

Preliminary Report on Continuous Stimulation vs. Intermittent Stimulation of Latissimus Dorsi Muscle in Chronic Canine Model of Cardiomyoplasty

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Abstract

In dynamic cardiomyoplasty (CMP), over-utilization leads to extensive muscle damage, which may explain the observed minimal systolic assistance with latissimus dorsi muscle (LDM) stimulation. Thus, we compared intermittent to continuous stimulation in CMP. In mongrel dogs, myocardial dysfunction was induced by intracoronary microsphere injections and vascular delay of the LDM was performed. After two weeks, a standard CMP was performed. LDVI was progressively conditioned using continuous stimulation (Group CS; $n = 3$) or intermittent stimulation (Group IS; $n = 3$, 10 hours on/14 hours off per day). After 9 weeks, the effects of the LDM stimulation were examined. Significant hemodynamic increases were observed in both groups with LDM stimulation. In group CS, LDM stimulation increased peak left ventricular systolic pressure (8.7 ± 1.4 mmHg), peak aortic systolic pressure (10.1 ± 0.5 mmHg), stroke volume (2.3 ± 1.0 ml), stroke work (5.0 ± 1.6 gm-m), and peak aortic flow (1.5 ± 0.5 ml/min). In group IS, LDM stimulation increased peak left ventricular systolic pressure (19.1 ± 1.4 mmHg), peak aortic systolic pressure (15.9 ± 2.2 mmHg), stroke volume (4.5 ± 2.7 ml), stroke work (14.2 ± 4.4 gm-m), and peak aortic flow (5.9 ± 1.8 ml/min). However, these changes were significantly greater in the IS group compared with the CS group. Preliminary report suggests that intermittent stimulation can increase the cardiac augmentation with LDM stimulation.

Key words: cardiomyoplasty, vascular delay, continuous stimulation, intermittent stimulation, left ventricular dysfunction.

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In cardiomyoplasty (CMP), over-utilization of the skeletal muscle can lead to extensive LDM damage. This damage may explain why many chronic CMP studies have observed little or no systolic assist with LDM stimulation [10, 12, 16]. In sheep, Arpesella showed that 24 hour/day stimulation caused fiber atrophy by $> 40\%$ and loss of most LDM contractile function after one year. In contrast, 10 hours/day stimulation for one year caused only minimal fiber atrophy (10%) and minimal fat infiltration with fibrosis [2]. In goats, Iannuzzo et al [11] compared continuous stimulation (24 hours per day) to intermittent (12 hours/12 hours rest/day) LDM stimulation. Intermittent stimulation preserved the muscle architecture and resulted in less muscle damage, larger fiber areas, and lower connective tissue concentration as compared with continuous stimulation. Unfortunately, neither study examined the hemodynamic effects of intermittent stimulation in CMP. The present canine study gives our preliminary results on the

hemodynamic benefits of intermittent versus continuous stimulation in CMP.

Materials and Methods

The animals (weighing 22-27 kg) were divided in two groups, continuous stimulation (Group CS; 24 hours/day) and intermittent stimulation (Group IS; 10 hours on/14 hours off per day). All the animals underwent the surgical procedures in compliance with the "Principles of Laboratory Animal Care" formulated by the National Society for Medical Research and the "Guide for Care and Use of Laboratory Animals" prepared by the National Academy of Sciences and published by the National Institute of Health [NIH publication 85-23, revised 1985].

Vascular delay

All the animals were fasted overnight and anesthesia was induced by intravenous sodium thiopental (Pentothal sodium 15-25 mg/kg) and intramuscular atropine (0.01mg/kg). After intubation and ventilation by a ventila-

tor (Quantiflex, VMC Anesthesia Machine, Orchard Park, NY), anesthesia was maintained by 2% isoflurane (Isoflurane Vaporizer, Oharda, Isotec 3, Aushell, GA), 0.5-1.0% nitrous oxide, and oxygen. ECG (Hewlett Packard Model NO. 78346A) and oxygen saturation were monitored continuously. Preoperatively, all animals received 500 mg of cefazolin sodium, I.V. (Marsam Pharmaceutical Inc., Cherry Hill, NJ) and 75 mg of gentamicin, I.M. (Gentocin™ Ayerst Laboratories Inc., Rouses Point, NY. Lactated Ringer's solution intravenously (250 ml - 350 ml/hr) was given per-operatively. Under sterile surgical condition, a 15-20 cm long oblique cutaneous incision was made from left axillary region towards the posterior iliac crest. The anterior border of the left LDM was identified and then all the perforating collateral branches supplying the muscle were severed and ligated [1, 4]. The spinal border of the muscle was identified and partially mobilized. The wounds were closed in layers using absorbable sutures.

LV dysfunction

The animals were then moved to the adjacent angiography operating suite, to induce left ventricular dysfunction by intracoronary microspheres injections [15]. Using a percutaneous approach, the left femoral artery was cannulated by a 7 Fr. Catheter sheath through which a 6 Fr. Left Coronary Amplatz #1 catheter was advanced into the left main coronary artery under fluoroscopy. Contrast material (Renografin® -76 Bristol-Myers-Squibb Co) was injected to verify the catheter position. Latex microspheres (3.0-6.0 x 10⁵ ± 2 (j. diameter, latex microspheres, Polyscience Inc. Warrington, PA), mixed in 10 ml of normal saline, were injected into coronary artery in bolus dosages until left ventricular systolic pressure decreased by at least 20%. The catheter and sheath were removed. The femoral artery was compressed externally for 20-30 minutes to stop the bleeding. All the animals survived the intra-coronary microspheres injections. The animals were treated with intravenous injection of Lasix 0.75 mg/kg and rapid infusion of 500 ml Ringer's Lactated saline solution. Post-operatively, the animals were treated with sedative (Acepromazine 0.5 mg, I.V.) and analgesics (Buprenex hydrochloride, 0.3 mg, I.V.) as needed. All the animals were allowed 2 weeks for recovery and vascular remodeling.

Surgical procedure

In all animals, a standard CMP procedure was performed using the technique well established in our laboratory [6, 7]. Under general anesthesia, as described earlier, with the animal in the left lateral position, a left lateral incision in the mid-axillary line was performed. The LDM was dissected out and mobilized from the surrounding tissue and distal insertions, proximally preserving the thoracodorsal neurovascular bundle. The tendon of the LDM was then carefully isolated and severed. Two epimysial leads (model YY38403403 Medtronic Inc., Minneapolis, MN) were implanted on the pedicle with nylon sutures; the cathode (-) was placed proximally on the muscle and with the anode (+) placed 6 to 8 cm distally. The stimulation

threshold of the leads was determined by an A-V Pacing System Analyzer 5311 (Medtronic Inc., Minneapolis MN).

A 4-5 cm section of the anterior portion of the left 3rd rib, including periosteum, was resected to allow the translocation of the LDM flap into the anterior mediastinal space. The proximal parts of a sensing myocardial lead and an aortic flow probe (20 mm) were dropped into the mediastinum for later implantation into the RV anterior wall and ascending aorta, respectively. All the epimysial and myocardial leads were tunneled and connected to a dual chamber synchronous cardiomyostimulator (SP 1005, Medtronic Inc., Minneapolis, MN) which was implanted in a subcutaneous pocket fashioned in the left side. The LDM flap was then fixed to the periosteum of the second rib by poly-braided suturing material, 3/0 dextran to avoid the tension to the muscle and the wound was closed in layers.

With the animals in supine position, the heart was exposed through a median sternotomy. After pericardiotomy, the ascending aorta was mobilized and an aortic flow probe (A-series 20-mm flow probes; Transonic Systems Inc., Ithaca, NY) was placed around the ascending aorta with a merocel sponge positioned between the flow probe and the aorta. The distal end for the aortic flow probe was placed before subcutaneously for later access. A posterior myocardial wrap was performed in a clockwise fashion using the left LDM and fixing it to the pericardium. Bilateral chest tubes were inserted and connected to a water-seal drainage system. The sternum was closed using four or five wire sutures parasternally on both sides. All the wounds were then closed in layers.

The animals were extubated. Post-operative analgesics and sedation were given routinely (Buprenorphine hydrochloride, 0.3-0.6 mg, I.V. and Acepromazine maleate, 0.25-0.5 mg, I.M.). Animals were positioned to lie on their right side overnight. Chest tubes were removed on the first post-operative day. Antibiotics (Cefazolin 500 mg, I.V. and Gentamicin 75 mg, I.M. every 12 hours) were used for 72 hours post-operatively.

Stimulation protocols

The SP1005 cardiomyostimulator was turned on the 2nd postoperative week and the LDM was progressively conditioned starting at 2 Hz and then gradually increasing up to 33 Hz (pulse width = 180 μ s, delay = 25 msec, bursts duration = 180 to 210 ms) until 9th post-operative weeks. The LDM was stimulated on every other heart beat. In Group CS (N = 3), the cardiomyostimulator was on 24 hours/day. In Group IS, the cardiomyostimulator was turned on for 10 hours a day and then off for 14 hours.

Hemodynamic evaluation

Nine weeks after surgery, the dogs were anesthetized with sodium pentothal (10-15 mg/kg IV) and intubated avoiding atropine. Each dog was ventilated via endotracheal tube with a positive-pressure respirator followed by 2% isoflurane, 1-2% nitrous oxide and oxygen. A 7 Fr. catheter sheath was introduced into the left femoral artery

and the side arm was connected to a fluid transducer for the aortic pressure measurement. A 6F pigtail micromanometer tipped catheter with lumen (MILLAR® Instruments Inc. Houston, TX, model no. SPC 464D) was advanced through the catheter sheath, and placed into the left ventricle under fluoroscopic guidance. Analog signals from the pressure transducers were obtained using an amplifier (PM-1000, CWE Inc., Admore, PA). The epimysial leads were disconnected from the SP1005 pacemaker and connected to an external muscle stimulator (Model 8800, Grass Systems Inc., Quincy, MA). A tachometer detected the QRS waveform from the analog ECG signal and triggered the muscle stimulator. This resulted in synchronized LDM stimulation with the R wave. To measure aortic flow, the aortic flow probe lead was dissected out and connected to a flow meter (Model No. 206T, TRANSONIC® Systems Inc., Ithaca, NY).

Data were recorded simultaneously on the chart recorder (Model TA-11, Gould Instrument Systems Inc. Cleveland, OH) as well as on a computer (MICRON computer, Micron Inc., model no. M55PLUS2-P200-MT). The pressure, flow, and ECG signals were digitized using an A/D circuit board (model AT-MIO 16.0E-10, Labview, National Instruments, Austin, TX). The data were acquired using software LABVIEW, version 4.0. The stimulator pulse train duration was adjusted between 150-190 ms, pulse duration at 0.5 ms, pulse frequency at 50 Hz, with an inter-pulse interval of 15-20 ms and pulse train delay after the R wave at 20-80 ms. Data were taken for 3 consecutive times and each data run was 30 seconds long with the ventilator switched off during data acquisition to avoid respiratory variations. After the procedure, the anesthetized animal was euthanized using 20 ml of KC1, administered intravenously.

Data analysis

Using software developed in Visual Basic for Excel (Microsoft Excel 7.0, Microsoft Inc., Redwood, WA), hemodynamic variables were extracted from a digitally stored data file. Ectopic beats and post ectopy beats were excluded from the analysis. For each beat, the end-diastolic pressure, the peak ventricular systolic pressure, the peak positive and negative first derivative of the left ventricle pressure (+ dP/dt, - dP/dt), peak and end-diastolic aortic pressures were determined, and stroke volume, stroke work, and stroke power were calculated. Both the absolute magnitudes of the changes and percent changes were calculated. The hemodynamic parameters of stimulated beats were compared with the non-stimulated beats immediately preceding it. An unpaired Student's t-test was used to compare the percent changes between the two groups, p is considered significant when < 0.05. Data were expressed as mean ± standard error of the mean.

Results

From one continuous LDM stimulation experiment. Figure 1 shows the typical data trace for aortic flow, aortic and

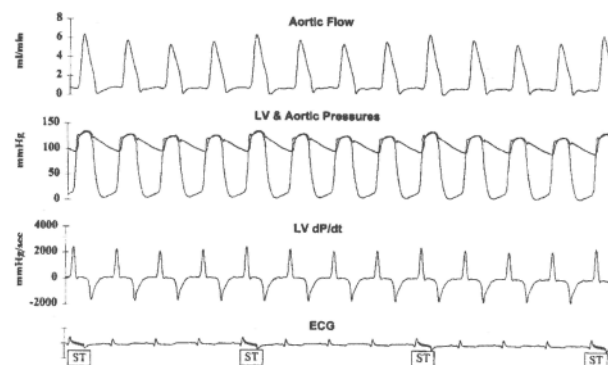


Figure 1. Typical data tracings from continuous stimulation experiment (IS). ST Beats: Stimulated beats. Aortic flow (ml/min); LV & Aortic Pressure (mmHg); LVdP/dt (mmHg/sec); ECG.

left ventricular pressures, left ventricular dP/dt, and ECG. The LDM was stimulated on every 4th beat as seen on the ECG. Figure 2 shows the typical data from an intermittent LDM stimulation experiment. In both figures, LDM stimulation caused moderate to large increases in left ventricular and aortic pressures, left ventricular dP/dt, and aortic flow. However, the increases were more pronounced in the intermittent stimulation experiment as compared with the continuous stimulation experiment.

Figure 3 shows the percent changes in continuous and intermittent stimulation groups. In both the groups, LDM stimulation significantly increased peak aortic systolic pressure, peak left ventricular systolic pressure, peak positive LV dP/dt, stroke volume, stroke work and peak aortic flow. In the continuous stimulation group, LDM stimulation increased peak aortic pressure by 10.1 ± 0.5 mmHg, left ventricular pressure by 8.7 ± 1.4 mmHg, peak positive LV dP/dt by 162.9 ± 82.2 mmHg/sec, stroke volume by 2.3 ± 1.0 ml, stroke work by 5.2 ± 1.6 gm-m, and aortic flow 1.5 ± 0.5 ml/min. In the intermittent stimulation group, LDM stimulation increased peak aortic pressure by 15.9 ± 2.2 mmHg, left ventricular pressure by 19.1 ± 1.4 mmHg, peak positive LVdP/dt by 304.2 ± 168.1 mmHg/sec, stroke volume by 7.5 ± 2.7 ml, stroke work by 14.2 ± 4.4 gnvm,

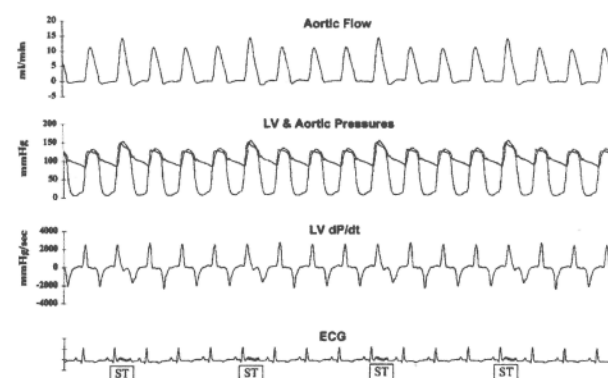


Figure 2. Typical data tracings from intermittent stimulation experiment (CS). ST Beats: Stimulated beats. Aortic flow (ml/min); LV & Aortic Pressure (mmHg); LV dP/dt (mmHg/sec); ECG.

Cardiomyoplasty with continuous vs. intermittent stimulation

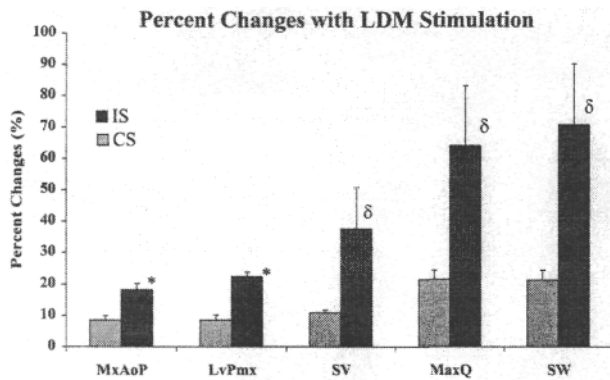


Figure 3. (bar graph) Differences of the percent change in continuous and intermittent stimulation experiments. CS: continuous stimulation; IS: intermittent stimulation; LvPmx: maximum peak left ventricular systolic pressure and MxAoP: maximum peak aortic systolic pressure, SV: stroke volume, SW: stroke work; and MaxQ: maximum peak aortic flow; (* $p < 0.05$ and $^{\delta} p < 0.10$ when compared to continuous stimulation group).

and aortic flow 5.9 ± 1.8 ml/min, respectively. Table 1 shows mean and individual absolute values in each animal of continuous and intermittent stimulation. However, the magnitude of these increases was much larger in the intermittent stimulation group.

Discussion

Since the first clinical case in 1985, CMP has been performed in over 700 patients worldwide as a surgical treatment for congestive heart failure. Most clinical studies show a significant improvement in functional class status [5]. Carraro et al showed improved long-term outcome in human CMP with morphological and molecular analysis of the muscle indicating preserved muscle mass and patent vessels with normal endothelial and smooth muscle walls [3]. However, augmentation in cardiac function by LDM

stimulation is not consistently observed. Distal muscle atrophy and loss of functional contractile properties have been observed [9, 10, 17]. The occurrence of muscle degeneration and necrosis compromise the contractile assist function and might explain the variable results [7, 14].

CMP surgery involves severing the perforating intercostal arteries to the LDM. The muscle is then transferred inside the chest as a rotational flap, cutting off most of the blood supply to the distal muscle [8]. Associated with these flow decreases, LDM damage has been reported by Cheng et al who examined full-thickness biopsies of the left ventricle and the LDM [6]. The proximal LDM was normal. However, in the distal LDM, a large band of fibrosis was observed with extensive degeneration of the LDM. In goats, Lucas et al. has shown that damage to the LDM correlated with poor hemodynamic outcome [16]. Clinically, Kalil-Filho et al. used magnetic resonance imaging to evaluate the LDM chronically [13]. The thickness of the LDM decreased from 19.6 mm at 15 days after surgery to 7.6 mm at 24-52 months post-operatively. Additionally, the signal intensity of the LDM was comparable with thoracic skeletal muscle shortly after surgery, but by 24 months the signal intensity resembled that of subcutaneous fat. Yoshiya et al, using echocardiographic assessment to evaluate the LDM, also observed muscle atrophy [20].

Several studies have examined vascular delay as a means to preserve the LDM. In this procedure, some of the arteries supplying a muscle or tissue are ligated. The muscle is left in its original position for several days (delayed) before being moved. This procedure stimulates revascularization. In dogs, Isoda et al. demonstrated that a 1-month vascular delay period significantly enhanced LDM flap perfusion at rest and during exercise [12]. After 10 day vascular delay, Carroll et al. wrapped the LDM around a silicone tube simulating CMP [4]. After 2 weeks, they demonstrated that vascular delay improved fatigue resistance and perfusion to the middle and distal LDM during exercise.

Table I. Data of mean and absolute changes in each individual animal of continuous and intermittent stimulation groups. CS: continuous stimulation; IS: intermittent stimulation; [^]CV absolute changes; LvPmx: maximum peak left ventricular systolic pressure and MxAoP: maximum peak aortic systolic pressure, Max L V dP/dt: maximum left ventricular contractility; SV: stroke volume, SW: stroke work; and MaxQ: maximum peak aortic flow.

	Stimulation Pattern	No. of animals	LVPmax (mm Hg)	MaxdP/dt (mmHg/sec)	SV (ml)	SW (gm·m)	Max-AoP (mm Hg)	Max Flow (ml/min)
[^] C	CS	1	6.00	-1	1.50	3.9	10.3	0.9
		2	9.40	242	4.40	8.30	9.20	2.50
		3	10.70	247	1.10	3.45	10.80	0.99
		Mean	8.7 ± 1.4	163 ± 820	2.3 ± 1.00	5.2 ± 1.60	10.1 ± 0.50	1.5 ± 0.5
[^] C	IS	1	21.20	574	12.80	22.70	20.30	9.20
		2	19.70	344	5.20	11.70	14.20	5.10
		3	16.50	-4	4.40	8.30	13.10	3.30
		Mean	19.1 ± 1.4	304 ± 168	7.5 ± 2.7	14.2 ± 4.4	15.9 ± 2.2	5.9 ± 1.8

You et al. performed vascular delay of the LDM followed by CMP and showed that vascular delay of the LDM preserved its normal muscle architecture [21]. This resulted in significant increases in peak left ventricular elastance and stroke volume with LDM stimulation. However, the effects of LDM stimulation were only observed immediately after surgery.

In our group, we have already established the efficacy of vascular delay procedure in chronic Cardiomyoplasty [1]. Measured at two weeks after the CMP, dogs with vascular delay of the LDM showed marked increases in peak aortic pressure (23.9%), peak left ventricular pressure (23.5%), and maximum dP/dt (49.4%) for LDM assisted beats when compared to non-stimulated beats. These increases were significantly greater than the increases without vascular delay. This is why we used vascular delay in the present study. However, in that study, the LDM was not electrically conditioned and was thus a fast, untrained muscle.

Another approach to prevent or minimize LDM damages and prevent total conversion to slow type fiber (Type I) is intermittent stimulation. Iannuzzo et al [11] compared continuous (24 hours/day) versus intermittent stimulation (16 hours 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. He also showed that percentage of slow type I fibers was almost the same: intermittent (80%) vs continuous stimulation (91 %), thus preventing the overuse atrophy by decreasing LDM damage. In sheep, Arpesella et al stimulated the LDM for either 24 hrs/day or 10 hrs/day for one-year [2]. Isomyosin analysis showed that after one year, LDM stimulation for 24 hrs/day caused gross atrophy (> 40%) and contained only MHC1, typically slow type isoform of fatigue-resistant muscle fibers. But 10 hrs/day stimulation caused only 10% fiber atrophy and it contained 23% MHC2A, the isoform of fast-oxidative fibers, less prone to fatigue than the type 2B isoforms.

In this study, we compared the effects of intermittent stimulation (10 hours on /14 hours off per day) vs. standard continuous stimulation of LDM. In the continuous stimulation group, LDM stimulation caused moderate increases in peak aortic pressure (8.6%), left ventricular pressure (8.6%), peak positive LV dP/dt (14.2%), stroke volume (11.0%), stroke work (21.0%), and aortic flow (21.6%). In intermittent stimulation group, LDM stimulation caused significantly larger percent increases compared to continuous stimulation group, in peak aortic pressure (18.3%), left ventricular pressure (22.4%), peak positive LV dP/dt (25.9%), stroke volume (37.6%), stroke work (70.8%), and aortic flow (64.2%).

Conclusion

These preliminary results suggest that intermittent stimulation (10 hours on and 14 hours off per day) is superior to continuous (24 hours/day) stimulation. In a previous study, we showed the advantage of LDM preconditioning by vascular delay [1]. This combination, vascular delay plus

intermittent stimulation, leads to very large increases in left ventricular pressure and outflow with LDM stimulation. Obviously, additional experiments are needed to substantiate these results and to identify the mechanisms involved in intermittent stimulation. However, these preliminary results suggest that future clinical application of vascular delay plus intermittent stimulation in CMP should be considered.

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