Passive Containment and Reverse Remodeling by a Novel Textile Cardiac Support Device

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Background—Progressive remodeling and dilation of cardiac chambers is responsible in part for myocardial dysfunction in chronic heart failure. Preclinical studies with suitable animal models indicate that a passive cardiac constraint device can promote reverse remodeling, with improvement in cardiac function. We hypothesize that such a device could provide benefit for stable heart failure patients in New York Heart Association (NYHA) class II and III.

Methods and Results—From April 1999 to March 2000, 27 patients received Acorn’s Cardiac Support Device (CSD) during an initial safety/feasibility study. In 11 patients, the only surgical measure was CSD placement. Most patients suffered from idiopathic cardiomyopathy; 4 were in NYHA class II, one was in class II/III, and 6 were in class III. All were stable on intensive medical treatment. The CSD, a textile polyester device, was fitted snugly around the heart during surgery. All patients survived surgery and recovered smoothly. Three months after surgery, 56% of patients were in NYHA class I, 33% were in class II, and 11% were in class II/III. Echocardiography showed an improvement in left ventricular ejection fraction from an average of 22% to 28% and 33% at 3 and 6 months, respectively. Simultaneously, the left ventricular end-diastolic dimension decreased from 74 mm to 68 mm and 65 mm, respectively. Mitral valve regurgitation (on a scale of 0 to 4+) decreased from 1.3 to 0.7 by 3 months. Quality-of-life indices correlated with the apparent reversal of ventricular remodeling. Preoperative cardiac medications remained virtually unchanged after implant.

Conclusions—In the short- and intermediate-term, CSD implantation seems to ameliorate symptoms and improve cardiac and functional performance in heart failure patients. Worldwide randomized trials are currently underway. (Circulation. 2001;104[ suppl I]:I-270-I-275.)

Key Words: cardiomyopathy ■ heart-assist device ■ heart failure ■ remodeling

Heart failure is a progressive disease characterized by increasing left ventricular dilation and cardiac dysfunction. The initiating cardiac injury may be due to a variety of causes, including myocardial infarction, infection, or an idiopathic cause. Early compensatory mechanisms such as ventricular dilation and neurohormonal activation are thought to restore adequate cardiac output and tissue perfusion. However, the long-term influence of these mechanisms leads to progressive deterioration in myocardial structure and function, which is known as ventricular remodeling. The remodeling process continues, with worsening cardiac function, until end-stage heart failure is reached.

Pharmaceutical therapy for heart failure has recently focused on treating the remodeling process, not just the relief of patient symptoms. New devices and surgical therapies have also been developed to halt ventricular remodeling and complement pharmacological heart failure therapy. One new surgical means is ventricular volume containment, as provided by the Cardiac Support Device (CSD), a mesh-like device surgically positioned around the heart to provide end-diastolic ventricular support. The device is intended to reduce wall stress and myocyte overstretch during end-diastole and periodic volume overload conditions. Thus, by limiting or reducing these key remodeling stimuli, the remodeling process may be halted or reversed.

Preclinical studies have demonstrated that passive ventricular containment with a CSD halts progressive ventricular remodeling. In these studies, which used various heart failure models and degrees of heart failure, results showed that the CSD prevented further ventricular dilation and promoted improvements in cardiac function. Further studies showed improvements in myocyte function and structure, as characterized by enhanced myocyte contraction and relaxation, decreased myocyte hypertrophy, and less interstitial fibrosis in the CSD-treated animals compared with controls. Biochemical analysis revealed downregulation of cell stretch receptor proteins, which are promoters of hypertrophy, and improved calcium handling within the sarcoplasmic reticu-
lum.7 These changes are clear indicators of reverse remodeling. No adverse events or safety issues were identified in these preclinical studies.

The current clinical study was undertaken to examine the safety and potential efficacy of passive ventricular containment using the CSD in patients suffering from dilated cardiomyopathy.

Methods

Patient Selection

From April 1999 to March 2000, the CSD (Acorn Cardiovascular, Inc) was implanted in a series of 27 patients with idiopathic or ischemic dilated cardiomyopathy in a nonrandomized safety study. The study protocol had been approved by the institutional review committee, and all patients provided informed consent before study enrollment. Sixteen of these patients received concomitant cardiac surgery, principally mitral valve repair or replacement. The remaining 11 patients received the CSD with no additional surgery (CSD-only), and they form the basis for this report. Patients enrolled in the study were in New York Heart Association (NYHA) class III, early class IV, or class II (only if they had had a history of at least one NYHA class III/IV episode). A left ventricular end-diastolic dimension of 60 mm, as based on echocardiographic measurements, was also an inclusion criterion. Patients were on stable drug therapy at the time of enrollment in this study. Candidate patients were excluded if they had patent coronary artery bypass grafts or severe adhesions from previous cardiac surgery, uncontrolled hypertension, arrhythmias, systemic disease (renal, hepatic, or pulmonary dysfunction), hypertrophic obstructive cardiomyopathy, pregnancy, or an estimated survival <1 year.

Device Implantation

Figure 1 illustrates the CSD implantation procedure. A standard sternotomy was used in all surgeries. After pericardiotomy, the patient was prepared for cardiopulmonary bypass, although cross-clamping was not actually used during surgery on any patient in the CSD-only patient group. Cardiopulmonary bypass was used in these initial patients to facilitate lifting the heart to place the posterior tacking sutures without the concern of hemodynamic compromise. The heart size was measured (apex to base and circumference) to select a CSD of proper size. The CSD was provided in 6 different sizes, with the final fit being accomplished by the surgeon. The CSD was positioned on the heart, with the device’s hemline positioned adjacent to or just above the atrioventricular groove. The device was stabilized in position by the application of interrupted tacking sutures at several places along the hemline, starting on the posterior surface. Care was taken to avoid compromising any epicardial coronary artery. After posterior stabilization of the device was achieved, custom fitting was accomplished by gathering and removing excess fabric from the anterior surface. Transesophageal echocardiography was used intraoperatively to monitor the fitting process. The CSD was adjusted with the goal of producing a short-term reduction of up to 10% in end-diastolic dimension, as based on transesophageal echocardiographic measurements, without evidence of hemodynamic compromise. Heart rate and rhythm, pressures (systemic, pulmonary, right atrial or central venous, and wedge), and cardiac output were monitored while fitting the CSD and throughout the entire implant procedure. In addition to heart size, left ventricular ejection fraction and mitral regurgitation were monitored while fitting the CSD and throughout the entire implant procedure. In addition to heart size, left ventricular ejection fraction and mitral regurgitation were monitored while fitting the CSD and throughout the entire implant procedure. In addition to heart size, left ventricular ejection fraction and mitral regurgitation were monitored while fitting the CSD and throughout the entire implant procedure.

Patient Follow-Up

Evaluations before and after surgery included measurements of heart size, ejection fraction, and the extent of mitral valve regurgitation by echocardiography, as well as maximal exercise testing, including recordings of blood pressure, and heart rate/rhythm by electrocardiography. Cardiac functional status was assessed using the Minnesota Living with Heart Failure6 and Uniscale7 questionnaires. Assessments were also scheduled for 3 and 6 months after surgery, with optional ongoing evaluations every 6 months. In addition, all adverse events were documented.

Statistical Analysis

Parametric data were analyzed using 2-tailed Student’s t tests on paired samples. Nonparametric data, which included estimates of NYHA class, mitral valve regurgitation, and quality-of-life indices were analyzed using the Wilcoxon signed-rank test. Statistical significance was defined as $P=0.05$. All data are expressed as mean±SE.

Results

Preoperative Evaluation

Table 1 summarizes the presurgical profile of CSD-only patients enrolled in this series. The patient group consisted of
10 men and one woman aged 37 to 71 years at surgery (mean, 55.9±3.2 years). The primary cause of heart failure was idiopathic cardiomyopathy (10 of 11 patients), but one patient had a history of anterior myocardial infarction. Patients had a heart failure duration averaging 3.7 years. All patients enrolled were in NYHA functional class III or IV or had experienced at least one episode of NYHA functional class III or IV. At the time of surgery, patients were in NYHA functional class II (n=4), class II/III (n=1) or class III (n=6). All had been on a stable cardiac medication regimen for at least 1 month before CSD implantation: 100% were on ACE inhibitors, diuretics, and digoxin; 81% on β-blockers; and 54% on additional cardiac medications.

Additional presurgical test parameters of the group were characteristic of progressive dilated cardiomyopathy, including a relatively large left ventricular end-diastolic dimension (range, 64 to 86 mm), a limited left ventricular ejection fraction (range, 13% to 28%), and a compromised peak oxygen consumption during exercise (average, 13.8±1.2 mL kg⁻¹ min⁻¹). Additional characteristics included general evidence of mitral valve regurgitation (10 of 11 patients; range, 1 to 3 on a scale of 0 to 4), and an average pulmonary capillary wedge pressure of 21.4±3.0 mm Hg.

### Surgery
The total time required for surgical implantation of the CSD was similar to conventional cardiac surgery, requiring an average of 2.2±0.2 hours of skin-to-skin time during a total anesthesia time of 3.3±0.2 hours. Patients were placed on instrumentation for cardiopulmonary bypass for an average of 24.8±1.2 minutes, during which time the CSD was implanted. Cross-clamp time was zero for all patients. An average of 10.3±0.4 tacking sutures were used to stabilize the CSD on the hearts of patients in this series. The average distance between sutures was 3.5±2.0 cm.

### Adverse Events and Patient Survival
All CSD-only patients enrolled in this series recovered from surgery and were released from the hospital. During the course of hospitalization, 4 of the 11 patients experienced adverse events (none was device-related), which included arrhythmia requiring cardioversion, compromise of renal function requiring hemofiltration or hemodialysis, and/or pulmonary compromise requiring puncture and drainage. After initial hospitalization, 5 of the 11 patients experienced adverse events, including 2 deaths (none was device-related) during an average follow-up of 12.2±1.1 months. One patient died at home during the night in the context of decompen-sated heart failure after refusing readmission for medication adjustments (this patient had also received a pacemaker 2 months after CSD implantation). Another patient died 7 months postoperatively of pneumonia (this patient had also received an implantable cardiac defibrillator 3.5 months after CSD implantation). Other adverse events included cardiac defibrillator implantation, diagnosis of lung cancer, and a car accident. No adverse event during or after initial hospitalization was considered device-related by an independent Safety Review Board.

### Follow-Up
Paired data reflecting changes in various test parameters for CSD-only patients over the period of 3 and 6 months after implantation of the CSD are shown in Table 2. Parametric indices, including left ventricular end-diastolic dimension (74.0±2.1 mm before implantation versus 68.4±1.6 mm at follow-up) and ejection fraction (21.7±1.5% before implantation versus 27.6±3.2% at follow-up), showed significant changes at 3 months after CSD implantation (P<0.02 and P<0.04, respectively). Figure 2 represents the changes in left ventricular end-diastolic dimension and ejection fraction, expressed as percentages, after CSD implantation.

Nonparametric indices, including estimates of mitral valve regurgitation (1.3±0.3 before implantation versus 0.7±0.2 at follow-up) and NYHA functional class (2.5±0.2 before implantation versus 1.6±0.2 at follow-up), also showed significant changes (P=0.05 and P=0.005, respectively) at 3 months of follow-up. The changes noted in left ventricular end-diastolic dimension, left ventricular ejection fraction, valve regurgitation, and NYHA functional class suggest a potential for improvement in cardiac structure and function after CSD implantation. Similar trends for improvement are indicated at 6 months of follow-up as well, although only the changes in ejection fraction (21.6±1.6% versus 32.8±4.9%, P<0.04) and NYHA functional class (2.5±0.2 versus 1.7±0.2, P=0.025) were significant.

Maximal exercise testing indicated that peak oxygen consumption was maintained at 3 months of follow-up compared with values before implantation, and it increased at 6 months of follow-up, although this change did not reach statistical significance. Blood pressure values did not change significantly during the course of follow-up. Heart rate, however, seemed unchanged at 3 months but showed a significant decrease (P<0.05) at 6 months. Results obtained from the Minnesota Living with Heart Failure and Uniscale questionnaires both indicated an overall improvement in quality of life.

### TABLE 1. Patient Characteristics and Test Results Before Implantation

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>55.9±3.2</td>
</tr>
<tr>
<td>Men, %</td>
<td>91</td>
</tr>
<tr>
<td>NYHA class*</td>
<td>2.6±0.1</td>
</tr>
<tr>
<td>Indication, %</td>
<td>9</td>
</tr>
<tr>
<td>Ischemic</td>
<td>91</td>
</tr>
<tr>
<td>Duration of HF, y</td>
<td>3.7±1.1</td>
</tr>
<tr>
<td>LVEDD, mm</td>
<td>73.5±2.0</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>20.8±1.4</td>
</tr>
<tr>
<td>MR, 0–4+</td>
<td>1.5±0.3</td>
</tr>
<tr>
<td>PCWP, mm Hg</td>
<td>21.4±3.0</td>
</tr>
<tr>
<td>Peak VO₂, mL · kg⁻¹ · min⁻¹</td>
<td>13.8±1.2</td>
</tr>
</tbody>
</table>

Data are mean±SE or percent. n=11 patients. NYHA indicates New York Heart Association; HF, heart failure; ACE, angiotensin converting enzyme; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; PCWP, pulmonary capillary wedge pressure; and peak VO₂, peak oxygen consumption.

*All patients were in NYHA functional class III or IV or, if in class II, had a history of at least one episode of class III or IV.
for patients at 3 and 6 months follow-up, with changes becoming statistically significant at the later time point.

All patients continued to receive nearly equivalent cardiovascular medication regimen throughout their follow-up, with 100% of patients continuing on their ACE inhibitors and diuretics. In 2 patients, other medications were increased slightly; in 5 patients, other medications were reduced slightly; and in 4 patients, medications were unchanged.

**Study Limitations**

The general study was undertaken as a nonrandomized safety study. Many of the patients enrolled in the study received concomitant cardiac surgery, primarily mitral valve repair or replacement. However, to better assess potential CSD efficacy, patients receiving the CSD only (no concomitant cardiac surgery as a confounding variable) were analyzed in this specific study. Nevertheless, given the relatively small sample size and nonrandomization, caution must be exercised in drawing any conclusions concerning device efficacy.

**Discussion**

The progressive clinical syndrome of heart failure is characterized by structural and functional changes to the heart that are known as remodeling. The initiating event may be relatively insignificant from a clinical perspective. However, once the remodeling process has begun, it is autoinductive, leading to further ventricular dilation and cardiac dysfunction. Factors that can stimulate the remodeling process include neurohormonal activation and mechanical stress. The resulting ventricular dilation increases biomechanical wall stress and initiates stretch of the cardiac myocytes. Such stresses cause maladaptive gene expression, stimulation of local neurohormonal activity, adverse changes in the extracellular matrix, and possible myocyte apoptosis. The CSD was designed to be surgically positioned around the heart and to fit to produce a slight, short-term reduction in heart size. The implanted CSD provides ventricular support and unloads the stresses associated with end-diastole, especially during periodic hemodynamic overload conditions, such as the transient increases in preload seen during even mild exertion. Thus, by reducing wall stress and myocyte overstretch, the CSD may halt the remodeling process and allow the heart to undergo reverse remodeling.

Preclinical study results with the CSD have been reported from 2 different heart failure models and degrees of heart failure. Sabbah et al, using a microembolic canine model, have shown reduced left ventricular volumes and improved cardiac function parameters in CSD-treated animals compared with controls at 3 and 6 months of follow-up. Power et al have shown similar results in a high-rate pacing ovine model. Heart size was maintained and cardiac function was improved in the CSD-treated animals. Functional improvements were seen when the CSD was implanted in animals with both moderate or more severe heart failure.

### Table 2. Test Results at 3- and 6-Month Follow-Up Intervals

<table>
<thead>
<tr>
<th></th>
<th>Changes at 3 mo After Implant</th>
<th>Changes at 6 mo After Implant</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pretreatment</td>
<td>3 mo</td>
</tr>
<tr>
<td>LVEDD, mm</td>
<td>74.0±2.1</td>
<td>68.4±1.6</td>
</tr>
<tr>
<td>LVESD, mm</td>
<td>65.5±2.2</td>
<td>62.8±1.7</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>21.7±1.5</td>
<td>27.6±3.2</td>
</tr>
<tr>
<td>MR, 0-4+</td>
<td>1.3±0.3</td>
<td>0.7±0.2</td>
</tr>
<tr>
<td>Peak VO₂, mL · kg⁻¹ · min⁻¹</td>
<td>14.7±1.5</td>
<td>14.8±1.4</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>82±4.1</td>
<td>82±3.9</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>113±5.2</td>
<td>118±5.2</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>78±2.6</td>
<td>82±3.0</td>
</tr>
<tr>
<td>NYHA class</td>
<td>2.5±0.2</td>
<td>1.6±0.2</td>
</tr>
<tr>
<td>MN living with HF</td>
<td>28.8±7.3</td>
<td>24.4±7.7</td>
</tr>
<tr>
<td>Uniscale</td>
<td>3.8±0.5</td>
<td>6.4±1.1</td>
</tr>
</tbody>
</table>

Data are mean±SE. n indicates number of patients. Patient cohorts may differ for each parameter and time point on the basis of available data and follow-up duration. LVEDD indicates left ventricular end-diastolic dimension; LVESD, left ventricular end-systolic dimension; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; peak VO₂, peak oxygen consumption; BP, blood pressure; NYHA, New York Heart Association; MN living with HF, Minnesota Living with Heart Failure quality of life questionnaire (a higher score indicates worse quality of life and daily functioning); and Uniscale, quality-of-life assessment (a higher score indicates better quality of life).

*Wilcoxon signed-rant test; other P values are paired t test.
†Insufficient data.
advanced heart failure. No adverse issues were noted, including no evidence of constrictive physiology.

Histological analysis revealed that animals treated with the CSD had less myocyte hypertrophy and less interstitial fibrosis. CSD-treated animals also demonstrated enhanced myocyte function (percent shortening and peak velocity of contraction and relaxation) compared with controls. Sabbah et al also examined other biochemical factors that may provide insight into the CSD’s mechanism of action. They reported that several proteins associated with stretch-mediated signal-transduction pathways (such as p21Ras, c-Fos, and p38a/β-mitogen-activated protein kinase) were at lower levels and Ca2 cycling was improved in the CSD-treated group compared with controls. These findings suggested that the CSD may halt or minimize unwanted alterations in gene expression and phenotypic transformation. In summary, these preclinical studies indicated that fitting the CSD to provide diastolic ventricular support, with only a very slight short-term heart size reduction, can reduce stretch-mediated stress and thus halt and potentially reverse the long-term process of progressive remodeling. This would be expected to result in an improved functional status for CSD-implanted patients.

Modern intensive pharmaceutical therapy for heart failure involves addressing multiple signal-transduction pathways and requires myriad drugs. Typical drugs include high-dose ACE inhibitors, nitrates, and β-blockers. Although this approach has the potential for promoting reverse remodeling, a recently published report suggests that improvement is not secure. Reversal was only sustained in two-thirds of patients during follow-up. The remainder showed a progression of heart failure despite optimal medical management. Patients enrolled in the CSD clinical study displayed functional status improvement after CSD implantation beyond what had been achieved by pharmacological means before implantation (100% on ACE inhibitors, diuretics, and digoxin; 81% on β-blockers; and 54% on additional cardiac medications). It may well be that these patients’ medical therapy was unable to address all aspects of remodeling, particularly those associated with biomechanical stress in the ventricular wall, and the CSD therapy provided an additional means to address remodeling. Ventricular remodeling, which is promoted by ventricular wall stress, must be viewed as both a consequence and a cause of heart failure progression.

The therapeutic concept of passive cardiac containment is derived from preclinical studies and clinical experience with cardiomyoplasty. Clinical observations and preclinical studies indicated that the primary benefit of the cardiomyoplasty procedure was derived from the passive component of the therapy.

Results from this study suggest that the CSD functions in the manner for which it was designed and presents no safety concerns. On the basis of a substudy involving 15 patients from both this series and the overall safety study, Kleber et al reported no evidence of constrictive physiology or impairment of coronary blood flow reserve due to the presence of the device at 3, 6, and 12 months of follow-up. Pressure-volume loop analysis revealed that patients receiving the CSD demonstrated no increases in diastolic filling pressures or chamber stiffness, while showing improvement in contraction and relaxation. In addition, a recent preliminary clinical safety study involving implantation of the CSD with concomitant coronary artery bypass surgery concluded that the device was safe and did not impair coronary grafts or produce diastolic dysfunction.

In summary, the CSD is designed to address an important aspect of chronic heart failure, namely, the increased mechanical wall stress associated with cardiac chamber dilation. The device represents a passive, physical means for treating the multifaceted syndrome of cardiac failure. The CSD may address a limitation in the current patient management strategy and provide an important tool in the treatment of heart failure. In the study reported here, the CSD implant procedure was uncomplicated, and the therapy demonstrated safety with positive trends for potential device efficacy, as shown by statistically significant improvements in left ventricular ejection fraction, NYHA class, and quality of life indices and a reduction in heart size. The CSD is now being evaluated in randomized, prospective, clinical trials in Europe, the United States, and Australia.

Acknowledgments

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References

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