Cardiomyoplasty
A Critical Review of Experimental and Clinical Results

Reida M. El Oakley, FRCS, Jonathan C. Jarvis, PhD

Skeletal muscle cardiac assist (SMCA) is emerging as a promising form of surgical treatment for end-stage heart failure. In one form, cardiomyoplasty, the muscle is wrapped around the heart and then activated by electrical stimulation to augment myocardial contraction.1

Cardiomyoplasty has been performed in more than 400 cases worldwide with variable degrees of success. Despite excellent symptomatic improvement in the majority of patients surviving the procedure, objective hemodynamic effects have not been consistently demonstrated.2,3

The hemodynamic effect of cardiomyoplasty has been the subject of a great deal of experimental and clinical research over the past decade. This article discusses in detail the published results of experimental and clinical cardiomyoplasty, with particular emphasis on hemodynamic effects and limitations of the procedure.

Other forms of experimental SMCA, including aortomyoplasty, skeletal muscle ventricles, and biomechanical assist devices, were reviewed recently4-6 and therefore are not discussed here.

Need for Cardiac Assistance

Chronic heart failure is a clinical entity characterized by left ventricular dysfunction, impaired quality of life, and markedly shortened life expectancy.7 The overall 1- and 5-year survival rates are 57% and 25% in men and 64% and 38% in women, respectively.8 Survival rates in patients with new-onset heart failure after acute myocardial infarction are even lower, with only a small minority remaining alive at 5 years.9 Today, despite optimal pharmacological therapy, mortality due to congestive heart failure remains unacceptably high.10

Cardiac transplantation has revolutionized the management of end-stage heart disease,11 with 5- and 10-year survival rates of 66% and 52%, respectively.1 However, the disparity between the number of donor organs available and the number of transplant candidates limits this option to a minority of patients.12 Xenotransplantation offers a potential solution to the problem of lack of donor organs, but even in the primate model and using state-of-the-art immunosuppression, heart xenografts have not been successful.13,14

Total artificial heart and mechanical assist devices have been used successfully as a bridge to transplantation,15,16,17 but longer-term applications are hampered by the associated infective and thromboembolic complications.18

The idea of using skeletal muscle as a source of energy to augment failing hearts is appealing, because even patients suffering from terminal congestive heart failure have an abundance of skeletal muscle. These muscles are capable of developing large forces and generate their own immediate energy supply. They also provide a power source that is free of wires, pneumatic tubes, and complicated electromechanical parts. Furthermore, autografting generates no immune response, and the risk of infection is low. The latissimus dorsi muscle is generally considered to be the most suitable candidate for cardiac assistance because it is a large, nonessential muscle that has a predominant axial neurovascular bundle and is situated close to the heart.

Historical Perspective of SMCA

Kantrowitz and McKinnon19 were the first to exploit the contractile properties of skeletal muscle to increase the pumping power of the heart. Using a canine model, they wrapped the left hemidiaphragm around the distal thoracic aorta. The muscle was stimulated via its intact phrenic nerve. Short-lived diastolic pressure augmentation was achieved when the muscle was stimulated in diastole, but muscle fatigue was clearly a serious obstacle to the use of skeletal muscles for long-term cardiac assistance.20-22

By the mid 1970s, it was established that long-term, low-frequency electrical stimulation not only caused a transformation of fast muscle to slow but also increased its resistance to fatigue.23 This discovery revived interest in the concept of SMCA,24-26 The idea was applied clinically for the first time only 8 years ago.27 In this case, the left latissimus dorsi muscle was transferred into the chest cavity to patch a myocardial defect left after resection of a 1.5-kg cardiac tumor.

Adaptive Transformation of Skeletal Muscle

Salmons and Vrbova28 showed that skeletal muscles can adapt to their pattern of use. Chronic low-frequency electrical stimulation of mammalian skeletal muscles transforms the fast type II muscle fibers into the slow fatigue-resistant type I.29,30 The end result of such transformation is that ATP production can match ATP utilization in continuous working conditions.31

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From the Department of Cardiac Surgery (R.M.E.), Royal Brompton National Heart and Lung Hospitals, London Chest Hospital, Bonner Road, London; and the Department of Human Anatomy and Cell Biology (J.J.), PO Box 147, The University of Liverpool, Liverpool, UK.

Correspondence to R. El Oakley, Department of Cardiac Surgery, Royal Brompton National Heart and Lung Hospitals, London Chest Hospital, Bonner Rd, London E2 9JX, UK.

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The fast-to-slow transformation is associated with a significant loss of muscle mass and power. It is estimated, however, that the remaining power is more than adequate for cardiac assistance, if delivered efficiently to the cardiovascular system. A further undesirable effect of muscle transformation is the striking reduction in contractile speed. Type I fibers are slow to contract and to relax; they cannot match the dynamics of the native heart. Slow relaxation, for example, could impair ventricular filling in cardiomyoplasty. Alternative stimulation techniques that have recently been applied in experimental animals transformed type Ib fibers to the intermediate type Ila fibers, which are fast yet resistant to fatigue. Such techniques have not yet been applied in cardiomyoplasty.

Cardiomyoplasty Techniques

The surgical techniques of clinical cardiomyoplasty were described by Chachques et al. and previous experimental research was performed using similar methodology. The operation is performed with the patient under general anesthesia with a single endotracheal tube. The patient is initially put in the right lateral position. A flank incision extending from the axilla to the mid point of the 12th rib is performed. The latissimus dorsi muscle is freed from its distal attachment, but the proximal neurovascular pedicle is left intact. The tendinous attachment to the humerus is divided, and two intramuscular electrodes are placed in the proximal part of the muscle. The anterior two thirds of the second rib are resected to allow the latissimus dorsi muscle flap (LDF) to be delivered into the left hemithorax. The proximal tendon is resutured to the periosium of the second rib, and the wound is closed in layers.

The heart is then exposed through a median sternotomy, the left pleura is opened, and the LDF is drawn into the pericardial cavity. The heart is gently lifted, the muscle is wrapped around it, and the flap is secured to the pericardium and/or the myocardium. Two epicardial sensing leads inserted on the right ventricle are connected to the cardiomyostimulator. The intramuscular electrodes are also connected to the stimulator, and the sternum is closed.

Complete wrap of the heart in a clockwise direction (looking at the apex of the heart) has been called "reinforcement cardiomyoplasty." If the muscle length is not adequate, a patch of the pericardium is sometimes used to allow a complete wrap. The muscle is wrapped so that its costal surface is in direct contact with the epicardium (cardiocostral wrap). This technique has been used in most clinical cardiomyoplasty operations. Substitution cardiomyoplasty is reserved for cases in which part of the myocardial wall is resected and patched with pericardium, and the muscle is sutured over the patch.

Two to 3 weeks of "vascular delay" without muscle stimulation has been advocated by Mannion et al. to allow the distal half of the muscle to recover from the loss of its blood supply; the delay period also allows the development of adhesions between the epicardium and the muscle flap. Graded muscle stimulation is then initiated to effect transformation of the muscle.

Experimental Basis of Cardiomyoplasty

Effects of Cardiomyoplasty on Healthy Hearts

Both reinforcement and substitution cardiomyoplasty have been shown to produce significant hemodynamic changes if applied to the right side of the heart. In contrast, the existence of objective hemodynamic effects of reinforcement cardiomyoplasty applied to the left side of the heart is not well established. It is therefore surprising that reinforcement cardiomyoplasty is being advocated as a therapeutic modality for patients with left ventricular failure, whereas right ventricular failure is considered a contraindication to the procedure.

The controversy regarding the validity of reinforcement cardiomyoplasty is more than 30 years old. Kantrowitz and McKinnon showed that wrapping the left hemidiaphragm around the heart and stimulating it in systole had no effect on systemic pressures. On the other hand, wrapping the muscle around the thoracic aorta and stimulating it in diastole generated significant diastolic pressure augmentation.

More recently, since the clinical application of reinforcement cardiomyoplasty, a number of researchers have attempted to document its hemodynamic effects. Chachques et al. reported hemodynamic measurements made 9 months after a complete muscle wrap in 10 healthy goats. A significant improvement in cardiac output was observed during burst electrical stimulation of the muscle flap. Cardiac output increased from 3.81 ± 0.16 L/min (with the cardiomyostimulator off) to 4.57 ± 0.19 L/min (with the cardiomyostimulator on in 1:1 heart-to-muscle contraction ratio). Other hemodynamic parameters measured with the stimulator on and off were not reported.

However, with the cardiomyostimulator in 2:1 mode, the peak velocity of blood flow in the descending aorta and the pulmonary artery were higher in the assisted than in the nonassisted beats. Similarly, the left and right ventricular stroke volumes were higher in the assisted than in the nonassisted beat. All hemodynamic measurements were based on Doppler ultrasound assessment except for cardiac output, when the thermodilution technique was applied.

The strength of this study is derived from the highly significant increase in cardiac output when the stimulator was switched on. This increased cardiac output was observed in goats with normal cardiac function up to 9 months after the operation, a finding that has not been reproduced by others (see below). Furthermore, the analyses of the results of ventricular stroke volumes and aortic and pulmonary peak flow velocities can be criticized on two grounds. First, comparing assisted with nonassisted beats in the 2:1 mode is less than ideal. Slow muscle relaxation (following the assisted beat) could impair venous return, thus reducing the next end-diastolic volume and consequently the stroke volume of the following unassisted beat. Second, increased aortic and pulmonary peak flow velocities may or may not be associated with an increase in the total blood flow.

Many others have failed to achieve such impressive results, particularly in animals with healthy hearts. In a long-term follow-up (12 to 35 weeks) after cardiomyoplasty, Lucas et al. found no significant change in cardiac output or left ventricular indexes of healthy
goats. The experimental protocol used was almost identical to that of Chachques et al. The lack of hemodynamic changes in 11 goats even after induction of acute heart failure was attributed to latissimus dorsi muscle damage, a finding not reported by Chachques et al. Thermel et al. have shown that cardiomyoplasty (partial wrap) in sheep was not associated with consistent improvement in ventricular function. The lack of hemodynamic improvement in this case was attributed to the possibility of cardiac diastolic displacement during latissimus dorsi muscle contraction.

Anderson et al. failed to show any significant hemodynamic changes in eight dogs 4 months after a partial cardiomyoplasty wrap. In four dogs, the muscles had been conditioned for 12 weeks after 3 to 4 weeks of vascular delay. At the time of hemodynamic assessment, three dogs were maintained on normothermic cardiopulmonary bypass, keeping left ventricular pressure at 20 mm Hg. Despite vigorous contraction of the muscle flaps, the aortic pressure remained unchanged, whereas the average left ventricular pressure increased by 15 mm Hg in two of three dogs.

**Effects of Cardiomyoplasty in Experimental Acute Heart Failure**

Chagas et al. realized that cardiomyoplasty may have little or no effect on a healthy heart. They performed a complete wrap in six dogs 6 to 8 weeks after left latissimus dorsi muscle conditioning. Acute heart failure was induced by high-dose intravenous propranolol. Multiple-gated equilibrium radionuclide angiography showed that pulse train stimulation increased the cardiac output from 1.4±0.1 to 2.0±0.2 L/min (P<.05). Similarly, the left and right ventricular stroke volumes increased by 49% and 39%, respectively. The mean systemic and pulmonary artery pressures remained unchanged.

In a similar study, Kao et al. showed that the clockwise muscle wrap had no consistent hemodynamic effects. On the other hand, wrapping the muscle in an anticlockwise direction produced a significant increase in cardiac output and aortic and pulmonary artery pressures. The improved hemodynamics in the anticlockwise wraps were attributed to skeletal muscle fiber orientation in relation to the heart. In the anticlockwise configuration, the skeletal muscle fibers are circumferential to the heart and perpendicular to the interventricular septum, which is in contrast to the clockwise arrangement in which the muscle fibers are parallel to the ventricular septum.

**Effects of Cardiomyoplasty in Experimental Chronic Heart Failure**

In clinical practice, cardiomyoplasty is being offered to patients in chronic heart failure. Experimental models with normal or acutely impaired cardiac function were therefore not the ideal test for cardiomyoplasty in many respects. Lee et al. induced chronic dilated cardiomyopathy by continuous rapid ventricular pacing in a canine model. Three to 4 weeks later, an anticlockwise left latissimus dorsi wrap was performed. Left ventricular pressure and major axis shortening were measured using pleoelectric sonomicrometric crystals. Dynamic cardiomyoplasty improved the systolic shortening in both axes and so enhanced the left ventricular stroke work. Although the peak systolic aortic pressure was increased by 11%, the mean arterial pressure remained unchanged. Since the muscles used were not conditioned, electrical stimulation was limited to short periods (15 to 25 seconds) to avoid muscle fatigue.

In another chronic heart failure model, cardiomyoplasty was induced in 10 dogs with doxorubicin. The hemodynamic effects of reinforcement cardiomyoplasty were analyzed 3 months after surgery. Radionuclide studies showed improved left ventricular global and regional ejection fractions with skeletal muscle assistance. The only significant change measured during cardiac catheterization was a reduction of left end diastolic pressure, which is an indirect measure of improvement of left ventricular systolic performance. The aortic and left ventricular pressures measured by micromanometer-tipped catheters were not altered.

Millner et al. reported a chronic heart failure model based on ligation of the "homonymous" and second diagonal coronary arteries in sheep. Using this model, the same group tested anterior "partial-wrap" cardiomyoplasty in a number of chronic experiments. Four months after the procedure, there were no significant hemodynamic differences between control, adynamic, or dynamic cardiomyoplasty in normovolemic animals. Only with volume overload did the dynamic cardiomyoplasty group have a significant improvement of cardiac output, pulmonary artery wedge pressure, and stroke volume.

Nakajima et al. have attempted to simulate the clinical application of cardiomyoplasty by performing the procedure in animals that had chronic heart failure at the time of cardiomyoplasty. Ten to 12 weeks after induction of ischemic ventricular dysfunction, by ligation of the left anterior descending and the second diagonal coronary artery, an anterior cardioscostal wrap was performed in five sheep. Hemodynamic assessment was performed 2 months after cardiomyoplasty. No significant change in cardiac output or in systemic pressure was detected after surgery. The same group also studied the left ventricular pressure-volume relation using a conductance catheter to estimate ventricular contractility (E-max) and myocardial oxygen consumption (pressure-volume area). Both measures improved after cardiomyoplasty over postinfarction pre-cardiomyoplasty values. However, there was no significant change in either E-max or pressure-volume area between the pacemaker off and on setting. It was concluded that cardiomyoplasty may prevent the progression of ventricular dilation and therefore improve left ventricular systolic function. These findings support those of Capouya et al., who found that even an unstimulated latissimus dorsi muscle wrap significantly attenuated the left ventricular enlargement, the increase in left ventricular volume, and the decrease in ejection fraction in a canine heart failure model.

**Results of Clinical Cardiomyoplasty**

Between 1985 and 1990, 78 dynamic cardiomyoplasties were performed in patients with chronic heart failure. Preoperative diagnosis was ischemic heart disease in 50%, idiopathic in 35%, Chagas' disease in 9%, congenital heart disease in 3%, and other diagnoses in 3%. The majority suffered from severe left or biventricular failure (46% in NYHA class IV, and 53% in class III). Twenty-three patients had a concomitant proce-
bypass graft class III and 33% occurred functionally.

III ment improved from 3.5

improved from 3.5 to 2.1). Direct hemodynamic assessment failed to show comparable improvement in left ventricular functions.

The symptomatic improvement after cardiomyoplasty could be attributed to the placebo effect of the procedure and to the overall improvement in patient care. However, detailed quality of life assessment of 14 patients before and 13 to 19 months after cardiomyoplasty suggests that the operation significantly reduced the degree of limitation of physical and social activities (Borghetti-Maio et al).

More positive data on hemodynamic improvement has been published by a group from Sao Paulo. In a nonrandomized trial on two comparable groups of patients with dilated cardiomyopathy, 15 patients underwent cardiomyoplasty and 17 patients continued to receive medical treatment. The cardiomyoplasty group not only improved their exercise tolerance but also had significant improvement in the left ventricular ejection fraction demonstrated by echocardiography and radioisotope ventriculography. Furthermore, the 18-month actuarial survival was significantly higher in the surgical than in the medically treated group (80% versus 31%). The only technical variation that Moreira’s group adopted was to suture the muscle directly to the epicardium. Despite suggestions that direct cardiac suturing is associated with an increased operative mortality, Moreira’s group reported no perioperative deaths in their series.

Magovern et al has retrospectively analyzed the outcome of 119 patients undergoing surgery for heart failure. Sixty-one patients had heart transplant, 27 had CABG, and 31 had cardiomyoplasty. The operative mortality was 7% for cardiac transplantation, 4% for CABG, and 16% for cardiomyoplasty. The 1-year survivals for those who were discharged alive were 94%, 91%, and 65% respectively. Although these three groups of patients were by no means comparable, cardiomyoplasty was associated with higher early and late mortality rates than transplantation or CABG.

Carpentier’s group has recently published the largest single-unit experience of clinical cardiomyoplasty from 52 patients with mean preoperative NYHA class of 3.3 and mean left ventricular ejection fraction of 16%. An associated procedure was performed in 23 patients. Ten had ventricular aneurysmectomy, 9 had valve surgery, 8 had coronary artery bypass grafting, and 3 had tumor resection. The overall preassist (up to 8 weeks after surgery) mortality rate was 23% although when the early experience was excluded (13 patients in the first 3 years), the early mortality rate was significantly less (12%). The late mortality (mean follow-up of 21 months) was 20%. The mean NYHA of 32 long-term survivors was 1.8. Cardiac catheterization performed in 20 patients showed an increase in mean ejection fraction from 24% to 30.6%. Pulmonary capillary wedge pressure and left ventricular end-diastolic pressure were unchanged.

These collective data imply a prohibitively high early and late mortality in class IV patients because cardiomyoplasty in its current form does not offer any immediate assistance to the failing heart. It is now recommended that patients undergoing the procedure should have enough residual ventricular function to carry them through the perioperative period, until complete muscle transformation is achieved. This practically limits the application of cardiomyoplasty to patients in NYHA class III.

Lack of Direct Hemodynamic Effects of Cardiomyoplasty

Significant subjective improvement is a common outcome in almost every clinical report, but it is not always accompanied by an objective improvement in left ventricular function. The question remains, therefore, why a muscle that would normally be able to generate more than 10 times the power output of a resting heart fails to alter beat-to-beat performance of a failing heart.

Lee et al suggested that latissimus dorsi wrap acts like an extra layer of myocardium, reducing the left ventricular wall stress and consequently increasing the velocity of circumferential shortening. This hypothesis is supported by Sigura’s mathematical model of cardiomyoplasty. Based on the assumption that a skeletal muscle wrapped around the heart behaves as a time-varying elastance that is connected in series with another time-varying elastance, “the native heart,” they predicted that cardiomyoplasty may augment myocardial contractility by increasing the slope of the end-systolic pressure-volume relation (E-Max).

The procedure may also improve ventricular function in an indirect fashion. Capouya et al have recently shown that a nonstimulated latissimus dorsi wrap significantly attenuates the progression of left ventricular enlargement and limits further deterioration of the ejection fraction. They concluded that this “girdling” effect of cardiomyoplasty may be of some importance in preventing further loss of function of dilated ventricles. Similar findings were reported by Nakajima et al in 1994. In clinical practice, removal of the cardiomyostimulator has been reported to be associated with deterioration in patients’ symptoms even in those who had no direct hemodynamic benefit after cardiomyoplasty (Carpentier et al, Moreira et al, and Acker et al, unpublished data). Such anecdotes are the only clinical evidence of the so-called “girdling” effect of cardiomyoplasty.

The lack of consistent long-term direct hemodynamic effects of cardiomyoplasty can partially be explained by the suboptimal loading of the grafted muscle, but it may also be result of progressive muscle damage. Lucas et al found that goat latissimus dorsi used for cardiomyoplasty are likely to develop severe muscle damage. Fourteen of 16 goats had “extensive lipomatosis” of the latissimus dorsi wrap within 12 weeks after surgery. This extent of muscle injury was reflected in poor muscle performance. The fate of latissimus dorsi muscle used in clinical cardiomyoplasty is not well known. In a recent series of 21 patients who had cardiomyoplasty, muscle damage was assessed by measuring CK levels at 38±18 hours after surgery, the mean peak value was 984 IU. Of 4 patients who had peak values above 1500 IU, 1 patient...
died 2 months after surgery, and postmortem histological examination of the latissimus dorsi flap showed evidence of muscle replacement by fibrous tissue. The other 3 patients had poor muscle flap contraction under pulse train stimulation. The same investigators61 performed NMR imaging of latissimus dorsi in 6 patients who had cardiomyoplasty 2 years previously. They found that significant parts of the six muscles were used by fatty tissue. El Oakley et al62 showed that structural muscle damage of latissimus dorsi muscles in the context of experimental cardiomyoplasty is due to the combined effects of chronic electrical stimulation, muscle ischemia, and loss of resting tension. Chronic electrical stimulation of skeletal muscles with preserved vascular supply and normal tension causes only a small amount of muscle damage.63

Another undesirable effect of cardiomyoplasty is the disturbing influence of the muscle on the heart, a phenomenon that has been observed both clinically and experimentally. Delahaye et al delineated the borders of human latissimus dorsi using metal clips before the muscle wrap was performed. Fluoroscopic examination in the postoperative period showed that the muscle pulled the inferior and the posterior left ventricular wall upward. Angiographic and radionuclide left ventricular ejection fraction did not improve in these patients. Similar experimental observations were made by Cho et al,57 who used radiofrequency pulse-tagged MRI images to generate three-dimensional reconstructions of the left ventricle throughout the cardiac cycle after cardiomyoplasty. They found that right anterior cardiomyoplasty produced marked translation of the left ventricle in the short-axis plane and rotation and displacement along the long axis. Since the muscle is fixed to the skeleton at one end and to the relatively mobile pericardium and heart at the other, such displacement is not surprising.

The lack of objective hemodynamic effect of cardiomyoplasty is probably multifactorial; however, the most apparent at present are muscle damage, the cardiomyoplasty-induced cardiac displacement.

Various configuration have been proposed as alternatives to the present clinically applied technique pioneered by Carpenter and Chachques. Virtually every technique is claimed to provide greater hemodynamic improvement.49,64-66 None of these procedures, however, deal with the problem of poor muscle preservation in the long term or the improvement of power transfer from the latissimus dorsi muscle to the heart.

Conclusions

SMCA is an attractive therapeutic option for patients with end-stage heart failure. Cardiomyoplasty was introduced as a method of dynamic assistance; it appears that in many patients, the relatively “passive” role of preventing ventricular enlargement may be useful in its own right. Further research efforts must aim to improve current surgical techniques and to preserve the structural and functional integrity of the grafted muscle. Meanwhile, the procedure should be offered only to patients in NYHA class III heart failure and in whom conventional surgical procedures and/or cardiac transplantation are contraindicated.

References


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