

## Strategies for Examining Dynamic Cardiomyoplasty

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### Abstract

Typically, in cardiomyoplasty (CMP) experimental studies, a new intervention is examined only after 3 months of latissimus dorsi muscle (LDM) training. We believe that this has been a major mistake. In our approach, we sequentially measured the effects of LDM stimulation in CMP. Our experimental results showed that the effects of LDM stimulation were variable, and that this variability was present shortly after surgery.

Accordingly, we tried a number of approaches (LDM training before surgery, LDM stimulation early after surgery, wrapping the LDM in a Gore-Tex membrane, etc.), all of which failed. Our last approach was to try vascular delay, and to evaluate LV function in a terminal study 2 weeks after CMP surgery. Preconditioning the LDM with vascular delay resulted in improving performance of the LDM with consistent increases in LV hemodynamics.

**Key words:** review, cardiomyoplasty, latissimus dorsi muscle.

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Chronic heart failure continues to be a major cause of morbidity and mortality in the United States, with approximately 300,000 new cases each year. 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 "donor"; rejection is not a problem and immunosuppression is not necessary. Stephenson suggested that CMP supports the damaged myocardium, thus preventing systolic bulging [19]. Laks suggested that CMP "girdles" the ventricle, thereby inhibiting progressive ventricular enlargement [4]. Both mechanisms probably contribute to the subjective decrease in symptoms experienced by CMP patients. More importantly, these mechanisms might explain the results of the phase II clinical CMP trials, in which, end-diastolic volume was unaltered (progressive left ventricular [LV] enlargement was inhibited). However, both in experimental and clinical studies, systolic augmentation of LV function by the latissimus dorsi muscle (LDM) is rarely observed: LV ejection fraction and peak systolic pressure are almost identical with the pacemaker on versus off [13, 14, 17].

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 flow outflow. The clinical study of Jondeau et al. [17] is consistent with the data from Stephenson's and Lak's groups: after cardiomyoplasty, left ventricular

ejection fraction and functional class increased. However, stopping LDM stimulation had no effect on cardiac index, or left ventricular systolic and diastolic pressures. Similarly, Hagege et al. [14] 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). In a recent multi-center retrospective study [13], LV ejection fraction only increased from 0.20 to 0.23. This increase is within measuring errors for ejection fraction, and is physiologically insignificant.

It is, and has been, the goal of our laboratory to achieve large pressure and flow increases with LDM stimulation. Our approach is to systematically examine this problem by sequentially measuring the effects of different interventions. After an in depth review of the CMP literature, we could not find a single study that has reported these sequential measurements. Typically, the experimental CMP studies try some intervention, and only examine the effects of this intervention at the end of 3 months of LDM training. We believe that this has been a major mistake in this field, and has actually slowed progress. Important improvements may have been missed. It is our view that we should maximize the response at two weeks after surgery (which we have already accomplished). Then from this foundation, obtain

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the best results at 1, 2, and 3 months with the conversion to a fatigue resistance muscle.

In this paper, we will review our initial studies showing the effect of cardiomyoplasty with and without prior conditioning of the LDM [1, 2, 9, 10, 18].

### Results

#### Standard cardiomyoplasty

In the first experiment, without prior preconditioning, the effects of LDM stimulation were examined 2 weeks after CMP surgery; clinically this is when the stimulation is initiated. Table 1 summarizes the results, comparing the stimulated beat to the immediately preceding non-stimulated beat. For the 11 experiments, the LDM stimulation showed very little effect on the left ventricular function. Stroke volume, stroke work, and +LVdP/dt did not change significantly. With LDM stimulation, only peak left ventricular systolic pressure increased by 2.7%, while the absolute value of peak negative LVdP/dt decreased by 6.6%.

However, the effects of LDM stimulation varied between animals. Based on the peak left ventricular systolic pressure changes with LDM stimulation, the experiments were divided into responders (n = 7) and non-responders (n = 4). In the responders, LDM stimulation increased peak left ventricular pressure by  $6.1 \pm 1.8$  mmHg (4.3%), +LVdP/dt by  $185 \pm 47$  mmHg/sec (8%), stroke work by  $4.5 \pm 1.9$  gm·m (29.5%); while the absolute value of the -LVdP/dt decreased by  $168 \pm 43$  mmHg/sec (7.8%). The increases of peak left ventricular systolic pressure, stroke volume and stroke work and the decrease of absolute value of -LVdP/dt implied that in the responding group, LDM stimulation improved systolic function, but

limited the diastolic relaxation. In the non-responders, no changes were found to be significantly different between the stimulated and non-stimulated beats.

By gross estimation, the ischemic area of LDM after complete mobilization of the muscle was 23% for all 11 animals. However, the ischemia area in the non-responding group (28%) was significantly bigger than that in the responding group (21%).

#### Preconditioning

Our experimental results showed that the effects of LDM stimulation were variable. This variable effect is present shortly after surgery, and before the LDM is converted into a fatigue resistant muscle. Moreover, even in the responders, the net changes in stimulated vs non-stimulated beats were small. Thus, with the conventional CMP approach (no LDM preconditioning), much of the potential benefit is already lost by 2 weeks.

This study suggested that adhesions between the LDM and chest wall or LDM precondition may contribute to the variability and the failure of LDM stimulation to provide physiologically important LV assistance. We reasoned that we needed to drastically improve the results at 2 weeks, if we were to have any hope of significant improvements after the conversion to a fatigue resistant muscle at three months. We proposed that preconditioning and/or revascularization was needed if the LDM is to provide consistent and physiologically important cardiac assistance. Accordingly, we tried a number of approaches (LDM training before surgery, LDM stimulation early after surgery, wrapping the LDM in a Gore-Tex membrane, etc.), all of which failed [1]. Our last approach was to try vascular delay, and to evaluate LV function in a terminal study 2 weeks after CMP surgery

Table 1. Left ventricular function 9-12 days after CMP surgery.

|                     | All (n = 11) |            | Responders (n = 7) |             | Non-responders (n = 4) |           |
|---------------------|--------------|------------|--------------------|-------------|------------------------|-----------|
|                     | nSB          | SB         | nSB                | SB          | nSB                    | SB        |
| -LVdP/dt (mmHg/sec) | -1767±292    | -1651±271* | -2165±408          | -1996±418*  | -1170±134              | -1133±140 |
| EDP (mmHg)          | 16.3±2.2     | 16.6±2.3   | 12.8±2.4           | 13.4±2.4    | 22.4±2.4               | 22.1±2.3  |
| PLVP (mmHg)         | 132.7±7.8    | 136.3±8.7* | 140.5±9.8          | 146.6±10.6* | 118.9±9.7              | 118.2±9.6 |
| SV (mL)             | 9.9±2.2      | 11.7±2.7   | 11.2±2.5           | 14.0±3.1    | 7.5±3.9                | 7.9±4.1   |
| SW (gm·m)           | 12.0±2.5     | 14.9±3.3   | 15.3±2.5           | 19.9±3.4*   | 6.1±3.5                | 6.2±3.6   |
| +LVdP/dt (mmHg/sec) | 2062±326     | 2159±350   | 2315±393           | 2500±427*   | 1681±499               | 1648±489  |

Data expressed as mean±standard error

SB – Stimulated beats                      nSB = Non-stimulated beats

EDP – End-diastolic pressure; PLVP – Peak LV Pressure; SV – Stroke Volume; SW – Stroke Work

\* p < 0.05 (Stimulated beats vs. Non-stimulated beats)

[2, 18].

#### Vascular delay

Vascular delay is a procedure, in which, 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. Vascular delay stimulates revascularization, which may prevent the observed LDM damage.

Reconstructive surgeons have used this term for over 300 years [11] to describe a procedure whereby a pedicled flap is elevated in two or more stages separated by a delay period of 1 to 3 weeks. The end result is that a greater flap length will survive than if the flap had been completely elevated at the first operation [11]. In the first stage, the tissue is made sub-lethally ischemic and this ischemia stimulates revascularization. These vascular changes play a major role in protecting the tissue when it is exposed to the second, more severe, ischemic insult at the definitive flap transfer. In contrast to this "vascular delay" technique, in the CMP literature a period of rest after elevating the LDM on a single, thoracodorsal pedicle and wrapping it around the myocardium is termed "delay". This "delay" was originally incorporated to allow the LDM to "heal" around the myocardium [8]. This "delay" in pacing the LDM cannot therefore be considered a "vascular delay" since it does not include an initial sub-lethal ischemic insult to the LDM.

Thus, we examined the vascular delay approach. Standard cardiomyoplasty was performed in 6 dogs in the control group, while in 6 other dogs CMP was carried out after a vascular delay. The vascular delay procedure was performed two weeks prior or CMP by severing the perforating vessels to the LDM. Evaluation experiments were undertaken 14 days after CMP.

Table 2 summarizes the hemodynamic changes with LDM stimulation, comparing the LDM stimulated beats to the immediately preceding non-stimulated beats in the control and vascular delay groups. In the vascular delay group, LDM stimulation increased peak aortic pressure by 18.7%, peak left ventricular pressure by 19.3%, peak positive LV dp/dt by 31%, stroke volume by 44%, and stroke work by 69%. These increases were significantly greater than the control responses. Compared with controls, in the vascular delay group, LDM stimulation caused a 205% greater increase in peak aortic pressure, a 227% greater increase in peak left ventricular pressure, a 202% greater increase in peak positive LV dp/dt, a 138% greater increase in stroke volume, and a 142% greater increase in stroke work.

## Discussion

#### Comparison to literature

Vascular delay is a procedure in which some of the arteries supplying a muscle or tissue are ligated. This

Table 2. Controls versus vascular delay, hemodynamic changes with LDM stimulation.

|                                          | Control<br>(n = 6) | Vascular Delay<br>(n = 6) |
|------------------------------------------|--------------------|---------------------------|
| AoP (mmHg)                               | 11.4±3.6           | 21.5±3.8*                 |
| PLVP (mmHg)                              | 10.2±3.5           | 22.1±4.1*                 |
| +LVdP/dt (mmHg/sec)                      | 209±84             | 512±163*                  |
| SV(mL)                                   | 5.5±1.8            | 10.4±2.3*                 |
| SW (gm-m)                                | 10.0±1.2           | 22.1±5.4*                 |
| Data expressed as mean ±standard error   |                    |                           |
| * p < 0.05 (Vascular delay vs. Controls) |                    |                           |

causes sublethal ischemia and microvascular remodeling. The muscles is left in its original position for 1-3 weeks (delayed) before being transferred. Vascular delay stimulates revascularization, which prevents the observed LDM ischemia/necrosis.

Tobin et al. [21] examined intramuscular vascular territories from fresh human cadavers and from canine LDMs. In these studies, humans had an average of 15 perforating vessels to the muscle from intercostal arteries. 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 [12]. 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, Carroll et al. hypothesized that muscle function would be improved by a vascular delay procedure that increases distal muscle perfusion of the LDM [5]. 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 before and after elevation as flaps. 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.

In a follow-up study, canine LDMs were subjected to a 10 day vascular delay period followed by a simulated CMP [6]. Two weeks after simulated CMP, LDM perfusion and function was 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, Carroll et al. used angiogenic growth factors to stimulate vascular change [7]. Basic Fibroblast Growth Factor (bFGF), a potent angiogenic growth factor, has been shown to be upregulated in the presence of tissue hypoxia. They hypothesized that this upregulation of bFGF would occur with vascular delay and that giving 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 µg of human recombinant bFGF, into the thoracodorsal 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. [16] also demonstrated that a 1-month vascular delay period significantly enhanced muscle flap perfusion at rest and during exercise. In dogs, You et al. [22] ligated collateral blood vessels to the LDM 2 weeks before cardiomyoplasty. 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 to 1.00 mmHg/ml and stroke volume from 6.3 to 8.3 ml. This study shows promising results. However, the effects of LDM stimulation were observed immediately after surgery.

### Summary

Typical experimental CMP studies try some intervention, and only examine the effects of this intervention at the end of 3 months of LDM training. We believe that this has been a major mistake. In our approach, we sequentially measured the effects of LDM stimulation in CMP. Our experimental results showed that the effects of LDM stimulation were variable, and that this variability was present shortly after surgery [10]. Moreover, even in the responders, the hemodynamic changes in stimulated vs non-stimulated beats were small. Thus, with the conventional CMP approach without LDM preconditioning, much of the potential benefit is already lost by 2 weeks.

Accordingly, we tried a number of approaches (LDM training before surgery, LDM stimulation early after surgery, wrapping the LDM in a Gore-Tex membrane, etc.),

all of which failed [1]. Our last approach was to try vascular delay, and to evaluate LV function in a terminal study 2 weeks after CMP surgery [2, 9].

Preconditioning the LDM with vascular delay resulted in improving performance of the LDM with consistent increases in LV hemodynamics. Vascular delay of the latissimus dorsi can significantly improve muscle performance in cardiomyoplasty and could provide hemodynamic assistance early after surgery. For long term cardiomyoplasty studies with the conversion of the LDM to a fatigue resistant muscle, additional strategies, such as activity-rest regimen, may be needed to maintain the cardiac assistance provided by the LDM [1, 15].

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