Current status of cardiomyoplasty as surgical alternative for end-stage heart failure

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Summary. Heart transplantation is the best option for surgical treatment of end-stage congestive heart failure. However, when heart transplantation is not possible, other surgical options are available, and one of them is cardiomyoplasty. Below is a new multi-step approach for improving cardiomyoplasty results according to our clinical and experimental data. In order to decrease the length of time and damage of cardiomyoplasty operation one can use a lateral approach to mobilize the latissimus dorsi muscle and wrap the heart. In order to receive long-term fatigue resistance in the latissimus dorsi muscle of older patients one can increase the length of time of the pre-assist training of the latissimus dorsi muscle using a more cautious regimen. In order to improve hemodynamic results after muscle conditioning the cardio-synchronization regimen can be changed from 1:2 to 1:4. In order to prolong the period of effective latissimus dorsi muscle performance the electrical stimulation may be switched off at night or changed to a rate of 1:8. New cardiomyostimulator LD-PACE II may be used to change day/night regimen. In order to prevent sudden cardiac death in the patient with severe cardiac arrhythmia it is possible to combine cardiomyoplasty with implantable cardioverter defibrillator (ICD) implantation. In order to implement cardiac assist immediately after cardiomyoplasty it is possible to start with cautious electrical stimulation regimen just after cardiomyoplasty or use cardiac assist in work-rest regimen several hours daily. In order to prevent ischemia-reperfusion damage of latissimus dorsi muscle after subtotal mobilization, the latissimus dorsi muscle can be treated with an application of fibrin sealant with added aprotinin, pyrrolostatin, or deferoxamine. In order to accelerate angiogenesis and indirect myocardial revascularization, fibrin sealant with own endothelial cells can be administrated between the latissimus dorsi muscle and the myocardium.

Despite significant advances in medical management, profound refractory heart failure usually results in death within five years of onset, which makes it a significant mortality risk. Cardiac transplantation, a routine surgery 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. For hundreds of thousands of patients worldwide, pre-end or end-stage congestive heart failure means death within one year. Those who live where there are no heart transplantation programs have no hope of receiving a donor heart. Where there are active transplantation programs, the demand alone leaves little chance of receiving a donor heart for many people. Since there is no conclusive answer regarding which surgical option is best, we need to concentrate on alternatives.
**Chronic heart failure**
In the United States alone, recent data has shown the prevalence of chronic heart failure to rise steadily to an estimated 4–5 million people with 400,000 new cases presenting annually – an estimated 2,000 new cases per 1.5 million people (1). For patients with New York Heart Association (NYHA) functional class II or III congestive heart failure, modern pharmaceutical support can prolong life expectancy considerably. But for those in NYHA functional class IV, mortality risk increases to 82% at two years (2). In patients with new onset heart failure after acute myocardial infarction survival rates are even lower, with only a small minority remaining alive at five years (3).

**Cardiac transplantation will not resolve the problem**
Cardiac transplantation remains the proven therapeutic modality in patients who have end-stage heart failure. In a new Stanford University study of 954 transplant patients, 46% survived for 10 years with cyclosporine and monoclonal antibody therapy (4). In a retrospective analysis of 952 patients undergoing cardiac transplantation, R. John et al (5) found that only 43 patients (4.5%) underwent cardiac re-transplantation 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 (6). 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% (2).

**Dynamic cardiomyoplasty**
**Background**
Dynamic cardiomyoplasty is defined as a surgical procedure in which the subtotally mobilized latissimus dorsi muscle is wrapped around the heart and stimulated 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. 1985 that Carpentier in Paris (7) and Magovern in Pittsburgh (8) performed the first successful clinical cases of dynamic cardiomyoplasty. In both instances, skeletal muscle was grafted to a heart and stimulated with a cardiac stimulator to contract in synchrony with the heart. First cardiomyoplasty in former USSR was performed by A. Dumcius in 1988 (9,10) Since then, cardiomyoplasty has been performed in more than 1000 patients worldwide (11).

**Overcoming muscle fatigue as an obstacle to stimulation training**
Prior to the realization of dynamic cardiomyoplasty, 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 cardiac muscle, but it tires quickly when worked at a rate similar to that of the heart.

Studies have shown, however, that skeletal muscle can be transformed into a highly fatigue-resistant muscle by using a low-frequency electrical stimulation regimen, which is gradually increased over several weeks time (12). After eight weeks of electrical stimulation, 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 (13), 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.

**Surgical approach for cardiomyoplasty**
Cardiomyoplasty can be performed using either a single-stage or double-stage approach. The most recommended single-stage approach involves the detachment of the latissimus dorsi muscle 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. After that, a posterior heart wrap is performed through a medial sternotomy using the technique perfected by A. Carpentier (14). Two stay sutures are placed on the edge of the muscle and used to slide the flap behind the heart. The distal stay suture is 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 G. J. Magovern (15) 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 be-
ginning ES training 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 six 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.

Recently, C. Y. Luo et al (16) showed that even after three-week delay of regional blood flow in the mobilized latissimus dorsi muscle did not revert to baseline. Maybe in the future it will be necessary to increase the delay time to avoid the muscle damage by electrical stimulation.

**How does cardiomyoplasty improve left ventricular function?**

Ventricular function after cardiomyoplasty improves because of two mechanisms: enhancement of left ventricular systolic function by the direct contraction of the wrapped latissimus dorsi muscle, and the elastic girdling effect caused by the muscle participating in chamber remodeling. Evidence of the direct influence of muscle contraction on left ventricular performance has been shown when stimulated and nonstimulated beats were compared (17). Improvement in left ventricular function also led to decreasing ventricular wall stress, and reduction in myocardial oxygen consumption (18). However, other reports demonstrated more significant alterations in diastolic rather than systolic function after cardiomyoplasty (19).

**Where are we now?**

During the past 14 years, cardiomyoplasty has been performed over one thousand times, and it is believed by some that it is potentially low risk with advantageous clinical results and a mortality rate similar to other available means (20). Others believe that it has only limited value (21). During the first ten years, some authors (22, 23) have reported no operative deaths after cardiomyoplasty. The results of L. F. P. Moreira et al (23) (no deaths after 32 operations) are the most impressive. Some surgeons (6, 24) have reported a 7–14% mortality rate. Data from South America (25) (112 patients; 8%) and from the US (26) (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 (20) shows no mortality.

Results on late mortality also vary. Some surgeons (25, 26) have reported a mortality rate of 0–10% at one to five year follow up. At eight to ten year follow-up, the rate varies from 29 to 38% (27). These are very exceptional results when one considers that before cardiomyoplasty, these patients had an expected survival rate of only two to three years.

The survival rate for 272 cardiomyoplasty patients in New York Heart Association (NYHA) functional class II–III was 60% after three years compared with 40% in class IV after two years (25). Patients treated only with medical therapy had considerably worse actuarial survival rates (27–30%) after 24 months compared with 60–80% after cardiomyoplasty (28, 29). The one-year survival rate after cardiomyoplasty is 60–86% (6, 25, 30); the two-year survival rate is 60–87%, (28, 29) the three- to five-year survival rate is 42–71% (25, 29) and after five to seven years it is 54% (27).

Most cardiomyoplasty patients show improvement in daily activities, mental acuity, and the ability to participate in social activities (27). In all reports (24, 25) NYHA class changed from III or higher (3.0–3.6) to II or lower (1.6–2.0). Started in September of 1994, a perspective, randomly assigned trial of 103 patients with an operative mortality of 4% showed functional class six months after randomization of 79 versus 25% in favor of the cardiomyoplasty groups as compared to the medical therapy patients. However this study failed to show statistically significant improvement in survival at one year for the cardiomyoplasty group. The systolic functional data such as ejection fraction and maximal oxygen consumption also were not statistically significantly different (31).

Most concern centers on the issue of hemodynamic results after cardiomyoplasty, with some concluding from literature review that there is no significant improvement in hemodynamic status after cardiomyoplasty. There is also an opinion that the girdling effect of the muscle wrap is the only benefit from cardiomyoplasty. Recently, E. Monnet (32) showed that the girdling effect associated with a myocardial sparing effect together revealed a more preserved myocardial contractile reserve. Clinical results with hemodynamic evaluation after cardiomyoplasty were controversial.
Some authors reported that after a period of improvement, left ventricle ejection fraction and left ventricle end diastolic volume reverted to preoperative levels (6). Conversely, data from A. Carpentier et al. (29) showed that three years after cardiomyoplasty, left ventricle ejection fraction continued to be greater than before surgery especially during exercise. Several authors, including a combined study from the US and Canada, reported a 2–6% increase in ejection fraction (24). Others (6, 29, 33, 34) have reported a 7–20% improvement in left ventricle ejection fraction.

It was from these results that it was reported that left ventricle ejection fraction only increased by 2–16%, and there was no significant improvement in hemodynamics after cardiomyoplasty. If the data truly suggests a non-desirable outcome, then maybe cardiomyoplasty is not an alternative for heart transplantation. However, there is not enough donor hearts available for the all the patients worldwide with pre-end and end-stage heart failure. For these patients who are likely to die from heart failure without a viable treatment option, and for whom heart transplantation is false hope, the slowing of the deterioration of hemodynamics for several years that cardiomyoplasty offers would be a great benefit. So, dynamic cardiomyoplasty remains a promising surgical option for patients with moderate to severe congestive heart failure (35). As L. F. Moreira and A. Leirner concluded in 2001 (36), it does not seem to yet be the time to have dynamic cardiomyoplasty dismissed as only an interesting idea rather than a warranted alternative treatment for patients with advanced cardiomyopathy. J. C. Chachques et al (37) also concluded that cardiomyoplasty could be recommended as an alternative to heart transplantation including patients with large ventricular tumors.

**Multi-step approach to improve cardiomyoplasty results**

**A lateral approach for latissimus dorsi muscle mobilization and cardiomyoplasty**

Although cardiomyoplasty is performed more easily through a medial sternotomy, in very sick patients with pre-end stage congestive heart failure, 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. Furthermore, a minimally invasive approach for dynamic cardiomyoplasty was recently described in which the latissimus dorsi muscle was harvested and the subsequent wrapping procedure was performed using video assistance through small incisions (38).

**Electrical latissimus dorsi muscle prestimulation**

Prestimulation is significantly more effective than vascular delay in preserving distal blood flow. Because it is less invasive and initiates metabolic transformation before muscle mobilization, this technique should allow cardiac assistance to be introduced at an earlier postoperative stage without compromising the viability of the grafted muscle (39). Partial mobilization of the latissimus dorsi muscle performed at the same time as placement of electrodes for preconditioning may better prepare the latissimus dorsi muscle for demands of cardiomyoplasty. Moreover, H. Lammuller, et al (40) advised, that muscle splitting and mobilization followed by vascular delay and in situ conditioning as a concept of muscle prefabrication should be strictly avoided. They also showed that preconditioning of the unaffected latissimus dorsi muscle in situ resulted in a complete muscle fiber transformation with no signs of degeneration or necrosis.

**Electrical stimulation regimen for elderly patients**

In some older patients, poor hemodynamic results after cardiomyoplasty may be associated with a lack of response by the skeletal muscle to electrical stimulation. With age, connective and fat tissues replace muscle fibers, making muscle transformation using electrical stimulation more difficult. Clinically, it is important to discern the differences between young adult skeletal muscle and older adult skeletal muscle and to alter the electrical stimulation protocol for elderly patients. It was shown (41) that after fatigue testing, the older muscle’s contractile force was only 53% of its pre-training level compared with 73% in younger muscle. 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, use a more cautious training regimen, and allow the older muscle longer rest periods between contractions after the training period.

**Latissimus dorsi muscle rest at night (intermittent stimulation)**

It is necessary 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. The damage to the latissimus dorsi...
muscle after cardiomyoplasty due to continuous electrical stimulation without rest may be prevented by periodic cessation of stimulation without any impairment in hemodynamic results (42). It was also shown (43) that intermittent stimulation considerably increases the left ventricular assistance (peak left ventricle pressure, stroke volume, stroke work, and stroke power).

**Changing the cardio-synchronization ratio from 1:2 to 1:4**

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. Skeletal muscle may atrophy and be replaced by fat when stimulation is synchronized to every cardiac beat. Excessive stimulation rates could be detrimental to ventricular contractility (44). As a variant of a slow rate of synchronization, a demand stimulation protocol was introduced in order to avoid complete latissimus dorsi wrap transformation caused by the continuous stimulation protocol, and for homogenizing patient response. The insertion of a rest period during chronic electrical conditioning preserves an area of myofibril cross-section and produces fatigue resistant fiber distributions. Intermediate levels of transformation improved the function of the latissimus dorsi muscle (45).

**Partial cardiac assistance immediately after cardiomyoplasty**

The traditional electrical stimulation protocol requires the latissimus dorsi muscle not to be stimulated for the first two weeks postoperatively (delay period), then to be stimulated with one or two impulses every other heart beat for the next four weeks. It was shown that it is possible to begin electrical stimulation two hours after latissimus dorsi muscle mobilization using single impulses and 15 contractions per minute (46). It is also possible to add to the protocol real muscle contraction in work-rest regimen (twice daily for 30 minutes). The usual ischemic state of the post mobilization muscle was not aggravated with the new protocol. These investigations bring cardiomyoplasty closer to a long-sought goal: electrical stimulation training beginning immediately after latissimus dorsi muscle mobilization and cardiomyoplasty, thus providing partial cardiac assistance immediately after surgery if needed.

**Combining implantable cardiac defibrillator implantation with cardiomyoplasty**

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 cardiomyoplasty follow-up, i.e., a 15–50% risk of recurrent cardiac arrest. Combining placement of an implantable cardiac defibrillator with cardiomyoplasty may be extremely useful for these patients. This combination was performed in five patients at the Milwaukee Heart Institute (47). There were 87 total arrhythmic episodes among the five patients during the follow-up period, 33 of which were ventricular and needed a defibrillator discharge. This means that the added benefit of an implantable cardiac defibrillator implant saved lives many times over.

**Increasing latissimus dorsi angiogenic potential**

Perhaps due to ischemia-reperfusion injury to the latissimus dorsi muscle after mobilization, hemodynamic results of cardiomyoplasty do not support clinically seen subjective improvements. S. M. Carrol et al (48) showed that administration of basic fibroblast growth factor during vascular delay after latissimus dorsi muscle mobilization, augment muscle flap perfusion and function. Autologous biological glue with added aprotinin (natural inhibitor of serine proteinases with the potential for preventing proteolytic degradation) was tested (49). Analysis revealed that muscle treated with autologous biological glue, either alone or with aprotinin, had less leukocyte margination, fibrosis, calcified necrosis, and fibrous degeneration than in controls, and considerable increase in capillarization. Autologous biological glue with added autologous endothelial cells between the heart and the muscle flap for the purpose of revascularizing the ischemic myocardium from the latissimus dorsi muscle was tested (50). After eight weeks, 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 if autologous biological glue was not used (control).

**Extraaortic counterpulsation and skeletal muscle ventricle: progress of cardiomyoplasty?**

Currently new publications the application of skeletal muscle in extraaortic counterpulsation and creation bioassist ventricle model (51–54). Similarly to cardiomyoplasty, extraaortic counterpulsation used the latissimus dorsi muscle to envelope the ascending or descending aorta. Hemodynamic results are roughly equivalent to the intraaortic balloon pump. Skeletal muscle ventricle model is connected to the left ventricle ...
ple apex with a valved conduit and then to the aorta by a second valved conduit (54, 55). This is the most hemodynamically effective skeletal muscle assist device we have tested. At time of implantation, skeletal muscle ventricles stimulated at 33 Hz and in a 1:2 ratio with the heart significantly decreased left ventricular work by 56% (p<01) (Stephenson LW, Wayne State University, Detroit, U.S.A.).

Using the LD PACE II cardiomyostimulator at a 1:2 cardiosynchronization ratio for extra-aortic counterpulsation, we compared continuous stimulation and work-rest stimulation regimens. The best regimen of electrical stimulation employs work-rest and can be started immediately post procedure for up to 100 min of cardiac assist (56, 57).

Conclusions
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 another surgery, including transplantation, is not feasible.

Kardiomioplastika – alternatyvus širdies nepakankamumo chirurginio gydymo metodas

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