Activity–rest stimulation protocol improves cardiac assistance in dynamic cardiomyoplasty

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Abstract

Objective: No data have ever been published regarding cardiac assistance in demand dynamic cardiomyoplasty (DDCMP). We tested the efficacy of the Doppler flow wire in measuring beat-to-beat aortic flow velocity and evaluating cardiac assistance in demand cardiomyoplasty patients. Methods: The technique was tested in seven patients (M/F = 6/1; age = 57.1 ± 6.2 years; atrial fibrillation/sinus rhythm = 1/6; NYHA = 1.4 ± 0.5). Measurements were done using a 0.018 inch peripheral Doppler flow wire advanced through a 5F arterial femoral sheath. Three 1-min periods with the stimulator off and three 1-min periods with clinical stimulation were recorded. We measured peak aortic flow velocity in all beats. Latissimus dorsi (LD) mechanogram was simultaneously recorded. Results: Comparison between pre-operative and follow-up data showed significantly higher values of tetanic fusion frequency (TFF) and ejection fraction at follow-up, whereas mean NYHA class was significantly lower. Statistical analysis showed an increase in aortic flow velocity not only in assisted versus rest period, but also in assisted versus unassisted beats (8.42 ± 6.98% and 7.55 ± 3.07%). A linear correlation was found between the increase in flow velocity and LD wrap TFF (r² = 0.53). Conclusions: In DDCMP, systolic assistance is significant and correlated to LD speed of contraction; demand stimulation protocol maintains muscle properties and increases muscle performance. © 2002 Elsevier Science B.V. All rights reserved.

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1. Introduction

Dynamic cardiomyoplasty (DCMP) uses the latissimus dorsi (LD) muscle to create an active girdle effect that not only reverses the progressive dilatation of the failing heart but also improves global heart energetics. One of the factors that limit the systolic assistance provided by DCMP is muscle performance after full conditioning following FDA phase II trial stimulation protocol. The fast, powerful (but early fatiguing) LD is transformed by continuous stimulation into a slow-contracting muscle, which is fatigue-resistant at moderate contraction forces. This means that the contraction–relaxation cycle of a fully conditioned LD may last longer than the heart systole. Thus, long-term continuous stimulation causes significant degeneration of the LD wrap. This explains the failure of this technique to provide satisfactory long-term results [1–3] after the positive early experience [4,5].

In order to maintain long-term partial transformation of the LD wrap avoiding excessive muscular degeneration and an extremely long contraction–relaxation cycle, fewer impulses per day than in standard clinical stimulation should be delivered. This can be obtained by providing the LD wrap with daily periods of rest (demand stimulation protocol), based on a heart rate cut-off [6].

Despite the encouraging preliminary results in sheep and humans [6,7], there are no definitive data on the real systolic assistance that demand dynamic cardiomyoplasty (DDCMP) offers, limiting its acceptability by cardiologists. There are two main difficulties in the assessment of DDCMP assistance in vivo using non-invasive methods such as echocardiography. Firstly, the movement of the ascending aorta during assisted beats does not allow correct alignment of the Doppler signal during transthoracic echocardiography. Secondly, beat-by-beat measurements during normal stimulation are relatively inaccurate because they are greatly
dependent on variations in stroke volume. In order to overcome these difficulties, we measured the aortic flow velocity with an intravascular Doppler flow wire. This is a 0.018 inch wire with a Doppler transducer near its tip that permits the measurement of blood flow velocities inside the coronary and peripheral vessels [8]. We describe our experience on the use of the Doppler flow wire in the evaluation of the systolic assistance provided to the heart by cardiomyoplasty in a series of seven patients; in these patients, demand protocol was introduced, in some between 6 and 12 months after operation and in others after years of continuous stimulation.

2. Patients and method

Surgery was done according to the Broussais Hospital procedure [1]. All patients had idiopathic left ventricular cardiomyopathy (age 57.1 ± 6.2 years; NYHA class 1.43 ± 0.5; time between DCMP and beginning of demand stimulation protocol 32.6 ± 17.6 months).

In three patients who came from the Department of Cardiovascular Disease of Legnago General Hospital, Verona, Italy and were operated at the Institute of Cardiovascular Surgery of the University of Padua, the LD was stimulated with a single impulse at a 1:3 synchronisation ratio after a healing period of 10–14 days. An impulse was added every week at a 23-ms pulse interval (43 Hz) for a final burst of four impulses with a cardiac amplitude >5 V and pulse width of 1.5 ms. After 6–12 months of this ‘light’ daily stimulation, the patients were submitted to the ‘demand regime’ allowing the LD wrap a daily period of rest.

The remaining four patients were referred to us from the Cardiology Rehabilitation Center, IRSS Fondazione Maugeri, Montescano, Pavia, Italy, due to their clinical deterioration. They had been operated several years before in another institute. Demand stimulation protocol was introduced in these patients after many years of continuous stimulation (6 pulses at 31 ms of interval, 5–100 ms of synchronisation delay, LD/heart ratio 1:2–1:4, cardiac amplitude >5 V, cardiac pulse width 1.5 ms). Individual data are showed in Table 1.

2.1. Heart rate-dependent demand stimulation

In order to provide the LD wrap with daily periods of rest, 24-h Holter study was first performed to determine the average heart rate during sleeping hours. The pacing parameters of the cardiomyostimulator (Transform, Model 4710, Medtronic Inc., Minneapolis, MN, USA) were programmed at a rate of 70–80 bpm with minimum pulse amplitude (<1 V) and pulse width (<0.05 ms). Muscle output was programmed to ‘Sense’ thus occurring only with sensed cardiac events and not with paced events. In this way, the lower rate was set just above average nocturnal heart rate and the cardiomyostimulator worked in resting hours at an energy level well below that required for capturing the heart. During these pacing episodes, muscle output was inhibited. The result was that muscle stimulation was inhibited during resting hours and occurred at the programmed synchronisation ratio during active hours, providing an activity–rest stimulation regimen.

After having obtained informed consent, a mechanogram registration was performed to establish the LD wrap properties. Contractile characteristics of LD wrap were monitored using a standard polygraph (MegaCart or Mingophon, Siemens Elema, Solna, Sweden): the electrocardiogram and pressure changes due to LD contraction were simultaneously recorded as described previously [9]. The dynamic characteristics of the LD wrap were determined from the LD response to stimuli delivered at increasing frequency up to tetanic fusion frequency (TFF). In this way, a smooth contraction curve was plotted: the faster the fibres, the higher the TFF.

A 0.018 inch peripheral Flex™ Doppler flow wire (Cardometrics Inc, Mountain View, CA, USA) was 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-min periods with the stimulator off and three 1-min periods with the stimulator on (ratio of assisted:unassisted beats = 1:3) were recorded, avoiding haemodynamic changes due to external factors. Quantitative data were expressed as percentage variation and calculated as mean ± SD. Continuous values were compared using the Student’s t-test and Pearson’s correlation coefficient. A value of P < 0.05 was considered significant. Individual data are shown in Table 1.

3. Results

A significant increase in mean peak aortic velocity (MPAV) in assisted period versus rest and in assisted versus unassisted beats (Fig. 1) was recorded, respectively, 8.42 ±
Fig. 1. Aortic flow velocity spectrum during unassisted and assisted beats (asterisks) in patient no. 1: peak aortic flow velocity increases during the assisted beat due to the increase in cardiac output during LD wrap contraction.

6.98% and 7.55 ± 3.0%. Individual data are shown in Table 2.

A positive correlation between the frequency of tetanic fusion and the percentage increase in MPAV in the assisted period versus rest was found ($r^2 = 0.53$; Fig. 2).

The LD was stimulated at the standard demand synchronisation ratio (1:3). During measurements, the myostimulator was switched to the continuous mode and to standard muscle activation threshold, the maximal threshold that does not cause patient discomfort related to the sensation of wrap activity in the chest. This threshold was determined using the mechanogram, measuring peak contraction at different amplitudes of stimulation current (from 1 to 8 V).

Mean NYHA class at follow-up was significantly lower when compared with pre-operative and post-DCMP: 1.4 ± 0.5 versus 3 ± 0 ($P < 0.01$) and 2.0 ± 0.8 ($P = 0.03$) whereas mean EF at follow-up was significantly higher: 37.7 ± 5.8% versus 26.8 ± 4.4% ($P < 0.01$) and 27.1 ± 2.1% ($P = 0.004$), respectively (Fig. 2). Moreover, the value of TFF was significantly higher at follow-up (23 ± 8.9 versus 35 ± 7.2 Hz, $P < 0.05$), (Table 3; Fig. 3).

As expected, there was no difference between pre-DCMP and pre-operative data.

### Table 2

Results of mechanographic and Doppler flow wire measurements

<table>
<thead>
<tr>
<th>PT no.</th>
<th>HR (Hz)</th>
<th>TFF (Hz)</th>
<th>MPAV (cm/s)</th>
<th>% Increase (P-value)</th>
<th>MPAP (cm/s)</th>
<th>% Increase (P-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rest</td>
<td>Activity</td>
<td></td>
<td></td>
<td>Assisted</td>
<td>Unassisted</td>
</tr>
<tr>
<td>1</td>
<td>74</td>
<td>43</td>
<td>97.4 ± 3.0</td>
<td>106.6 ± 1.2</td>
<td>+14.6 (0.001)</td>
<td>130.4 ± 9.2</td>
</tr>
<tr>
<td>2</td>
<td>68</td>
<td>43</td>
<td>65.2 ± 4.1</td>
<td>70 ± 3.0</td>
<td>+9.5 (0.010)</td>
<td>70.6 ± 5.0</td>
</tr>
<tr>
<td>3</td>
<td>70</td>
<td>32</td>
<td>96 ± 2.0</td>
<td>110 ± 2.1</td>
<td>+15.2 (0.028)</td>
<td>92.9 ± 5.1</td>
</tr>
<tr>
<td>4</td>
<td>76</td>
<td>32</td>
<td>80 ± 7.8</td>
<td>80.4 ± 5.6</td>
<td>+0.14 (0.416)</td>
<td>70.7 ± 6.8</td>
</tr>
<tr>
<td>5</td>
<td>58</td>
<td>43</td>
<td>96.2 ± 11</td>
<td>108 ± 8.2</td>
<td>+15.7 (0.001)</td>
<td>107.1 ± 11</td>
</tr>
<tr>
<td>6</td>
<td>60</td>
<td>26</td>
<td>101.5 ± 4.3</td>
<td>115.9 ± 6.5</td>
<td>+2.4 (0.416)</td>
<td>110 ± 5.4</td>
</tr>
<tr>
<td>7</td>
<td>62</td>
<td>26</td>
<td>98.7 ± 5</td>
<td>100.1 ± 3.7</td>
<td>+1.4 (0.426)</td>
<td>101.9 ± 7.4</td>
</tr>
</tbody>
</table>

*HR, heart rate; MPAV, mean peak aortic velocity; PT, patient; TFF, tetanic fusion frequency.

Mean fluoroscopy time was < 1 min and mean procedural time was < 15 min. No complications were observed during and after the procedure.

### 4. Discussion

DCMP has recently regained interest because of the high costs of mechanical assistance and the lack of organ donors in Europe. In order to improve the disappointing results of classic DCMP, the demand stimulation protocol [6,7–9] and the vascular delay approach [10,11] have been suggested.

There are two principal hypotheses on the mechanism by which DCMP relieves symptoms in patients who benefit from it: limited heart dilatation and enhanced systolic contraction [12–15]. The enhancement of systolic contraction has been suggested but not proven by measurements of ejection fraction [16,17], stroke volume [17,18] and study of the P/V loops [19] in DCMP patients. Unfortunately, despite their results these studies were unable to explain the great variability in the response to classic cardiomyoplasty, probably related to graft degeneration.

Demand stimulation protocol was introduced [6,17] in order to avoid complete LD wrap transformation caused by the continuous stimulation protocol of the FDA phase II trial in use by the American Cardiomyoplasty Group [5] and to homogenise the patient response. Up to now, no proof of real systolic assistance using this protocol has been produced.
It is well established that a muscle fully transformed by continuous stimulation displays significant loss in power, generally attributed to fibre-type change or loss of type 2 myofibrils (fast contracting myofibrils). The insertion of rest periods during chronic electrical conditioning preserves myofibril cross-sectional area and produces fatigue-resistant fibre distributions; thus, a more powerful fatigue-resistant muscle is created. The improved performance of such a LD is thought to be due to the maintenance of an intermediate level of transformation of the LD wrap, thanks to the demand regimen. Moreover, the differences in TFF between patients who started the demand regimen 6–12 months after operation and those who switched to it after years of continuous stimulation support our theory: activity–rest stimulation protocol is superior to daily continuous stimulation in minimising incremental activity-induced muscle damage and thus maintaining an intermediate level of LD transformation.

Due to the difficulty in measuring a parameter directly correlated to stroke volume and cardiac output by standard echocardiography, we decided to assess the efficacy of the flow wire technique in measuring aortic blood flow velocity in a feasibility study [20]. In fact, aortic flow velocity is a term in the simplified continuity equation: \( Q \) (cardiac output) = \( V \) (aortic flow velocity) \( \times A \) (cross-sectional area of the vessel). The flow wire was chosen as a technique that is independent of aortic movements secondary to LD contraction and capable of beat-to-beat measurements. In this feasibility study, the flow wire technique was tested in non-heart failure patients. Every two normal cardiac contractions, an ectopic ventricular beat was introduced using a temporary cardiostimulation catheter: the flow wire was sensitive enough to measure the changes in cardiac output between normal and post-ectopic beats, with an excellent correlation to transthoracic Doppler echocardiographic findings.

Our data suggest that flow wire measurements in DDCMP patients are able to reveal the real improvement in cardiac assistance provided by the powerful, partially transformed LD. The activity–rest demand stimulation protocol based on heart rate seems to enhance muscle capabilities over time, reversing fast-to-slow muscle transformation.

Combined mechanographic evaluation proved that cardiac assistance is related to LD properties: the equation ‘resistant muscle = good muscle’ could be changed to ‘faster muscle = improved systolic assistance’. In fact, comparison between pre-operative and follow-up data demonstrated a consensual increase in EF, TFF and improved NYHA class.

One limit of our study may be the late initiation of demand stimulation in the last four patients that came from centres other than our own. This could explain certain dispersion in our data. Moreover, in our study application of the protocol was not done in patients immediately after surgery: on one hand, geographical dispersion of the centres involved in the research on DCMP made immediate post-operative inclusion in the protocol impossible; on the other hand it was decided to introduce the demand protocol after a period of ‘light’ stimulation in order to partially condition the LD and provide sufficient benefit in the early post-operative period.

Another limit is the lack of a direct comparison of flow wire data between the FDA and demand protocol. On the one hand, at the time of the application of the FDA protocol, the Doppler flow wire technology available in non-academic hospitals such as our own did not permit such measurements. On the other hand, in the previous years there has been a lack of interest in DCMP, which still remains an experimental technique.

**5. Conclusions**

In DDCMP, systolic assistance is measurable by means of Doppler flow wire and is significantly higher to the assistance provided by the FDA stimulation protocols. We believe that demand stimulation could replace previous protocols in DCMP: our data suggest that the demand protocol conserves LD wrap properties and can even enhance them, providing a significantly improved systolic assistance.

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