monitored to determine whether contraction of the LDM would alter the position of the animal. No movement of the animal was detected. For shortening studies, the platform was loaded with weights totaling 50% of the peak isometric force of the muscle.

Stimulation protocol. Four pulse trains were tested (Fig. 2). Train 1, the stimulation pattern currently used in clinical cardiomyoplasty, was a 6-pulse CFT with a 33-ms interpulse interval. The time between the first pulse and the final pulse in the train (train duration) was 165 ms. Train 2 was a...
where F is the force measured at the force transducer in newtons, and \( \Delta D \) is the incremental displacement of the mass in meters. Instantaneous power \( P \) (in W), the rate of work, was calculated as

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P = F \cdot \frac{dD}{dt}
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where \( dD/dt \) is the time derivative of displacement (velocity) of the platform in meters per second. Peak power was the maximum power attained during the contraction. Mean power was calculated from the onset of contraction to peak platform displacement (when velocity equaled 0).

Both mean and peak power were calculated because it was hypothesized that these two measures might be influenced differently by the stimulus patterns being tested. Peak power tended to be influenced largely by the interpulse intervals at the beginning of the stimulus train when the muscle is shortening most rapidly. In contrast, mean power is influenced by all of the interpulse intervals within the train. Thus, there was concern that the results would be “unfairly” biased in favor of VFT stimulation if only peak power was calculated because the VFTs chosen for this study had two shorter interpulse intervals (higher stimulus frequency) at the beginning of the train.

Displacement, work, and peak and mean power (which were collectively termed performance measures) were calculated for each contraction and matched with the corresponding stimulus pattern. For the baseline, the performance measures for all contractions produced in response to each stimulus pattern were averaged to give mean muscle performance attributable to that pattern in the nonfatigued muscle. Similarly, for the fatigued muscle, the last 20 s of data represented the fatigued state. Each stimulus pattern occurred 10 times over the final 20-s period. The mechanical performance for the last 10 contractions of each pattern was averaged to give mean muscle performance attributable to that train in the fatigued muscle.

Muscle performance elicited by the four stimulus trains at baseline and after 5 min of repeated muscle contraction was compared by using repeated-measures one-way analysis of variance (ANOVA). Data that failed normality were compared by using Friedman repeated-measures ANOVA on ranks. For this study, peak and mean power after repeated muscle contractions failed normality. When significant differences were found, a Student-Newman-Keuls test for multiple comparisons was used. \( P < 0.05 \) was considered significant. Data are reported as means \( \pm \) SE.

## RESULTS

Figure 3 shows sample records of force, displacement, and stimulus pulses while the muscle was stimulated with the 6-pulse CFT and VFT at baseline (A) and after fatigue (B). The first stimulus pulse in each record occurred at time 0. At baseline, after the pulse-train onset, force developed rapidly. The VFT maintained the initially higher rate of force development for a longer time than did the CFT. When the muscle force exceeded the force needed to lift the load (38 N), muscle shortening began (≈60 ms). Between 60 and 140 ms, force was >38 N because the load was being accelerated. From 140 to 200 ms, the load was displaced with nearly zero acceleration. After 200 ms, the load decelerated with peak displacement occurring at 270–300 ms. The CFT produced greater displacement than did the VFT. Interestingly, for both stimulation patterns, the load was lifted for ≈100 ms after cessation of the stimulation. This was because the mass continued to be displaced upward until the muscle force was equal to
the load being lifted. After 300 ms, the weighted platform fell toward the laboratory jack. Force was approaching 38 N when the weighted platform contacted the laboratory jack at 400–420 ms, resulting in a precipitous drop in force.

Compared with baseline, the data after muscle fatigue (Fig 3B) show diminished peak force, peak displacement, and velocity. The small difference in muscle preload between the two samples from the fatigued muscle are due to the high contraction rate. That is, the closely timed consecutive contractions did not always allow the measured force to settle completely to the preload value. This does not influence data analysis, however, because the muscle does not shorten during this time. The VFT generated greater peak force compared with the CFT. Peak force during CFT stimulation occurred later in the record in the fatigued muscle compared with CFT stimulation at baseline. The rate of displacement was similar between the two stimulus trains and was reduced compared with baseline. Compared with CFT stimulation, the VFT elicited greater displacement from the fatigued muscle. Despite achieving greater displacement, the load returned to its baseline sooner during VFT stimulation because of the shorter train duration.

The time course of the changes in muscle performance during 5 min of high-rate contractions was similar among performance measures (Fig. 4): peak potentiation at ~20 s (40 contractions) followed by rapidly decreasing performance in the first 2 min transitioning to stable performance toward 5 min. In a comparison of the results among the stimulus trains and performance measures early in the test, it was found that the 6-pulse CFT produced the greatest displacement and work (Fig. 4, A and B) while the 6-pulse VFT was ranked second. After potentiation,
these two rankings switched, with the work and displacement produced by the 6-pulse VFT being greatest for the remainder of the record. Similarly, for the two 5-pulse trains at the beginning of the fatigue test, the CFT produced greater work and displacement than did the VFT, and after potentiation the situation reversed.

At beginning of the test, the two VFTs elicited similar peak and mean power, and both were greater than power elicited by the two CFTs (Fig. 4, C and D). The greater peak and mean power associated with VFT stimulation persisted throughout the test. After potentiation, the 6-pulse VFT produced greater peak and mean power compared with the 5-pulse VFT.

In a comparison of performance of the stimulus pattern among all dogs, at baseline no significant differences were found in the displacement, work, or mean power produced by the four stimulation patterns (Fig. 5, A, B, and D). Only the peak power showed significant differences among the stimulation patterns tested, with both VFTs producing greater peak power than the 6-pulse CFT (Fig. 5C).

After repeated high-rate contractions, all muscle performance measures decreased to 64–77% of their initial values (Fig. 5, E–H). When the muscle was fatigued, the 6-pulse VFT was significantly better than the 5-pulse CFT for all performance measures and produced significantly greater peak power and mean power than did the 6-pulse CFT. In addition, the 5-pulse VFT produced significantly greater peak power and mean power than did the 5-pulse and 6-pulse CFTs. Overall, the VFTs elicited 25% greater peak power and 15% greater mean power than did the CFTs.

**DISCUSSION**

Cardiomyoplasty is a new surgical treatment in which the LDM provides cardiac assistance for chronic heart failure. After cardiomyoplasty, the LDM traditionally has been stimulated with a CFT. For this study, the LDM was stimulated with VFTs in a manner potentially useful for cardiomyoplasty. The CFTs and VFTs tested were limited in duration so that they would allow muscle contraction to be completed within a single cardiac cycle. Three of the four trains tested were of shorter duration than the train now used for cardiomyoplasty (Fig. 2). During the baseline testing, small and nonsignificant differences were observed for the displacement, work, and mean power elicited by the four stimulation patterns tested (Fig. 5). The VFTs achieved greater peak power compared with the CFTs. In contrast, after the muscle was repeatedly stimulated, the VFTs significantly improved muscle performance compared with the CFTs.

In ~50% of cardiomyoplasty patients, the LDM must be stimulated on every other heart beat (1:2 mode) to prevent the impairment of diastolic filling due to slow or incomplete muscle relaxation (14). The present data show that a muscle stimulated with shorter duration VFTs can produce comparable or greater mechanical performance than when CFT stimulation is used. The accomplishment of cardiac assistance during a shorter time within the cardiac cycle may allow greater cardiac filling and greater cardiac assistance. The benefits from using VFT stimulation should be greater at elevated heart rates, when the cardiac cycle shortens and less time is available for muscle contraction and relaxation.

It has been suggested that the rate of fatigue may be related to the number of pulses used to stimulate the muscle (3, 17, 20). Because a 5-pulse VFT in this study performed similarly to the 6-pulse CFT at baseline and gave greater mechanical performance after repeated contractions, it may be possible to stimulate the LDM with fewer pulses and thereby reduce muscle fatigue. This is especially important in the early postoperative period after the cardiomyoplasty procedure. If muscle fatigue could be diminished by using appropriate VFT stimulation, earlier assistance might be possible.
For this study, fatigue was caused by a collection of four pulse patterns; therefore, the fatiguing effects of individual patterns cannot be discerned. To compare the rate of fatigue attributable to a particular train would require stimulating the muscle with that train alone for the entire fatigue test. Although the study presented here did not include such an experiment, data from preliminary studies suggest that the 5-pulse VFT reduced muscle fatigue compared with stimulation using the 6-pulse CFT (23).

VFT stimulation has been shown to increase performance compared with CFT stimulation in the slow motor unit of the cat triceps surae muscle (7), in fast and slow motor units of the cat gastrocnemius muscle (8), in the cat soleus muscle (24), and in the rabbit tibialis anterior muscle (18). These studies did not measure VFT effects after repeated muscle stimulation. In the present study, the VFTs gave greater performance, relative to the CFTs, after repeated muscle contractions. Relatively greater VFT performance after repeated contractions is consistent with previous research in human quadriceps femoris muscle (3, 5) and cat hindlimb skeletal muscle motor units (2).

The normal canine LDM is a mixed muscle, composed of slow, fatigue-resistant type I fibers and fast, fatigueable, type II fibers (21). It is possible that the muscle performance at baseline was dominated by the contribution from the type II, fatigueable fibers; however, as fatigue progressed, the contribution of the type I fatigue-resistant fibers became proportionally greater. Our results are consistent with earlier work showing that VFT stimulation produces greater augmentation in slow-twitch motor units than in fast-twitch motor units (8). This suggests that in the fully conditioned LDM, transformed into slow type I fibers, VFT stimulation may be useful.

It is encouraging that muscle performance can be manipulated and potentially enhanced by adjusting the interpulse intervals within the stimulus pattern. A beneficial effect of VFT stimulation was demonstrated in this study even though the stimulus patterns that were tested may not have been optimal and the VFTs
were of shorter duration than the 6-pulse CFT used for cardiac assistance (9). Systematic optimization could identify pulse patterns for improving muscle performance. Most likely the optimal stimulus pattern will depend on the performance characteristic(s) to be optimized. For example, one pattern may be best for maximizing work while another might maximize power. Preliminary data from our laboratory suggest that stimulus trains with interpulse intervals equal to or greater than the twitch contraction time maximize the isometric force-time integral (6), whereas power during isokinetic contraction is maximized by stimulation at interpulse intervals equal to 50% or less of the twitch contraction time (unpublished observation).

Skeletal muscle in the chronic heart failure patient is different from an individual without heart failure. In chronic heart failure, skeletal muscle has reduced mitochondrial content, ATP synthesis, and metabolic efficiency; increased fatigability; poorer perfusion; and impaired vasodilatory response (12). Although the results of this study may differ when applied to muscle in chronic heart failure patients, we believe that these maladaptive effects make it even more important to optimize force generation and potentially reduce fatigue in this population.

The mechanism of VFT augmentation is not yet known, partly because we do not yet completely understand the mechanics of muscle force generation. It has been proposed that the initial high-frequency component overcomes the elastic stiffness of the muscle (24) or that nonlinear summation results from intensified Ca$^{2+}$ release (13). The Ca$^{2+}$ mechanism is controversial because researchers have yet to document a link between Ca$^{2+}$ and the force enhancement during catchlike muscle contractions.

Conclusion

These results suggest that rearranging the stimulus pulse pattern to form a VFT that takes advantage of the catchlike property of skeletal muscle for activation of the canine LDM can produce greater power than the CFTs traditionally used during cardiomyoplasty. This benefit occurs even when there is one less pulse in the VFT. Use of VFT stimulation that takes advantage of the catchlike property of skeletal muscle holds promise for improving muscle contractile performance, reducing contraction duration, and reducing muscle fatigue. The trains tested in this study were not necessarily optimal; systematic investigation into the effects of pulse patterns on muscle mechanics for skeletal muscle cardiac assist is warranted.

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