

Ventricular and Skeletal Muscle Function in Cardiomyoplasty: Experimental Observations

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Abstract

After nearly a decade of clinical application consisting of over 400 cases worldwide, dynamic cardiomyoplasty, as a clinically applicable surgical technique for heart failure, is still in its infancy. In cardiomyoplasty a muscle mass is first added to the heart and then the muscle is conditioned to convert it into a more heart-like muscle. The unique nature of cardiomyoplasty is that, unlike coronary artery bypass surgery or angioplasty, it does not provide immediate relief for the failing heart. Rather, cardiomyoplasty is more like an exercise program in which beneficial outcomes require weeks and months to attain. Our laboratory has been working to understand the progression of cardiac function following cardiomyoplasty surgery and how skeletal muscle electrical stimulation influences cardiac assist.

Keywords: Cardiomyoplasty, Hemodynamics, Skeletal Muscle, Electrical Stimulation.

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In biomechanical cardiac assist, skeletal muscle, typically the latissimus dorsi muscle (LDM), is utilized to augment function of the failing heart. Several types of skeletal muscle cardiac assist are under investigation, including: skeletal muscle ventricles in which the muscle is formed into an independent ventricle [1, 57] or hydraulic assist device [15, 31]; aortomyoplasty, in which skeletal muscle is wrapped around the aorta [10, 49]; and cardiomyoplasty [7, 12, 29, 39, 46, 48] in which the LDM is wrapped directly around the heart. Presently, cardiomyoplasty is undergoing worldwide clinical trials and is the only skeletal muscle cardiac assist technique FDA-approved for clinical evaluation in the United States.

Among these techniques, cardiomyoplasty is unique in that the assisting skeletal muscle is applied directly to heart epicardium. This eliminates the risk of thrombosis from blood-material interface or through blood stasis. After the surgery, the LDM remains unstimulated for 2 weeks to allow revascularization and adherence to the epicardium [42]. During this time the LDM cannot provide active cardiac assistance. Thereafter, a progressive electrical stimulation regime converts the LDM to a more heart-like muscle capable of contracting at sinus rhythm. The physiological "miracle" leading to successful application of cardiomyoplasty is that by chronic electrical stimulation,

skeletal muscle adapts to an increased contraction rate, modifies its genetic expression, and increases its fatigue resistance [19, 26, 43, 44, 50, 51]. The muscle conversion process takes several months. Once the skeletal muscle becomes fatigue resistant, it is capable of contracting along with the heart to provide direct cardiac assistance.

For this manuscript we will confine our discussion to experimental studies in cardiomyoplasty, the most clinically relevant technique today. For descriptions of other skeletal muscle cardiac assist modalities, we refer the reader elsewhere [1, 8, 10, 14, 15, 31, 49, 57].

Early-Postoperative Function/Static Cardiomyoplasty Experimental

In current cardiomyoplasty practice, the LDM is not stimulated during the first two postoperative weeks. At this time, the effect of the muscle wrap is passive (static cardiomyoplasty). Recent experimental studies suggest that static cardiomyoplasty causes slight-to-moderate depression of preload-dependent measures of left ventricular (LV) function [16, 22, 23, 25, 38].

Magovern's group performed left, right, and bilateral LDM cardiomyoplasty in dogs and measured depressed ventricular function immediately following each procedure [22, 38]. They reported significant decreases in peak right ventricular (RV) systolic pressure, peak positive RV

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dP/dt, peak LV pressure, and peak aortic pressure and flow. Peak LV systolic pressure decreased 19% with the left wrap and 27% with the bilateral wrap. Similarly, left and bilateral wraps decreased peak LV dP/dt by 26% and 39%, respectively [38]. The depression of these preload-dependent measures of LV systolic function was similar between the left and right LDM wraps, with bilateral cardiomyoplasty causing the most severe depression [22]. LV dimensions were not reported in these studies, so constrictive pathophysiology cannot be ruled out and changes in LV end-diastolic volume might have occurred.

In our laboratory, static cardiomyoplasty caused mild LV diastolic dysfunction [16]. In normal canine hearts instrumented by sonomicrometry and micromanometry, we measured LV function before and after wrapping the heart with the left LDM. A typical baseline beat, a beat after LDM wrap without stimulation, and a stimulated beat are R-wave matched in Fig. 1. A decrease in the rate of LV pressure decay and its prolonged duration are evident in the LDM-wrapped beats compared with baseline beats. Systolic pressure was augmented during LDM stimulation.

Data from 6 hearts is summarized in Table 1. After the LDM wrap, the peak rate of filling (dA/dt), and LV end-diastolic area and pressure were unchanged. The time constant of diastolic pressure decay increased by 39%, the constant of chamber stiffness increased eight-fold, and the

maximum rate of diastolic pressure decay (-dP/dt) was reduced 19%. Thus, comparing pre and post wrap diastolic function showed that, although end-diastolic areas and pressures were unaltered by the LDM wrap, sensitive indices suggested the presence of mild diastolic dysfunction.

Table 1. Diastolic Functional Data Following Acute Cardiomyoplasty.

Variable	Baseline	LDM wrap	
		No Stimulation	Stimulation
EDP	3 ± 2	5 ± 1*	6 ± 2*
EDA	7.3 ± 2.3	7.5 ± 2.3	7.4 ± 2.1
dA/dtmax	18.1 ± 6.7	16.3 ± 8.9	16.6 ± 4.1
b	0.2 ± 0.2	1.6 ± 0.7*	2.1 ± 1.0*
dP/dtmax	-1560 ± 370	-1260 ± 330*	-1120 ± 420*
τ	38 ± 5	53 ± 10*	62 ± 11*

EDP, end-diastolic pressure (mm Hg); EDA, end-diastolic area (cm²); dA/dtmax, maximal rate of diastolic area increase (cm²/sec); b, constant of chamber stiffness (1/cm²); dP/dtmax, maximal rate of LV pressure decay (mm Hg/sec); τ, constant of diastolic pressure decay (ms). * p < 0.05 compared with baseline.

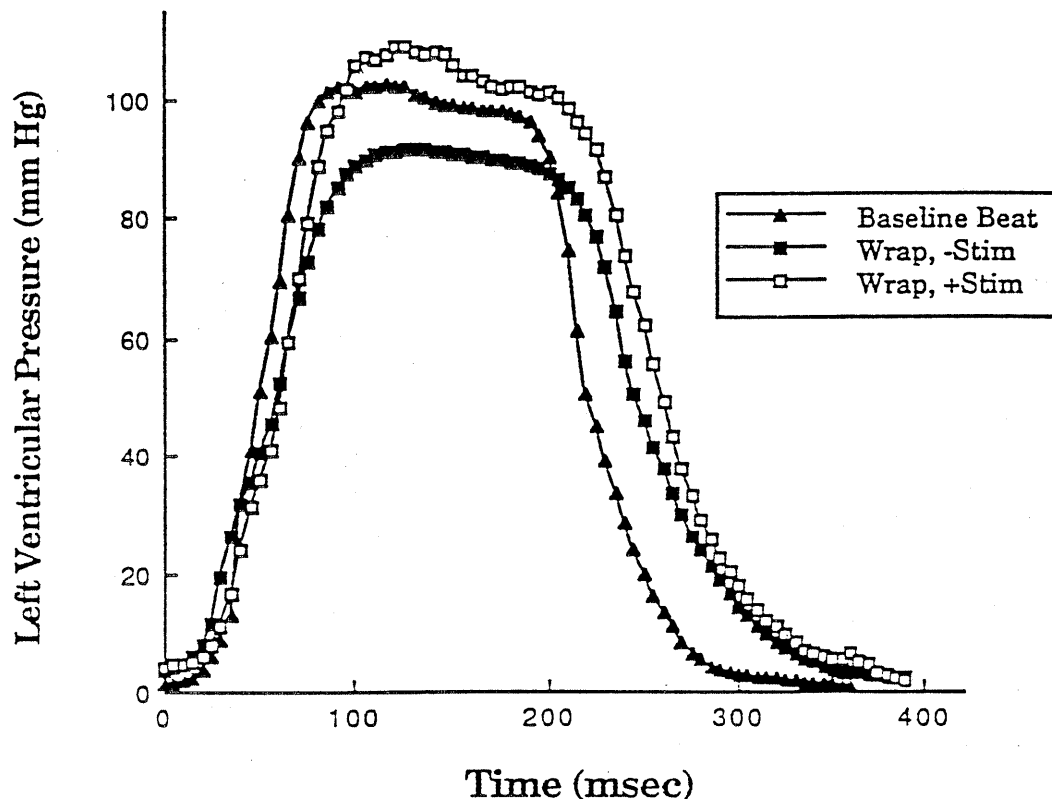


Figure 1. Sample baseline, wrapped but unstimulated, and wrapped with LDM stimulation beats are superimposed, time-matched to the ECG. Both beats after LDM wrap demonstrate a prolonged period of pressure decay compared with the baseline beat, with reduced maximal rate of pressure decay. Increase in systolic pressure with LDM stimulation compared to nonstimulated beat is evident.

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In another study, canine hearts were instrumented by sonomicrometry and micromanometry and ventricular function was acutely depressed with propranolol [25]. LV pressure and short axis dimensions were recorded at baseline and during vena caval occlusion. Fig. 2 shows sample LV pressure-area loops and the linear fit to the end-systolic pressure-area relation, an analog of the end-systolic pressure volume relation, as measured immediately before (left panel) and then after wrapping the heart (right panel). From these data, both preload-dependent and preload-independent measures of systolic function were calculated. Table 2 gives summary results from six dogs. Static cardiomyoplasty caused some depression of preload-dependent measures of LV systolic function, however, preload-independent measures were not significantly affected. The muscle wrap had no effect on E_{max} . Preload recruitable stroke work tended to decrease with the LDM wrap, but this change was not statistically significant.

The aforementioned studies were done acutely on normal or acutely depressed hearts. To the best of our knowledge,

the early postoperative effects of static cardiomyoplasty in a chronic heart failure model remain unknown.

Mechanism of Functional Impairment

We believe that the passive muscle wrap increased effective LV mass and thus caused the observed depression in LV systolic and diastolic function. The mass of the LDM in contact with the heart is comparable to the mass of the heart (unpublished observations). Consistent with this hypothesis, Magovern's group measured greater decreases in LV systolic performance in the bilateral wrap which has, about twice the muscle mass applied to the heart, compared with the left or right wrap alone. In our studies, the observed diastolic dysfunctional changes are similar to those observed with increases in LV mass, such as with LV hypertrophy [34]. As per systolic function, our data show that intrinsic LV myocardial contractility was unaltered while preload-dependent indices (peak LV systolic pressure, dP/dt) were depressed. The increased effective heart mass, leading to increased inertial effects, could explain this LV systolic dysfunction.

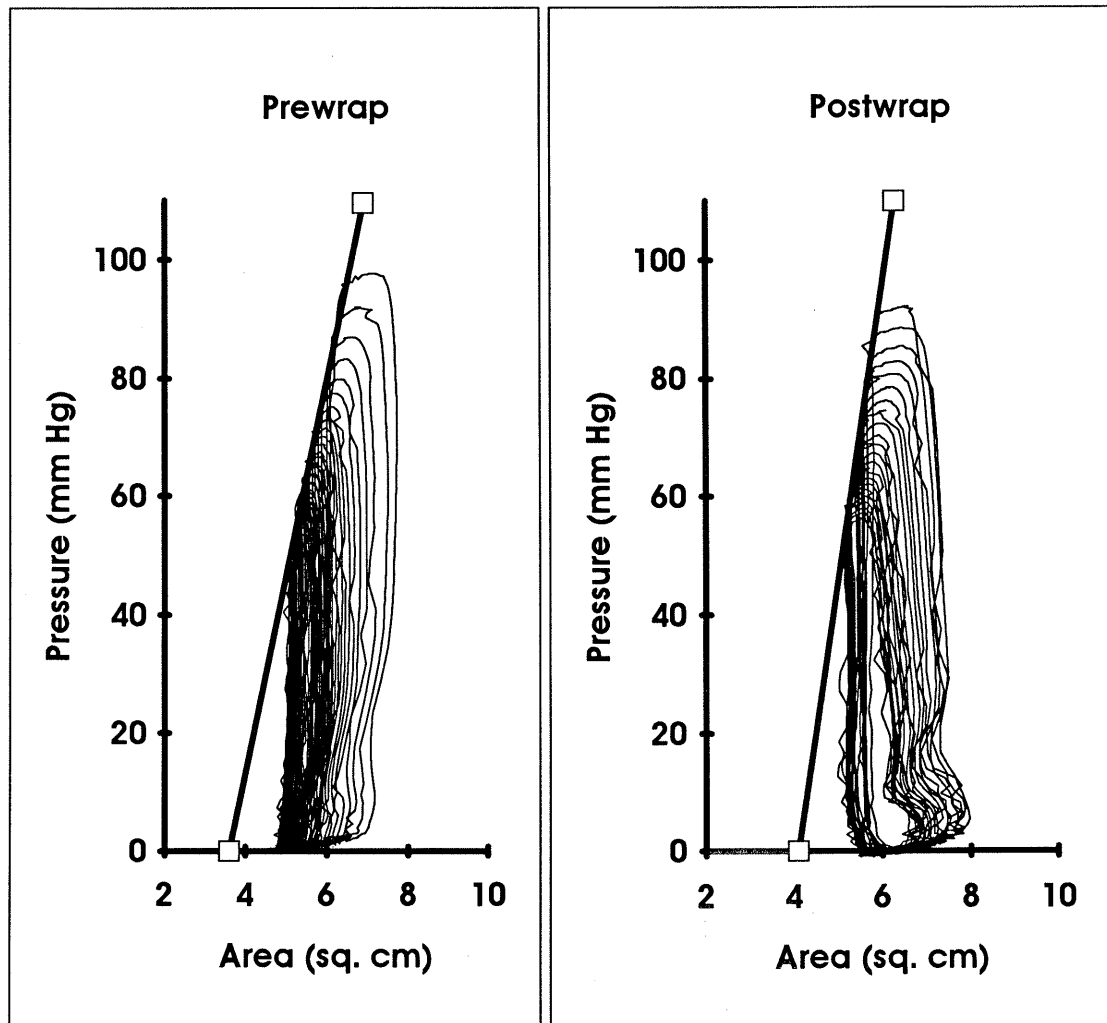


Figure 2. Pressure-area loops during vena caval occlusion as calculated from data obtained before and after static cardiomyoplasty. Left panel shows loops from before the muscle wrap and the right panel shows loops immediately after the muscle wrap. The end-systolic-pressure-area relations are shown.

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Table 2: Hemodynamics and Contractility Measures During Static Cardiomyoplasty.

Variable	Baseline	Prewrap	Postwrap
EDA (cm ²)	5.7 ± 0.9	6.9 ± 1.2*	6.3 ± 1.3
EDP (mm Hg)	5.8 ± 0.4	7.8 ± 0.8*	6.7 ± 0.7
LVP (mm Hg)	100 ± 7	89 ± 7	79 ± 8
LV dP/dt (mm Hg/sec)	1540 ± 129	1159 ± 94*	934 ± 115**
E _{max} (mm Hg/cm ²)	96 ± 5	59 ± 8*	65 ± 15
Ao (cm ²)	3.4 ± 0.9	3.2 ± 1.0	3.4 ± 1.0
RSW (mm Hg)	80 ± 18	70 ± 16	57 ± 15
Aw (cm ²)	4.0 ± 0.8	4.2 ± 0.9	4.4 ± 1.1

EDA: end-diastolic area, EDP: end-diastolic pressure, LVP: left ventricular pressure, LV dP/dt: time derivative of LV pressure, E_{max}: maximum systolic elastance, Ao: x-intercept of the end-systolic pressure-area relation, RSW: preload recruitable stroke work, Aw: x-intercept of the stroke work-EDA relation, data reported as mean ± the standard error of the mean, * p < 0.05 compared with baseline, ** p < 0.05 compared with prewrap.

Clinical

Because of the risk and difficulty in assessing a patient's hemodynamic state early after a surgical procedure, there are no reports of hemodynamic measurements in the first two weeks following the cardiomyoplasty procedure. However, New York Heart Association (NYHA) class IV patients have a poorer prognosis following the cardiomyoplasty procedure than NYHA class III patients [27]. This may be due to the combination of some early postoperative cardiac depression and the length of time until active cardiac assistance occurs. It is now thought that patients must have sufficient "cardiac reserve" to overcome the lengthy surgical procedure and then the time required to convert the muscle to a fatigue resistant type [7, 39, 48].

Dynamic Cardiomyoplasty in Chronic Heart Failure Models

Biventricular Cardiomyoplasty

Ventricular Function

Relatively few studies exist whereby cardiomyoplasty was applied to a chronic heart failure model [12, 13, 28, 33, 45, 47]. In our study, we induced chronic heart failure, in dogs with Adriamycin (1 mg/kg/week) for 10 weeks [12, 13]. Cardiomyoplasty surgery was then performed, and the skeletal muscle conditioned. After completion of the muscle conditioning protocol (3 months), the dogs underwent radionuclide ventriculography (MUGA) studies and cardiac catheterization. Full thickness samples of the LV and LDM were taken for histological analysis.

Table 3 shows hemodynamic data with and without LDM stimulation. LV peak systolic pressure and LV dP/dt were unchanged, while LV end diastolic pressure de-

creased slightly with LDM assistance. RV peak systolic pressure increased significantly with LDM assistance, while RV dP/dt and RV end diastolic pressure were unchanged. Dynamic cardiomyoplasty significantly improved LV and RV ejection fractions with LDM assistance. Phase analysis of the radionuclide ventriculograms showed that, with skeletal muscle assistance, standard deviation (SD, "spread") decreased from 31.6 ± 17.4° to 20.0 ± 15.4°; p < 0.06, while skewness ("symmetry") was unchanged, suggesting LDM stimulation synchronized LV chamber contraction.

Morphology

The LV epicardial surface was in close contact with the LDM along the entire epicardial border. There did not appear to be any diminution or compromise of the epicardial vasculature of the LV. The distal portions of the LDM remained in close proximity to the LV, however a large band of fibrosis was observed between the LV epicardium and the LDM (Fig. 3). Representative micrographs were taken at progressive distances from the muscle pedicle. Sections taken proximal (2-4 cm) to the pedicle revealed a homogenous distribution of muscle cells surrounded by a fine band of collagenous matrix tissue. These bands of extracellular material divided the muscle cells into well-defined fascicles. In the samples taken nearer to distal LDM, zones of fibrosis became more frequent with wide spread fibrosis, continued atrophy, and dissolution of muscle cells was greatest at the most distal region. The relative progression of fibrosis from the proximal to distal portion of the LDM showed that the proximal portion (2-4 cm) contained a normal amount of extracellular matrix material while the percent area occupied by extracellular material significantly increased in the distal portion. The average cross sectional area of muscle fibers decreased

Table 3. Hemodynamics After Cardiomyoplasty in Chronic Heart Failure.

Variable	0 V	5 V	10 V
Peak Emptying (EDV/sec)	2.07 ± 0.95	3.10 ± 0.67*	3.34 ± 0.89
Peak Filling	1.81 ± 0.9	2.67 ± 1.18	3.11 ± 0.65*
Global EF	18.4 ± 7.2	26.2 ± 3.7*	31.0 ± 5.4*
Peak LVP	92.0 ± 23.4	95.8 ± 22.5	98.2 ± 21.3
Peak LV dP/dt	1302 ± 355	1450 ± 413	1568 ± 455
EDP	11.2 ± 1.5	10.4 ± 2.3	9.6 ± 1.5*

EDV, end-diastolic counts; EF, ejection fraction (%); LVP, left ventricular pressure; dP/dt, time derivative of pressure; EDP, end-diastolic pressure; 0 V, without muscle assistance; 5 V and 10 V, 5 V or 10 V LDM stimulation. Data reported as mean ± SD, * p < 0.05 compared with 0 V.

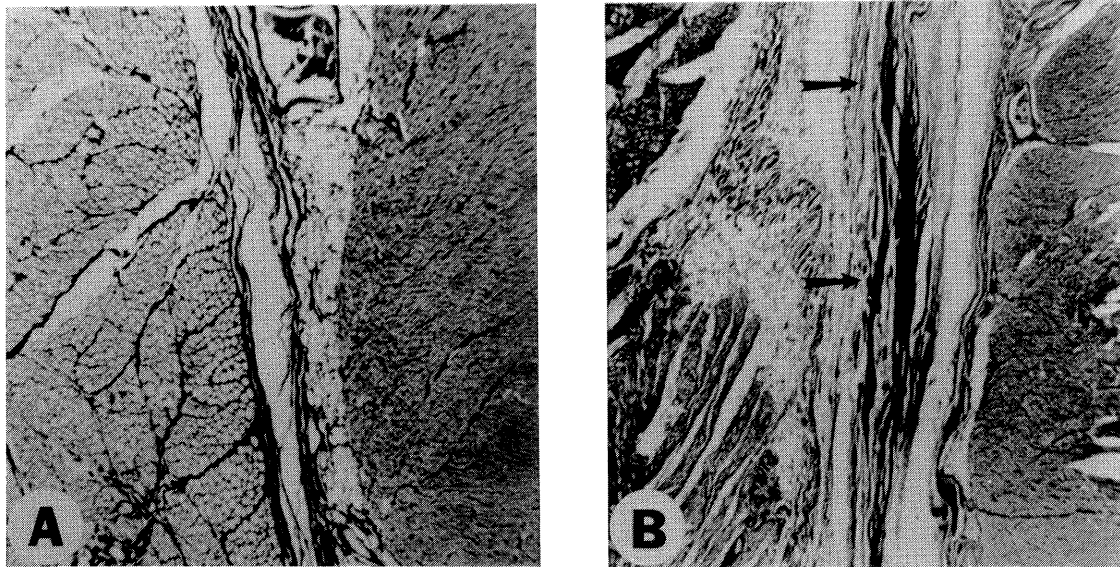


Figure 3. (A) Representative low power micrograph of a cross section of LV (right) and LDM (left) taken from a proximal (2-4 cm) region with respect to the muscle pedicle. The LV epicardium and LDM are in close proximity along the entire surface with no apparent compromise of coronary vasculature. (B) Representative section taken from a distal (10 cm) region of the LDM. While the relationship between the LV epicardial surface (right) and LDM (left) was maintained, a large band of fibrosis was evident (arrows). In addition, large areas of fibrosis within the LDM were observed. Original magnification 50X; silver impregnation stain with alcian blue counter stain.

significantly when taken from progressive distances from the LDM pedicle, suggesting distal region muscle atrophy.

Guiraudon and colleagues produced a chronic RV failure model in the dog by ligating all coronary arteries to the RV free wall [28]. The right LDM was placed over the right ventricle and the muscle conditioned for 12 weeks. Skeletal muscle assist produced significant increases in RV peak systolic pressure and dP/dt. Lee and colleagues induced chronic dilated cardiomyopathy in dogs rapid ventricular pacing for 3 to 4 weeks [33]. Acute dynamic cardiomyoplasty increased cardiac output and systolic shortening, and decreased mean systolic wall stress.

Morita produced dyskinetic segments of the LV by ligation of the left anterior descending artery in dogs [47]. A LDM graft was placed on the LV during the cardiomyoplasty procedure. The muscle was conditioned for 12 weeks. Systolic bulging was present in the ischemic area when the graft was not stimulated. Pacing resulted in passive segmental shortening of the ischemic segments. They concluded that the LDM graft has the ability to contract in systole against the LV wall stress, and to augment regional LV performance in dyskinetic segments.

Millner studied cardiomyoplasty and chronic LV failure in sheep [45]. Heart failure was induced by coronary artery ligation. After a conditioning protocol, volume loading was used to produce function curves. Dynamic cardiomyoplasty produced significant improvements in cardiac

output, LV end-diastolic pressure, pulmonary artery capillary wedge pressure, stroke volume and cardiac power. Significant improvements were also seen when the dynamic cardiomyoplasty sheep were compared to a control and static cardiomyoplasty group.

Summary

Basic research studies suggest slight perioperative depression of ventricular function following cardiomyoplasty. Ventricular function during the muscle conditioning protocol has not yet been extensively measured. After completion of muscle conditioning, the LDM is adhered to the heart, with the distal position showing fibrosis and atrophy. LDM stimulation in the late postoperative stage augments ventricular function.

Skeletal Muscle Stimulation

An integral part of skeletal muscle cardiac assist is how the skeletal muscle is electrically activated. The ultimate success of cardiomyoplasty depends on the health and strength of the assisting skeletal muscle. In turn, the muscle properties and contractile dynamics are dependent upon the mode of electrical stimulation. In cardiomyoplasty, the understanding and implication of the physiology of electrical stimulation continues to evolve. Starting from cardiac tissue, where the problem is in detecting electrical activity and stimulation is less difficult - once threshold stimulus is reached, all the cardiac myocytes are activated (all-or-none). In skeletal muscle stimulation, two mechan-

Table 4. RV Patch Study, Summed Results.

Variable	Unstimulated	Stimulated
RVP	23.2 ± 0.95	25.1 ± 1.5*
Peak RV dP/dt	226 ± 13	309 ± 12
RVEF	51.5 ± 13.5	66.5 ± 14.5

RVP, right ventricular pressure; RV dP/dt, time derivative of right ventricular pressure; RVEF, right ventricular ejection fraction, Data expressed as mean ± SEM, *p < 0.05 compared with baseline.

isms determine muscle performance: recruitment and summation. Skeletal muscle contraction can summate by delivering a train of pulses, and the stimulating voltage can be increased to recruit additional muscle fibers. Recent advances in skeletal muscle electrical stimulation also show that the pattern of the pulses within the pulse train influences skeletal muscle contractile dynamics.

Stimulus Voltage

As mentioned before, we measured ventricular function during biventricular cardiomyoplasty in a chronic heart failure model [12, 13]. Table 3 shows that peak LVP, peak LV dP/dt, LV end-diastolic pressure, and RV and LV ejection fractions are a function of the stimulus voltage. Each hemodynamic measure was related to stimulus voltage level (some linearly), suggesting that increased stimulus voltage may lead to greater cardiac assist.

In an earlier work, we examined the ability of skeletal muscle to function as a partial myocardial replacement [55]. Full-thickness right ventricular cardiomyoplasty was done in a chronic canine model (Fig. 4). Table 4 shows the summed results for the five dogs studied. Mean RV systolic pressure increased 8%, and RV dP/dt increased 37% with LDM stimulation. RV ejection fraction increased from 51.5% to 66.5% with stimulation. In some studies, the effects of varying the skeletal muscle stimulation parameters on hemodynamic performance and LDM contractile performance were also measured. In one dog, RV peak systolic pressure and RV dP/dt were increased as stimulus voltage was increased from 3.5 to 10 V. LDM shortening increased from 3.2 to 15.5% as stimulus intensity increased from 5 to 10 V.

The effects of stimulating voltage level were investigated in more detail in another study [24]. Rabbit LDMs were wrapped around a compliant balloon to form skeletal muscle ventricles and the ventricles were filled to a constant preload pressure. The LDM was stimulated with long bursts to cause full tetany. The threshold voltage causing a visible twitch was noted and then developed pressure was recorded as the LDM was stimulated with pulse trains at integer increments of threshold voltage. The pressure-voltage relation (Fig. 5) showed the typical sigmoidal response - as voltage was increased there was at first a large increase in developed pressure - at greater voltages, pres-

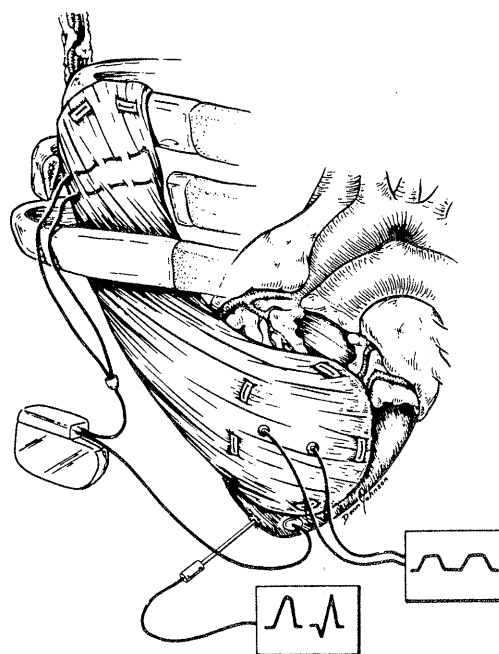


Figure 4. Diagrammatic representation of right ventricular latissimus dorsi dynamo cardiomyoplasty at terminal study. A micotransducer-tipped catheter is seen entering the right ventricular apex, measuring right ventricular pressure and dP/dt. Ultrasonic crystals are placed on the latissimus dorsi in one animal; they overlie the repaired ventricular defect and are parallel to the direction of latissimus dorsi muscle fiber.

sure development peaked. The threshold-normalized voltage at maximal muscle contraction varied widely (5.7 ± 2.0 , mean $\pm$ SD, range 3.1 to 9.3).

Guiraudon and colleagues [28] investigated RV free wall dynamic cardiomyoplasty in a canine model of RV failure. They found that when the stimulating voltage was increased from 3 to 6 V, a statistically significant increase in RV systolic pressure and RV dP/dt resulted. If one plots their results as a function of stimulating voltage, one finds that the cardiac performance-stimulating voltage relationship was highly linear ($r > 0.98$).

Malek and Mark [41] considered the role of stimulus voltage in isolated LDMs after 2 months of chronic stimulation. In a skeletal muscle ventricle pumping against a constant resistance, they observed a strong voltage dependent increase in peak pressure. Kunov and colleagues [32, 58] reported a 10-fold increase in hydraulic pouch pressure development as stimulus voltage was increased from 0.4 to 20 V.

These studies suggest that we should stimulate the skeletal muscle with the strongest possible voltage. However,

Voltage Dependent Performance of SMV

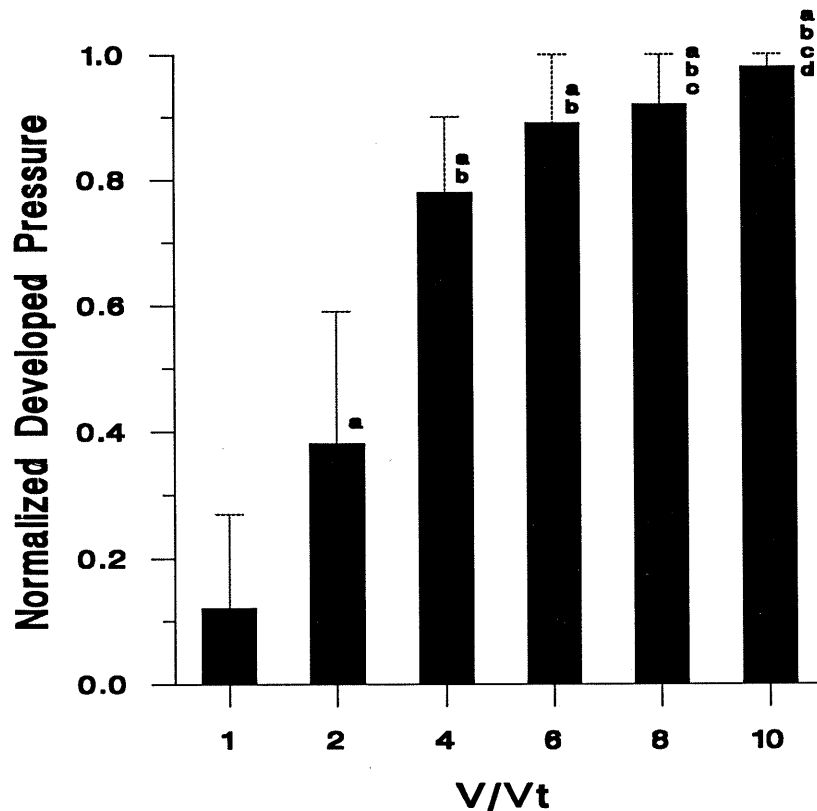


Figure 5. Summary data from hydraulic pouch study. Mean normalized pressure at each level of threshold-normalized stimulating voltage (V/V_t). As stimulating voltage is increased, greater developed pressure is achieved. a: $p < 0.05$ compared to $V/V_t = 1$; b: $p < 0.05$ compared to $V/V_t = 2$; c: $p < 0.05$ compared to $V/V_t = 4$; d: $p < 0.05$ compared to $V/V_t = 6$.

in chronic application, the overall goal for skeletal muscle cardiac assist is to get the best performance from the muscle but to scrupulously avoid stimulation-induced muscle damage. Therefore, stimulus intensity may ultimately be determined by considerations of long term skeletal muscle health. If chronic stimulation with high intensity stimuli causes permanent muscle damage, we must reconsider the stimulus level. Although it is clear that acute increases in stimulating voltage results in greater LDM contractile strength and cardiac assist, the long term effects of higher stimulus intensities are less well described. In skeletal muscle cardiac assist, it has been suggested that the muscle not be stimulated with greater than 5 V or 50 Hz pulse frequency [19]. It is often difficult to set safety standards for chronic stimulation due to differing pulse patterns, electrode configurations, and neuronal configurations from the many varied application of functional electrical stimulation. Maximum current densities thought to not cause neuromuscular damage have been reported [17, 52, 53], however, these can only be approximations - ultimately, one must directly measure the effects of chronic electrical stimulation with the exact configuration

for a given application. Finally, although the literature clearly suggests that increased stimulus intensity leads to increased muscle performance, it is difficult to determine the optimal stimulus voltage in a clinical setting [24].

Advanced Muscle Stimulation

More recently, our laboratory has been working to determine if modifying the pulse pattern within the burst can give better LDM dynamic performance [18, 20, 54]. In the manner of van der Veen and colleagues [36, 59], we developed a mechanical system to measure the isometric and shortening performance of the canine LDM during functional electrical stimulation [18]. In present cardiomyoplasty practice, the skeletal muscle is activated by burst of 6 pulses with a constant interpulse interval of 33 msec. We hypothesized that improved muscle performance could be elicited from the LDM by rearranging the pulses in the burst [4, 6, 56]. We compared the skeletal muscle performance elicited by pulse trains with non-uniform interpulse interval, to the performance achieved with the standard 6 pulse train.

Fig. 6 shows a sample time-matched contraction pattern for two contractions: one elicited by the constant frequency

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train (CFT) used in cardiomyoplasty (6 pulses at 30 Hz) and a second elicited by a variable frequency train (VFT). The first two interpulse intervals of the variable frequency train were at 10 msec (100 Hz) and the second two intervals were 42 msec (24 Hz). In this way the variable frequency train was composed of an initially high frequency segment, followed by a lower frequency segment. The muscle was stimulated with the two bursts at a rate of 120 bursts/min

for 7 minutes. The top panel shows shortening contractions as measured at the beginning of the test; the bottom panel after 7 minutes. For illustration, the top plot shows the VFT pattern and the bottom plot shows the CFT pattern. The VFT-induced contraction shortened more rapidly and attained greater peak shortening. The VFT returned to baseline more quickly, because the VFT was shorter in duration than the CFT. More rapid relaxation may be

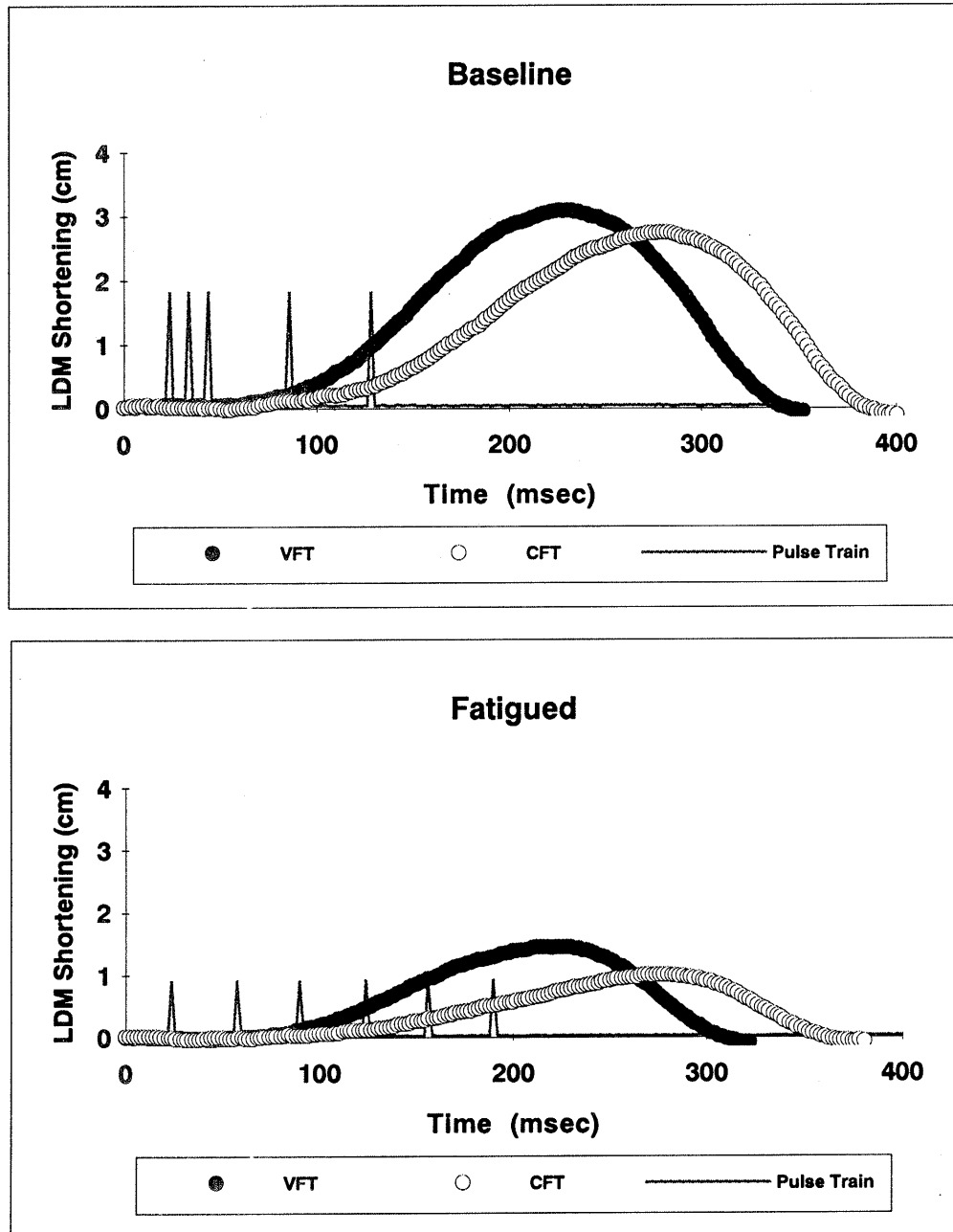


Figure 6. Sample records from an in-vivo latissimus dorsi stimulation study. The muscle was stimulated with a constant frequency train (CFT) and a variable frequency train (VFT) while working against a constant load. The top panel shows displacement of a mass lifted by the dog at baseline. The traces are time matched to the onset of the pulse train with the VFT pattern given. The VFT elicited greater shortening and did so at a higher rate, compared with the CFT-induced contraction. After the muscle was subjected to repeated contraction (bottom panel), shortening decreased for each pattern. Here, we show the CFT pulse pattern. The VFT-induced contraction had greater peak shortening and greater rate of shortening.

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especially useful in preventing impairment of diastolic filling, an important clinical concern. At the end of the fatigue-inducing stimulation, the VFT elicited even greater shortening, relative to the CFT.

Fig. 7 shows the shortening, work, and power generated by each pulse train over the 7 minute fatigue test. The VFT elicited higher performance than the CFT in each measure of contractile dynamics, both at baseline, and after the muscle was subjected to repeated contraction. At the beginning of the test, the VFT-induced contraction shortened a further 3%, accomplished 10% greater work, and generated 47% greater power than the CFT. At the end of the test shortening was 18% greater, work was 14% greater, and power elicited by the VFT was 35% greater. Note that the VFT had only 5 pulses compared with 6 pulses for the CFT. Thus, in this study, we were able to achieve improved muscle performance while using one fewer pulse. In general, VFT stimulation may have the two-fold benefit of giving greater cardiac assist through increase muscle performance and may allow for earlier stimulation following

the cardiomyoplasty surgery because of the reduced demand on the LDM.

Conclusions and Future Directions

At present, cardiomyoplasty is still a developing surgical technique for heart failure. Current worldwide research efforts are ongoing to both understand the mechanism of cardiomyoplasty and to learn how it can be improved upon. Advances in surgical technique and muscle training may be keys to cardiomyoplasty's continued success and general acceptance in medical practice.

Many aspects of cardiomyoplasty remain unclear and would benefit from further investigation. The disparity between the observed functional class improvements in clinical cases and the lack of objectively measured hemodynamic function improvement, suggests that we do not yet understand the mechanism of cardiovascular improvement following cardiomyoplasty. There is little documentation of ventricular function during the muscle conditioning process and how this may impact on early postoperative management. Furthermore, there is a paucity of cardiomyoplasty studies using chronic heart failure models.

Recent reports suggest that wrapping the heart with the right LDM, instead of the more commonly used left LDM, may be better [22, 37]. Some researchers suggest using a two-step surgical procedure in which the muscle is first isolated and then the muscle wrap is done at a later date [2, 11, 39, 55]. However, save for dividing the surgical protocol into two shorter procedures for the benefit of patients who cannot tolerate a long surgical procedure [9, 40], the hemodynamic benefits of the two-step procedure have not been compared with the single day procedure. Modifications in postoperative management have also been proposed to reduce the time delay between the wrap procedure and muscle stimulation. Epicardial-to-LDM adhesion can be promoted with fibrin glue [35] and pharmacological means of reducing early post-operative muscle fatigue have been proposed [21].

Although interest in improving skeletal muscle performance is strong, there is no consensus on how this can most effectively be accomplished and clinically implemented. The present conditioning protocol efficiently converts the mixed fiber type LDM into a fully type-I fatigue resistant muscle. It was originally believed that the fully fatigue resistant muscle was necessary to augment function at the cardiac rhythm. However, the great loss of muscle contractile performance following the chronic stimulation [51] is causing reexamination of this belief [5]. New manners of skeletal muscle stimulation, including mixing bursts with twitches [3], a more gradual conditioning regime [30], resting the muscle for part of the day [30], and advanced stimulus patterns [20], offer the hope of improving skeletal muscle performance and ultimately the amount of cardiac assist.

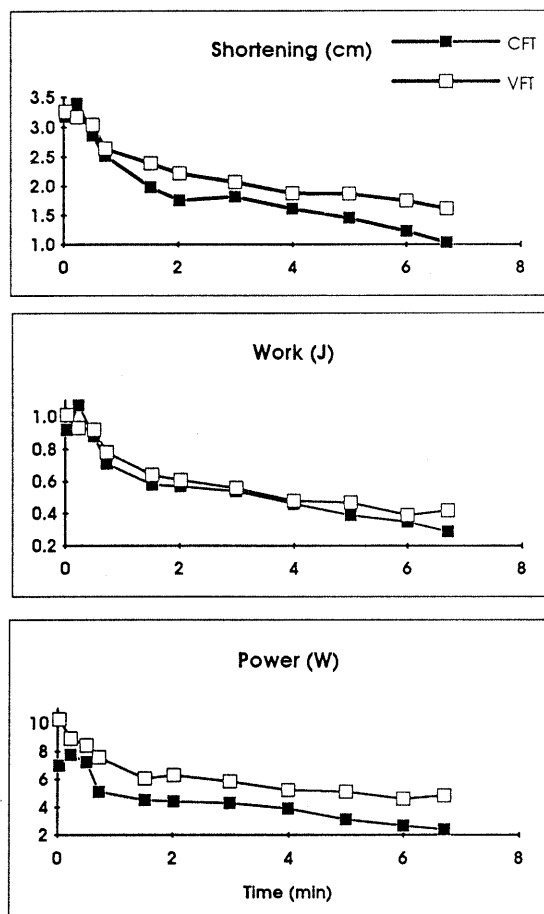


Figure 7. LDM performance during fatigue test. The muscle received the pulse trains at 120 bursts/min while lifting a mass. The VFT generated greater shortening, work, and power.

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