

Optimization of Programming in Dynamic Cardiomyoplasty: Enhancing Synchronization of Muscle Wrap and Ventricular Contractions

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Abstract

Introduction: To obtain maximal benefit from dynamic cardiomyoplasty, stimulation parameters of the cardiomyostimulator need to be optimized. The two components for optimization include the muscle channel and the synchronization channel. This study looks at the issue of timing muscle contraction to ventricular contraction. Specifically, we compared 2 methods of obtaining optimal synchronization delay, 1) using the current clinical method of echocardiographic assessment of mitral valve closure with onset of burst stimulation, and 2) simultaneous open measurements of muscle and ventricular pressure generation.

Methods: A left latissimus dorsi (LD) cardiomyoplasty was performed in 4 dogs. Using a previously established protocol for muscle transformation, the LD muscle was continuously stimulated over 4 weeks with an epineural cuff and the Irel II myostimulator. After the training period, a Cardiomyostimulator (model #4710) was used for assist, and optimal synchronization timing was assessed. First, m-mode echocardiography was used to optimize timing of burst stimulation spikes with closure of mitral valve. Secondly, a median sternotomy was performed, and Millar pressure measuring catheters were inserted into the left ventricle (LV) and the LD muscle. Optimization of synchronization delay was again assessed with simultaneous measurement of ventricular pressure and the LD intramuscular pressure. Optimal delay for the open method was determined by best overlap of peak pressures of muscle and ventricle. Comparison was made between optimal synchronization obtained by echocardiography and the open method.

Results: All dogs survived the surgery without complication, and underwent the full period of muscle transformation, followed by optimization studies. One dog (#4) appeared to be in heart failure during the optimization study. In all dogs, optimal stimulation delay as measured by the catheter technique was shorter than that determined through m-mode echocardiography. Of note, 1) peak pressure (P_{Max}) generation of muscle occurred 70-100 msec after LV P_{Max} in 3 of 4 dogs (in one dog with failure, muscle P_{Max} occurred 10 msec after LV P_{Max}), and 2) in 3 of 4 dogs, duration of muscle contraction exceeded ventricular contraction, making diastolic impairment difficult to avoid.

Conclusions: From our results, we conclude that optimal synchronization delay occurs at a shorter delay than as determined by the echocardiographic method. In chronically stimulated muscle, P_{max} occurs later than LV P_{max} , and duration of muscle contraction is longer than LV contraction. A dilemma exists for optimizing timing of muscle contraction where maximal systolic assist is achieved with minimal diastolic interference. Because peak LV wall stress occurs early in systole, and most LV filling occurs early in diastole, we suggest that muscle contraction should occur as early as possible even at the cost of some late diastolic interference.

Key words: cardiomyoplasty, biomechanical assist, optimization of stimulation parameters in dynamic cardiomyoplasty.

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Optimization of muscle in cardiomyoplasty

Dynamic cardiomyoplasty (DC) is an alternative surgical procedure for managing patients with refractory congestive heart failure [4, 8]. In DC, the patient's latissimus dorsi (LD) muscle is wrapped around the heart, and is stimulated to contract in synchrony with cardiac systole. Although clinical improvements in symptoms and hemodynamics have been demonstrated, the role of DC in treating heart failure awaits the completion of a randomized clinical trial.

The success of any medical intervention depends on the application of optimal techniques for the method used. In DC, optimization of stimulation parameters of muscle contraction has been shown to be a critical component for obtaining good results [9-11, 18]. By optimizing stimulation parameters, various investigators have demonstrated further improvements in hemodynamics of up to 20% [9, 18]. One area to optimize is the timing of muscle contraction with cardiac systole. Poor synchronization of contractions can result in harmful diastolic interference, or ineffectual systolic assist.

Currently, the recommended method for setting the timing parameters is through m-mode echocardiography, looking at mitral valve closure with respect to onset of electrical stimuli of the muscle (figure 1) [10]. However, it is known that with chronic stimulation, skeletal muscle will show a decrease rate of response to pacing [17]. Therefore, tracking of the electrical stimulation activity may not reflect the real-time activity of muscle contraction. The purpose of this study was to obtain simultaneous measurements of ventricular and muscle contractions in response to electrical stimulation in a chronic animal model, and to compare these results with those obtained by using the current recommended method with m-mode echocardiography.

Methods

Studies were performed on 4 mongrel dogs weighing between 30-40 kg. All animals in this study received humane care as outlined in the Canadian Council on Animal Care guidelines.

Experimental model

The dogs were initially induced with a intravenous dose of Nembutal (30 mg/kg). During the surgery, anesthesia was maintained by the use of isoflurane (1-1.5%) during mechanical ventilation. Dynamic cardiomyoplasty was performed using the left latissimus dorsi (LD) muscle in the same manner as performed clinically. The left chest was shaved, then prepped and draped sterilely. The left LD was raised as a pedicled flap, with preservation of the thoracodorsal artery nerve bundle. After mobilization of the muscle, the LD was placed into the left chest through a window created by resection of a lateral segment of the 3rd rib. The insertion tendon of the LD was anchored to the 2nd rib, and a neural cuff lead (Medtronic) was placed around the thoracodorsal nerve for stimulation. The neu-

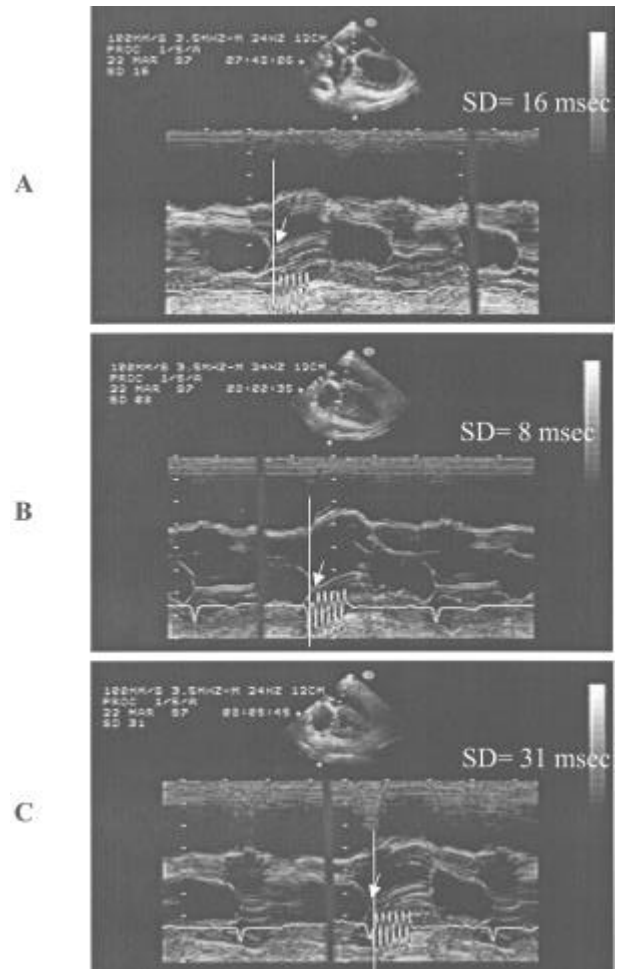


Figure 1. M-mode echocardiographic assessment of optimal synchronization delay. With a delay of 16 msec (fig. 1a), stimulation starts at the closure of the mitral valve (arrow). This is in contrast to a delay of 8 msec (fig 1b), which is too early. While with a delay of 31 msec (fig 1c), the onset of contraction is too late. (SD: synchronization delay; LV: left ventricle; ECG: electrocardiogram).

ral cuff lead was connected to an Irel II (Medtronic) myostimulator situated in a subcutaneous pocket in the left upper abdomen. The incision was closed in two layers. Next a median sternotomy was performed to wrap the muscle around the heart. The pericardium was opened, and the LD brought out from the left thorax. The LD was wrapped around the heart in a clockwise direction as viewed from the cardiac apex, and anchored in place onto the heart with sutures. The wrap was placed loosely, to avoid any interference with cardiac filling. The sternum was closed, and the animal was allowed to recover from surgery. Two weeks after the surgery, muscle training was started. The Irel myostimulator was set to the following parameters: 2 Hz continuous stimulating cycle (0.1 sec. on; 0.4 sec off), burst frequency of 36 Hz, pulse width of 210 μ sec, and voltage of 1-3V, as required to get palpable LD contractions. Stimulation was maintained at

Optimization of muscle in cardiomyoplasty

these settings for 4 weeks. These settings were chosen since our previous studies have shown this to result in complete muscle transformation, similar to that observed in the clinical situation [12].

Studies

After completion of the muscle training period, the animals were returned to the laboratory for functional studies. Under endotracheal anesthesia with isoflurane, a right jugular vein cutdown was performed. An intravenous pacing lead (Medtronic 4012) was passed under fluoroscopic guidance into the right ventricle. This lead was used as a sensing lead for the cardiomyostimulator (Medtronic 4710 Transform). The previously inserted thoracodorsal neural lead was attached to the cardiomyostimulator, and used to stimulate the LD muscle. The cardiomyostimulator was set to fire 6 pulses/burst, with a pulse interval of 31 msec, and a burst duration of 28% of the R-R interval of the ECG.

Optimal synchronization delay was first determined by surface echocardiography using a 3.5 MHz transducer. Under m-mode, burst stimulation was timed to start immediately after mitral valve closure as currently recommended. After determining the optimal delay with m-mode, a median sternotomy was performed. Millar Mikro-Tip pressure catheters were inserted into the LV through the apex, and one was inserted intramuscularly into the LD muscle. Optimal delay was then assessed using this open method by adjusting delay to provide best overlap between LD muscle and LV peak pressures. Comparisons were made from results obtained by m-mode and the open method within the same animal.

Results

All animals survived the dynamic cardiomyoplasty procedure and completed the chronic stimulation period for muscle transformation. Of note, the 4th dog appeared to develop ventricular dysfunction as evidenced by a decrease in ejection fraction on echocardiogram during the functional study. The etiology for the fall in LV function was not known, but the dog remained hemodynamically stable to determine optimal synchronization delay using both methods.

An example of the m-mode study and open measurement tracing are shown (figure 1 & 2). Optimal synchronization delay, as determined by the two methods, in the animals studied are provided (table 1 and figure 3). Of note, delay as determined by the open method was shorter than as determined by the m-mode method in all animals. This was due to the significant lag period between LD stimulation and peak muscle contraction. The LV was able to achieve peak pressure 70-100 msec faster than the transformed muscle (except for the animal which demonstrated ventricular dysfunction where the difference was only 10 msec). Diastolic overlap was observed in 3 of the dogs despite optimizing of the delay period.

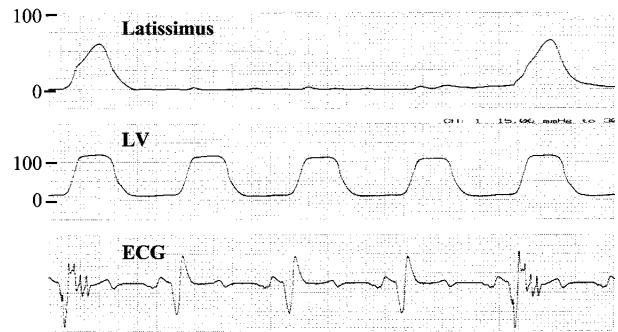


Figure 2. Sample tracing of simultaneous pressure measurement of latissimus dorsi muscle and left ventricle. Note the slower rate of contraction and relaxation in the muscle. (SD: synchronization delay; LV: left ventricle; ECG: electrocardiogram).

Discussion

The importance of optimizing the stimulation parameters in DC was demonstrated by Geddes in an acute animal model [9]. In the study, untrained LD muscle was wrapped around the heart, and hemodynamics were measured with and without assist. The hemodynamic endpoints used included aortic flow and pressure, LV pressure, and stroke volume. By varying synchronization delay, they demonstrated from minimal changes to improvements in hemodynamics of up to 40% with optimal timing.

The effects of optimizing stimulation parameters was demonstrated clinically by Schreuder [18]. Studying patients 6-24 months after DC, they were able to further improve stroke volume by a mean of 20% through adjustments in the stimulation parameters. Additionally, they observed a possible detrimental effect if parameters were not correctly set. Similar clinical observations of hemodynamic improvements were shown by others after optimization of synchronization delay of LD contraction.

Optimization of stimulation parameters for DC can be divided into two areas of focus. One area includes improving force of contraction (such as adjustment of voltage and burst frequency), while avoiding muscle injury. The other area of focus is optimization of timing of muscle contraction with the cardiac cycle. This study looked at the issue of muscle contraction timing. There are two reasons to optimize synchronization delay. They are to avoid interference of diastolic filling, and to maximize systolic assist. It is currently recommended that muscle contraction should not occur until after closure of the mitral valve, where muscle contraction would occur only after completion of ventricular diastole [10, 11, 13].

The current recommended method for obtaining optimal synchronization delay is through m-mode echocardiographic assessment [10]. Using a parasternal long-axis view, the mitral valve leaflets are visualized with a simultaneous display of the ECG tracing. Synchronization delay is set by timing the start of the pulse train stimulation with mitral valve closure. When using this method to

Optimization of muscle in cardiomyoplasty

Table 1

Dog	Synchronization Delay		Response Rate	
	M-Mode (msec)	Open Measurement (msec)	QRS to LV _{Peak} (msec)	Burst to LD _{Peak} (msec)
1	16	8	110	180
2	16	8	100	200
3	16	8	120	200
4	23	16	170	180

adjust delay, the assumption is made that electrical stimulation of the muscle correlates temporally with mechanical activation. That is, there should be no lag period between stimulation and contraction of the muscle. However, it is known that skeletal muscle which has been trained to be fatigue resistant demonstrate a reduction in response rate from stimuli to peak contraction [17]. Timing using the electrical stimuli signal would then result in actual muscle contraction occurring late in systole, with some loss of benefit of cardiomyoplasty. Additionally, because of slow relaxation in trained muscle, cessation of burst stimuli may not allow complete muscle relaxation prior to diastole. These issues were addressed in our labo-

ratory study.

Our results demonstrate that trained muscle, as currently used in DC, show a slower rate of contraction compared to the heart. Because of this characteristic, assessment of optimal synchronization delay by the m-mode method resulted in settings where peak muscle contraction occurred later in cardiac systole, than what appeared optimal through direct measurement of muscle contraction. Optimal delay as assessed by the m-mode echo technique was 8 msec. longer than as assessed by direct measurement. Despite the lowest set delay period for the cardiomyostimulator (8 msec.), peak muscle contraction still occurred 70-100 msec after peak LV pressure in most of the animals studied. Even with modification of the cardiomyostimulator, to allow firing immediately upon R wave sensing, there may not be sufficient time for peak muscle contraction to occur with LV peak pressure. Some innovative means to trigger muscle stimulation, such as using the p-wave, may be required if peak-to-peak superimposition is desired. Interestingly, in one animal that developed cardiac deterioration during the study, peak pressure superimposition between muscle and LV was possible. This was due to a decreased rate of LV pressure generation in the animal. One could assume that in clinical heart failure, a similar situation would occur and superimposition of peak pressures would be possible. It was observed that with the burst duration set at 28% of the R-R time interval, there was incomplete relaxation of the muscle prior to the onset of diastole in 3 of the animals. This slow relaxation response is seen in trained muscle, and makes it difficult to avoid some diastolic interference. Another factor which would affect the extent of diastolic interference would be heart rate. The faster the rate, the greater the chance that the LD muscle would have less opportunity to relax completely prior to onset of diastole. This would provide additional incentive to closely control heart rate in patients with heart failure. Although heart rate was not controlled in this study, the adaptive feature of the cardiomyostimulator would compensate the burst duration according to the changing R-R interval of the ECG.

Several issues are apparent from our results. First, because of the lag period between onset of stimuli to peak muscle contraction, optimization by m-mode echocardiography will tend to overestimate the ideal delay period. However, this conclusion is based on our assumption that

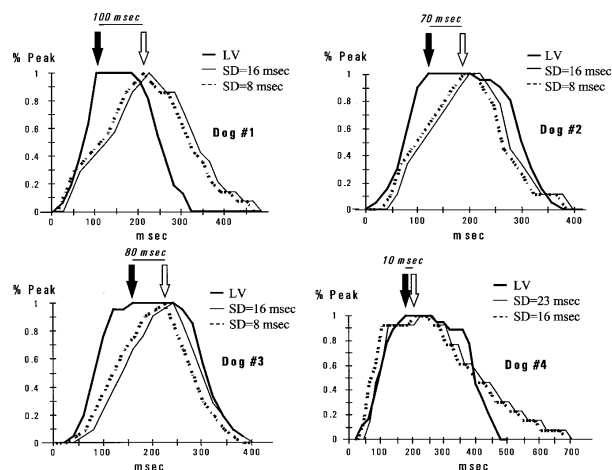


Figure 3. Results of simultaneous pressure measurements of latissimus dorsi muscle (thin-solid and dashed lines) and LV (thick-solid lines) in all 4 dogs. Graphs show % of peak contraction with time after triggering event by the QRS complex. Comparisons are made between optimal delay as determined by m-mode (thin-solid lines) and direct pressure measurements (dashed lines). Note that despite minimal delay of 8 msec, peak muscle contraction occurred 70-100 msec after peak LV contraction. In the 4th animal, LV dysfunction was present (delayed peak contraction to 200 msec), and close peak-peak superimposition was possible (10 msec). Because of decreased muscle relaxation rates, encroachment into early diastolic phase was seen in 3 animals (#1,2,4). (SD: synchronization delay; LV: left ventricle).

optimal timing requires superimposition in time of the peak LV and muscle contraction. We chose to use peak pressure superimposition because a major beneficial effect of DC is likely through a myocardial sparing effect by decreasing ventricular wall stress during systolic assist [7, 14, 16]. Since wall stress is greatest during the pre-ejection phase of systole, peak assist from DC would be most beneficial at this time period. In acute laboratory studies, DC was shown to decrease transmural pressures by over 40%, and was associated with a decrease in myocardial oxygen consumption while maintaining the same level of work [5, 6]. Analysis using a mathematical model also described a 40% improvement in hemodynamics with DC after optimizing timing of contractions [15]. Interestingly, the authors predicted that having the muscle contract too early during the cardiac cycle detracted minimally to the benefit of DC, as opposed to having the muscle contract late during the cardiac cycle where there would be a significant decrease in assist. Simply stated, it is better to have the muscle start contracting during late diastole, rather than have it extend into the early phase of diastole. Intuitively this is reasonable since most of ventricular filling occurs during early diastole. It should be noted that in their model, an assumption was made that the profile of the muscle contraction curve was identical to that of the ventricle.

The second issue demonstrated in this study is that the muscle contraction curve profile does not always follow that of the ventricle. This is due to the decrease in rate of activation and relaxation of fatigue trained muscle, and makes diastolic interference hard to avoid. One way to address this issue would be to have LD muscle contraction occurring early during the cardiac cycle, as suggested above. This would result in some late diastolic interference, but would assure peak force generation early during systole, with minimal interference during early diastole. Alternatively, the burst stimulus duration could be decreased to allow greater time for muscle relaxation, but it would come at the cost of decreasing peak muscle force. Another option may be to modify the training protocol to produce a LD muscle with different functional properties.

The present protocol used for training the muscle for clinical DC results in complete transformation to slow twitch fibers. A fully converted muscle can show an eight fold reduction in peak power output, with a fivefold reduction in shortening velocity. Fortunately, it has been shown that fatigue resistance can be induced, while maintaining the properties of fast twitch fibers including its greater force and rate of contraction. A protocol of "interval stimulation" was suggested by Carraro, where the muscle is allowed to rest during periods of low activity (as during the night while the patient is asleep), and is stimulated during the day with increased activity [2]. With this regimen they demonstrated fatigue resistance while preserving muscle force and velocity, leading to

improved benefit from DC. Chronic animal studies from Carraro's laboratory have demonstrated preservation of muscle contraction velocity and muscle mass with this intermittent training regimen while still maintaining qualities of fatigue resistance [1].

Possible criticisms of this present study include the limited number of animals studied and the variability observed in the muscle response to stimuli. We believe the number of animals studied are sufficient to emphasize that reliance on stimuli signal as a temporal marker of muscle contraction is poor, especially with fully transformed muscle. In all dogs, open measurement indicated optimal delay to be shorter than that obtained via m-mode echocardiography. In addition, individual variability of muscle and ventricular contraction occur in patients, and forms the basis for the need to tailor optimal stimulation parameters to each patient. As discussed above, peak-to-peak superimposition could not be achieved in most of the animals, but this may be unique to this experimental setup where normal hearts were used. Using a heart failure model may have allowed better timing to be achieved as seen in one of our animals. Another issue is the validity of using peak-to-peak superimposition for the ideal timing. The mechanism for benefit from systolic assist with DC most likely results through a myocardial sparing effect due to decrease in transmural wall pressure and stress. Since stress is highest at or just prior to ejection, it is reasonable to attempt to provide greatest muscle assist during this time. Although Chen has demonstrated, by measuring transmural wall pressure, most benefit with optimal timing in an acute model; these results should be confirmed in the chronic model [5]. Finally, concern may arise on the use of intramuscular pressure measurement as a temporal reflection of muscle force generation. A study by Cestari compared intramuscular pressure generation with force production in the latissimus dorsi muscle of the dog [3]. They observed that intramuscular pressure was linearly related to force generation.

Future studies are needed to further define the methodology for optimizing stimulation parameters in DC. The optimal time for muscle contraction to occur during the cardiac cycle needs to be investigated in chronic models. It may be feasible to develop a fatigue resistant muscle which maintains its force and velocity of contraction to improve the results of DC. These muscle training protocols need to be defined and verified. Because of individual variability, a more precise way of noninvasively assessing muscle contraction clinically is critical, if optimization of stimulation parameters is to be achieved. Some preliminary work using the apicocardiogram to monitor latissimus dorsi muscle contraction has shown promise as a means to noninvasively follow muscle function. Other methods to monitor muscle function in DC, including intramural balloons, have been suggested.

In conclusion, our study shows that m-mode echocardiographic assessment of optimal delay does not correlate well with real time muscle contraction due to a lag period between stimuli and peak muscle contraction. Because of a decrease in rate of contraction and relaxation in the chronically stimulated muscle, some diastolic interference may be difficult to avoid. However, recent physiological studies suggest that these issues can be overcome. Because of individual variability, optimization would need to be tailored to each patient. Further investigations are needed on the approach of optimizing stimulation parameters to obtain maximal benefit from DC.

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Optimization of muscle in cardiomyoplasty

catheter and aortic model flow in cardiomyoplasty

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