Latissimus Dorsi tetanic fusion frequency in clinical settings: Monitoring fast to slow and slow to fast muscle transformation during follow-up of Demand Dynamic Cardiomyoplasty

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Abstract

Limited systolic assistance by Latissimus Dorsi (LD) weak power due to excessive slow speed of shortening has been considered a problem of Dynamic CardioMyoPlasty (DyCMP) after its creation by Carpentier and Chachques. To improve systolic assistance, and to reduce potential muscular damage, we introduced the concept of activity-rest stimulation, to deliver fewer impulses per day than with the clinical standard protocol. This was achieved by providing the LD wrap with daily periods of rest (demand stimulation) based on a heart rate cut-off. We here review how the demand protocol was introduced in 4 patients from the beginning and in 10 patients which had previously undergone continuous stimulation DyCMP. These ten subjects, with no short-term to mid-term prospect of heart transplantation, were switched to the demand stimulation for worsening of clinical conditions. Furthermore, we report how the Latissimus Dorsi long term changes in contraction speed had be monitored by Tetanic Fusion Frequency (TFF) analysis (Mechanographic interrogation). In the 10 2-year-switched subjects the TFF values were significantly higher (33 ± 8.0 versus 15.8 ±11Hz; $p< 0.0001$) than at the start of the demand protocol. Although the long-term survival in this small group is not comparable with the one of transplant patients, demand dynamic cardiomyoplasty showed encouraging results compared with classic cardiomyoplasty. Since heart transplantation after cardiomyoplasty procedure is still possible and feasible, the procedure could be revived as a biological bridge for persons in the transplant waiting list, in particular in those countries in which economic and cultural constrains strongly limit heart transplants.

Key Words: Demand Dynamic Cardiomyoplasty, DyCMP, Non-invasive monitoring of Latissimus Dorsi, LD, Tetanic Fusion Frequency, TFF

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Questionable systolic assistance and latissimus dorsi (LD) degeneration have been considered the main drawbacks of Dynamic cardiomyoplasty (DyCMP) after its creation by Carpentier and Chachques [4]. Many authors only recognize the passive girdle effect of DyCMP to be its mechanism of action [3, 9, 15, 19]. To hopefully improve LD power and expected systolic assistance, fewer impulses per day were delivered than with the standard clinical stimulation protocol in successful preliminary sheep experiments [1]. This was then achieved in humans by providing the LD wrap with daily periods of rest (demand stimulation) based on a heart rate cut-off [1, 6]. Our studies proved that effective measurable systolic assistance is possible in patients who early undergo a demand stimulation protocol. Its value was high when the demand protocol was started early after surgery and much lower to virtually absent when the demand protocol was started several months/years after continuous burst stimulation [2, 5, 6, 20, 21]. Unfortunately, despite this encouraging results and evidences, the program was stopped due to the scarce interest of companies in developing “ad hoc” cardiomyostimulators.

Materials and Methods

The demand protocol was electively introduced in 4 patients from the Italian Trial of Demand Dynamic Cardiomyoplasty and in 10 patients who had previously undergone DyCMP for worsening of clinical conditions during DyCMP continuous stimulation with no short-term to mid-term prospect of heart transplantation. Informed consent to the intervention or change in stimulation protocol (continuous to demand) was obtained from all patients. The stimulator was programmed for demand stimulation at the Department of Cardiology, Cardiomyoplasty Project Unit-Center for Advanced Heart Failure, Legnago Teaching Hospital, Verona, Italy, whereas follow- up was performed at this center as well as at the Division of Cardiology and Rehabilitation, Montescano Medical Center, Maugeri Foundation, Montescano, Pavia, Italy.

Demand Stimulation Protocol

The demand stimulation protocol was introduced [1, 6] in hopes of avoiding complete LD wrap transformation caused by the continuous stimulation protocol of the US Food and Drug Administration phase 2 trial used by the American Cardiomyoplasty Group [12]. It is well known that a muscle that has been fully transformed by continuous stimulation displays significant loss of power, generally attributed to fiber type change or loss of type 2 myofibers (fast-contracting myofibers) [22]. The inclusion of daily rest periods during chronic burst electrical conditioning maintains myofiber cross-sectional area and produces fatigue-resistant myofibers of faster contraction speed, and creates a more powerful fatigue-resistant muscle. The improved performance of such LD is because of the maintenance of an intermediate level of LD transformation, thanks to the activity-rest regimen on demand [1, 12, 13, 16]. The LD was stimulated with a single impulse at a 1:3 synchronization ratio after a healing period of 10 to 14 days. An extra impulse was then added every week at a 23-ms interval (43 Hz) for a final burst of four impulses, with a cardiac amplitude more than 5 V and pulse width of 1.5 ms. After 6 to 12 months of this light daily stimulation, the patients took part in the demand regimen, which gave the LD wrap a daily period of rest [2]. To provide the LD wrap with daily periods of rest, a 24-hour Holter study was performed first to determine the average heart rate during sleep. The pacing variables of the cardio-myostimulator (Transform, model 4710; Medtronic, Inc, Minneapolis, MN) were programmed at a rate of 70 to 80 beats/min, with minimum pulse amplitude ($\leq$1 V) and pulse width ($\leq$0.05 ms). Muscle output was programmed to “Sense,” occurring only with sensed cardiac events, not with paced events. In this way, the lower rate was set just above the average nighttime heart rate and the cardiomyostimulator worked during resting hours at an energy level well below requirements for activating the heart. During these pacing episodes, muscle output was inhibited. The result was that muscle stimulation was inhibited during the resting hours and occurred at the programmed synchronization ratio during activity, providing an activity-rest stimulation regimen [6].

Non-invasive monitoring of Latissimus Dorsi Wrap Function: The LD Mechanogram

Dynamic contractile characteristics of the LD wrap, i.e., speed of contraction and relaxation, can be monitored using a standard polygraph (MegaCart or Mingophon, Siemens Elema, Solna, Sweden). Electrocardiogram and pressure changes caused by LD contraction can be simultaneously recorded as previously described [1, 5, 6]. The dynamic characteristics of the LD wrap are determined by the LD response to stimuli delivered at increasing frequency up to tetanic fusion frequency (TFF).

In this way, a smooth contraction curve can be plotted: the faster the fibers, the higher the TFF. This method is also used for monitoring cardiac/LD contraction synchronization. At low stimulation frequency, the mechanogram shows that some relaxation occurs in between in-burst impulses (unfused tetanus). At higher stimulation frequency, a smooth curve is recorded (fused tetanus), which lasts as long as the tetanic contraction is maintained (200 ms with four impulses delivered at 43 Hz). The higher the TFF, the faster the contractile characteristics of the LD wrap. The normal value of TFF for human LD muscle is 43 Hz; the fused tetanus is obtained with in-burst impulses delivered at 23-ms intervals [6]. Usually, the normal value of TFF for human muscle is expected to be 43 Hz (the tetanic contraction with pulses delivered at 23 msec intervals). The mechanogram is also useful to precisely synchronize the LD wrap contraction to cardiac systoles. The value of 43-Hz TFF, which characterizes a fast-contracting muscle, provides systolic assistance, whereas a TFF less than 26 Hz, characterizing a slow-contracting muscle, provides a very low or immeasurable systolic assist [20, 21].

Systolic Assistance Measurement: Doppler Flow-wire

In order to assess the effective contribution of demand dynamic cardiomyoplasty to systolic assistance expressed by increasing in the aortic peak velocity, we tested the usefulness of a .018 inch peripheral Flex™ Doppler flow wire (Cardiometrics, Inc Mountain View, California, USA) advanced under fluoroscopy into the descending thoracic aorta through a 4F catheter introduced via a 5F femoral sheath. The catheter served to maintain the wire at a steady position, coaxial to the vessel throughout the entire cardiac cycle. A peripheral type flow wire was chosen for its stiffness and easy parameter setting for aortic measurements. It was connected to its digital display and registration of aortic flow velocity was performed at standard settings. Three 1-minute periods with the stimulator off and three 1-minute periods with the stimulator on (ratio assisted: unassisted beats = 1: 3) were recorded, avoiding hemodynamic changes due to external factors.

Quantitative data were expressed as % variation and calculated as mean ± SD.

Statistical Analysis

Paired Student's *t* test was used to compare data before and after demand DyCMP, whereas frequencies were compared using the Chi-square test. A *p* value less than 0.05 was considered significant. Clinical and laboratory data were expressed as mean ± standard deviation or as percentage.

Results and Discussion

Seven patients had TFF more than 26 Hz (DemDynWrap) and the other 7 had TFF less than 26 Hz (adynamic girdling). At the start of the demand protocol, the two groups were comparable for sex, age, dilated cardiomyopathy cause, NYHA class, and left ventricular ejection fraction (Table 1). At follow-up, the DemDynWrap group showed a better NYHA class, higher LVEF, and TFF, and a better survival (85.7% versus 28.6%; p = 0.037) than the adynamic-girdling group. Event-free survival rate was not significantly higher (50% versus 45%; p = 0.217) in the DemDynWrap patients. Duration of continuous burst stimulation correlates directly with TFF (r =0.64; p = 0.014) and indirectly with LVEF (r = 0.61; p = 0.009) values, suggesting that the longer the duration of continuous stimulation, the smaller is the systolic assistance.

Table 1. *Data of DemDyn and Adynamic girdling groups and results comparison at 5-year follow-up.*

	DemDyn	Adynamic	p
Male/female	6/1	6/1	-
Age (years)	58.4± 5.3	58.1±5.9	ns
Chronicle stimulation (months)	18.9±10.2	47±22.4	0.012
Mean decrease in NYHA class	2.14±0.7	0.43±0.5	0.007
Mean percent increment of LVEF	13.7±7.1	5.3±2.4	0.002
Actuarial survival	85.7%	28.6%	0.037
TFF (Hz)	38.3±5.8	24.3±2.9	0.002

LVEF: left ventricle ejection fraction on transthoracic echocardiography; TFF: tetanic fusion frequency.

Measurements of increase in aortic peak velocity were performed in seven patients (M/F= 6/1; age= 57.1±6.2 years; atrial fibrillation/sinus rhythm= 1/6; follow-up= 40±12 months) with previous demand dynamic cardiomyoplasty. Statistical analysis showed an increase in aortic flow velocity not only in assisted versus rest period, but also in assisted versus unassisted beats (8.4±7.0% and 7.5±3.0%). A linear correlation was found between increase in flow velocity and LD wrap tetanic fusion frequency (r^2=0.53). According with these results, the mean NYHA class at follow-up was significantly lower when compared with pre-operative one: 1.4±0.5 versus 3±0 (p<0.01), whereas the mean value of EF at follow-up was significantly higher: 37.7 ±5.8% versus 26.8± 2.4% (p<0.01), respectively. Moreover, the value of TFF was significantly higher at the follow-up (23±8.9 versus 35±7.2 Hz, p<0.05) rather than before the starting of demand stimulation, suggesting that in demand dynamic cardiomyoplasty, systolic assistance is significant and correlated to latissimus dorsi speed of contraction.

Although the results of demand dynamic cardiomyoplasty in Italy at the end of the follow-up may be considered scarce (manuscript in preparation), we believe that some important points could be kept in mind.

The evaluation of correct mechanism of work in patients with demand dynamic cardiomyoplasty is probably the main achievement of our experience. In DyCMP, there are two possible mechanisms to explain improved clinical results: limited heart dilation (heart remodeling) and the enhancement of systolic contraction. Systolic assistance has been suggested, but not proven by studies revealing low-to-moderate increase in LVEF and stroke volume [11, 18]. Nevertheless, a notable improvement in NYHA class, usually from class III or higher to class II or lower, has been reported worldwide, although improvements in LVEF seem to be limited to early follow-up periods [8, 12, 11, 17]. Therefore, there is a general consensus that only a passive girdle effect occurs long term with classic DyCMP. Contractile characteristics and fat and fibrotic degeneration of the LD wrap, described in a few autoptic cases after continuous burst stimulation, may play an important role in this general opinion. From pathologic and morphologic studies [1, 13], it appears that muscle degeneration, previously related to surgical dissection of the muscle and/or chronic stimulation is indeed mainly the result of contraction load imposed to an ischemic muscle [10, 22-26]. While a 2-week delay in stimulation after cardiomyoplasty was introduced to attenuate early damage, it may indeed contribute to muscle atrophy and loss of function [14]. These studies led to the concepts that a period of low-frequency pre-stimulation before LD transfer have a protective effect on the grafted LD [10, 22-26], and that intermittent burst stimulation may result in a long-term fatigue-resistant, fast-contracting LD wrap, contributing to more-effective cardiac support. The latter is the reason to introduce Demand Stimulation, i.e., activity-rest patterns of LD stimulation [1, 2, 6, 13, 20, 21], to improve results of classic DyCMP [7]. Our data shows that the amount of systolic assistance correlate well to muscular properties and are maintained with time [20, 21]. Altogether, these results explain the higher TFF values and the improvements in NYHA class and in LVEF value, as well as the good survival rate in the DemandDynWrap group of Italian patients. Moreover, in the patients in whom demand protocol was started after several years of the continuous burst stimulation protocol, the TFF not only maintained its initial value, but in many cases surprisingly increased. This is sound evidence of muscle plasticity in humans, and supports the opinion that muscle degeneration is not a necessary outcome of long-term continuous burst stimulation of LD wrap in DyCMP.

All together, these results points to Demand DyCMP as a potential alternative to other bridge to Heart Transplant, a procedure that without the heavy limitation of heart donors could have solved the increasing problems that population senescence accumulate in the affluent countries. Of course, Demand DyCMP would be an even more important option in those countries in which economic and cultural problems strongly decrease total heart transplants.

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