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Multicenter Trial of Dynamic Cardiomyoplasty for Chronic Heart Failure

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Objectives. **The purpose of this study was to prospectively assess the effect of dynamic cardiomyoplasty in patients with symptomatic chronic heart failure.**

Background. **Since the first procedure was performed in 1985, dynamic cardiomyoplasty has been developed for use in patients with chronic heart failure. The aging population in developed countries has made heart failure a growing public health concern. Heart transplantation is appropriate or available for only a small proportion of these patients because of limited donor supply. Effective alternatives to transplantation are needed.**

Methods. **Eight centers in North and South America performed 68 cardiomyoplasty procedures between May 1991 and September 1993. Data were prospectively collected every 6 months and compared with preoperative values using paired *t* tests, chi-square tests and actuarial survival analyses.**

Results. **Patients had a mean (±SD) age of 57 ± 1 years and were predominantly male (53 [78%] of 68). Heart failure etiology was classified as idiopathic in 47 (69%) of 68 patients and ischemic in 21 (31%). The in-hospital mortality rate was 12% (8 of 68), and the survival rate at 6 and 12 months was 75 ± 5% and 68 ± 6%, respectively. Objective improvements were seen at 6 months (n = 49) in left ventricular ejection fraction (23 ± 1% vs. 25 ± 1%, p = 0.05), stroke volume (50 ± 2 vs. 56 ± 3 ml/beat, p = 0.02) and left ventricular stroke work index (26 ± 1 vs. 30 ± 2 g/m^2 per beat, p = 0.01). Improvements in mean New York Heart Association functional class (3 ± 0.04 vs. 1.8 ± 0.1, p = 0.0001) and activity of daily living score (59 ± 3 vs. 80 ± 2, p = 0.0001) were also observed. There were no significant changes at 6 months in peak oxygen consumption (15 ± 1 vs. 16 ± 1 ml/kg per min), cardiac index (2.26 ± 0.08 vs. 2.33 ± 0.08 liters/min per m^2), pulmonary capillary wedge pressure (19 ± 2 vs. 18 ± 1 mm Hg) or heart rate (87 ± 2 vs. 82 ± 3 beats/min).**

Conclusions. **These data suggest that dynamic cardiomyoplasty improves ventricular systolic function, reduces symptoms of heart failure and improves objective measures of quality of life in patients with congestive heart failure. This improvement occurred without changes in peak exercise capacity, ventricular filling pressure or actuarial survival.**

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Each year ~400,000 people in the United States are added to the population of 2.3 million patients already diagnosed with heart failure. Approximately 2,300 heart transplantations are performed in the United States annually. Most of the remaining patients are managed with medical therapy. Despite significant advances in the pharmacologic treatment of heart failure, many patients realize little improvement in quality of life or cardiac morbidity, and mortality rates are still high. Adjuvant therapies to enhance the quality of life of these terminally ill patients are still needed. Dynamic cardiomyoplasty is one possible therapy.

Dynamic cardiomyoplasty is a surgical procedure in which a pedicled latissimus dorsi muscle flap is transposed into the chest and wrapped around the ventricles of a failing heart. The muscle flap is then electrically stimulated to contract in synchrony with ventricular systole. Latissimus dorsi muscle stimulation is incrementally increased over a period of 10 weeks, causing gradual transformation of muscle fibers from Type II (anaerobic, fatigue prone) to Type I (aerobic, fatigue resistant) fibers.

Clinical dynamic cardiomyoplasty is the result of >50 years of scientific advancements in our understanding of anatomy, muscle physiology and microcircuit technology. In the 1930s, several surgeons began experimenting with skeletal muscle repair of the heart (1–3). In the 1950s, Kantrowitz and McKinnon (4) stimulated diaphragm muscle wrapped around the aorta and demonstrated increased blood flow for a short period before muscle fatigue. In the 1960s, independent efforts in Europe by Termet et al. (5) and in the United States by Hume (6) led to the use of electrically stimulated latissimus dorsi wrapped around the heart. Meanwhile, Buller et al. (7) used cross-innervation studies to demonstrate that muscles could be transformed from "fast-twitch" fatigable to "slow-twitch" fatigue-resistant fibers. In the 1970s, Salmons and

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Streter (8) showed that this same muscle transformation could be accomplished using electrical stimulation. Macoviak et al. (9) experimentally applied this concept using single-pulse stimulation of the diaphragmatic pedicle graft to the heart in laboratory animals. DeWar and Chiu (10) later incorporated the concept that multiple, sequential electrical pulses (a "pulse-train") greatly increased muscle recruitment and power, and they worked with Medtronic, Inc. to develop an external cardiomyostimulator for use in the procedure. These advancements culminated in the first clinical application of dynamic cardiomyoplasty in 1985 in Paris, France by Carpentier and Chachques (11) using a fully implantable system.

Between 1985 and 1991, ~185 cardiomyoplasty procedures were performed in 17 countries worldwide. Reports published during this period documented significant, subjective, clinical improvements; objective improvements were inconsistently noted or were often not reproduced (12–16). The present study, approved by the U.S. Food and Drug Administration (FDA), was designed to more objectively quantify the efficacy of dynamic cardiomyoplasty.

Methods

Study organization. The FDA-approved Phase II study was conducted at five U.S. centers, two Canadian centers and one Brazilian center (see Appendix). Data were collected and analyzed centrally. A steering committee, consisting of principal investigators from each center, developed and implemented the protocol. A clinical events review committee, consisting of investigators and independent consultants, evaluated all deaths and monitored the progress of the study. The study was approved by the institutional review boards of each hospital, and the patients gave written informed consent.

Patient eligibility. Patients were eligible for the study if they 1) had heart failure due to dilated cardiomyopathy or ischemic heart disease that had not improved despite attempts to optimize drug therapy; 2) were in New York Heart Association functional class III; 3) had left ventricular ejection fraction (LVEF) by radionuclide ventriculography <40%; 4) had left ventricular end-diastolic pressure or pulmonary capillary wedge pressure ≥15 mm Hg; and 5) had an intact latissimus dorsi muscle.

Patients were excluded from the study if they 1) were <18 or >80 years old; 2) had arrhythmias requiring a pacemaker or implantable cardioverter-defibrillator; 3) had poor lung function with forced vital capacity <55% of predicted value; 4) were dependent on intravenous inotropes; 5) had a life-threatening noncardiac disease; 6) had creatinine clearance <30 ml/min; or 7) had unresolved drug or alcohol abuse.

Study protocol. Patients underwent dynamic cardiomyoplasty as a single-stage procedure in which the left latissimus dorsi muscle was wrapped around the heart in a posterior cardiocostal or cardiosubcutaneous fashion (17). A variance in operative technique was allowed for 13 patients treated with right latissimus anterior cardiocostal myoplasty (17) at a single center. Analyses comparing the right and left latissimus cardiomyoplasty subgroups showed no clinically relevant preoperative or postoperative differences. Therefore, the two groups were combined for these analyses.

Ten-week muscle stimulation protocol was designed to gradually transform the latissimus dorsi from Type II to Type I fatigue-resistant muscle. Details of the surgical and latissimus dorsi stimulation techniques have been described elsewhere (18–20).

Every 6 months postoperatively the patients repeated the following preoperative tests: radionuclide ventriculography, right heart catheterization, respiratory gas exchange with concomitant exercise testing, chest X-ray film, 12-lead electrocardiogram, 24-h Holter monitor, functional class and a quality of life questionnaire (21). In addition to results of these tests, investigators also reported medications, complications and hospital admissions during each evaluation period.

Each center in the study was also asked to enroll nonrandomized, medically treated reference patients from their medically treated heart failure population with the following characteristics: heart failure due to dilated cardiomyopathy or ischemic heart disease; functional class III; LVEF by radionuclide ventriculography <40%; age between 18 and 80 years. These patients were assessed at 6-month intervals using the same quality of life questionnaire and were likewise followed up with respect to survival, hospital admission rate, functional class and medication use.

Statistical analysis. Data were analyzed using SAS software. There were no statistical adjustments for multiple testing. Paired *t* tests were used to test improvement in continuous variables over time. Two-sample *t* tests were used to compare the treatment and reference group baseline characteristics and improvements over time. The Fisher exact and chi-square tests were used on dichotomous and polychotomous variables, respectively. Survival curves were produced using the actuarial (life table) method and compared by the Mantel-Haenszel test.

Results

Patients. Sixty-eight patients underwent dynamic cardiomyoplasty between May 1991 and September 1993. The patients were 56.6 ± 1.4 years old, and were predominantly male (78%). The etiology of heart failure was classified as idiopathic in 47 (69%) and ischemic in 21 (31%). Their mean functional class was 3.00 ± 0.03, and mean duration of heart failure symptoms was 3.6 years. A history of arrhythmias was reported in 36 patients (53%), and atrial fibrillation was present in 13 (19%). At the time of enrollment, all patients were receiving digoxin and diuretic drugs, and 61 (90%) were taking angiotensin-converting enzyme inhibitors. Other vasodilators were used in place of angiotensin-converting enzyme inhibitors in three of the remaining seven patients. Fourteen patients (21%) received long-term antiarrhythmic therapy.

Table 1 details the preoperative measurements of cardiac performance and exercise tolerance for all 68 postoperative patients. Left ventricular ejection fraction by radionuclide ventriculography was 21.9 ± 0.8%. Baseline cardiac index was

Table 1. Preoperative Measurements of Cardiac Performance and Exercise Tolerance in 68 Study Patients

	Mean ± SE
Functional assessment	
NYHA	3.00 ± 0.03
Peak $\dot{V}O_2$ (ml/kg per min)	14.8 ± 0.6
Radionuclide measures	
LVEF (%)	21.9 ± 0.8
RVEF (%)	40.9 ± 2.4
Hemodynamic measures	
HR (beats/min)	85.7 ± 1.7
CI (liters/min per m^2)	2.26 ± 0.06
LVEDP (mm Hg)	22.1 ± 1.1
PCWP (mm Hg)	20.1 ± 1.1
MPAP (mm Hg)	29.6 ± 1.3
SV (ml/beat)	52.0 ± 1.9
LVSWI (g·m/m^2 per beat)	24.6 ± 1.3

CI = cardiac index; HR = heart rate; LVEDP = left ventricular end-diastolic pressure; LVEF = left ventricular ejection fraction; LVSWI = left ventricular stroke work index; MPAP = mean pulmonary artery pressure; NYHA = New York Heart Association functional class; PCWP = pulmonary capillary wedge pressure; RVEF = right ventricular ejection fraction; SV = stroke volume; $\dot{V}O_2$ = oxygen uptake.

2.26 ± 0.06 liters/min per m^2, with a concomitant pulmonary capillary wedge pressure of 20.1 ± 1.1 mm Hg. Peak oxygen consumption during exercise testing was 14.8 ± 0.6 ml/kg per min.

Table 2 compares the patients who underwent dynamic cardiomyoplasty with the reference patients.

Operative data. Of the 68 patients who underwent dynamic cardiomyoplasty, 3 had a concomitant surgical procedure (coronary artery bypass grafting in 2, mitral valve repair in 1). The postoperative mortality rate was 12% (8 of 68), and death occurred at a median of 11 days. Causes of death included primary cardiac failure (6 patients), aspiration pneumonia (1 patient) and sepsis (1 patient).

Table 2. Preoperative Demographic and Quality of Life Scores for Patients Undergoing Cardiomyoplasty and Reference Patients

	Cardiomyoplasty Group (n = 68)	Reference Group (n = 58)	p Value
Age (yr)	56.6 ± 1.4	57.0 ± 1.3	0.85
Male	78%	78%	1.00
Etiology			0.53
Ischemic	31%	36%	
Idiopathic	69%	64%	
NYHA	3.00 ± 0.03	2.98 ± 0.0	0.42
LVEF	21.9 ± 0.8	20.2 ± 0.9	0.18
Quality of life scores			
ADL	59.4 ± 2.4	64.4 ± 3.2	0.20
Social activity	46.0 ± 4.1	52.7 ± 4.9	0.29
Quality of interaction	76.4 ± 2.5	76.1 ± 2.3	0.93
Mental health	67.2 ± 2.5	67.3 ± 2.9	0.97

Data presented are mean value ± SE or percent of patients. ADL = basic activities of daily living; other abbreviations as in Table 1.

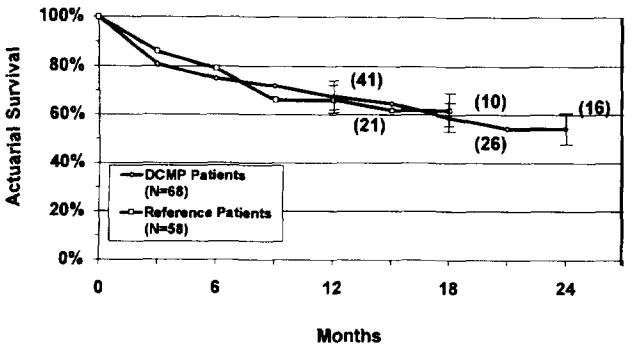

Figure 1. Actuarial survival curve for the 68 patients undergoing cardiomyoplasty versus 58 reference patients drawn from seven of the eight investigation sites. DCMP = dynamic cardiomyoplasty.

A total of 13 additional patients (13 [19%] of 68) experienced one or more major, nonfatal postoperative complications (20 complications in total). Four patients (4 [6%] of 68) developed severe hemodynamic deterioration requiring insertion of an intraaortic balloon pump. One of these four patients failed to hemodynamically recover and underwent successful cardiac transplantation at 1.4 months postoperatively. Seven patients (7 [10%] of 68) required prolonged mechanical ventilation or reintubation. Six patients (6 [9%] of 68) required defibrillation, cardioversion or overdrive pacing. Two patients (2 [3%] of 68) required dialysis, and one (1 [1%] of 68) developed sepsis.

Six- and 12-month evaluation. Figure 1 depicts the actuarial survival curve for the 68 postoperative patients compared with 58 reference patients over a 2-year period. There was no significant difference in survival between the treatment and reference groups at any time point during the 12-month evaluation period.

Measurements of cardiac performance and exercise capacity for the surviving patients are shown in Table 3. Significant improvements were seen in LVEF by radionuclide ventriculography, stroke volume and left ventricular stroke work index at 6 and 12 months. By 12 months, heart rate was also significantly lower. Subjective assessment tools also indicated a significant improvement in heart failure symptoms; functional class significantly decreased, and the basic activities of daily living score increased. This was, likewise, a persistent finding through the first 12 months. There was no change in peak aerobic capacity as measured by peak oxygen consumption.

Discussion

Study rationale. To our knowledge, this report represents the results of the first multicenter study designed to investigate the short and long-term effects of dynamic cardiomyoplasty in patients with chronic heart failure. Earlier experience at single institutions has helped to define patient selection and operative technique. In 1991, Grandjean et al. (12) reported on 78 patients operated on between 1985 and 1990, 46% of whom had functional class IV heart failure. Twelve percent of

Table 3. Postoperative Measures of Cardiac Performance and Exercise Tolerance

	12-Month Comparison			6-Month Comparison		
	No. of Pts	Preop (mean ± SE)	12 mo (mean ± SE)	No. of Pts	Preop (mean ± SE)	6 mo (mean ± SE)
Functional assessment						
NYHA	32	3.0 ± 0.1	1.7 ± 0.1*	49	3.0 ± 0.04	1.8 ± 0.1*
Peak $\dot{V}O_2$ (ml/kg per min)	29	15.8 ± 0.8	16.0 ± 1.1	44	15.4 ± 0.7	15.8 ± 0.9
Radionuclide measures						
LVEF (%)	31	22.7 ± 1.0	25.5 ± 1.9*	49	22.7 ± 0.9	24.6 ± 1.3*
RVEF (%)	24	40.3 ± 3.9	40.8 ± 3.9	42	40.9 ± 3.0	41.3 ± 3.0
Hemodynamic measures						
HR (beats/min)	23	87.2 ± 2.8	79.1 ± 3.3*	41	86.6 ± 2.0	82.2 ± 2.7
CI (liters/min per m^2)	31	2.26 ± 0.1	2.37 ± 0.1	46	2.26 ± 0.1	2.33 ± 0.1
PCWP (mm Hg)	22	19.2 ± 1.9	20.4 ± 1.5	41	19.0 ± 1.5	18.1 ± 1.3
MPAP (mm Hg)	31	28.8 ± 1.8	32.0 ± 1.8*	47	27.6 ± 1.5	27.8 ± 1.4
SV (ml/beat)	31	48.2 ± 2.4	56.9 ± 3.6*	45	50.0 ± 2.3	55.7 ± 2.9*
LVSWI (g·m/m^2 per beat)	23	25.0 ± 1.7	31.8 ± 2.9*	41	25.8 ± 1.5	30.0 ± 1.8*

*$p \leq 0.05$ versus preoperative (Preop) values; Bonferroni's correction was not applied. Pts = patients; other abbreviations as in Table 1.

patients in functional class III and 33% of those in class IV died during the initial hospital stay. Notwithstanding, functional status improvement was observed in 85% of the surviving patients despite the investigators' inability to demonstrate salutary hemodynamic changes. In contrast, Moreira et al. (22,23), from Sao Paulo, Brazil, have consistently detailed hemodynamic improvement. Moreover, they have shown (15) significant and beneficial changes in exercise tolerance, as well as survival, in a nonrandomized trial. Carpentier et al. (24) published a review of their 52-patient experience, citing an early mortality rate of 54% during 1985 to 1987 and 12% during 1988 to 1992, with a late mortality rate of 20%. A subset of patients showed an improved LVEF, but no change in cardiac filling pressure; functional class was markedly enhanced in the survivors. Thus, at the onset of the present study, investigators worldwide had noted a prohibitively high mortality rate in functional class IV patients. This finding was frustrating in light of the fact that these same patients were the most likely to benefit from the procedure. However, because a safe clarification of the effects of cardiomyoplasty on cardiac performance and quality of life, including exercise tolerance was needed, the present multicenter trial was restricted to patients with functional class III heart failure.

The present study involved 68 patients who entered into a protocol that was similarly followed by investigators at eight institutions. Patients were, by selection, somewhat less hemodynamically compromised than those in previous studies and had moderately severe heart failure, as evidenced by an LVEF of 21.9 ± 0.8% and a peak oxygen uptake of 14.8 ± 0.6 ml/kg per min. Correspondingly, the in-hospital mortality rate was lower at 12%. Some measurements of cardiac performance indicated significant improvement, including a sustained increase in LVEF and augmentation of stroke volume and stroke work index. Perhaps more important, an objective assessment of quality of life suggested a significant lessening of heart failure symptoms, with a simultaneous enhancement of well-being.

Study significance. The clinical significance of these results should be determined by the same criteria that are used to judge the efficacy of heart failure therapy. The view that the syndrome of congestive heart failure secondary to dilated cardiomyopathy is primarily one of central hemodynamic abnormalities has evolved in the past decade (25). Earlier efforts to improve cardiovascular hemodynamic variables at rest did not always result in a reduction of patient symptoms (26). Subsequently it was thought that a therapeutic agent must improve cardiovascular hemodynamic variables not only at rest but also during exertion for the agent to have a meaningful effect (27). However, multiple drugs failed to effect sustained clinical benefit during large-scale, controlled trials (28). The current hypothesis argues that hemodynamic alterations are not the only pathophysiologic abnormality in heart failure that must be corrected for a therapeutic agent to be successful. Alterations in skeletal muscle metabolism, local vascular tone, respiratory muscle function and neurohormonal responses must all be normalized.

How, then, should a therapy for heart failure be judged? Perhaps most important, definitive trials must be undertaken in a placebo-controlled or case-controlled, randomized manner (29), which was not done in the present study. One valid criticism of the present study might be the nonrandomized nature of our control group. In addition, other factors not easily accounted for may make the treatment and reference groups noncomparable. Accordingly, a randomized trial design is currently under way for the cardiomyoplasty procedure.

In addition to definitive controlled trials, multiple end points must be analyzed. Patient symptoms, often legion in heart failure, can be chronicled subjectively and objectively. An accurate measurement of aerobic capacity, the peak oxygen uptake has been shown to reflect hemodynamic status (30) and predict clinical stability (31) and survival (32) in patients with heart failure. Measurement of LVEF has become routine in heart failure trials, although it has infrequently been shown to improve (33,34). However, improvement in LVEF, when it has

occurred, has correlated with improved survival (33,34). Finally, and ultimately, survival of the patient with heart failure must be prolonged if a therapeutic approach is to be judged efficacious.

Using these criteria, the cardiomyoplasty procedure was an effective therapy for the patients in the present study. Patients undergoing cardiomyoplasty had reduced symptoms and an improved LVEF. Peak oxygen uptake, although not improved, was maintained for at least 1 year. Survival was not measured against a randomized, control cohort but was as good as a reference group collected at the investigating centers. These data certainly complement an earlier study showing enhanced survival (15).

Mechanistic hypotheses. If dynamic cardiomyoplasty is a beneficial therapy for patients with chronic heart failure, which of the potential mechanisms of action are responsible for the benefit observed? Various hypotheses have been suggested. Lee et al. (35) proposed that the muscle wrap acts to reduce left ventricular wall stress and thereby augments myocardial shortening. Capouya et al. (36), as well as Mott et al. (37), suggested that the procedure serves to halt progressive left ventricular dilation. Both proposals would be consistent with the observed data (i.e., little change in cardiac filling pressures but alterations in volume–pressure relation and stability of exercise tolerance). Single-center reports also support these concepts. In the largest single-center series to date, Carpentier et al. (24) reported a stable cardiothoracic ratio up to 3 years after cardiomyoplasty. Moreira et al. (38) reported clinical evidence of reduced wall stress, reduced left ventricular chamber stiffness and increased left ventricular maximal elastance after cardiomyoplasty. Kass et al. (39) reported a striking clinical benefit associated with reverse chamber remodeling in three case studies using pressure–volume analysis.

Some researchers have shown (22,23,40,41) that a loss of muscle integrity in the cardiomyoplasty flap correlates with a lack of hemodynamic efficacy, underscoring the importance of this central mechanism for the procedure. Ongoing research is addressing long-term muscle optimization (42–45). Also relating to latissimus dorsi contribution, several reports (46–51) have been recently published on the ability of optimal stimulation timing to significantly improve outcome in cardiomyoplasty.

Patient selection. As with any new operative procedure, considerable exploration into proper patient selection must be undertaken, both to reduce surgical risk and to improve long-term outcome (52). A better understanding of surgical risk in cardiomyoplasty is emerging from several single-center publications (13,22,23,37,53–55) and multicenter analyses (56,57); the largest multicenter report to date (57) with a total of 166 patients includes the 68 patients from the present report. With regard to long-term outcomes, it is possible that a certain stage of heart failure may be altered more successfully by cardiomyoplasty. Alternatively, dynamic cardiomyoplasty may be most efficacious when used in conjunction with concomitant surgical procedures, such as high risk coronary bypass procedures or repair of regurgitant lesions. Many of these issues remain unresolved.

Conclusions. Dynamic cardiomyoplasty may improve symptoms and cardiac performance in patients with chronic heart failure. Operative techniques have been refined, and optimal patient selection has resulted in decreased hospital mortality. The ultimate role of this procedure for the thousands of patients with dilated cardiomyopathy awaits the results of the current case-controlled, randomized trial.

Appendix

Participating Centers and Investigators

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