

Recent Findings on Cardiomyoplasty Management and Mechanisms of Action: Implications for Patient Selection, and Postoperative Care

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Abstract

The use of skeletal muscle power to assist the failing heart in the clinical setting has been limited to the cardiomyoplasty procedure, apart from very preliminary clinical experience with skeletal muscle external aortic counterpulsation. Because of several drawbacks in patient selection, operative technique, and postoperative management, the patient outcome faced extremely variable results throughout the years. Most recent experiences have underlined the importance of refined patient inclusion criteria, appropriate strategy in surgical decision-making, and thorough patient follow-up to optimize postoperative results. The use of sophisticated techniques to evaluate cardiac performance disclosed subtle changes secondary to skeletal muscle support which are shedding new light on the understanding of mechanisms of action, and delineating the role of such a procedure in the therapeutic scenario of chronic heart failure.

The present paper provides a useful overview on the recent advances in patient selection, the surgical technique, postoperative management, and probable mechanisms of action, based mainly on the personal experimental and clinical experiences.

Key words: cardiomyoplasty, patient selection, surgical procedure, postoperative care.

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Dynamic cardiomyoplasty has been introduced in the clinical practice since 1985 [7]. The use of mobilized and chronically stimulated skeletal muscle proved to be suitable for reinforcing or substituting the failing myocardium. Previous experimental studies had shown that muscle fibres have the capability to adapt to a new functional demand and to respond to chronic electrical stimulation by transforming contractile fatiguable fibres to fatigue resistant units [10, 43]. Nonetheless, several drawbacks progressively appeared in the clinical application, and substantial refinements have been applied in the management of such a biomechanical cardiac support [9, 12, 35, 39]. This article presents our personal experience and attitude in the application of cardiomyoplasty in the treatment of chronic heart failure patients, and provides some interpretation of cardiomyoplasty effects based on recent findings.

Selection of candidates

Initial experiences with cardiomyoplasty faced the cumbersome issue of treating patients affected by terminal stage of chronic heart failure, that is, patients in New Heart Association Class (NYHA) IV [7, 37, 38]. This indication

soon appeared to exert disappointing results in terms of operative mortality and dismal long-term prognosis [9, 13]. It was clear that skeletal muscle support could not represent a valuable therapeutic option for these patients. Amongst other factors, the presence of biventricular failure and pulmonary hypertension showed to be additional negative predictors for patients outcome after surgery [12]. Besides a few further criteria, no major advances in terms of patients selection has been provided by the investigators in the last 2-3 years.

It is important to note that despite clear evidences in terms of direct relations between etiology of the underlying cardiomyopathy and prognosis in patient following heart transplantation [17, 21], this did not seem to be relevant in cardiomyoplasty. Nonetheless, in our experience ischemic cardiomyopathy did play a major negative role in terms of morbidity and mortality [35]. It is conceivable that in our opinion ischemic heart disease requires an extensive evaluation. Indeed, besides the search for adequate myocardium viability to predict functional recovery after revascularization [27], an attempt to objectivate the myocardial response induced by potential ischemic insults should be ruled out (figure 1). Stress test by dobutamine infusion under tran-

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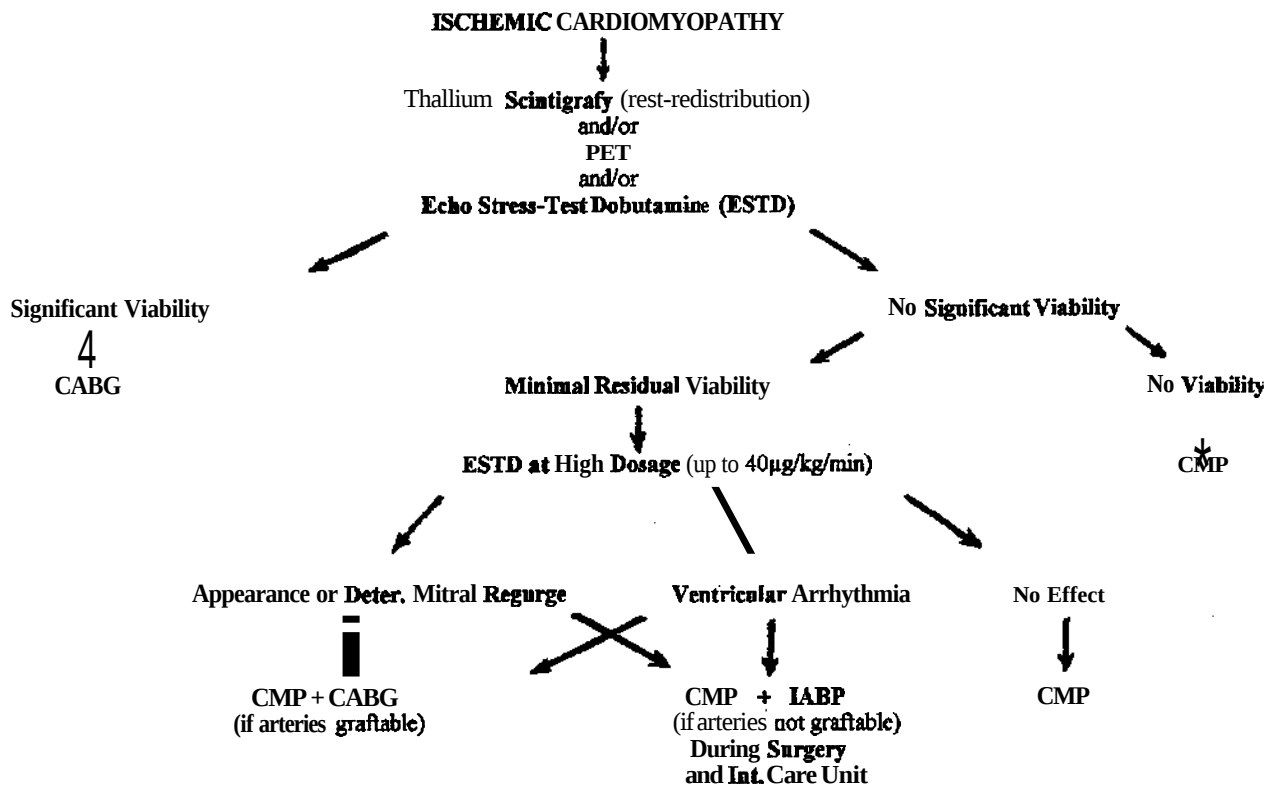


Figure 1. The figure shows the diagnostic iter adopted to decide the kind of therapeutic intervention in ischemic cardiomyopathy, and plan the intra and postoperative management in a patient affected by ischemic dilated cardiomyopathy. PET: Positron Emission Tomography; CABG: Coronary Artery Bypass Grafting; CMP: Cardiomyoplasty; IABP: Intraaortic balloon counterpulsation.

esophageal echo monitoring is used to analyse at high dosages of dobutamine (up to 40 $\mu\text{g/kg/min}$) the evoked myocardial response. The appearance or deterioration of mitral insufficiency, and the occurrence of malignant ventricular arrhythmia, will be important clues for avoiding such events during the operative procedure or in the Intensive Care Unit when maximal pharmacological support may be needed to counteract common episodes of low cardiac output. If the test is positive, an early use of intraaortic balloon pump will be mandatory to prevent adverse effects induced by ischemic response of the myocardium, or concomitant CABG may be considered for the target vessels if graftable [20].

Surgical procedure

In terms of technical details, the introduction by Carpentier and Chachques of the so called "no-touch technique" for the wrapping maneuver [8], unquestionably reduced the surgical difficulty, avoiding long-lasting heart lifting while suturing the muscle superior border to the atrio/ventricular groove. Besides this innovative and outstanding contribution, little has changed in the last years. Despite some experimental reports [11, 23] regarding possible modification, the left LDM cardiocostal wrapping represents the worldwide standard in cardiomyoplasty procedure. The use of the right LDM has been introduced by

Magovern and associates, with little evidence concerning a likely benefit if compared with the left LDM [37]. Our group recently proposed a modification of the right cardiomyoplasty technique [33], with an attempt to reproduce the Carpentier maneuver used for the left LDM cardiomyoplasty operation. Another crucial aspect may be represented by severely enlarged hearts (> 85 mm of end-diastolic diameter). In these cases an incomplete ventricular wrapping is likely. Chachques and Carpentier proposed the pericardial patch or flap to fill the muscular gap [8]. We have been recently adopting a modified wrapping technique for such a peculiar case. The superior LDM margin is somehow extended by suturing two patches of bovine pericardium together (along the shorter border) and then suturing (along the longer margin) this wide patch to the LDM. In this way, the wrapping surface is substantially enlarged, avoiding the use of the native pericardium (which can be used as a coverture over the mediastinal course of the muscle reducing the adhesions with the above sternum), with crucial ease for the muscle to be slipped posteriorly to the heart.

Another important aspect is the use of intraaortic balloon pump during cardiomyoplasty operation. Such a mechanical assistance has witnessed a wider application in the latest years in cardiomyoplasty experiences. It is our belief that in presence of poor cardiac reserve (e.g. EF $<$ than 15-

20%), or with a positive preoperative echo stress-test, the use of IABP is mandatory to ensure a smooth perioperative management. In this situation, IABP can be safely and easily introduced at the beginning of the 2nd step (after mid sternotomy) of the ongoing procedure. Furthermore, the presence of the IABP in Intensive Care Unit may allow an easier control of hemodynamics, with subsequent reduced need of inotropic or vasoretic drugs which may induce untoward effects (reduced renal or muscle perfusion, increased vascular resistance, and so forth).

The last controversial issue is represented by a recent concern in patient outcome. Sudden death constitutes a relevant problem in cardiomyoplasty [5, 35]. The use of concomitant implantable defibrillators is a matter of discussion, but we believe that, seen the stabilization effects of patient clinical condition, it would be reasonable to have the opportunity to counteract the often fatal arrhythmia. A combined device (cardiomyostimulator plus implantable defibrillator) seems to be soon available. In the mean time, the concomitant application of an AICD and of a cardiomyostimulator has been shown to be feasible [15], and should be taken into account in the decision making.

Postoperative care

The early use of IABP in surgery or Intensive Care Unit is the most important advance, and has been discussed in the previous section. Further potential problems, usually encountered in the perioperative phase, are represented by arrhythmia and low cardiac output syndrome. Supraventricular arrhythmia (sinus tachycardia or atrial fibrillation) are a common finding in the first few hours, but ventricular arrhythmia may also occur, and usually linked with worse prognosis. Therefore, following continuous infusion in the operative theatre, lidocaine is maintained for the first 3-4 hours, then gradually discontinued, whereas amiodarone infusion is instituted. Such an approach usually allow an effective prevention of ventricular disturbances, provided that other usual factors (potassium level, pH, and pO₂) are within acceptable range. It is worth noting that these patients usually require higher loading than preoperatively likely due to the small changes in diastolic properties induced by the wrapped muscle, even if no diastolic impairment has been shown just following cardiomyoplasty [4].

Low cardiac output syndrome may occur during the following hours (from 6-7 up to 1 or 10 days postop), probably induced by the further burden of the wrapped muscle on an already failing heart. This event is particularly evident when the cardiac reserve is low. In these patients, cardiocirculatory compensatory mechanisms have already been present since a long time, and, often, the hemodynamic homeostasis is based on very weak balance, with high likelihood of deterioration just after surgery. As mentioned before, use of intravascular mechanical assistance is the first choice, but use of inotropes (preferably dobutamine) and vasodilator (nitroprusside) may be necessary and generally effective to treat the ongoing hemody-

namic worsening. If low cardiac output persists a tight wrapping (right ventricle) or slight compression on the posterior a/v groove may be the potential explanation, and transesophageal echoardiography evaluation is mandatory to indicate any need of surgical revision. Nonetheless, with strict adherence to precise and appropriate selection criteria, irreversible cardiac failure is unlikely. Temporary renal failure which progressively leads to definitive impairment of function, and need of permanent dialysis, may be encountered, especially if preoperative chronic dysfunction was present. High level of muscle phosphocreatine kinase may be observed, and not invariably linked to irreversible muscle damage [35], with transient myoglobinuria and kidney failure, but it has usually a benign course. Pulmonary complications (atelectasia or edema) may be related to the surgical procedure itself (lung compression by the muscle passage along the left pleural cavity) or to the cardiac performance. Other untoward events are quite uncommon (bleeding, muscle edema due to narrow thoracic window, etc.), but should be taken into account.

As far as postoperative attitude, we would like to underline the necessity to use antiarrhythmic and anticoagulant drugs. Amiodarone proved to be effective in significantly reducing the ventricular arrhythmic events in dilated cardiomyopathy patients [16], and low dosages of Warfarin may further reduce the formation of intraventricular or intraatrial (brief episodes of atrial fibrillation are very frequent in such patients) thrombi [42], with undisputable prevention on cerebral or coronary emboli and related morbidity.

Optimization of wrapped muscle represents another critical factor. Indeed, correct heart/LDM interaction has been shown to substantially influence cardiac performance and, therefore, cardiomyoplasty result. Muscle contraction timing is currently programmed to intervene at the moment of the closure of the mitral valve. Nonetheless, the optimal effect of muscle support may occur later in the systolic phase. Therefore, it would be advisable to monitor, by transthoracic echocardiography, the hemodynamic effects (aortic flow) of different LDM activation times at the end of the conditioning protocol. This evaluation should be performed during the follow-up since the mechanical properties of the wrapped muscle changes (prolonged contraction/relaxation time) with potential detrimental effects on the beat following the assisted one (impairment of the early ventricular filling by a still contracted LDM).

Results

Our experience (25 patients) show that cardiomyoplasty actively influence the progression of the underlying cardiomyopathy [35]. Direct and contractile benefits on cardiac performance may be observed in some patients. Traditional hemodynamic parameters were improved at short term (6 and 12 months), whereas no further significant changes have been observed at long term. More often, clear hemodynamic changes during wrapped LDM can be documented at higher amplitude than clinical setting [44],

whose evoked muscle contraction cannot be stand by the patient. Concomitantly, a positive effect on ventricular dilatation is exercised, with significant ($p < 0.05$) reduction of left ventricular end-diastolic diameter up to 2 years postoperatively (73.24 mm, 69.30 mm, e 72.45 mm, at 6, 12, and 24 months, respectively). Subsequently, we observed a low progression of the ventricular dilatation which was nevertheless stable ($p = \text{NS}$) thereafter (figure 2). A less effective contribution of the LDM [22, 36], or a progression of the cardiomyopathy should be taken into account. It is worth saying that at 4 years after cardiomyoplasty, no additional increase in left ventricular volume is achieved, with undoubt advantage on patient prognosis. Quality of life is generally considerably improved as reported by most of the worldwide clinical experiences.

Complications

Perioperative complications have been discussed in the postoperative care section.

Late complications are frequently related to arrhythmia (atrial fibrillation or sudden death). This factor requires prudent approach, and use of Amiodaron and slight anticoagulant therapy should be undertaken in all the patients in an attempt to reduce the incidence of ventricular arrhythmia and atrial and/or ventricular thrombi [5, 42]. Worsening of heart failure may represent the terminal evolution of the underlying myocardial disease. This event occurs in the minority of the patients in our experience, and it was more common in the initial phases of cardiomyoplasty experience (NYHA Class IV patients). The postoperative course of these patients show a rather stable clinical condition, with some periods of increased medical therapy, but definetly less frequent episodes of acute heart failure [35]. It is important to underscore that heart transplantation following

cardiomyoplasty has been performed in several cases [19], and may represent an additional option for patients with refractory heart dysfunction.

Bacterial infection is an unfortunate complication following cardiomyoplasty. It can occur involving any electrical portion or related structure (abdominal pocket) or can be limited to the area of muscle dissection. Electrical material explantation is often required [1, 9], since conservative approaches are frequently unsuccessful. Some minimally invasive techniques to approach the infected material and reimplant the pacing system have been designed (figure 3) and carried out by our institution [32]. Mechanical problems involving the electrical system are extremely rare, but may occur. The break of muscle lead can be easily managed, as well as the epicardial sensing electrode malfunctioning [34].

Heart failure may of course represent an additional complication and a terminal event. Usually, following cardiomyoplasty the episodes of acute cardiac dysfunction are substantially reduced [9, 35]. Conversely, these patients may have cyclic phases of clinical conditions. This situation may require adjustment of medical therapy, provided that correct heart/muscle interaction has been investigated [14, 30] and that no other factors intervened in the meantime.

Interpretation of mechanisms of action

The lack of homogeneous hemodynamic improvements has been representing the major source of debate in the interpretation of cardiomyoplasty mechanisms of action [46]. Evaluation of traditional parameters (EF, CO, VO_2max , and so forth) have been not showing clear benefits, except a few reports [9, 28, 40], and thereby prevented a wide acceptance of the technique. Initial experimental and clinical data seemed to validate the contractile properties of the wrapped skeletal muscle, despite some cautious

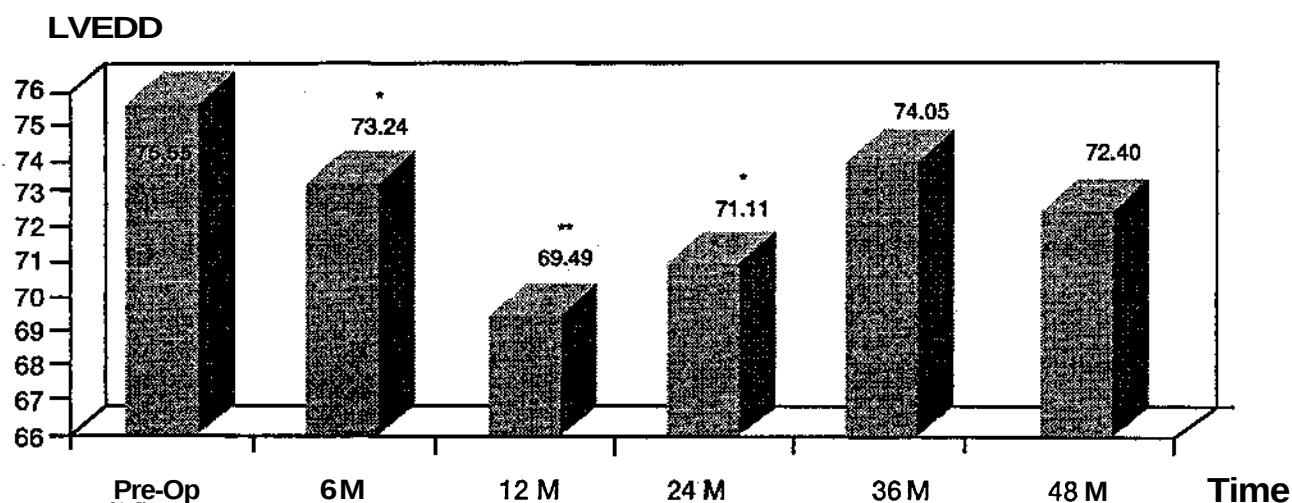


Figure 2. This figure shows the changes during time (months) of left ventricular end-diastolic diameter (LVEDD). It is important to underline the significant reduction of left ventricular dimension up to 2 years after cardiomyoplasty. * $p > 0.05$, ** $p < 0.01$.

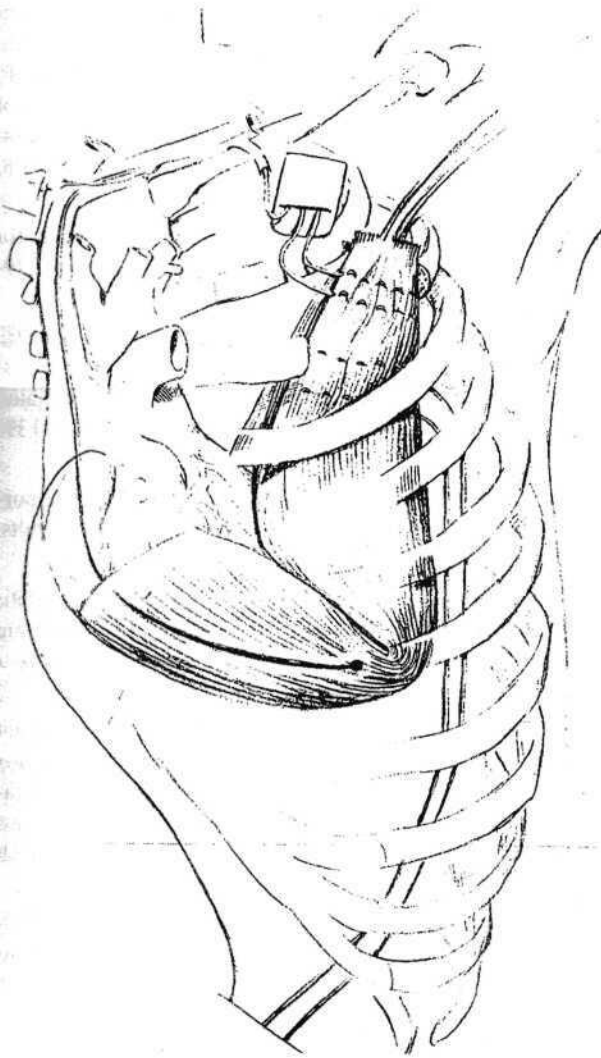


Figure 3. Replacement of the infected cardiomyostimulator with a new device positioned at the pectoral level is shown. Two new intramuscular leads have been implanted at the thoracic window, following careful dissection of the proximal part of the transposed muscle graft, and tunneled to the new thoracic pocket. The sensing lead is placed endocardially through the cephalic vein.

approach by the most [2]. Nevertheless, recent data obtained by accurate analysis of cardiac performance during muscle assistance ensured a better understanding of the LDM contribution. The use of pressure/volume relations using the conductance catheter [3] represented in cardiomyoplasty evaluation a major breakthrough. Indeed, experimental and clinical studies clearly documented different effects. Nakajima and coworkers showed an hypothetical explanation by using pressure/volume relations [41]. The experiments of Capouya further evidenced the constraint effect provided by the wrapped muscle, by preventing the heart dilatation following high rate ventricular pacing [61]. The concept of "girdling effect" was therefore

introduced in the process of interpretation of potential mechanisms of action. Lee had previously hypothesized this mechanism by showing the reduced myocardial consumption of the supported myocardium during cardiomyoplasty [29]. Kaulbach and associates confirmed the constraint effect exerted by the wrapped muscle on dilated hearts in animals achieved by continuous iatrogenic chronic overload (arterial-venous fistula) [25], and elegantly demonstrating that a passive muscular girdle was sufficient to halt the progressive cardiac dilatation, whereas muscle stimulation was required to effectively and progressively decompress the enlarged ventricles. Subsequently, Kass showed in a clinical report of 3 cases the effects of cardiomyoplasty on ventricular dimensions [24], and recently Schreuder and collaborators documented clear LVEDD reduction at 6 and 12 months after surgery as compared with preoperative data in a limited clinical series [45].

Perspectives

The latest period has been featured by the efforts of investigators and researchers to better define mechanisms of action. Concomitantly several studies have been undertaken to improve some of the major concerns appeared along the clinical and experimental experiences. The major advances, apart from a clearer understanding of the benefits of the current technique, will likely come from the improvement of the overall quality of the transposed muscle, either in respect to preoperative condition [31] or to stimulation protocol [18, 26], which appears to significantly affect the postoperative outcome. Likewise, the search for any influence on long-term morbidity and a potential reduction of mortality is ongoing, and the combined cardiomyostimulator/portable cardiodefibrillator device will be a major advance in this respect, with intuitive benefit on patient outcome.

Comment

Relevant progresses are undergoing in terms of understanding and management of cardiomyoplasty. Recent sophisticated studies allowed fine evaluation of the active and passive support of the wrapped skeletal muscle. Some other issues remain unsolved, and constitute the major limitation of patient outcome. Postoperative arrhythmia may be counteracted by combined implantation of portable defibrillator. Other matters like effectiveness of right versus left LDM, the exact tension of the wrapping tightness, the exact role of muscle structure in terms of hemodynamic performance, the role of preoperative muscle condition for postoperative muscle performance, need still extensive investigations.

In conclusion, cardiomyoplasty represented an innovative and "conservative" surgical treatment of patients affected by refractory heart failure. Heart transplantation is the gold standard treatment option in these cases, but the well known limitation of the access to such a therapy or the presence of contraindications, call for alternatives, even if

palliative. Cardiomyoplasty proved to exert a wide range of positive effects on the failing hearts, and to improve patient clinical condition. Ongoing studies, and randomized trials may add final information for the exact role of such a treatment.

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