

Latissimus Dorsi Stimulation in Dynamic Cardiomyoplasty: How Should We Proceed?

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Abstract

Improved understanding of the mechanisms of action in dynamic cardiomyoplasty (DCMP) and continued research in the stimulation of the latissimus dorsi muscle (LDM) contribute to the development of new stimulation strategies aimed at improving DCMP outcomes. Cautious initiation of LDM stimulation sooner after surgery than currently practiced may provide the patient earlier hemodynamic assistance. During training and chronic stimulation, adjustment of stimulation amplitude, number of pulses in a burst, the interval between pulses, the synchronization ratio and the synchronization delay will all have important effects on the acute and chronic contractile properties of the LDM, thus impacting its capacity to improve cardiac function. Allowing the LDM periods of rest each day can be extremely beneficial to the muscle and may ultimately improve clinical outcome. Non-invasive monitoring of LDM contraction is essential to implementing and testing new stimulation regimes. Recent development of such monitoring techniques allows safe clinical evaluation of experimentally validated concepts. This review considers each LDM stimulation parameter in terms of improving LDM function and optimizing DCMP benefit during both training and chronic stimulation phases. Post-operative stimulation techniques currently possible with today's technology are discussed in light of recent research and clinical findings.

Key words: cardiomyoplasty, Latissimus dorsi, electrical stimulation.

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The premise that fatigue-resistant skeletal muscle could assist or replace the systolic function of the failing myocardium formed the conceptual foundation of dynamic cardiomyoplasty (DCMP). The feasibility of DCMP using the latissimus dorsi muscle (LDM) has been demonstrated through early research and clinical work [9, 10, 14, 53, 56, 64]. The early protocols, for experimental work and clinical evaluation, were designed based on this original premise of systolic assist. The LDM needed to contract vigorously during cardiac systole, and it should work continuously, 24 hours per day, contracting with every or every-other heart beat. To measure the benefit provided, standard indices of left ventricular systolic function were monitored. Numerous centers have reported clinical success using the original techniques with improvements in functional class, ejection fraction, and exercise capacity being documented [8,17,42,47, 48, 58,71]. However, increased knowledge in how DCMP works [57, 60], and how the LDM responds to chronic electrical stimulation allows us to reassess the early protocols and make improvements. The goals that guided the development of the first training and stimulation protocols were: 1) achieve maximal systolic assistance by stimulating the LDM to forcefully contract within the systolic phase, 2) completely transform the LDM

to fatigue-resistant, type 1 fibers, in order to 3) maintain beat-to-beat assistance 24 hours per day.

Recent clinical and experimental studies have taught us that the mechanisms of DCMP leading to a patient's clinical improvement are much more complicated than originally thought. Systolic assistance may not be the primary mechanism in improving a patient's well-being, particularly when the muscle used becomes fully transformed with reduced power capacity. Analysis of pressure-volume relations in patients and evaluation of myocardial energetics in animals indicate that the chronic girdling and the dynamic effects of cardiomyoplasty combine to cease or reverse the myocardial remodeling process and improve its working efficiency [2, 7, 45, 62, 67, 68]. The reversal of the dilatation process may largely depend on the dynamically contracting LDM for wall tension reduction [2, 23, 62, 67, 68], but the LDM contraction, as DCMP is practiced today, may be ineffective in significantly augmenting systolic measures of left ventricular function on a beat-by-beat basis in many patients [38].

With this better understanding of how dynamic cardiomyoplasty is presently working, the goals of LDM training and chronic stimulation need to be reset, and the protocols redefined accordingly. Now the goals might be

more accurately stated as: 1) stimulate the LDM in a way that preserves its mass and function for long-term dynamic myocardial support, thereby stopping or reversing the disease process, 2) maintain a more powerful, fast-contracting LDM with greater potential for providing systolic assistance, but 3) provide such hemodynamic assistance only when necessary for the patient, such as in the early post-operative phase or during periods of activity, to avoid chronic muscle overuse.

While numerous approaches for improving LDM function for DCMP exist, such as pharmacological enhancements [27,63,55], preconditioning by electrical stimulation [3, 15] or exercise training [16, 50], this review will focus on post-operative stimulation techniques currently possible with today's technology. An attempt is made to consider each LDM stimulation parameter in terms of improving LDM function and optimizing DCMP benefit, during both training and chronic stimulation phases.

When to Start Stimulation

Conventionally, a two-week healing period is allowed following the surgical procedure, prior to muscle activation. This period has commonly been called a "vascular delay", but it should be noted that this terminology is somewhat inaccurate. The original terminology of "stimulation delay" or "pre-assist period" may be more appropriate [14]. To clarify, the term "vascular delay" originates from the plastic surgery practice of performing a muscle or skin flap transfer in two surgical procedures, separated by a few days or weeks. This averts ischemic necrosis of the flap by avoiding complete and irreversible regional ischemia due to collateral vessel ligation during surgery. This true "vascular delay" may have substantial benefits in DCMP as well as described in detail by Santamore and colleagues elsewhere in this issue [66].

The conventional two-week recovery period practiced in cardiomyoplasty is based on two assumptions: 1) time is necessary to allow adhesions to form between the LDM and epicardial surface to prevent dislodgment or displacement of the muscle wrap, and 2) the LDM must have time to recover from the surgical injury. A two-week period of time is supported by the experimental work of Chachques who evaluated the recovery process following various lengths of ischemic episodes [12]. Fourteen days after three to six hours of total ischemia, muscle fiber regeneration had occurred. Mannion's work also supports the practice of leaving the muscle undisturbed for the first couple weeks after surgery [54]. He found that immediately after mobilization, stimulation of the LDM did not induce the normally expected rise in blood flow to the muscle. After three weeks, a normal hyperemic response to stimulation was regained. Based on these studies of fiber regeneration and restoration of normal blood flow, a two week recovery period seems prudent.

Other clinical factors may also support this cautious approach [14]. Besides the surgical dissection of collateral blood flow, the LDM perfusion is already subject to the effects of low cardiac output. During post-operative care, the patient may be supported by inotropic agents which will further limit LDM blood flow and threaten viability

particularly under imposed contractile activity. Muscle relaxants may also be given which would impair normal LDM contractile function anyway. Disuse atrophy associated with heart failure will also limit the early capacity of the LDM for assistance. This can be at least partially remedied by pre-operative exercise training [16, 50]. For these reasons, stimulation during the immediate post-operative phase could be ineffective.

On the other hand, a two-week recovery period, perceived to be necessary for the muscle, is a major limitation of DCMP. It prevents early delivery of cardiac assistance to the patient. Several investigators have examined the real risk of early stimulation. Lorusso and colleagues reported that stimulation beginning one day post-op at a synchronization ratio of 1:3 produced no signs of fiber degeneration as assessed two weeks later [49]. To avoid LDM displacement, a fibrin sealant had been used. Likewise, Guldner and associates have initiated stimulation immediately after experimental cardiomyoplasty procedures in goats [37]. They demonstrated that muscle function could be maintained and histological fiber damage could be avoided with cautious stimulation regimes and close monitoring of muscle function.

Prior to these experimental studies, clinicians in Russia were already activating the LDM immediately after the DCMP procedure [1, 19]. The ability to use a very low synchronization ratio of 1:16 in the Russian-made stimulators allowed this attempt in delivering immediate assistance to be made cautiously. In these cases and in the first clinical case in Korea [61], no mention of using fibrin glue is made with no reports of complications due to muscle displacement.

In fact, the two weeks of no stimulation intended to allow ischemic recovery of the muscle may be detrimental to the muscle in another way. Following any limb injury that limits mobility, disuse atrophy of the affected limb is easily observable within two to three weeks. This consequence in DCMP was studied by You and colleagues [74]. Muscles that underwent tendonectomy and left inactivated for two weeks had an almost 50% reduction in fiber diameter. Though it is unclear how much stretch was applied to the tenotomized muscle during that time, the effect of disuse atrophy surely has impact on the LDM morphology during the two week "recovery" period in the clinical setting.

Just as in almost any situation encountered, the law of moderation should probably be applied. No stimulation at all does not benefit the patient and will cause some degree of disuse atrophy and deconditioning of the muscle, thereby limiting the future potential for cardiac assist as well. On the other hand, immediate stimulation for 24 hours per day should be considered overly aggressive (with the possible exception of extremely low contraction rates).

The best scenario must be somewhere in between-one that provides some assistance, but does not overexert the muscle. Chekanov has performed systematic studies to determine just how much stimulation can be safely applied to the muscle without producing muscle injury experimen-

tally [20]. A review of his laboratory's past and most recent results are presented in this issue [21]. Short periods of powerful contractions are possible without muscle injury and with the potential to provide relevant cardiac assist to the patient during the critical post-operative phase. The muscle is still a fast contracting muscle at this time so powerful contractions will be possible with only a few pulses per burst, for example three to four. Since the patient typically remains hospitalized for the first 10 to 14 days after surgery, it is quite practical to administer such brief periods of stimulation, to potentially help the patient hemodynamically and to preserve LDM mass.

Training Protocols

The standard clinical training protocol was based on providing a progressive training regime that could be synchronized to cardiac function. By beginning with a single pulse and progressively increasing the number of pulses a progressive demand is placed on the muscle to allow it to condition over time. Early experiments designed to develop a training protocol for producing fatigue-resistant muscle that was clinically applicable in fact used a progressively increasing rate of pulse trains per minute [13]. Due to technical specifications of first generation cardiomyostimulators (specifically a fixed burst duration and synchronization modes of 1:1 or 1:2 with upper rate safety limits), the pulse interval was the only variable that could be flexibly programmed. Progressive iterations in pulse number, therefore, were performed by shortening the pulse interval over time to allow more pulses to fall within the fixed burst duration.

This means that when the second pulse is added, it is delivered at an interval much greater than the fusion frequency of the muscle resulting in two distinct twitches [14]. While this approach provides a mild increase in demand over time, it is not necessarily physiological in the sense that pulses are delivered well below normal motoneuron firing frequencies and thus produce quite different contractile activity than normal, intrinsic skeletal muscle function. To work efficiently, summation of the muscle twitch response to each individual pulse should occur. Therefore, potential force generation is wasted when two pulses are delivered below the tetanic fusion frequency [28].

Technological advances now allow much greater flexibility in the programming of the cardiomyostimulator [33]. The pulse number can be programmed at a wide range of pulse intervals, and progressive increases can be made in the synchronization ratio. Clinical implementation of progressively adding pulses at a fixed pulse interval of 31 msec or less (33 Hz or more) has already occurred in some centers. In Padova, stimulation is initiated one week after surgery with one pulse [59]. Pulses are added each week at an interval of 23 msec (43 Hz) for four weeks for a final regimen of only 4 pulses per burst delivered at 1:3. Clinical outcome with this approach has been excellent so far.

With the large number of stimulation parameters that can be varied, such as pulse amplitude, pulse train frequency,

the number of pulse trains per minute, the duration of the pulse train, the hours per day that the muscle is stimulated, etc., deciding the best approach for designing a progressive training protocol can seem overwhelming. Alternatives include using a progressive number of contractions per minute rather than progressively increasing the number of pulses in the burst. This approach was used in Russia and was compared to the standard training regime in an animal study, as well as a regime in which pulses were added at a fixed pulse interval [28].

The results led to the same endpoint: complete fiber-type transformation and an overall reduction in power capacity. This reduction occurs rather early on in the postoperative period, say within the first two months after surgery, so the potential power available for cardiac assistance is already limited by the end of the conditioning period.

The goal of the conditioning period is simply to prepare the muscle to be fatigue resistant to avoid later injury due to overexertion. However, it is more desirable to prevent a full transformation to fatigue-resistant type 1 fibers which may be too slow for optimal coupling to the cardiac cycle and too weak to produce meaningful hemodynamic assistance [65]. An intermediate state of transformation to type 2a fibers which have improved fatigue-resistance with maintained force capacity is more suitable.

Salmons' laboratory has shown that two weeks of 2 Hz continuous stimulation preconditions the muscle to resist damage when higher stimulation frequencies are later applied [43]. They have also shown that the overall degree of transformation is related to the "average aggregate frequency" [41]. These concepts when applied clinically, support the standard clinical practice of beginning with a single pulse delivered at every or every other heart beat for two weeks before proceeding to trains of pulses. The oxidative capacity of the muscle will already be increased during this time [43], making the muscle more fatigue-resistant and preparing it to tolerate a higher stimulation demand. The next steps in training the muscle are more crucial to the aim of preventing full transformation. Choosing parameters which lower the average aggregate frequency should be considered. This can be done by using fewer pulses per burst, lower synchronization ratios, and perhaps most effectively by intermittent stimulation [5].

With these basic guidelines, the individual stimulation parameters in terms of exact pulse number or synchronization ratio may not be so important as far as training is concerned; most important is to what degree the combination of these parameters produce overall activity over a 24 hour period. Patterning it in a way that utilizes the available muscle power most effectively and as early as possible for cardiac benefit will ultimately define how each parameter should be programmed. For example, maybe a synchronization ratio of 1:8 for 24 hours per day is roughly equivalent to using a 1:4 synchronization ratio for twelve hours per day in terms of LDM properties. However, if assistance is provided primarily during active daytime periods, it may provide the greatest clinical benefit and allowing the LDM

to rest during the night may *be* better for the muscle long-term.

In 1993, Lexell and associates in Salmons' laboratory found that intermittent stimulation at 10 Hz produced less fiber damage in rabbits than continuous 5 Hz stimulation despite an equivalent 24 hour aggregate frequency [46]. Ferguson et al. compared stimulation periods of 8 and 24 hours per day using either 10 Hz continuous stimulation or a 30-Hz phasic (burst) pattern, which was equivalent to an average of 10 Hz in the number of pulses delivered [26]. Stimulation was applied for 90 days. Muscles stimulated with the 30-Hz phasic pattern retained greater tetanic tension and muscle mass with fewer pathologic changes than 10-Hz continuous groups for either the 8- or 24-hour per day stimulation periods. Eight-hour per day stimulation led to an intermediate state of transformation: more than 60% type 2a fibers and the remaining 30 to 40% type 1 fibers. Twenty-four hour stimulation led to nearly complete type 1 transformation. The greatest muscle mass, tetanic tension, and contraction and relaxation velocities were achieved with the 30 Hz burst pattern delivered 8 hours per day.

As early as 1991, Magovern's group evaluated a training protocol in sheep utilizing intermittent periods of stimulation at the onset which progressively increased to 24-hour per day stimulation [44]. They report preserved force and mass after four months of stimulation compared to control, non-stimulated muscle. It is somewhat surprising that after several weeks of 24 hour per day stimulation, force did not begin to decrease more significantly with an assumed conversion to type 1 fibers. Even earlier than that study, Badyalak and colleagues evaluated continuous 2 Hz stimulation versus intermittent periods of 15 minute episodes of burst stimulation, and a combination of both [6]. While the 2 Hz stimulation led to greatest fatigue resistance and power loss, the intermittent stimulation produced the greatest force retention and least fatigue resistance, but the combination of both led to fatigue resistance and force retention.

Ianuzzo and colleagues found that intermittent burst stimulation used to train a mobilized goat LDM preserved fiber size and prevented increased fibrosis when compared to continuous stimulation [40]. Arpesella reported that this morphologic preservation and maintained power capacity can be sustained up to one year by intermittent stimulation [5]. Most recently, Duan and colleagues present in this issue the striking results of increased force and stroke work capacity associated with fiber hypertrophy and intermediate fiber type conversion in muscles trained intermittently compared to non-trained control muscles [25].

Though individually each of these studies evaluated quite different sets of stimulation parameters, all support the basic concept that intermittent stimulation can effectively maintain power for cardiac assistance while improving fatigue resistance and preserving muscle morphology. Furthermore, if applied cautiously, for short daily periods, such stimulation could be initiated earlier than two weeks after surgery.

The goal of LDM training is not necessarily to achieve chronic state of 6 pulses per burst at a 1: 2 synchronization ratio but to lead to clinical improvement. If this can be done at a lower synchronization ratio or pulse number there is no reason to impose higher demands on the muscle, discussion of how to select the final clinical settings for stimulation parameters follows.

Chronic Stimulation Settings

The process of choosing stimulation parameters during and after training is currently evolving with increase knowledge of the chronic effects of these parameters on both LDM and cardiac function and with the introduction of new techniques for monitoring LDM function. Factors to be considered and recent advances are described for each parameter individually, but since their effects are obviously not independent some overlap is made in the following discussion.

Stimulation amplitude

Initial selection of muscle stimulation amplitude takes into account the twitch threshold measured at the time of electrode implantation. This threshold can of course change as electrodes become encapsulated or if their relative position to the nerve branches changes. To verify threshold amplitude postoperatively, the simple means of palpation in the axillary region for sensation of the muscle twitch at the lowest possible amplitude is commonly used. The full recruitment amplitude for intramuscular electrodes in the LDM is typically 2 to 2.5 times the palpation threshold. The programmed stimulation amplitude can be selected according to these basic guidelines and taking into consideration patient comfort.

Obviously this technique does not allow accurate determination of a desired recruitment level, tailored to individual patient response. George and colleagues demonstrated experimentally how variable the maximal recruitment amplitude can be between individual subjects [32]. Furthermore, significant differences in maximal pressure development during muscle contraction can occur with small increases in stimulation voltage which will certainly affect the degree of cardiac assist attained.

Clinically, Schreuder *et al.* found significant improvement in systolic parameters only after adjusting the appropriate synchronization delay and increasing the stimulating voltage 1.5 to 3 V higher than the chronic clinical setting [67]. Conceivably, increasing the stimulation amplitude temporarily recruits more powerful motor units previously not stimulated and therefore not transformed. This auxiliary recruitment likely has more than a trivial contribution to the assisting action. Nonetheless, this result emphasizes the importance of having a stronger, faster muscle contraction in order to achieve meaningful hemodynamic augmentation.

Catheterization required for pressure-volume analysis is not plausible for all patients just for the selection of stimulation amplitude. A straight-forward, non-invasive technique is needed for determining the strength of contraction

associated with amplitude settings. Van der Veen and colleagues have proposed a fluoroscopic technique of monitoring the degree of shortening that occurs between the intramuscular electrodes in response to different stimulation settings [73]. Tissue velocity imaging using echo Doppler techniques can also indicate contractile response to stimulus strength which can then be related to the level of myocardial wall velocity augmentation [34]. The latest method proposed, and perhaps the simplest and most accessible, is the "mechanogram" technique using early polygraph technology as described in this issue [11].

Having a tool for monitoring the degree of contraction in response to stimulus strength, however, still does not answer an underlying question: what degree of recruitment is necessary for clinical effect but safe for long-term muscle performance? In Padova, a conservative approach is taken in selecting a stimulus amplitude half-way between the determined threshold and the maximal amplitude comfortable for the patient [11]. This approach certainly leaves some motor units not recruited, but, as suggested by the authors, it leaves additional muscle usable for the future if greater assist becomes necessary. Although this is still a somewhat subjective method, it perhaps emphasizes that the stimulation energy does not have to produce a maximal contraction to have clinical benefit.

The more important objective is to maintain fast-contracting, powerful fibers, even in the motor units that are recruited, in order to have proper coupling of the mechanical events of LDM contraction and cardiac ejection. As a consequence of the power loss due to transformation, a lower amplitude used to stimulate a fast muscle might provide greater cardiac assistance than a maximal amplitude used to stimulate a fully transformed muscle. Furthermore, rather than increasing stimulation amplitude, other muscle parameters can be adjusted to provide a more vigorous contraction, such as pulse interval, as will be described in the next sections.

Pulse number

The number of pulses in a burst certainly affects the degree of LDM shortening and the muscle's ability to generate pressure for performing actual hydraulic work [30, 73]. Using 6 pulses approximately doubles the stroke work performed in a single contraction compared to three pulses [30]. However, this is only true when the overall contraction rate stays low, say less than 60 contractions per minute. At higher rates, a longer burst length will compromise blood flow and lead to fatigue due to inadequate relaxation time between contractions. As the rate goes higher, a shorter burst is necessary to achieve a sustainable level of work. This situation is easily solved by using the automatic adaptation feature available on second generation cardiomyostimulators [30].

The effect of pulse number on muscle mechanics and blood flow is one concern, but obviously another major factor to be considered when selecting pulse number is the duration of the induced contraction in relation to the duration of cardiac systole. The actual mechanical contraction

will lag the onset of the electrical impulses; the peak muscle contraction will occur up to 100 msec after the pulse train ends, and the relaxation may not be complete for another 200 to 400 msec [30, 36]. The actual duration of the contraction-relaxation cycle measured in chronic cardiomyoplasty patients has been found to sometimes exceed cardiac systole, and even exceed an entire cardiac cycle [36, 73].

Several centers have begun using a lower pulse number, three or four pulses, while still achieving good clinical outcome [59]. Grubb has measured that maximum LDM shortening velocity can be achieved within only three to four pulses (100 msec) [36], again supporting the concept of a short burst. In fact, if the muscle retains its fast properties, it may be capable of generating greater power when stimulated with only three or four pulses than a fully transformed muscle stimulated with 6 pulses. Increasing the pulse number to six during the conditioning period may only be leading to more complete transformation due to an overall increased aggregate frequency and ultimately decreasing the power available long-term rather than increasing it.

Thus, acutely it may be true that more pulses will generate a stronger contraction, but it is a misconception that using more pulses chronically will sustain powerful contractions and provide the greatest hemodynamic benefit long-term. If clinical improvement is recognized during the course of the training period, it is not an absolute necessity to continue increasing the number of pulses in order to reach the standard "full burst" of six pulses.

Pulse interval

Adjustment of the pulse interval to induce more forceful contractions has been largely overlooked in both clinical and experimental settings. Most studies evaluating LDM contractile function and the resulting systolic assist focus on synchronization delay, pulse number, synchronization ratio, or stimulation amplitude. Indeed, shortening the pulse interval can be very effective in increasing the strength of the contraction, and it will shorten the overall pulse train duration.

The first general principle that should be understood is that to induce the strongest contraction given a fixed amplitude and pulse number, the pulses must be delivered above the frequency required for smooth summation of the individual twitch response to each pulse. This basic principle is not employed in the conventional training protocol which uses pulse intervals longer than the tetanic fusion frequency during the first weeks. Potential muscle power is not fully harnessed [28]. An analysis of the tetanic fusion frequency for trained and untrained LDM is given by Chachques and colleagues [13]. After training, a smooth contraction requires approximately 25 Hz stimulation (40 msec pulse interval), meaning that at the beginning of training an even higher frequency is needed for a fused contraction of the untrained muscle. In the standard clinical training protocol, when two pulses are delivered a 102 msec interval, only

10 Hz, is used. Using at least a 31 msec interval (33 Hz) from the beginning of training would be more practical.

Even after the conditioning period, a shorter pulse interval than the standard 31 msec (33 Hz) can produce a stronger contraction. This has been measured in our laboratory at the University of Minnesota (previously unpublished). For a given burst duration, canine skeletal muscle ventricles conditioned for 12 weeks using the standard training protocol generated 25% more pressure during 50 Hz stimulation than 30 Hz stimulation ($n = 8$, $p = 0.001$). Soberman and colleagues have measured the increase in ventricular ejection fraction and dP/dt in response to varying stimulation amplitude, burst duration, and burst frequency using conditioned LDM [69]. The greatest increases in ejection fraction and dP/dt were observed in response to increases in amplitude (5.0 V to 7.5 V) and frequency (30 Hz vs. 85 Hz) while duration had little effect (185 msec vs. 240 msec). Since both duration settings studied are already relatively long, it is not surprising an increased effect was not measured, but it is important to note that a frequency of 30 Hz was less effective than a higher frequency in augmenting hemodynamics.

Davies et al. found maximal shortening to occur at 36 Hz in conditioned muscle, only slightly higher than the conventional 33 Hz [24]. It has been a general assumption that 33 Hz is close to the fusion frequency of the conditioned muscle and will induce a maximal contraction, but the above observations of greater augmentation with even higher frequencies is also supported by others. Skeletal muscle ventricle performance evaluated in Stephenson's laboratory is superior at 85 Hz than at 30 Hz [4]. In patients, Carraro and colleagues have measured a greater degree of contraction by decreasing the pulse interval from 31 to 23 or 16 msec (33 Hz, 43 Hz, and 63 Hz respectively) [11]. Muneretto has adopted a 23 msec pulse interval clinically [59]. Using only four pulses per burst and this slightly higher frequency, short powerful contractions can be contained within the systolic ejection phase. Marked clinical improvements were already observed within six months of follow-up in a small group of patients.

Decreasing the pulse interval, rather than increasing the stimulation amplitude, can be considered in order to increase contractile force. Increasing the summation of the recruited motor units may be a more conservative approach than increasing stimulation energy. When stimulation amplitude is increased, muscle fibers and nerve branches near the stimulating electrodes are exposed to a higher energy density, and more motor units are recruited reducing the "spare muscle" available for future use. Increasing frequency only increases the net summation of already recruited muscle fibers without exposing them to a higher energy density.

Decreasing the pulse interval, rather than decreasing the pulse number, can also be considered for shortening the overall contraction duration. The onset of LDM contraction should be tuned to the start of the desired systolic phase. If the required delay setting results in LDM contrac-

tion extending too long into diastole, the pulse train needs to be shortened. If this is done by decreasing pulse number, the contraction will be weaker. If the pulse interval is decreased alone or at the same time as pulse number, the LDM contraction-relaxation cycle can be shortened with less loss of force generation.

Synchronization ratio

The optimal synchronization ratio has been a subject of much discussion. Originally, when the mechanism of cardiomyoplasty was hypothesized to be one of pure systolic assist, it was assumed that the muscle should provide assist on every cardiac cycle. One-to-one synchronization was quickly realized to be too aggressive experimentally and clinically based on evaluations of LDM perfusion [29, 72], bioenergetics [31], histology [57], contractile performance [30] and hemodynamic augmentation [4, 70]. Perhaps 1:1 stimulation is feasible with an extremely short burst duration and at low heart rates, but it is not necessary for clinical improvement [22].

Soltero and colleagues compared the net cardiovascular effects of 1:1 versus 1:2 stimulation in experimental heart failure [70]. Net hemodynamic results averaged over several cardiac cycles (both assisted and unassisted for 1:2) were similar for both synchronization ratios. In patients, higher synchronization ratios of 1:4 to 1:6 have been reported to provide the greatest increases in cardiac index and stroke index [22]. Guldner reports that hemodynamic assistance completely diminishes when chronic 1:2 stimulation is used whereas considerable assistance is maintained with 1:8 stimulation and muscle fiber damage avoided [37].

The ideal synchronization ratio depends on what the primary actions of DCMP are in producing clinical benefit. If a hemodynamic effect is desired, a lower synchronization ratio seems to be more effective by avoiding muscle fatigue and perhaps maintaining faster fiber properties. This is contradictory to the original thought of systolic assistance on every beat. If, however, it is more beneficial to utilize cardiomyoplasty as a "time-varying elastic wall stress reducer [68]," a higher synchronization ratio of very short bursts, maybe only two or three, could achieve the greatest affect by relieving wall stress on more frequent beats in order to have a cumulative chronic impact on myocardial energetics and ventricular remodeling.

Experimental investigations measuring cardiac energetics by Patel et al. have shown greater contractility during 1:1 stimulation than 1:2 stimulation [62]. Significant reductions in transmural myocardial wall stress were found by Chen and colleagues to occur only on stimulated beats [23]. However, both of these investigations have some limitations. In the study by Patel et al., 1:1 stimulation was only tested during monitoring procedures; the ability for the muscle to sustain the improvement measured at 1:1 long-term is questionable [61]. In this chronic study, however, cardiac dilatation due to experimental induction of heart failure was halted by the dynamic girdling action of a 1:3 stimulated muscle wrap. The muscle was not conditioned in the study by Chen et al. and in a later study by

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conditions has produced an accumulation of knowledge, much of which is not yet used in regular clinical practice. Advancements in cardiomyostimulator technology allow greater flexibility in the programming of stimulation parameters within safe limits. Safe clinical evaluation of new approaches in stimulation can occur today using already developed, non-invasive methods of LDM monitoring. Future developments in the use of growth factors, anabolic agents and the recent clinical introduction of vascular delay may add to the hemodynamic benefits achievable. In the meantime, there is no need to wait longer for testing new stimulation approaches such as shorter bursts and lower synchronization ratios. Experimental and clinical evidence convince that old ideas need to be rethought and simple changes tested immediately. Less stimulation may indeed mean more in terms of patient benefit. The feasibility phase of DCMP is long over with successful clinical outcomes justifying the potential value of this therapy in the armamentarium of heart failure treatment. New concepts, now validated experimentally, need to be implemented and tested clinically to continue the evolution of this therapy.

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