

Demand Dynamic Cardiomyoplasty: Improved Clinical Benefits by Non-Invasive Monitoring of LD Flap and Long-Term Tuning of Its Dynamic Contractile Characteristics by Activity-Rest Regime

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Abstract

To many authors, cardiomyoplasty is a clinical reality, founded on the basis of its girdling effect which limits and/or reverses the progressive dilatation of a failing heart. Load-independent measurements of cardiac function demonstrate a real improvement of the heart energetics when analyses are compared before and after cardiomyoplasty. Standard indices of systolic function are not consistently improved. One of the factors limiting the systolic assistance of cardiomyoplasty is muscle performance after full conditioning of LD. Clinically, it is accepted that LD benefits the patient's quality of life only if its activation is optimally delayed after the sensed QRS complex in order to avoid mitral regurgitation. Since maximum instantaneous power of a fully conditioned LD is smaller than the peak power of the left ventricle, the grafted muscle could assist the heart during mid and late systolic phases. Such a short time window requires a fast, powerful contraction which is not delivered by a fully transformed LD. Monitoring LD function is essential for evaluating and implementing new concepts aimed at improving LD function for greater systolic benefit. We have developed a simple non-invasive method to analyse the dynamic characteristics of the LD flap during conditioning and chronic stimulation using a standard polygraph. To perform this monitoring we have implemented the basic concept of tetanic fusion frequency analysis. By monitoring changes in fusion frequency over time, we hoped that it would be possible to adjust daily stimulation parameters in order to maintain a faster, more powerful muscle. In fact, this has now been achieved by implementing an activity-rest regime. After months of continuous daily stimulation it is possible to reverse the fast-to-slow transformation by a "demand" stimulation protocol which allows the LD flap to rest during periods of low-activity, both day and night. With this lighter stimulation regime, now used in patients at more than one-year of follow-up, substantial improvement in quality of life has occurred with a reduction in heart failure symptoms from N.Y.H.A. Class III to I. If these preliminary data can be substantiated by long-term results in these patients and in future patients in an Italian Trial of Demand Dynamic Cardiomyoplasty (DDC), we are confident that DDC could offer longstanding benefits to manage pharmacologically-intractable heart failure.

Key words: Demand Dynamic Cardiomyoplasty, improved clinical benefits, non-invasive monitoring, human LD flap, dynamic contractile characteristics, activity-rest regime.

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To many authors, cardiomyoplasty is a clinical reality [8-10] which founds its basis on a girdle effect which limits and/or reverses the progressive dilatation of a failing heart, since load independent measurements demonstrate a real amelioration of the heart energetic when analyses are

compared before and after cardiomyoplasty [21, 24]. One of the factors limiting systolic assistance of cardiomyoplasty is muscle performance after full conditioning. After a few weeks of stimulation, Latissimus Dorsi (LD) mitochondrial content and capillary/myofiber ratio

increase, but intracellular calcium handling became less efficient and therefore the contraction-relaxation cycle significantly slows; finally slow myosin substitutes fast myosins, so that a fast, powerful (but early fatiguing) LD is transformed in a slow contracting muscle which is fatigue resistant at moderate power [11]. Furthermore, in the actual prudent management of the clinical stimulation protocol of dynamic cardiomyoplasty, the conditioning period of LD lasts two months, reducing the potential benefit during the critical post-operative period.

Clinically, it is fully accepted that LD benefits the patient's quality of life only if its activation is critically delayed after sensed QRS to avoid mitral regurgitation [18, 20, 24]. Since maximum instant power of a fully conditioned LD is smaller than the peak power of the left ventricle [1-7, 13, 17], we share the opinion [5] that the grafted muscle could assist the heart principally during mid and late systolic phases. Of course, such a short window asks for a fast, powerful contraction which is not delivered by a fully transformed LD. Monitoring is essential to take advantage of the new concepts, so we developed a simple non-invasive method to analyse dynamic characteristics of LD flap during conditioning and regime stimulation. We have obtained such a worth result by implementing the basic concept of tetanic fusion frequency analysis. Using a doublet of stimuli delivered at increasing frequency rate it is possible to estimate the contraction-relaxation cycle of the transposed LD during conditioning and long-term clinical stimulation. Furthermore, after months of continuous daily stimulation it is possible to reverse the fast-to-slow transformation by an activity-rest stimulation protocol based on a frequency cut-off at around 80 bpm, so that the LD flap is rested during low-activity periods during both day and night.

Materials and Methods

Dynamic Cardiomyoplasty is performed in selected subjects according the actual guide-lines [8-10, 15], but shortening the conditioning period to one month by adding an impulse up to four every week, and stimulating the LD every third cardiac cycle [22]. The subject's LD flap is monitored at bed-side using a standard polygraph (Siemens MegaChart or Mingophon). ECG and heart sounds are recorded simultaneously with the pressure changes due to LD flap contraction-relaxation measured near the rib window [25]. We determine: i) the activation threshold, measuring the peak contraction at different amplitude of the stimulating current (from 1 to 8 Volts); ii) the good clinical LD flap activation (we use the voltage at half the difference between the threshold and the maximal contraction accepted without discomfort for the subject. Of course this is not the maximal activation, but in such a way the non activated portion of the flap is a "spare LD", available in case of long-term-activity muscle damage); iii) the dynamic characteristics of the LD flap. Using doublets of stimuli delivered at increasing frequency rate we determine the tetanic fusion frequency and/or measure the

percent of relaxation between two stimuli delivered with 100-200 msec interval. Of course, faster the LD flap higher the extent of muscle relaxation between the two impulses; iv) duration of the mechanical event (we use four impulses at 23 msec intervals (or less) to have a contraction-relaxation cycle from 200 msec (for LD flap before conditioning) to 300 msec (after long-term, i.e. six-month, daily stimulation); v) the best synchronisation between cardiac cycle and contraction of LD flap. This can be done either using the mitral and aortic tones using phonocardiogram parameters, or even better connecting the polygraph signals to an EchoDoppler device with resolution of the cardiac events and direct measurement of the left ventricle out-flow. The activity-rest stimulation is obtained by decreasing the amplitude of the cardiac channel under the threshold (from 5 to 0.9 V) and increasing the cardiac rate of the Transform 4710 (Medtronic, Inc.), from 50 bpm to a figure (usually 80 bpm) established after a Holter analysis of the subject's daily cardiac frequency.

Results and Discussion

Actual clinical protocol make the LD very resistant to fatigue, but meanwhile its dynamic characteristics ask for improvements. With a 185 msec stimulation train of six impulses the contraction-relaxation cycle of a fully conditioned LD may last longer than the heart systole [16, 23], so correct timing of flap contraction frequently became a challenge. Thanks to experimental results in sheep of the Arpesella's team [3-5], we planned in the setting of our first clinical procedures a "lighter" regimen of LD stimulation after a shortened conditioning periods. We chose to select and operate the patients in pair, unaware of what Dr. Silver and the Lajolla group did, but the goal is the same. We encourage patients to meet during screening and pre- and post-operation muscle training. It proved to be an excellent tool of mutual support, especially in the post operative period. In June 1996 two patients (a 48 year man and a 46 year old woman) have been operated. After the healing period their LD flap were stimulated with single impulse, and every next week one impulse up to four was added to the burst stimulation of the wrapped LD at 23 msec intervals (43 Hz).

The presence of a strong left axillary muscle twitch was used in the past to clinically determine the continue presence of muscle contraction and test stimulation voltage threshold of LD [14]. Results were substantiated with fluorography of heart displacement during assisted beat and shortening of the distance between intramuscular electrodes or metal clips sutured on the LD flap, and finally with cardiac catheterism and PV loops analyses [24]. Only after introduction of M-mode echocardiography, optimisation of muscle synchronization after cardiomyoplasty became rational and easily repeatable [18]. On the other hand, by echocardiography LD contraction timing is based on delay between sensed QRS and spikes of the electrical impulses delivered by the muscle stimulator [8-10, 18, 20, 24, 25], and evaluation of dynamic characteristics of the

LD flap needs tissue imaging approach and off-line calculations [19].

Figure 1 shows that muscle contraction became a non fused tetanus when the impulses are delivered at 55 msec intervals (18 Hz). Indeed changing the interpuls intervals it is easy to determine the frequency at which the tetanus is fused (TFF, tetanic fusion frequency), i.e., the dynamic characteristics of the LD flap. Figure 2 shows that using the approaches described in methods it is easy to demonstrate that the dynamic characteristics of the LD flap change during the conditioning periods and even more

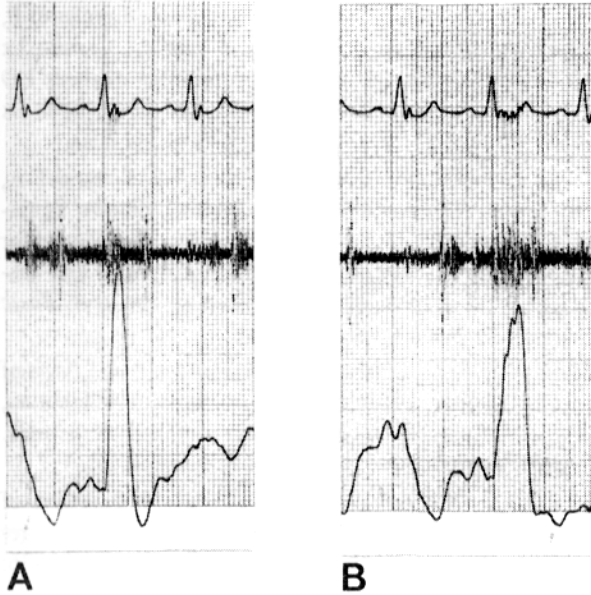


Figure 1. Mechanogram of the LDflap. A, tetanic contraction with four impulses at 23 msec interpuls intervals (43 Hz); B, non fused tetanic contraction with four impulses at 55 msec intervals (18 Hz). Upper trace, electrocardiogram; Middle trace, phonocardiogram; Lower trace, LD flap mechanogram. Heart/LD ratio 3:1.

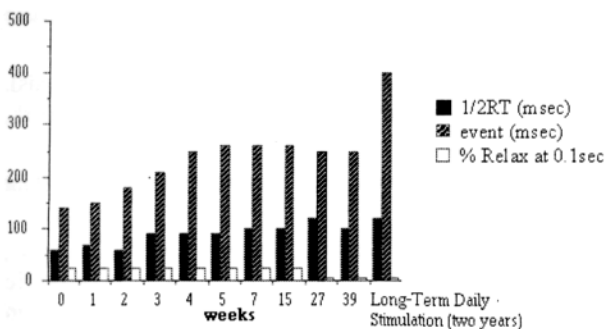


Figure 2. Dynamic characteristics of the LDflap by shortened and lighter clinical stimulation. Subject Pd02DeRo; Long-Term Daily Stimulation (2 years), mean data from three subjects of Dr. Lorusso, Brescia, Italy. 1/2 RT, Half relaxation time (msec); Event, Contraction-relaxation time(msec); % relax at 0.1 sec, percent of LD flap relaxation between two impulses at 10 Hz, i.e., delivered at intervals of 0.1 sec.

during the first few months of daily stimulation regime [12]. While the fast to slow transformation is evident, its extent is very limited during the conditioning period and afterwards. It is worth noting that these LD flaps, i.e., stimulated lighter than usually, are faster than those of a cohort of Italian patients stimulated up to four years, of which an example is included in Figure 2 [25].

Activity-rest stimulation regime by Demand Stimulation

After six-months of continuous daily stimulation it is

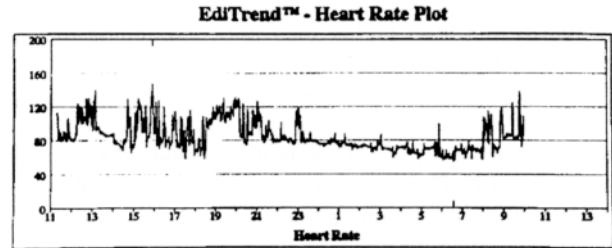


Figure 3. Daily heart rate plot of subject Pd()2DeRo. Note that the frequency is lower than 80 bpm during night and even several hours during daily activity.

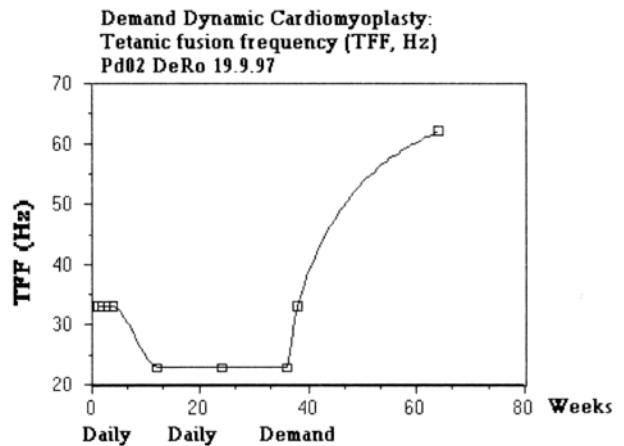


Figure 4. Fast-to-slow-to-fast transformation of the LD flap by activity-rest stimulation (demand regime). TFF (Hz), Tetanic Fusion Frequency of LD flap.

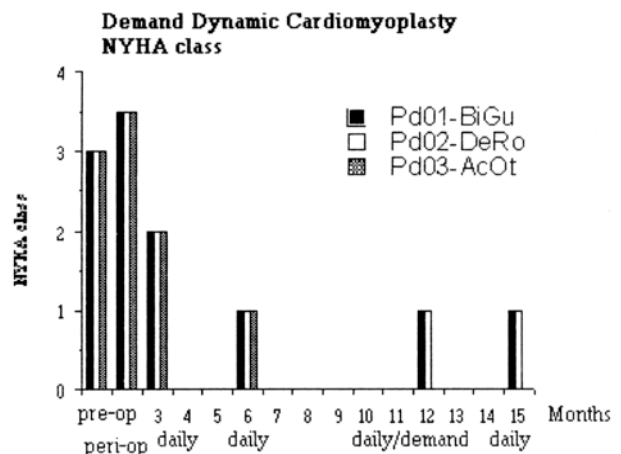


Figure 5. Heart failure symptoms (NYHA class) of patients after Demand Dynamic Cardiomyoplasty.

possible to reverse the fast-to slow transformation by an activity-rest stimulation protocol based on a frequency cut-off at around 80 bpm determined by Holter analysis of the daily cardiac frequency (Figure 3), so that every day the LD flap is rested during low-activity periods both during day and night (usually one-two hours afternoon, and seven-eight hours during night).

Patients enjoy the activity-rest regime, and, due to lighter LD stimulation, they have any sleeping problems. Figure 4 shows that the tetanic fusion frequency remains at a value of about 20 Hz from fifteen to forty weeks, and then increases to values higher than pre-conditioning during three months of demand stimulation.

In a second subject we observed that even after the reverse of the fast-to-slow transformation by activity-rest regime, two weeks of daily stimulation made slower once again the LD flap. Furthermore, after additional three months of demand stimulation the LD flap is faster than before conditioning. Since the results are essentially the same in the two patients we have subjected to demand stimulation, we are confident that tuning of dynamic characteristics of LD flap is no more a dream, but a clinical reality.

It is important to stress that, at least up to fifteen months (the longest period studied), with the demand stimulation regime patients' quality of life is substantially improved with reduction of heart failure symptoms from N.Y.H.A. class 3 pre-op to sustained class 1 after several months of demand stimulation (Figure 5). Anecdotaly, patients that have been submitted to continuous stimulation for at least six months, than submitted to the activity-rest regime, gave preference to remaining on the activity-rest regime due to their better feeling of general well-being.

If these preliminary data will be substantiated by long-term results in these patients and in future patients, we are confident that Demand Dynamic Cardiomyoplasty could offer long-standing benefits to manage pharmacologically-intractable heart failure. An Italian Trial of Demand Dynamic Cardiomyoplasty is currently underway to evaluate this approach in a larger group of patients. Such new stimulation approaches, and most importantly having a technique to monitor their effects, paves the way for important advances in how the therapy of Dynamic Cardiomyoplasty is delivered in the near future.

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