

Cardiomyoplasty: To Be or Not To Be? Review and Proposed Multi-Step Approach for Improving Results

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Abstract

Heart transplantation is the best option for surgical treatment of end-stage congestive heart disease. However, when heart transplantation is not possible, other surgical options are available: partial left ventriculectomy, assist devices, plastic cardiac binding, cardiomyoplasty (CMP). All of these operations have advantages and disadvantages and at present there is no consensus as to which one is the best. Below is a new multistep approach for improving cardiomyoplasty results according to our clinical and experimental data. In order to decrease the length of time and extent of damage of the CMP operation one can use a lateral approach to mobilize the LDM and wrap the heart. In order to build long-term fatigue resistance in the LDM of older patients one can increase the length of time of the pre-assist training of the LDM using a more cautious regimen. In order to improve hemodynamic results after muscle conditioning the cardiosynchronization regimen can be changed from 1:2 to 1:4. In order to prolong the period of effective LDM performance the electrical stimulation may be switched off at night or changed to a rate of 1:8-1:16. New cardiomyostimulator LD-PACE II was designed with the capability to program a different regimen for day use than for night use. In order to prevent sudden cardiac death in the patient with severe cardiac arrhythmia it is possible to combine CMP with ICD implantation. In order to implement cardiac assist immediately after CMP it is possible to start with a cautious electrical stimulation regimen (1:16-1:8) just after CMP or to use cardiac assist (work-rest regimen) several hours daily. In order to prevent ischemia-reperfusion damage to the LDM after subtotal mobilization, the LDM can be treated with an application of fibrin sealant with added aprotinin. In order to accelerate both angiogenesis and indirect myocardial revascularization, fibrin sealant enhanced with autologous endothelial cells can be administered between the LDM and the myocardium.

Key words: cardiomyoplasty, multi-step approach, work-rest regimen.

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Hamlet's question, "to be or not to be?" continues to be debated over the place of cardiomyoplasty (CMP) in the surgical treatment of congestive heart failure (CHF). The current shortage in the supply of cardiomyostimulators and consequent impact on ability to perform CMP threatens both further investigation and application of these approaches that could help many patients with New York Heart Association (NYHA) class III heart failure who are not sick enough to be transplanted, but who cannot be managed effectively with medication alone.

Despite significant advances in medical management, profound refractory heart failure is a significant cause of mortality (i.e., death within 5 years of onset). Cardiac transplantation, a routine operation in some clinics

worldwide that can improve the length and quality of life for the recipient, is not always the best solution; there simply are not enough hearts.

Employing the autologous skeletal muscle to assist cardiac function, dynamic CMP offers the potential of eliminating tissue mismatches, organ rejection, and thromboembolic complications. CMP is not donor dependent, is not prohibitively expensive, and it has few of the medical, religious, geographical, or other contraindications that can rule out transplant surgery for some patients.

Chronic Heart Failure

In recent years, the prevalence of chronic heart failure has risen steadily to an estimated 4-5 million people in

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the USA alone with 400,000 new cases presenting annually - an estimated 2,000 new cases per 1.5 million people annually [29].

For patients with NYHA class II or III CHF, modern pharmaceutical support can prolong life expectancy considerably. But for those in NYHA functional class IV, mortality rates increase to 66% at one year and 82% at two years [51]. In patients with new onset heart failure after acute myocardial infarction survival rates are even lower, with only a small minority remaining alive at 5 years [25].

Three key questions about CHF have yet to be resolved:

1. What are the challenges for cardiologists, heart failure specialists, and cardiac and transplant surgeons who manage today's CHF patient?
2. When should medical therapy give way to a surgical option?
3. What support must we have to facilitate CMP in clinical practice?

Cardiac Transplantation Will Not Resolve the Problem

Cardiac transplantation remains the proven therapeutic modality to achieve long-term survival in patients who have end-stage heart failure [34], despite the development of new surgical techniques for the treatment of end-stage heart failure, such as partial left ventriculectomy [44], improved mechanical assist devices [26], cardiomyoplasty [7], and progress in understanding the immunologic mechanisms in xenotransplantation [2].

In a new Stanford University study [52] of 954 transplant patients, 46% survived for 10 years with cyclosporin and monoclonal antibody therapy. In a retrospective analysis of 952 patients undergoing cardiac transplantation, John et al. [34] found that only 43 patients (4.5%) underwent cardiac retransplantation for cardiac failure resulting from transplant-related coronary artery diseases, rejection, and early graft failure.

But the prospect of transplantation proves a false hope for many patients because of the small number of donors and the strict selection criteria for recipients [43]. In the US, each year 25,000 patients are on the waiting list for 2,000 available donor hearts. There must be a better answer for the 23,000 patients who fail to receive a heart yet have a one-year mortality rate of 66%.

Dynamic Cardiomyoplasty: Background

Dynamic CMP is defined as a surgical procedure in which the subtotally mobilized latissimus dorsi muscle (LDM) is wrapped around the heart and trained through low frequency electrical stimulation (ES) to contract in synchrony with cardiac systole, thereby augmenting the ventricular function of a failing heart. This concept is not new: extensive work on cardiac reinforcement had been done previously. In 1933, Leriche [38] performed

experimental adynamic CMP, and, in 1935, Beck [3] used this option for patients with ischemic heart disease. By 1966, Petrovsky [49] reported on his experience of using the diaphragm to repair cardiac aneurysms in 100 patients. However it was not until 1985 that Carpentier [7] in Paris and Magovern [40] in Pittsburgh performed the first successful clinical cases of dynamic CMP. In both instances, skeletal muscle was grafted to a heart and stimulated with a cardiac stimulator to contract in synchrony with the heart.

Overcoming muscle fatigue as an obstacle to stimulation training

Prior to the realization of dynamic CMP, fatigue was a biological constraint that impeded the use of skeletal muscle in helping a failing heart. Skeletal muscle is a better generator of contractile work than is cardiac muscle but tires quickly when worked at a rate similar to that of the heart.

The anatomical structure of the myocardium is an interconnected syncytium, which responds to a single pulse of ES. Skeletal muscle is composed of individual fibers and motor units, which respond to a burst, or train, of pulses and then summates the contractile force [53]. Studies have shown, however, that skeletal muscle can be transformed into a highly fatigue-resistant muscle by using a ES regimen, which is gradually increased over several week's time [54]. After eight weeks of ES, skeletal muscle can be paced at a normal heart rate without fatiguing. The basic mechanism for this process is an alteration in the biochemical substrate that results from changes in gene expression [50].

Skeletal muscle is capable of changing its make-up in response to repeated ES (the conditioning process). Muscle expression is altered, which results in modification of the muscle's synthetic pattern for manufacturing proteins at the molecular level. This protein-processing alteration converts the skeletal muscle from a fast-twitch muscle to a slow-twitch muscle similar to that of cardiac muscle. The muscle also alters its manner of handling calcium, energy metabolism, and contraction. Together these changes result in a skeletal muscle that is more resistant to fatigue and that can contract repeatedly over a prolonged period of time without losing contractile force. Post-conditioning morphological and biochemical analyses have shown that skeletal muscle changes its morphological makeup to be more like that of cardiac muscle. In addition, the muscle's biochemical ability to synthesize the high-energy compounds necessary for these contractions has been altered to be more like that of cardiac muscle [50, 53, 54].

Surgical approach for cardiomyoplasty

Cardiomyoplasty can be performed using either a single-stage or double-stage approach. The double-stage approach, the one most recommended, involves placing the

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patient in a right lateral decubitus position and elevating the left arm. A vertical skin incision is made from the posterior edge of the axillary region to the midpoint of the twelfth rib. The LDM is detached from all insertions while carefully preserving the thoracodorsal neurovascular pedicle. The anterior third of the second rib is removed, creating a window into the chest. Stimulator electrodes are implanted in the muscle, and the muscle flap is transferred into the thorax. Subcutaneous tissue and the skin are then closed. The patient is then placed in a supine position and a median sternotomy is performed. Finally, a posterior heart wrap is performed using the technique perfected by Carpentier [8]. Two stay sutures are placed on the edge of muscle and used to slide the flap behind the heart. The distal stay sutures are secured to the pericardium in front of the inferior vena cava and at the level of the left atrial appendage.

If predominantly right ventricular insufficiency is present, then an anterior wrap technique developed by Magovern [42] is preferred in which the muscle is applied to the right ventricle, and the edge of the muscle is sutured to the pericardial sac as far posteriorly as possible.

Unfortunately, patients do not immediately reap benefits. A two-week delay is necessary prior to beginning ES so that the muscle can re-establish the collateral blood flow lost when it was detached from its insertions. Also during the early phase of muscle transformation only minimal ES is used. As a result, cardiac assistance is also minimal during the first 6 weeks after the procedure.

Stimulation protocol

After the two-week delay, a progressive eight-week protocol is begun: single impulses for the first two weeks, double impulses for the next two weeks, and triple impulses for the next two weeks. A single impulse invokes only moderate muscle contraction, whereas multiple burst impulses (beginning after week eight) produce a stronger muscle contraction. The contraction's duration is physiologically timed to ventricular systole. Initially, there is a 25% stimulation time and a 75% recovery time.

Where Are We Now?

For hundreds of thousands of patients worldwide, pre-end or end-stage CHF means death within one year. Those who live where there are no heart transplantation programs have no hope of receiving a donor heart. Where such programs are active, the chance of receiving a donor heart is slight. Since there is no conclusive answer regarding which surgical option is best, we need to concentrate on alternatives: CMP or partial ventriculotomy. Accepted benefits of dynamic cardiomyoplasty are: improvement in the quality of life, output augmentation, reduction of medical therapy, stabilization of the myocardial wall, and reversal of congestive failure.

During the past 14 years, CMP has been performed more than one thousand times, yet although some believe that it has a potentially low risk with advantageous clinical results and a mortality rate similar to other available means [9], others believe that it has only limited value [56].

Some authors [4, 23, 37, 39, 48] have reported no operative deaths after CMP. The results of Moreira et al. [48] (no deaths after 32 operations) are the most impressive. Some surgeons [22, 27, 43, 45] have reported a 7-14% mortality rate. Data from South America [46] (112 patients; 8%) and from the US [41] (57 patients; 12%) are probably the most realistic. However, we must remember that mortality rates were high early on because most patients had what are now considered contraindications to this procedure. Most of the later data [9] shows no mortality.

Results on late mortality also vary. Some surgeons [4, 22, 24, 46, 57] have reported a mortality rate of 0-10% at 1-5 years follow up. At 8-10 years follow-up, the rate varies from 29 to 38% [4, 11, 47], exceptional results when one considers that these patients had an expected survival of two to three years.

The survival rate for 272 CMP patients in NYHA class II-III was 60% after 3 years compared with 40% in class IV after 2 years. Moreira et al. [46] reported a survival rate of 60% after 54 months for patients in class III or intermittent class IV. Data from the same center [31] showed that patients treated only with medical therapy had considerably worse actuarial survival rates (27%) after 24 months compared with 60% after CMP. Carpentier et al. [6] also reported that after two years of medical treatment only 30% of patients were alive compared with 80% of CMP patients. The one-year survival rate after CMP is 60-86% [32, 33, 43, 46, 47]; the two-year survival rate is 60-87% [6, 31, 32, 47]; the three- to five-year survival rate is 42-71% [6, 46]; and after five to seven years it is 54% [11].

Most CMP patients show improvement in daily activities, mental acuity, and ability to participate in social activities [10]. In all reports [6, 14, 28, 35, 36, 47], NYHA class changed from III or higher (3.0-3.6) to II or lower (1.6-2.0).

Most concern centers on the issue of hemodynamic results after CMP, with some concluding from literature review that there is no significant improvement in hemodynamic status after cardiomyoplasty. It is very difficult, for example, to evaluate the effectiveness of the procedure when there is only slight improvement in LV diastolic volume and stroke volume after five years [10]. Magovern et al. [43] showed that after a short period of improvement, LV ejection fraction and LV diastolic volume reverted to preoperative levels. Moreira et al. [47] also showed that after six months of improvement, ejection fraction slowly reverted to baseline lev-

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els, but only after five years. Conversely, data from Carpentier et al. [6] showed that three years after CMP, LV ejection fraction continued to be greater than before surgery, especially during exercise. It seems that LV ejection fraction is perhaps the better marker of hemodynamic evaluation. Several authors, including a combined study from the US and Canada, reported a 2-6% increase in ejection fraction [4, 28, 35, 55]. Others [5, 6, 14, 30, 32, 33, 36, 39, 43, 47, 57] have reported a 7-16% improvement in LV ejection fraction.

However, for a patient who is highly likely to die from heart failure without treatment, even a stabilization of hemodynamics for several years is a great benefit. Started in September of 1994, a perspective, randomly assigned trial of 103 patients comparing dynamic CMP with medical therapy showed a decrease in operative mortality to only 4% [1], and 79% of CMP patients versus 25% of medical therapy patients improved by one or two NYHA functional classes 6 months after randomization [58].

Multi-Step Approach to Improve Cardiomyoplasty Results

More than 12 years of clinical and experimental investigations in CMP have led us to formulate the following 8-step approach for improving results.

Using a lateral approach for LDM mobilization and cardiomyoplasty [14, 22]

Although CMP is performed more easily through a medial sternotomy, in very sick patients with pre-end stage CHF two large incisions (a lateral incision for muscle mobilization and a medial sternotomy for the heart wrap) may be too much, especially when there is no immediate benefit from the cardiomyoplasty operation. A lateral approach for such patients allows the entire procedure to be performed through a single incision from the axilla to the costal border. After muscle mobilization, the heart wrap is approached through a 4th intercostal space thoracotomy, and the LDM graft is then sutured to the pericardium with two sutures to complete the heart wrap: one near the pulmonary artery and other at the inferior vena cava.

The left anterolateral thoracotomy approach for CMP was first used at the Bakulev Institute of Cardiovascular Surgery in Moscow in 1990. Fourteen patients were followed from six months to three and half years, (mean follow-up 14.6 months). Improvement in clinical status consisted of a decrease in signs of cardiac failure and in the NYHA functional class (from a mean of 3.8 to 2.2). In patients with ischemic heart disease, a decrease in the functional angina class was also noted (from a mean of 4.0 to 2.0). Tolerance to physical exercise doubled (from an average of 41.1 watts to 83.7 watts). LV end systolic volume (evaluated by echocardiography) decreased an average of 18% (from a mean of 222 ± 38 ml to 185 ± 33 ml) and LV end diastolic

volume decreased an average of 15% (from 310 ± 47 ml to 265 ± 38 ml). The LV ejection fraction increased an average of 10%, (from 30 ± 2% to 41 ± 2%), or one-third of the initial value.

ES regimen for elderly patients [13, 20]

In some older patients poor hemodynamic results after CMP may be associated with a lack of response by the skeletal muscle to ES. Clinically, it is important to discern the differences between young adult skeletal muscle and older adult skeletal muscle and to alter the ES protocol for elderly patients. In our study of differences between untrained skeletal muscle in one-year old and eight-year old sheep, we found no statistically significant ($p > 0.05$) differences in fatigue resistance (after 30 minutes of intensive stress testing), in lactate dehydrogenase (LDH) isoenzyme distribution, in the percent area occupied by mitochondria, and or in the number of nuclei and fibers per square millimeter. However we did find that the percent area occupied by muscle fibers was less in the older sheep. With age, connective and fat tissues replace muscle fibers, making muscle transformation using ES more difficult.

The first evidence that older skeletal muscle adapts less well to ES than does younger muscle was a considerable decrease in contractile force after 8 weeks of ES (67 ± 4% in older sheep compared with 81 ± 7% in young sheep). Even though all muscle pays for the acquisition of fatigue resistance with a decrease in force, a considerable loss of contractile force in older muscle is an early predictor of poor cardiac assist in the future. On the other hand, after 8 weeks of ES, the older muscle began to be more fatigue resistant, losing only 14 ± 5% of pre-testing contractile force after a 30-minute fatigue test. At first glance, this seems insignificant when compared with younger skeletal muscle, which lost only 8 ± 2% of its pre-testing contractile force. But after fatigue testing, the older muscle's contractile force 53% was of its pre-training level compared with 73% in younger muscle.

Another important consideration is the alteration of proportions of LDH fractions during transformation from quick-twitch to slow-twitch muscle. The process was slower in older muscle, i.e., a considerably smaller increase in proportions of LDH-1+ and LDH-2 and a smaller decrease in LDH-5.

There was also evidence that the transformation in older muscle is less complete: the number of nuclei per square millimeter in the older muscle was considerably less in completely transformed younger muscle, muscle fiber size decreased, and the number of fibers per square millimeter increased, whereas in older muscle the number of fibers was considerably less (391 ± 43 vs. 560 ± 47), and at least 35% of the older muscle was occupied by connective tissue and fat (that do not contribute to muscle contraction) after ES.

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An important consideration is that the ES protocol designed for healthy, young adult animals should not be employed in very sick, elderly human patients. This disparity may help explain why clinical CMP yields such poor hemodynamic results. Because older muscle transforms less completely and may perform less well in cardiac assist, it is advisable to lengthen the training protocol in older muscle, to use a more cautious training regimen, and to allow the older muscle longer rest periods between contractions after the training period.

Latissimus dorsi muscle rest at night [18, 19]

Because it is an appealing notion to be able to switch off or slow down the contraction rate of the cardiomyostimulator during periods of sleep and rest when a maximal assist effect is not needed, we investigated whether hemodynamic results after CMP were impaired when continuous ES was turned off for 12 hours a day. Using an animal model of chronic heart failure featuring arterial-venous anastomosis and doxorubicin administration and CMP, we found no significant differences between the group that had continuous ES and the one that had ES stopped for 12 hours a day. Hemodynamic measurements taken with the stimulator turned on were virtually the same, showing a heart rate of 126 ± 3 BPM with continuous ES vs. 127 ± 4 BPM with 12 hours of no ES, right atrial pressure of 8 ± 2 mm Hg vs. 9 ± 2 mm Hg, right ventricular pressure of 25 ± 4 mm Hg vs. 26 ± 3 mm Hg, pulmonary capillary wedge pressure of 14 ± 2 mm Hg vs. 14 ± 3 mm Hg, LV ejection fraction of $55 \pm 4\%$ vs. $55 \pm 5\%$, LV end diastolic volume of 21.1 ± 0.9 ml vs. 22.3 ± 0.7 ml, and LV endsystolic volume of 9.4 ± 0.6 ml vs. 9.8 ± 1.0 ml. Thus damage to the LDM after CMP due to continuous ES without rest may be prevented by periodic cessation of stimulation without any impairment in hemodynamic results.

Changing the cardio-synchronization ratio from 1:2 to 1:4 [21]

The process of muscle transformation in older patients with chronic cardiac failure is still not clear, and the risk of muscle damage in such patients is particularly high. Because the conventional cardiosynchronized muscle contraction regimen (1:2 mode) may be too damaging, we have proposed use of a 1:4 synchronization regimen in older patients. In following 10 patients for one to two years after CMP, we found that a 1:4 regimen had better results than the conventional 1:2 regimen: cardiac index was 5.1 ± 1.2 L/min/m² vs. 4.1 ± 0.9 L/min/m² using a 1:2 ratio, cardiac output was 4.7 ± 0.5 L/min vs. 4.5 ± 0.5 L/min, stroke index was 51.0 ± 4.5 mL/m² vs. 47.2 ± 3.8 mL/m². Changing the ES ratio from 1:2 to 1:4 clearly benefits elderly patients and preserves the LDM during long-term conditioning for cardiac assistance.

Partial cardiac assistance immediately after cardiomyoplasty [16]

The traditional ES protocol requires that the LDM not be stimulated for the first two weeks postoperatively (delay period), then be stimulated with one or two impulses every other heart beat for the next four weeks. In an experimental study, we investigated whether the LDM could provide assistance earlier than six weeks postoperatively. No ES was applied to the mobilized LDM in the control animals. In the first experimental series, ES was begun two hours after LDM mobilization using single impulses and 15 contractions per minute. In a second experimental series, ES mimicking cardiac assist (using a work-rest regimen) was added to the protocol twice daily for 30 minutes. In Group II animals (the protocol mimicking cardiac assist) following two successive 30-minute fatigue tests (two hours of rest between tests) using a work-rest regimen (10V, 30 Hz, 20 g/kg preload, 6 impulses per burst, one minute work-one minute rest for 30 minutes), contractile force changed minimally on days 6 ($98 \pm 3\%$), 11 ($100 \pm 2\%$), and 16 ($96 \pm 2\%$). In control animals after the same test, contractile force decreased to $85 \pm 3\%$, $78 \pm 3\%$, and $72 \pm 9\%$ respectively. The usual ischemic state of the post mobilization muscle was not aggravated with the new protocol. The percent area occupied by capillaries increased to $5.04 \pm 0.33\%$ (compared with $3.02 \pm 0.6\%$ in control muscle).

The investigation showed that a slow rate of contraction applied to the LDM immediately after mobilization does not further damage the ischemic muscle, rather it may accelerate the angiogenic response and vascular remodeling. Moreover, vigorous contractions do not damage newly mobilized LDM if used for a short period with at least two hours rest between intervals and a work-rest regimen with a slow rate of contraction. This investigation brings CMP closer to a long-sought goal: ES training beginning immediately after LDM mobilization and CMP, thus providing partial cardiac assistance immediately after surgery if needed.

Combining ICD implantation with CMP [12]

Even with advanced medical management (drug suppression of inducible arrhythmias, including the use of amiodarone), arrhythmic sudden cardiac death remains a major cause of death during long-term CMP follow-up, i.e., a 15-50% risk of recurrent cardiac arrest. By combining the technological knowledge of Medtronic, Inc. with our research expertise and clinical capabilities in electrophysiology, we created a new protocol that combined an implantable cardioverter-defibrillator (ICD) and CMP. Investigations were performed at the Milwaukee Heart Institute in Milwaukee, Wisconsin, in 5 patients with the following three scenarios: 1) ICD implantation soon after CMP, 2) ICD implantation several months after CMP (patients who have developed ventricular tachycardia), or 3) ICD implantation prior to

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CMP. The hemodynamic status of these patients before CMP was considered “borderline” when indications and contraindications for CMP were weighed.

All five patients were re-evaluated 1.5 years after CMP. NYHA functional class in four patients improved considerably (from 3.5 to 2.2) and remained the same in one. Hemodynamic indices showed an increase in LVEF from $16 \pm 3\%$ to $19 \pm 4\%$, an increase in RVEF from $29 \pm 4\%$ to $33 \pm 9\%$, a decrease in LV end diastolic volume from 381 ± 63 ml to 320 ± 56 ml, and a decrease in LV end systolic volume from 309 ± 51 ml to 257 ± 37 ml. There were 87 total episodes of supraventricular tachycardia among the five patients during the follow-up period, 33 of which needed a defibrillator discharge. This means that the added benefit of an ICD implant saved lives many times over.

Applying biological glue with added aprotinin [15]

Perhaps due to ischemia-reperfusion injury to the LDM after mobilization, hemodynamic results of CMP do not support subjective improvements seen clinically. Having tested autologous biological glue (ABG) as a protective layer around traumatized muscle, as a means for facilitating revascularization, and as a drug depot to reduce local ischemia-reperfusion lesions, we wanted to determine if this protective and revascularization effect could be enhanced by adding aprotinin, a natural inhibitor of serine proteinases with the potential for preventing proteolytic degradation. Three different post-mobilization scenarios were investigated: nontreated muscle (control), muscle applied with ABG, and muscle with ABG and added aprotinin. Fifty-six days later muscle biopsies were taken for light microscopy. Analysis revealed that muscle treated with ABG, either alone or with aprotinin, had less leukocyte margination, fibrosis, calcified necrosis, and fibrous degeneration than in controls. In the control muscle (after 56 days) capillaries occupied $3.6 \pm 0.7\%$ of area, and in muscle treated with ABG only, $5.5 \pm 0.2\%$ of area. In muscle treated with ABG and aprotinin, capillary area increased to $8.5 \pm 1.1\%$. This data confirms that aprotinin, when added to ABG, prevents further ischemia-reperfusion lesions after muscle mobilization and enhances capillary ingrowth in ischemic muscle.

Administering biological glue with added endothelial cells between LDM and myocardium [17]

Despite its advantages, CMP has unresolved problems that manifest because vascular supply is not re-established for 6-8 months after the operation: 1) poor angiogenic potential of the ischemic, traumatized skeletal muscle and damaged myocardium post-surgery and 2) incomplete surface-to-surface contact between the mobile myocardial wall and the transplanted muscle flap. CMP can provide capillary ingrowth to the myocardium, but it may be too late for some patients. Because the fibrin meshwork in ABG sufficiently mimics

the extracellular matrix and can support endothelial cell growth, we have proposed and studied the idea of using ABG with added autologous endothelial cells between the heart and the muscle flap for the purpose of revascularizing the ischemic myocardium from the LDM.

After we created a model of chronic myocardial ischemia in sheep by placing an ameroid constrictor around a branch of the circumflex coronary artery, CMP was performed, during which two separate pockets were created between the LDM and the myocardium. In one of the pockets, ABG with endothelial cells was introduced by simultaneously applying two separate solutions of fibrinogen (with endothelial cells) and thrombin between the skeletal muscle and myocardium. As a control, no ABG was introduced in the other pocket. After the operation the typical ES protocol for skeletal muscle training was begun.

After 8 weeks, the muscle flap and the myocardium of the left ventricle were examined. Extremely strong adhesions were noted between the LDM and the myocardium in the pocket where the ABG with endothelial cells had been applied. Histological examination showed new blood vessel growth of significant diameter. Transmission electron microscopy revealed that there were large bore capillaries and arterioles with well-formed endothelial cells. New capillaries were also found in the interlayer between muscle and myocardium. No adhesions had developed in the pocket in which ABG was not used (control pocket). In summary, significant new blood vessel structures are formed and strong adhesions are produced (promoting capillary ingrowth) between the skeletal muscle and the myocardium with the use of ABG with added endothelial cells. This finding may be helpful for patients undergoing CMP.

Conclusion

Based on the positive results of our studies described in this review, we believe that a multi-step approach will greatly improve results of cardiomyoplasty, making it a viable option for patients for whom surgery, including transplantation, is not feasible:

- Decreasing surgical trauma by using a lateral approach for mobilizing the LDM and wrapping the heart;
- Putting the mobilized LDM to work earlier by using a cautious ES regimen that includes beginning with a slow 1:16 cardio-synchronization ratio, changing the ratio from 1:2 to 1:4, and using strategies to rest the heart;
- Providing protection against sudden cardiac death by combining an ICD with CMP;
- Bonding tissues and accelerating both angiogenesis and indirect myocardial revascularization by applying biological glue with added endothelial cells between the LDM and myocardium; and

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- Adding aprotinin to the glue to decrease ischemia-reperfusion lesions and enhance capillary ingrowth in ischemic muscle.

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