Heart transplantation following cardiomyoplasty: a biological bridge*

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Abstract

Objective: Dynamic cardiomyoplasty (CMP) was proposed as a treatment for refractory heart failure; more than 2000 procedures have been performed worldwide. Heart transplantation was indicated afterwards in some CMP patients with recurrent heart failure symptoms. This study reviews the multicentric French experience with CMP followed by heart transplantation. Methods: From 1985 to 2007, 212 patients (mean age 53 ± 11 years) with refractory heart failure (LVEF = 22 ± 9%, mean NYHA 3.2) underwent CMP in France. Heart transplantation was performed in 26 patients (12.3%), mean age: 51 ± 11 years, within 2.3 ± 3 years after CMP. Transplantation was indicated for persistent heart failure, i.e. no immediate improvement after CMP (19%) and for recurring heart failure (81%). Results: The surgical technique of heart transplantation following cardiomyoplasty presents few particularities. Routine extracorporeal bypass was instituted between the vena cavae and the ascending aorta. As in most of these patients the CMP procedure had been performed without the need of extracorporeal circulation, hearts were free of previous cannulations for cardiopulmonary bypass. The latissimus dorsi muscle flap was divided as far as possible inside the left pleural cavity and its vascular pedicle was obturated. The proximal portion of the muscle as well as the muscular pacing electrodes were kept in place in the pleural cavity. The adhesions between the flap and the heart were not released so as to achieve an en bloc resection of the heart and the muscle flap. During removal of the recipient’s heart, care was taken not to injure the left phrenic nerve that was frequently in tight relation with the latissimus dorsi muscle. Heart transplantation was then performed in a routine manner, the donor heart being anastomosed to remnant atria and great vessels. Mean follow-up was 5.5 years (longest 13.5 years). Survival at 10 years was 40% for early heart transplantation (done within 4 months of CMP) and 57% for transplantation performed at 3 ± 2.8 years after CMP. Conclusions: Heart transplantation after CMP is technically feasible. Hospital mortality was higher when urgent transplantation was required. Long-term survival results are similar to those for primary heart transplantation. Cardiomyoplasty, when it fails, does not preclude transplantation, and when indicated, CMP could be considered as a biological bridge to heart transplantation.

Keywords: Heart failure; Heart transplantation; Cardiomyoplasty; Cardiac surgery; Cardiac bioassist

1. Introduction

Cardiomyoplasty (CMP) was originally proposed as a possible alternative treatment to heart transplantation in patients suffering refractory congestive heart failure and more than 2000 procedures have been performed worldwide [1–3]. However, it soon became obvious that it would not substitute heart transplantation and that both techniques were complementary [4,5]. At present, the respective indications and contra-indications of these two alternatives have been defined with more precisions [6–8]. Nevertheless, it has not yet been clearly established if the same patient could successively undergo cardiomyoplasty and heart transplantation throughout the different stages of his disease.

The goal of this study is to assess the feasibility and the potential drawbacks of heart transplantation in patients having undergone prior latissimus dorsi dynamic cardiomyoplasty. Heart transplantation was indicated in CMP patients with recurrent heart failure symptoms. We review the multicentric French experience with CMP followed by heart transplantation and analyse the indications, surgical approach and long-term survival. In this series, 26 patients underwent a CMP procedure and were subsequently transplanted 0–16.6 years later.

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2. Materials and methods

2.1. Patients

From 1985 to 2007, 212 patients (mean age 53 ± 11 years) with refractory heart failure (LVEF 22 ± 9%, NYHA functional class: II [8%], III [80%], IV [12%]) underwent cardiomyoplasty in France using the left latissimus dorsi muscle (LDM) flap wrapped around both ventricles. The predominant ventricular failure was as follows: left ventricle 76%, biventricular 19%, right ventricle 5%.

Indications and contraindications for cardiomyoplasty were the following:

- Inclusion criteria for CMP
  - Adult heart failure patients.
  - Idiopathic dilated or ischemic cardiomyopathies.
  - Severe heart failure (but not yet end-stage; i.e. patient has some cardiac reserve: peak VO₂ > 10 ml kg per min; radioisotopic LVEF > 15%).
  - Intact latissimus dorsi muscle.

- Contra-indications for CMP
  - Intractable NYHA IV status.
  - Preoperative dependence on IV inotropes or IABP.
  - Primary hypertrophic or restrictive cardiomyopathy.
  - Cardiac cachexia or neuromuscular disease.

After CMP, the LDM was chronically electrostimulated using specific electrodes and a pulse train generator (Cardiomyostimulator). Heart transplantation was performed in 26 patients (12.3%), mean age: 51 ± 11 years, within 2.3 ± 3 years (0—16.6 years) after CMP. Transplantation was indicated for persistent heart failure, i.e. no immediate improvement after CMP (19%) and for recurring heart failure (81%) mostly due to progression of the underlying cardiac disease. Indication for late heart failure etiology was mostly ischemic (50%) and idiopathic (42%).

2.2. Surgical techniques

2.2.1. Cardiomyoplasty

Cardiomyoplasty was performed in two successive stages (1):

**Stage 1, elevation of the LDM:**

The patient was placed in the right thoracotomy position. The left LDM was dissected free with preservation of its axillary neurovascular pedicle. Intramuscular pacing electrodes (Medtronic models 4750) were implanted. The cathode or proximal electrode was placed near the motor nerve branches. The second electrode was placed approximately 5 cm distally. The muscle flap and pacing leads were then transferred to the left thoracic cavity after segmental resection (6 cm) of the second rib. To avoid arm motion during electrostimulation and to allow for a bigger LDM surface inside the chest, the LDM humeral tendon was completely divided at its proximal end. This tendon was then secured to the third rib, in order to prevent traction injury to the neurovascular pedicle.

The heart was then exposed through median sternotomy and an inverse 'C' pericardiotomy overlying the ventricular silhouette. Cardiopulmonary bypass was not necessary for this procedure. Two epicardial electrodes (Medtronic models 4755) were then implanted into the ventricular wall for 'QRS' complex sensing. The LDM was wrapped clockwise around both ventricles and fixed with interrupted sutures to the pericardium. To avoid cardiac manipulation, the LDM was passed posteriorly around the ventricles using two long curved hemostatic clamps. Two mattress sutures were placed on the leading free edge of the LDM and then attached posteriorly to the pericardium near the pulmonary artery and also to the pericardium at the level of the diaphragm, medial to the inferior vena cava. Then the LDM was fixed anteriorly to itself in a pocket fashion. The wrapping was completed by fixing the anterior part of the LDM to the pericardial flap tailored from the right edge of the pericardiotomy. Multiple single sutures were placed to secure structures (Fig. 1).

![Fig. 1. Dynamic cardiomyoplasty using the left latissimus dorsi muscle flap transposed into the chest and fixed around both ventricles.](https://example.com/cardio.png)
Postoperative LDM electrostimulation: muscle pacing and heart sensing electrodes were coupled to an implantable pulse generator (cardiomyostimulator) which includes a heart monitor, a myostimulator and a synchronization circuit processing heart and muscle activities. It enables LD muscle stimulation synchronized on heart contractions (sensed or paced) using bursts of impulses.

2.3. Heart transplantation

Preoperative CT chest scans were performed to evaluate the degree of heart adhesions to the thoracic wall. In cases of ventricular adhesions to the sternum, the femoral vessels were dissected before sternotomy and prepared for immediate cannulation to initiate cardiopulmonary bypass.

The surgical technique of heart transplantation following CMP presents few particularities (Table 1). Usual technical precautions were observed at sternal re-entry. The adhesions located in the anterior mediastinum were released. The pericardial flap generally used to complete the LDM wrapping was incised and routine extracorporeal bypass was instituted between the vena cavas and the ascending aorta. As in most of these patients the CMP procedures were performed without the need of extracorporeal circulation, hearts were free of previous cannulations for cardiopulmonary bypass.

The LDM flap was divided as far as possible inside the left pleural cavity and its vascular pedicle was obturated. The proximal portion of the muscle as well as the muscular pacing electrodes were kept in place in the left pleural cavity. The adhesions between the flap and the heart were not released so as to achieve an en bloc resection of the heart and the muscle flap (Fig. 2). The LDM was divided using electrocautery; the incidence of bleeding from the skeletal muscle stump was generally low. During removal of the recipient’s heart, care was taken not to injure the left phrenic nerve that was frequently in tight relation with the latissimus dorsi muscle.

Heart transplantation was then performed in a routine manner, the donor heart being anastomosed to remnant atria and great vessels.

3. Results

Overall survival results after heart transplantation (mean follow-up: 5.5 years, longest follow-up: 13.5 years) are shown in Table 2 and for two sub-groups depending on the time of heart transplantation indication, i.e. no benefit after CMP (group 1: urgent heart transplantation done within 4 months, mean: 1 month, range 0.1—2.1 month) or benefit after CMP (group 2: heart transplantation after >4 months, mean: 3 years, range 0.5—16.7 years) (Fig. 3).

Hospital mortality was higher in the urgent group 1 than for group 2, i.e. 60% versus 17%. Early death causes were septicemia [2] and graft failure [5]. Late death causes were graft failure [4], reject [1] and gastric bleeding [1].

3.1. LDM histopathological studies

Microscopic analysis of the latissimus dorsi at the time of transplantation revealed preservation of the architecture of

Table 1

<table>
<thead>
<tr>
<th>Heart transplantation following cardiomyoplasty surgical procedure guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Preoperative chest CT scan: femoral cannulation in cases of ventricular adhesions to sternum.</td>
</tr>
<tr>
<td>• Standard fashion for cardiopulmonary bypass (previous CMP done without extracorporeal circulation).</td>
</tr>
<tr>
<td>• Heart and muscle wrap removed en-block.</td>
</tr>
<tr>
<td>• Proximal LDM and muscle pacing electrodes left in the chest.</td>
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<tr>
<td>• Careful preservation of the left phrenic nerve.</td>
</tr>
</tbody>
</table>

Table 2

<table>
<thead>
<tr>
<th>Survival</th>
<th>No. of patients</th>
<th>&lt;2 Months (%)</th>
<th>1 Year (%)</th>
<th>5 Years (%)</th>
<th>10 Years (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>26</td>
<td>73</td>
<td>61</td>
<td>57</td>
<td>50</td>
</tr>
<tr>
<td>Group 1 (HTx &lt; 4 months)</td>
<td>5</td>
<td>40</td>
<td>40</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>Group 2 (HTx &gt; 4 months)</td>
<td>21</td>
<td>80</td>
<td>76</td>
<td>67</td>
<td>57</td>
</tr>
</tbody>
</table>

Fig. 2. Heart and LDM of a transplanted patient 2 years after cardiomyoplasty. Thigh adhesions have been found between the muscle and the surface of the ventricles.
a normal muscle with slight hypotrophy and mild fibrosis in 11 patients. The ultrastructure of the LDM was remarkably well preserved without any fibrosis or fat infiltration in six patients (Fig. 4). Tight adhesions between the LDM and the heart were frequently observed (Fig. 5).

In nine patients, the study of the latissimus dorsi muscle wrap revealed severe ultrastructural impairment with muscle atrophy, extensive fibrosis and fat infiltration (Fig. 6A and B).

4. Discussion

A variety of invasive procedures have been utilized to reduce the burden on the left ventricle in order to slow or reverse the progressive changes of structural remodeling. These include mitral valve repair, left ventricular assist devices, left ventricular chamber reduction surgery, endo-vascular patchplasty, dynamic cardiomyoplasty, and a variety of prosthetic implants designed to inhibit remodeling either by constraining chamber enlargement or reducing wall stress to inhibit further growth. Resynchronization therapy and stem cell implantation also may favorably affect remodeling. The potential of these procedures to slow the progression of heart failure needs to be confirmed in prospective studies [9,10].

Cardiac bioassist procedures have been conceived for patients presenting heart failure, refractory to medical therapy. Cardiomyoplasty and aortomyoplasty were born in the 1980s from the use of skeletal muscle flaps from plastic and reconstructive surgery and by the demonstration of muscle-fatigue resistance induced by stimulation [1,11—13]. The biological support of these operations consists of chronic muscle electrostimulation that induces a physiological adaptation of skeletal muscle to cardiac work. The metabolism of the rapid glycolytic fatigue-sensitive muscle fibers (type II) are transformed into slow oxidative fatigue-resistant muscle fibers (type I).

The mechanisms of action of CMP include limitation of heart dilatation and augmentation of ventricular contractility, through the synchronization of LDM contractions with heart contractions. More than 2000 procedures have been performed worldwide. It was shown that CMP provided functional improvements in heart failure patients. Improvements in diastolic function and limitation of adverse LV remodeling may be responsible for the long-term clinical benefits observed in cardiomyoplasty patients [14,15].

Fig. 3. Long-term survival after heart transplantation in cardiomyoplasty patients.

Fig. 4. Histochemical study of the LDM of the case presented in Fig. 2, showing preserved structure and complete histochemical transformation into slow oxidative fatigue-resistant fibres (ATPase stain, original magnification ×400).

Fig. 5. Histological study performed at 8 years of cardiomyoplasty showing the heart (left), the interface adhesions and a preserved LDM cytoarchitecture (right). Hematoxylin–eosin stain, original magnification ×250.

Fig. 6. (A) (left): Atrophy and fat infiltration of the LDM at the moment of heart transplantation. Hematoxylin–eosin stain, original magnification ×350. (B) (right): Fibrosis and necrosis of the LDM in a cardiomyoplasty patient. Hematoxylin–eosin stains, original magnification ×400.
The most recent application of CMP is chronically depressed right ventricular function (e.g., arrhythmogenic RV dysplasia), which represents an unresolved therapeutic challenge [16], and ventricular reconstruction after tumor resection [17]. As for causes of death after dynamic cardiomyoplasty, heart-related deaths, particularly frequent sudden deaths due to arrhythmia have been observed. Thus implantation of an ICD has progressively been recommended in CMP patients to prevent sudden death caused by arrhythmia [18,19].

Indications of CMP in patients with congestive heart failure are now well defined; this therapeutic approach can be considered in patients in NYHA functional class III free of severe symptoms of right ventricular failure [3,20] or in isolated RV failure [16]. In our early clinical CMP experience some end-stage HF patients (irreversible NYHA FC 4) were included. Due to the high mortality, patient’s selection moved progressively to NYHA FC 3. It is important to remark that hemodynamic benefits of CMP can be only observed at the end of the LDM electrostimulation training protocol (i.e. 2 months after surgery).

The present study demonstrates that prior CMP does not preclude heart transplantation. Following CMP a patient may be placed on the waiting list for heart transplantation in two different clinical settings:

1. Early CMP failure where stimulation of the latissimus dorsi has never been effective.
2. Initial (and sometimes prolonged) period of improvement under dynamic CMP followed by progressive deterioration of the clinical status.

Five patients in this series belong to the early cardiomyoplasty failure group. The cause of CMP failure was in one case infection of the stimulation system resulting in complete removal of electronics, in another patient muscular lysis of the skeletal muscle secondary to viral hepatitis and in three cases lack of clinical improvement.

The other 21 patients in this series were significantly improved for a period of 0.5—16.7 years (mean 3.8 years). Secondary impairment of their functional status occurred probably due to the onset of arrhythmias triggered by a progression of the underlying heart disease. Intractable atrial fibrillation was the promoting factor in seven cases and ventricular arrhythmias associated to an increasing mitral valve insufficiency in eight cases.

Our series and previous case reports [21—23] illustrate the surgical therapeutic strategy that may be considered in patients suffering advanced congestive heart failure; CMP could be indicated as a first stage procedure in patients in functional class III, in case of secondary worsening of symptoms, heart transplantation still remains feasible and may provide satisfactory results. Due to the lack of donors, heart transplantation should remain restricted to patient in end-stage cardiac failure (NYHA class IV) [7,24,25].

In this series, the morphological aspect of the LDM at the time of transplantation was variable. The architecture of the skeletal muscle was either well preserved or severely impaired with fibrosis or fat infiltration. These microscopic findings are not fully surprising if one considers the fact that in some cases, at the time of explantation the latissimus dorsi had not been electrically stimulated for several weeks. Consequently, it seems extremely difficult to distinguish the histological lesions of the muscle secondary to the denervation from ischemic injury that could have been induced by the surgical procedure itself. It is noteworthy that in six cases, the latissimus dorsi was morphologically normal long-term after CMP.

Hospital mortality was high when urgent heart transplantation was required due to postoperative heart failure or to early inefficient cardiomyoplasty support. We can explain this mortality by the fact that the indication of heart transplantation in many of these CMP patients started in the late 1980s and the early 1990s. In those days mechanical assist devices were not easily available to be used as a ‘bridge to transplant’. It is certain that access to LV assist devices would have enabled a better transplant schedule and probably better donor organ selection. It is therefore likely that the constraints of urgency would have been eased and the mortality of ‘urgent transplantation’ after cardiomyoplasty would have been lower if those patients had been assisted with mechanical devices after early CMP failure. In 1999 a patient benefited from a mechanical bridge (Novacor System) during 2 months before heart transplantation, with successful outcome. Device implantation and heart transplantation were performed without technical difficulties.

For ‘not urgent transplantation’, long-term survival was similar to those for primary heart transplantation [7]. This analysis confirms that cardiac transplantation after CMP is technically feasible. Operative mortality is within expectations when transplantation is performed late after CMP due to progression of underlying cardiac disease resulting in CMP inefficiency.

In conclusion, cardiomyoplasty, when it fails, does not preclude heart transplantation. When indicated, CMP could be considered as a biological bridge to transplantation. The overall results are quite similar to normal transplant population.

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References


Appendix A. Conference discussion

Dr G. Laufer (Innsbruck, Austria): Are you still performing cardiomyoplasty?

Dr Chachques: We are still performing cardiomyoplasty for right ventricular failure which is as you know very difficult to treat. There are no medical treatments for isolated right ventricular failure. These patients are young with a normal left ventricle, they start with arrhythmias, but at long term they develop RV dilatation with severe tricuspid valve regurgitation. The only possibility is to make tricuspid valve annuloplasty and in addition also to limit the important dilatation of the right ventricle using the muscle flap. We have a 10-year follow-up of this series of 12 patients and, really, the results are quite good and we can control the symptoms and we can avoid heart transplantation in these patients having good LV function.

Dr Laufer: What do you think is the reason that you have such a high mortality in patients that are coming early with failed cardiomyoplasty within the first 4 months for urgent heart transplantation.

Dr Chachques: Probably it was a bad indication for cardiomyoplasty. These patients were closer to NYHA Functional Class 4 than Class 3. We did not evaluate well the clinical situation. And also, the main disadvantage with cardiomyoplasty is that it did not improve patients early after operation. We have to wait 2 months or more for the training of the muscle to expect hemodynamic improvements and modifications in LV remodeling. The use of inotropics drugs and balloon counterpulsation in the postoperative period can be useful, but can only be used for a short period. So I think that the main cause of this failure was poor indication.

Dr B. Jegden (Lyon, France): I think that in this group of patients, obviously, the cardiomyoplasty has allowed to delay the indication of the stage of heart transplantations. And I know that you are very involved in cell therapy now. Do you think that such therapy could afford the same results in this population of patients to delay the stage of heart transplantation in severe ischemic or dilated cardiomyopathy?

Dr Chachques: The goal of cardiomyoplasty was to operate patients that have some degree of contraindication for heart transplantation and to delay transplantation. Perhaps some patients should have been selected directly for transplantation and not for cardiomyoplasty. It was more in the early experience, but in time we learned that we have to select patients in stable NYHA Class 3. The best results of CMP were observed when we wrapped the LD muscle most of the left and right ventricular surfaces.

Presently we are developing intrainfarct stem cell therapy associated with a 3D cell seeded collagen matrix fixed onto the infarct zone. The goal is to regenerate the myocardium and to support the failing ventricle.