Strategies for Preserving Muscle Function for Improved Systolic Assist in Dynamic Cardiomyoplasty

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Abstract

Chronic heart failure continues to be a major cause of morbidity and mortality. Cardiomyoplasty (CMP) a surgical treatment for heart failure, has several potential advantages: skeletal muscle requires no external power source; each patient serves as his/her own "donor"; rejection is not a problem and immunosuppression is not necessary. This promising new technique appears to cause symptomatic improvement in patients with New York Heart Association class III heart failure. Objective improvement in systolic performance of the left ventricle appears small but remains to be further defined. Mechanisms of action may include a girdling effect that prevents progressive left ventricular dilatation. This effect may be independent of any role in augmenting systolic performance.

Although current efforts with Cardiomyoplasty have not produced the anticipated clear-cut benefits in cardiac function, consistent improvements in subjective function have resulted. Efforts in optimizing preconditioning protocols and skeletal muscle integrity should provide further improvements in Cardiomyoplasty.

Key words: Cardiomyoplasty, vascular delay, ventricular function, heart failure.

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In 1959, Kantrowitz and McKinnon reported the first attempted use of stimulated skeletal muscle to augment cardiac function [29]. Diaphragmatic muscle was wrapped around either the ventricle or the descending aorta. In 1966, Hume [22] in Louisville and Tennet [51] independently reported wrapping a latissimus dorsi muscle (LDM) flap around both ventricles. In one dog, LDM stimulation was able to sustain a systolic blood pressure of 80 mm Hg for 15 minutes even though the ventricles were in fibrillation [51].

Investigators have demonstrated the feasibility of transposing skeletal muscle to the heart in acute and chronic preparations. Shepherd utilized diaphragmatic muscle flaps to the right ventricle, as either inlay or overlay grafts [48]. Christ and Spira placed a LDM flap on the apex of a canine heart, covering a partial thickness ventricular defect [14]. Macoviak placed a diaphragmatic graft into the canine right ventricle [36]. Stimulation of the graft caused active tension development and muscle thickening.

In Stephenson's group, a ventricle or spiral-wrapped LDM was constructed and left *in situ* in the flank. After a three-week delay, the muscle was conditioned. The skeletal muscle ventricle was able to generate pressures equal to those of the left ventricle, even after 9 weeks of continuous pumping against an afterload of 80 mm Hg [1, 40].

In humans, Carpentier was the first to report successful LDM Cardiomyoplasty after removal of a large apical fibroma from the heart of a 37-year-old woman. A 23% increase in ejection fraction was demonstrated when the muscle was stimulated [5]. Moreira has reported surgical results in eleven patients [42]. There was one death due to congestive heart failure. Of the surviving patients, one patient remained in functional class III, but all others were reported to improve from class III to class II or I. Improvements in left ventricular ejection fraction, stroke volume, and cardiac output were reported in these patients following Cardiomyoplasty. In another study involving Cardiomyoplasty, it was found that patients with right ventricular ejection fraction < 40% had poor results, with three early and three late deaths, whereas no operative and one late death occurred in patients with right ventricular ejection fraction > 40% [38].

Other successful cardiomyoplasties have also been reported [25, 42]. Magovern et al. reported their experience with 119 patients with congestive heart failure [39]. Sixty-one had heart transplants, twenty-seven had coronary artery bypass and thirty-one had cardiomyoplasty. In the

cardiomyoplasty group, they reported an increase in left ventricular ejection fraction to 0.33 from 0.26. Likewise, Jegaden reported his experience with 12 patients undergoing cardiomyoplasty [26]. All patients were in NYHA class III. They reported no perioperative deaths. Left ventricular function was measured at 2 years. They demonstrated an improvement in left ventricular ejection fraction from 0.25 to 0.40 and a decrease in left ventricular end-diastolic pressure from 20 to 11 mm Hg. Furnary reported on 127 consecutive patients who underwent cardiomyoplasty [18]. There was a distinct improvement at 6 months in NYHA functional class (3.2 vs 1.7).

Mechanism of Cardiomyoplasty

Stephenson's group studied the mechanism of cardiomyoplasty. In sheep, left ventricular dysfunction was induced by occluding a coronary artery [44]. They measured left ventricular function before and after cardiomyoplasty, and observed a significant improvement in left ventricular function (Emax = 2.6 before and 5.1 after cardiomyoplasty). However, they did not observe any change in left ventricular function with or without LDM stimulation: left ventricular pressure and aortic flow were unaltered by LDM stimulation. Their results suggest that the effectiveness of cardiomyoplasty is due to support or constraint of the damaged myocardium by the LDM, thereby preventing systolic bulging.

Laks' group induced heart failure in dogs by rapid ventricular pacing [4]. Half the dogs received cardiomyoplasty. Of note, the LDM was not stimulated. Compared to controls, the cardiomyoplasty group had less left ventricular dilation and higher ejection fraction. Thus, the non-stimulated wrap significantly attenuated the degree of left ventricular enlargement, the increase in left ventricular volume, and the decrease in ejection fraction. Their observations suggest cardiomyoplasty may have an important "girdling" effect on the left ventricle that prevents dilation and deterioration of left ventricular function.

In our opinion, at present, cardiomyoplasty prevents or limits the progressive enlargement of the left ventricle and helps to reinforce ischemic segments. It does this without increasing left ventricular end-diastolic pressure. Both mechanisms probably contribute to the subjective decrease in symptoms experienced by cardiomyoplasty patients. More importantly, these mechanisms might explain the results of the phase II clinical cardiomyoplasty trials, in which, left ventricular ejection fraction increased and end-diastolic volume was unaltered (progressive left ventricular enlargement was inhibited). However, both in experimental and clinical studies, systolic augmentation of left ventricular function by the LDM is rarely observed: left ventricular ejection fraction and peak systolic pressure are almost identical with the pacemaker on versus off.

This is a major problem. Both in clinical and chronic experimental studies, active LDM contraction has not been shown to cause any important increases in LV pressure or outflow. The clinical study of Jondeau et al. is consistent with the data from Stephenson's and Lak's groups: after cardiomyoplasty, left ventricular ejection fraction and functional class increased [27]. However, stopping LDM stimulation had no effect on cardiac index, or left ventricular systolic and diastolic pressures. Similarly, Hagege et al. observed that when stimulation was stopped, there was no change in indexes of systolic or diastolic left ventricular function (peak systolic left ventricular pressure, left ventricular ejection fraction, peak positive dP/dt, peak negative dP/dt, or tau) [20]. In a recent multi-center retrospective study, LV ejection fraction only increased from 0.20 to 0.23 [18]. This increase is within measuring errors for ejection fraction, and is physiologically insignificant.

We have conducted a very thorough review of the cardiomyoplasty literature. Tables 1 and 2 summarize the key research studies and presents the changes in pressures, stroke volume, and stroke work caused by LDM stimulation. In acute studies, the effects of LDM stimulation were recorded at the time of cardiomyoplasty surgery. In chronic studies, the effects of LDM stimulation were evaluated at 1 week to 6 months after cardiomyoplasty surgery. As described below, 67% of the LDM is supplied by branches from intercostal arteries [53]. To move the LDM, these vessels must be cut, which causes ischemia in the distal LDM [21]. In acute experiments, we have shown that after moving the LDM, the mid and distal portions become ischemic and the muscle can only perform 30% of its normal work [17]. In chronic experiments, the LDM has had time for revascularization and time to be trained to become a fatigue resistant muscle. Thus, if anything, the acute experimental results should be much worse than the chronic studies. Yet, just the opposite is true. As shown in Tables 1 and 2, the results from the acute experiments are much better than the results from the chronic studies.

Studies from Lucas et al. [35] and Stephenson et al. [45, 47] highlight these differences. Both groups performed acute and chronic studies. In acute studies, Stephenson's group obtained an 18.2% increase in stroke volume and an 18.4% increase in peak LV pressure, while in the chronic experiments, stroke volume decreased by 9%, while peak LV pressure increased only 10.6%. In acute experiments, Lucas reported a 44% increase in stroke volume and a 24% increase in peak LV pressure, but no change in stroke volume and only a 2% increase in peak LV pressure in their chronic studies.

With the current approach to cardiomyoplasty, the LDM is over-utilized and has incomplete revascularization. This combination has led to gross LDM damage and atrophy experimentally. We were the first to report this damage [11]. In a chronic study, we examined full-thickness sections taken of the left ventricle and the LDM. We observed a progressive degeneration along the LDM. The proximal LDM was normal. However, in the distal LDM, a large band of fibrosis was observed and extensive degeneration of the LDM was noted.

Table 1. Review ofCMP studies. Hemodynamic responses: non-stimulated vs. stimulated. Acute studies.

REFERENCE		RVP	LVEDP	min dP/dt	LVSP	LVdP/dt	CO	EF	SV	AoP	N =
Lange	NS	XXX	11.6	XXX	XXX	1144	XXX	XXX,	10.4	75.6	5
J Card Surg 6:225	STIM	XXX	11.6	XXX	XXX	1632	XXX	XXX	13.2	93.0	
Lee	NS	XXX	18.0	XXX	94.0	867	1.0	XXX	XXX	XXX	7
JTCS 102:124	STIM	XXX	15.0	XXX	104.0	1254	1.2	XXX	XXX	XXX	
Magovem	NS	27.0	XXX	XXX	83.0	1291	XXX	XXX	XXX	80.0	8
AnnThorsurg52:1259	STIM	38.0	XXX	XXX	96.0	1413	XXX	XXX	XXX	86.0	
Corin	NS	XXX	5.0	-1260	91.0	XXX	XXX	XXX	XXX	XXX	7
JTCS 104:1662	STIM	XXX	6.0	-1120	106.0	XXX	XXX	XXX	XXX	XXX	
Lucas, Chp. 5 "The Use of	NS	25.5	9.6	XXX	78.0	1115	XXX	XXX	14.4	79.0	9
LDM for Card Asst," p 79	STIM	39.0	9.4	XXX	90.0	1240	XXX	XXX	18.4	88.0	
Furnary	NS	27.0	XXX	XXX	89.0	1660	XXX	XXX	XXX	86.0	8
Ann Thor Surg 55:72, part I	STIM	37.0	XXX	XXX	91.0	1700	XXX	XXX	XXX	86.0	
Furnary	NS	31.0	XXX	XXX	91.0	1625	XXX	XXX	XXX	84.0	8
Ann Thor Surg 55:72, part II	STIM	42.0	XXX	XXX	102.0	1856	XXX	XXX	XXX	93.0	
Takahashi	NS	XXX	XXX	XXX	73.0	1765	XXX	XXX	XXX	71.0	10
Artif Organs 17:9 14	STIM	XXX	XXX	XXX	87.6	247'1	XXX	XXX	XXX	85.2	
Aklog	NS	XXX	18.0	XXX	87.0	942	2.0	0.52	23.0	71.0	5
Circulation, 90:11 1 12	STIM	XXX	17.0	XXX	88.0	972	1.8	0.59	21.0	65.0	
Chen	NS	XXX	XXX	XXX	XXX	XXX	XXX	XXX	16.0	58.0	5
Ann Thor Surg 60: 1678	STIM	XXX	XXX	XXX	XXX	XXX	XXX	XXX	17.0	60.0	
AVERAGES	NS	27.6	12.4	-1260	85.8	1301	1.5	0.52	16.0	75.6	72
	STIM	39.0	11.8	-1120	95.6	1567	1.5	0.59	17.4	82.0	

Lucas et al. made similar observations. In 24 goats, the left LDM was wrapped around the heart [35]. The muscle was then subjected to progressive electrical stimulation, and histologic evaluation of the LDM were performed at > 12 weeks after the wrapping. Only two goats showed an increase in aortic and right and left ventricular pressures concomitant with increased aortic flow during LDM stimulation. This was accompanied by a preserved LDM structure. The remaining goats showed extensive lipomatosis in the LDM. These findings differed from those observed after long-term electrical stimulation of goat LDM in situ. Incomplete revascularization may explain this overuse atrophy.

Kalil-Filho et al. [28] used magnetic resonance imaging to evaluate chronic LDM in patients. The thickness of the LDM decreased from 19.6 mm at 15 days after surgery to 7.6 mm at 24 to 52 months after surgery. In addition, the signal intensity of the LDM was comparable with thoracic skeletal muscle shortly after surgery, but by 24 months the signal intensity was comparable with subcutaneous fat. Morphological changes in the wrapped LDM consistent with fatty degeneration evidently occurred after chronic stimulation. It is important to note that the patients evaluated in this study had been stimulated with a 1:1 synchronization ratio. Such overuse atrophy and damage could be partially controlled by avoiding overly aggressive stimulation patterns.

Ways to prevent LDM damage

Vascular delay is a procedure in which some of the arteries supplying a muscle or tissue are ligated. This causes sublethal ischemia and microvascular remodeling. The muscle is left in its original position for 1-3 weeks (delayed) before being transferred. Vascular delay stimulates revascularization, which prevents the otherwise observed LDM ischemia and necrosis.

Table 3 summarizes the key studies on vascular delay performed at the University of Louisville. Tobin et al. examined intramuscular vascular territories from fresh human cadavers and from canine LDMs [53]. In these studies, humans had an average of 15 perforating vessels to the muscle from intercostal arteries. Radiograph planimetry studies showed that these vessels supplied 67% of the area of the LDM. In dogs, these same vessels supplied 69% of LDM area. LDM mobilization in the canine resulted in poor perfusion in the distal zone, decreasing its blood supply by > 90%, and totally eliminating flow in the most caudal area.

Table 2. Review of CMP studies. Hemodynamic responses: non-stimulated vs. stimulated. Chronic studies.

REFERENCE		RVP	LVEDP	min dP/dt	LVP	LVdP/dt	CO	EF	SV	AoP	N =
Chagas	NS	29.8	18.0	XXX	127.0	XXX	1.5	XXX	XXX	XXX	6
Circulation 80:202	STIM	28.6	12.1	XXX	131.0	XXX	2.0	XXX	XXX	XXX	
Lorusso	NS	26.0	XXX	XXX	110.0	1740	XXX	XXX	XXX	118.0	7
BAM 1:83	STIM	30.0	XXX	XXX	112.0	1897	XXX	XXX	XXX	120.0	
Cheng	NS	21.0	11.2	XXX	92.0	1302	XXX	0.2	XXX	XXX	5
JTCS 103: 1207	STIM	26.0	9.6	XXX	96.0	1450	XXX	0.3	XXX	XXX	
Cho	NS	XXX	6.2	-1608	XXX	1319	1.3	0.3	10.7	XXX	5
Ann Thor Surg 56:38	STIM	XXX	6.4	-1543	XXX	1370	1.2	0.4	10.4	XXX	
Lucas	NS	27.0	14.0	XXX	110.0	130.0	XXX	XXX	XXX	111.0	13
JACC 22:758	STIM	29.0	14.0	XXX	112.0	1326	XXX	XXX	XXX	112.0	
Nakajima	NS	XXX	8.1	XXX	93.6	1084	2.2	XXX	19.6	84.6	5
Ann Thor Surg 57:407	STTM	XXX	10.2	XXX	95.7	1097	2.4	XXX	21.2	80.1	
AVERAGES	NS	26.0	11.4	-1608	104.1	1271	1.6	0.2	15.1	104.5	41
	STIM	28.4	10.3	-1543	107.5	1456	1.9	0.3	15.8	104.0	

In previous studies, our group has demonstrated a 100% incidence of distal muscle ischemia in acutely elevated rat [46], mouse [30], and canine LDMs [52, 53]. In the canine study, 5 days after acute flap elevation, the ischemic area had progressed to flank necrosis in 10 of 11 muscles. The combined areas of complete and partial necrosis equaled 27% of the flap, and always involved the distal muscle segment.

Table 3. Studies on vascular delay at the University of Louisville.

Tobin, 198la, b LDM flap ischemia/necrosis found and bipedicle principle delay developed.
Tobin, 1991 Vascular anatomic basis for LDM ischemia/necrosis defined.
Tobin 1991 100% incidence of distal muscle ischemia in acutely elevated canine LDMs
Hakami 1993 Confirmed LDM flap protected from necrosis by bipedicle principle delay.
Keelen, 1993 Rodent LDM flap protected by bipedicle principle delay.
Overgoor, 1995 100% incidence of distal muscle ischemia in acutely elevated rat LDMs
Cruz, 1997 Severe loss of LDM function after mobilizing and reattach-ing the muscle.
Carroll, 1997a Vascular delay increased perfusion in the middle and distal LDM and improved circumferential force generation and fatigue resistance during exercise.
Carroll, 1997b enhanced muscle flap perfusion at rest and during exercise.

Cardiomyoplasty surgery involves severing the perforating intercostal arteries to the LDM, detaching the LDM from its distal insertion, and wrapping it around the heart. At each step, Cruz and colleagues measured LDM force development, shortening, and blood flow in 6 dogs [17]. Loss of LDM function was most apparent after mobilizing and reattaching the muscle. Initial shortening, work, and power significantly decreased by 74%, 77%, and 74%, from their respective control values. During a fatigue test, final values for shortening, work, and power were all near zero. Resting blood flow decreased in the mid and distal LDM.

Based on the above studies, we hypothesized that muscle function would be improved by a vascular delay procedure that increases distal muscle perfusion of the LDM [21,6]. The LDMs of adult mongrel dogs were subjected to a vascular delay procedure on one side and a sham procedure on the other. Following 10 days of vascular delay, muscle perfusion was measured with a laser Doppler perfusion imaging system before and after elevation as flaps based only on their thoracodorsal neurovascular pedicles. The muscles were wrapped and sutured around silicone chambers (simulating CMP), a stimulating electrode was placed around each thoracodorsal nerve, and the muscles were stimulated to contract in both rhythmic and tetanic fashion. Circumferential (distal and middle LDM function) and longitudinal (proximal LDM function) force generation and fatigue rates were independently measured. Circumferential muscle force, circumferential and longitudinal fatigue rate, and distal, middle and overall perfusion were significantly improved in delayed muscle compared to non-delayed muscle.

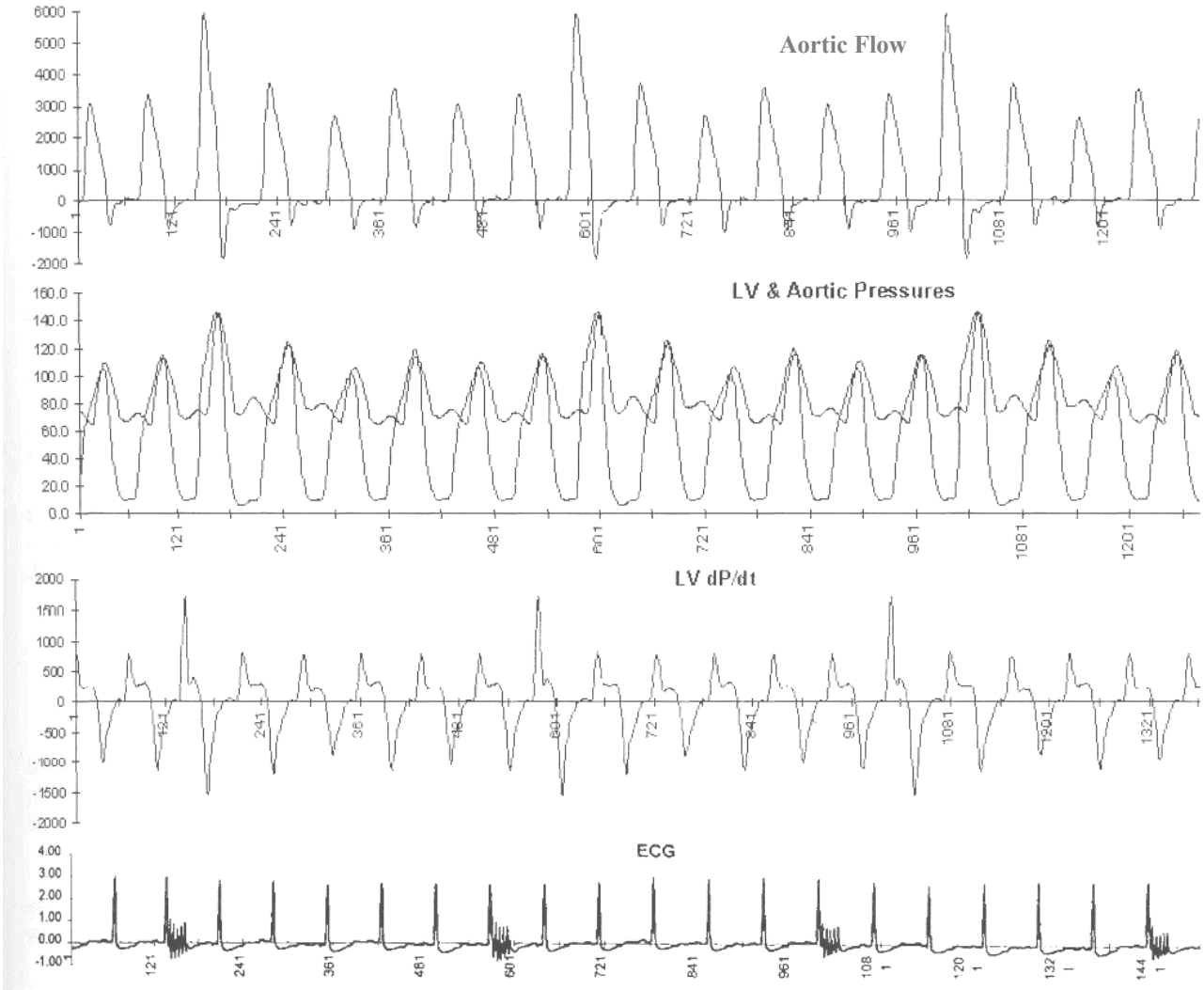

Figure 1. Plot of aortic flow (top panel), aortic and left ventricular pressures (second panel), LVdP/dt (third panel), and ECG (bottom panel) from a dog with vascular delay and early LDM stimulation after surgery [47],

In a follow-up study, canine LDMs were subjected to a 10-day vascular delay period followed by a simulated CMP [7]. Two weeks after simulated CMP (corresponding to the healing delay between CMP and the onset of LDM stimulation used in the clinical setting), LDM perfusion was measured and circumferential (distal and middle squeezing muscle function) and longitudinal (proximal pulling muscle function) force generation and fatigue rates were measured. Muscle perfusion was significantly greater in the distal and middle segments of vascularly delayed LDMs. Circumferential muscle force generation and fatigue rates were significantly improved in vascularly delayed LDMs.

In an effort to determine the mechanism of the vascular delay phenomenon, we used angiogenic growth factors to stimulate vascular change [8]. Basic Fibroblast Growth Factor (bFGF), one of the most powerful angiogenic growth factors currently isolated, has been shown to be upregulated in the presence of tissue hypoxia. We hypothesized that this upregulation of bFGF would occur in response to vascular delay and that administration of an exogenous supply of bFGF would further increase this production. In this study, both LDMs were vascularly delayed for 10 days and one LDM received a bolus injection 100 jig of human recombinant bFGF into the thoraco-dorsal artery at the time of vascular delay. The LDM perfusion, ratio of capillaries to muscle fibers, and force generation and fatigue resistance of the LDM was significantly increased by the administration of bFGF.

Other groups have also examined vascular delay. In dogs, Isoda et al. also demonstrated that a one-month vascular delay period significantly enhanced muscle flap perfusion at rest and during exercise [24]. In dogs, You et al. ligated collateral blood vessels to the LDM two weeks before cardiomyoplasty [54]. Histological examination confirmed that the two-stage procedure preserved normal LDM architecture. Immediately after cardiomyoplasty surgery, acute heart failure was produced, and LV function was evaluated. LDM stimulation increased Emax from 0.77 ± 0.14 to 1.00 ± 0.17 mm Hg/ml and stroke volume

from 6.3 ± 1.2 to 8.3 ± 1.1 ml. This study shows promising results for achieving more relevant systolic assist using a vascular delay. However, in this study the effects of LDM stimulation were observed immediately after surgery.

Recent Experimental Studies

We hypothesized that vascular delay of the LDM would prevent LDM ischemia, increase myocardial assistance, and provide assistance early after surgery [13]. Thus, in dogs, after a 14 day vascular delay, LDM stimulation was started on the first day after cardiomyoplasty surgery. Two weeks after surgery, global cardiac dysfunction was induced by injecting intra-coronary microspheres. From a typical experiment, Figure 1 shows the aortic flow, aortic and left ventricular pressures, LVdP/dt, and ECG. In this experiment, LDM stimulation dramatically increase aortic flow, left ventricular systolic pressure, and dP/dt. In this example, greater than 30 mm Hg increases in left ventricular systolic pressure were recorded. These are very large increases in pressure and flow.

Thus, in dogs with global LV dysfunction, cardiomyoplasty with vascular delay and early (48 hr.) LDM stimulation resulted in significant and consistent improvement in hemodynamic function measured two weeks after surgery. This improvement was not provided by single stage cardiomyoplasty with or without early stimulation.

Preservation of LDM integrity after surgery

lanuzzo et al. developed an approach to prevent overuse atrophy [23]. He compared continuous (24 hours/day) versus intermittent stimulation (16 hrs on/8 hrs off/day) of the LDM. Intermittent stimulation resulted in less muscle damage, in larger fiber areas, and in a lower connective tissue concentration than continuous stimulation. With intermittent stimulation, the fiber area was 228% greater than in the continuously stimulated LDM group. Yet, conversion to slow type I fibers was almost the same: intermittent (80%) vs continuous stimulation (91%). Thus, preventing overuse atrophy resulted in less LDM damage. In a similar experimental study, Arpesella et al. stimulated the LDM for 10 hours per day, with a rest period of 14 hours per day [3]. This stimulation pattern resulted in only minimal LDM damage and a LDM power that was equal to or bigger than the left ventricle.

Incomplete revascularization may explain the overuse atrophy observed in these studies. Mannion et al. determined whether fibroblast growth factor would improve the vascularity of the LDM [41]. In goats, myocardial ischemia was induced with an ameroid constrictor and cardiomyoplasty performed. The LDM was stimulated for 6 weeks and given 4 weekly bolus injections of fibroblast growth factor. The LDM blood flow rate was 3 times greater than that of historical controls (chronically stimulated LDM without basic fibroblast growth factor). Associated with the improved blood flow, less skeletal muscle fiber dropout and muscle fibrosis occurred in the animals treated with basic fibroblast growth factor.

Conclusion

Cardiomyoplasty represents an exciting surgical treatment for congestive heart failure. By using the patient's latissimus dorsi muscle as a ventricular assist device, it eliminates complications of other mechanical assist devices. It also has the potential to "bridge" a patient for a sufficient period of time to allow possible cardiac transplantation. If LDM assistance is sufficient, it may eliminate the need for transplantation.

Although much work has been done on cardiomyoplasty, many questions remain. Several groups have identified that the LDM muscle wrap prevents further ventricular dilation. Fewer have been able to demonstrate significant systolic augmentation as measured by left ventricular ejection fraction or dP/dt. In our laboratory, we observed severe degeneration of the LDM attached to the heart. This degeneration was due in part to incomplete revascularization. Vascular delay has been known to help revascularize tissue. Thus, we hypothesis that vascular delay used clinically will improve the long term viability of the LDM, thereby improving the ultimate systolic augmentation.

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