Worldwide surgical experience with the Paracor HeartNet cardiac restraint device

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Objective: An elastic ventricular restraint device has been developed for patients with heart failure who remain symptomatic despite treatment with standard therapies. The safety and efficacy of this device are under clinical investigation. Six-month data for the first 51 patients treated worldwide are reported. We hypothesize that the Paracor HeartNet device (Paracor Medical, Sunnyvale, Calif), placed through a minithoracotomy in patients with severe dilated cardiomyopathy, improves clinical and functional status.

Methods: Fifty-one patients with an ejection fraction of 35% or less, with a New York Heart Association class II or III, and receiving optimal medical therapy for at least 3 months, were selected at 15 sites (3 in Europe, 12 in the United States) to undergo implantation of the HeartNet device through a minithoracotomy. Patients were evaluated at baseline and at 6-month follow-up by echocardiography, the 6-minute walk test, cardiopulmonary exercise testing (partial oxygen pressure in mixed venous blood), New York Heart Association class, and (in the United States) the Minnesota Living with Heart Failure questionnaire.

Results: The average age was 52 years (30–73 years), with a preponderance of men and nonischemic cause of heart failure. Implantation was accomplished in 50 of 51 patients (98%). Adverse events included 2 in-hospital deaths secondary to pulmonary complications (4%), additional pulmonary complications in 7 patients (14%), arrhythmia in 14 patients (27%), epicardial laceration in 2 patients (4%), and empyema in 1 patient (2%). Six-month data demonstrated significant improvement in the 6-minute walk test (+65.7, $P = .002$) and Minnesota Living with Heart Failure scores (−15.7, $P = .002$) and improvement in echocardiographic findings.

Conclusion: The Paracor HeartNet device can be reliably implanted in patients with heart failure and marked reduction of left ventricular function. These data suggest a functional and clinical benefit, with a trend toward reverse remodeling, and support the conduct of a randomized controlled pivotal trial.

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Optimal heart failure therapy using neurohormonal blockade with angiotensin-converting enzyme inhibitors and beta-blockers in all patients, and biventricular pacing in certain patients who have prolonged QRS duration, represent the current standard of care for patients with symptomatic systolic heart failure. Despite reductions in morbidity and mortality with medical therapy, there are some patients in whom optimal medical and device-based therapy fail to halt the progressive course of this disease.[1] In the current era, patients with end-stage heart failure are considered for destination therapy with a left ventricular assist device or heart transplantation as a final option.[2] Multiple therapies have been used or are under investigation in an attempt to intervene earlier in the progression of this disease process. These efforts have centered on surgically reshaping the ventricle or using biventricular pacing to relieve mechanical and electrical asynchrony.[3-10] Recently, other mechanical therapies have been investigated to potentially halt the progression of the failing heart and

Abbreviations and Acronyms
LVEDD = left ventricular end-diastolic dimension
NYHA = New York Heart Association

allow for reverse remodeling in patients with stage C heart failure to possibly attenuate progression to end-stage heart failure.[11] In a sheep model, it has been shown that a myocardial constraint device can modify the left ventricular geometry after myocardial infarction.[12-14] Myocardial constraint devices have also been shown in an ovine model of tachycardia-induced progressive dilated cardiomyopathy to improve cardiac function, reduce left ventricular volume, and reduce mitral regurgitation.[15]

The Paracor HeartNet device (Paracor Medical, Sunnyvale, Calif) is an elastic ventricular restraint device that was developed for patients with heart failure who remain symptomatic with progressive cardiac remodeling or who continue to remodel without concomitant clinical deterioration, despite treatment with standard evidence-based therapies. It is implanted around the heart to apply a low level of epicardial pressure, thereby reducing wall stress and potentially inducing reverse remodeling. The safety and efficacy of this device are now under clinical investigation. We previously reported the initial US experience with the device.[16] This report details the current worldwide surgical experience and 6-month follow-up data for the first 51 patients treated and represents a comprehensive and consecutive series of all patients implanted with the device worldwide.

It was hypothesized that the HeartNet device could be safely implanted through a minithoracotomy in patients with heart failure and significantly reduced left ventricular systolic function and lead to improvement in clinical and functional status.

Materials and Methods

Fifty-one patients with an ejection fraction of 35% or less, with New York Heart Association (NYHA) class II or III, and receiving optimal medical and or device therapy for at least 3 months were selected at 15 sites (3 in Europe, 12 in the United States) to undergo implantation of the HeartNet device through a minithoracotomy. All US sites obtained investigational review board approval of the Food and Drug Administration-approved safety and feasibility trial and informed consent before patient enrollment. Criteria for enrollment included patients with symptomatic heart failure (College of Cardiology/American Heart Association stage C) caused by ischemic or nonischemic dilated cardiomyopathy and receiving stable medical and device therapy for heart failure for at least 3 months. This included pharmacologic therapy with angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, as well as beta-blockers, diuretics, and aldosterone inhibitors as tolerated. An ejection fraction of less than or equal to 35% and receiving optimal medical and device therapy, including resynchronization therapy as indicated, were additionally required for consideration. Patients with NYHA class IV heart failure, acute exacerbation of symptoms, and previous cardiac operations were excluded. Left ventricular end-diastolic dimension (LVEDD) of greater than 85 mm was subsequently added as an exclusion criterion after initiation of enrollment. Patients were evaluated at baseline and at 6-month follow-up by echocardiography, 6-minute walk test, cardiopulmonary exercise testing (partial oxygen pressure in mixed venous blood), NYHA class, and (in the United States) the Minnesota Living with Heart Failure questionnaire.

Operative Technique

All procedures were performed via a left anterior minithoracotomy under general anesthesia. Patients were positioned supine, and fluoroscopy was used to identify the cardiac apex. Minithoracotomy incision was performed 1 or 2 interspaces lower than the apex to allow the correct trajectory for the delivery system. Rib spreading was performed only to the extent necessary to accommodate the introducer sheath. The pericardium overlying the cardiac apex was opened and suspended with stay sutures. The introducer was inserted into the intrapericardial space and expanded (Figure 1, *A*). Frequently the previously placed stay sutures were tensioned along the introducer to keep the edges of pericardium from protruding in the path to the cardiac apex. An unobstructed path to the cardiac apex was ensured by direct visualization or by using a 10-mm thoracoscope through the introducer. After confirmation of the introducer positioning, the delivery system (Figure 1, *B*) was advanced through the introducer under fluoroscopic guidance. The apex was captured with the suction cup while the device was inserted and deployed. Once the delivery system was removed, either direct visualization or the thoracoscope was used synergistically with fluoroscopy to ensure appropriate device deployment and location (Figure 2). The pericardium was loosely approximated, and

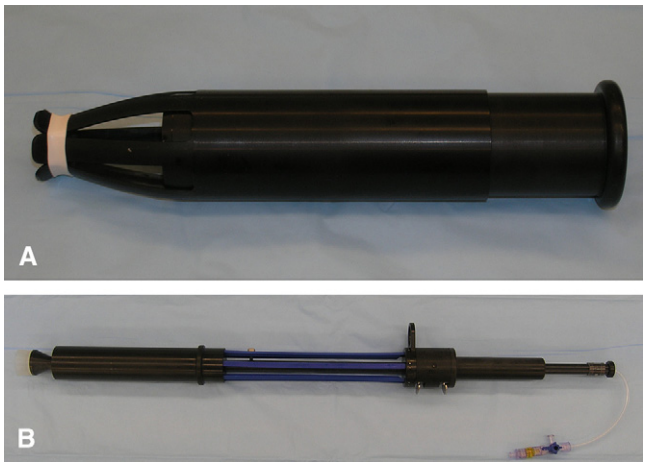

Figure 1. A, Introducer sheath used to maintain stable access to pericardial space. B, HeartNet delivery system (Paracor Medical, Sunnyvale, Calif).

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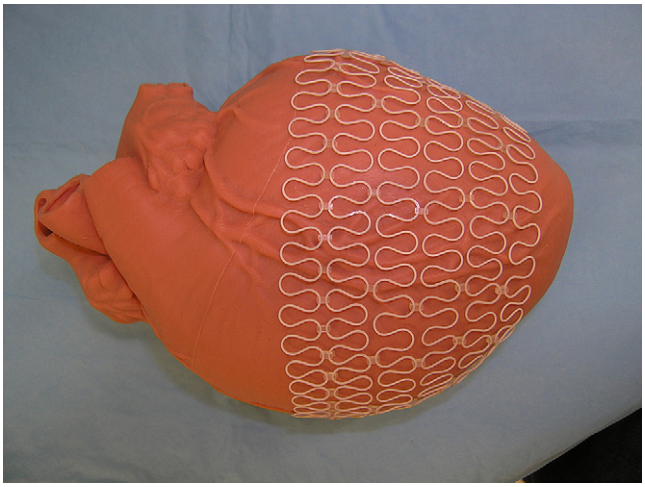

Figure 2. Paracor device implanted in heart model.

a chest drain was left in place. Thoracotomy closure was accomplished in standard fashion.

Results

The HeartNet device was successfully implanted in 98% (50/51) of the patients enrolled. The baseline demographics of the patients are listed in Table 1. There was a preponderance of male patients and those with a nonischemic cause of heart failure. All patients had been receiving optimal medical therapy for a minimum of 3 months. Clinical and functional parameters (Table 2) and baseline echocardiographic data (Table 3) demonstrated a moderately ill cohort of patients with NYHA class II and III heart disease. Eight patients (7 nonischemic, 1 ischemic) demonstrated greater than 2+ mitral regurgitation on preoperative transthoracic echocardiography.

Procedural Data

Successful implantation was accomplished via a left anterior minithoracotomy in 50 patients. In 1 patient, the tissue of the pericardium and epicardium was determined to be extremely friable. After an epicardial laceration necessitating suture control, the procedure was aborted. In the 50 patients with successful implantations, the average total anesthesia time was 191 minutes (76–818 minutes, median 164 minutes), although the skin incision to skin closure time averaged 78 minutes (26–233 minutes, median 73 minutes) (Table 4). The actual time to deploy the device and the fluoroscopy time constituted only a small part of the procedure duration.

Postoperative Course and Adverse Events

The average time to ambulation was 1.7 days (0–6 days, median 1 day), and the average intensive care unit stay was 2.9 days (1–16 days, median 2 days). The duration of patient hospitalization averaged 8 days (3–29 days, median 6 days) (Table 4). Perioperative pain-management strategy was selected by the individual surgeon. Strategies included the use of epidural catheters, intercostal nerve blocks, local anesthetic infusion pumps placed into the wound, and selected use of ketorolac.

Serious adverse events (Table 5) included 2 patients with unilateral diaphragmatic paresis and pleural effusion, 1 which resolved completely. One patient with diaphragmatic paresis also presented for follow-up with anemia 1 month after implantation and was found to have colonic polyps. This same patient returned a third time 3 months after implantation with a period of obtundation related to overmedication with narcotics. One patient (2%) required reexploration for bleeding secondary to persistently high chest tube outputs. At reexploration, the bleeding originated from an arterial branch to the diaphragm. Fourteen patients had postprocedure arrhythmias, including 8 patients who presented after discharge

TABLE 1. Baseline demographics

Parameter	n (percent)/mean (range) n = 51 unless otherwise indicated
Age (y)	52.3 (30.4–72.6)
Male gender	48 (94%)
Race (white)*	47 (92%)
Cause	
Nonischemic	41 (80%)
Ischemic	10 (20%)
Duration of heart failure (y)	6.2 (0.3–18.8)
Cardiac medications	
ACEI/ARB	50 (98%)
Beta-blockers	49 (96%)
Coreg	33 (65%)
Metoprolol	14 (27%)
Diuretics (other than spironolactone)	44 (86%)
Aldosterone inhibitors	30 (59%)
Digoxin	31 (61%)
Medical history and comorbidities	
Systemic hypertension	22 (43%)
Pulmonary hypertension	17 (33%)
Diabetes mellitus	20 (39%)
Myocardial infarction	7 (14%)
Ventricular tachycardia	15 (29%)
Atrial fibrillation	14 (27%)
Biventricular pacemaker†	2 (4%)
Biventricular ICD†	17 (33%)
Pacemaker alone†	0 (0%)
ICD alone†	14 (27%)

ACEI, Angiotensin-converting enzyme inhibitor; *ARB,* angiotensin receptor blocker; *ICD,* implantable cardioverter/defibrillator. *There were 3 African-Americans (6%) and 1 Hispanic (2%). †Only the active device was counted for patients with a history of more than 1 type of device.

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TABLE 2. Baseline exercise and quality of life

Parameter	n (percent)/mean (range) n = 51 unless otherwise indicated
NYHA class II*	18 (35%)
NYHA class III*	33 (65%)
Peak VO_2 (mL/kg/min)†	16.4 (6.9–26.3) n = 49
VE/VCO_2 slope†	32.1 (22.0–59.0) n = 36
6MWT (m)	360.2 (108.0–523.0)
MLHF (units)‡	56.4 (23.0–91.0) n = 38

NYHA, New York Heart Association; *6MWT,* 6-minute walk test; *MLHF,* Minnesota Living with Heart Failure; *VE,* ventilation; *VCO_2,* carbon dioxide output. *For NYHA class, because an independent assessment was not done for European patients, site assessment was used. †For Peak VO_2 and VE/VCO_2 slope, if core laboratory data were not available for European patients, the site assessment was used. ‡For MLHF, these data were only collected at US sites.

with recurrent arrhythmia, which necessitated an admission for heart failure management and arrhythmia treatment.

Two patients sustained epicardial lacerations during the procedure that required suture repair. In 1 patient the implantation proceeded uneventfully after repair of the laceration. In 1 patient (2%) it was thought that the friable nature of the epicardial and pericardial tissue precluded safe implantation of the device, and the procedure was aborted.

Four patients had a total of 11 episodes of worsening heart failure after implantation of the HeartNet device. Three of these patients progressed to decompensated heart failure at 4, 8, and 22 months after implantation of the HeartNet device.

TABLE 3. Baseline echocardiographic parameters

Parameter	Mean (range) unless otherwise indicated
LVEF (%)	22.1 (11.0–33.7) n = 49
LVEDD (mm)	7.3 (5.4–9.8) n = 46
LVESD (mm)	6.3 (4.2–8.8) n = 46
Diastolic LV volume (cm^3)	352.7 (193.2–651.5) n = 49
Systolic LV volume (cm^3)	278.3 (134.0–559.3) n = 49
MR > 2+ (No. of patients)	8 patients (17%) n = 47
Diastolic sphericity index ratio*	0.6 (0.3–0.9) n = 49

LVEF, Left ventricular ejection fraction; *LVEDD,* left ventricular end-diastolic dimension; *LVESD,* left ventricular end-systolic dimension; *LV,* left ventricular; *MR,* mitral regurgitation; *EDV,* end-diastolic volume; *EDL,* end-diastolic length. *Diastolic Sphericity = $EDV/\pi \cdot EDL3/6$.

TABLE 4. Index procedural information for 51 patients (range)

Parameter	Mean ± SD (range) Median
Anesthesia time (min)*	190.6 ± 114.3 (76.0–818.0) 164.0 n = 49
Skin to skin (min)*	77.7 ± 39.9 (26.0–233.0) 73.0 n = 51
Fluoroscopy time (min)	8.8 ± 8.9 (1.4–52.0) 6.1 n = 50
Implant time (min)	19.8 ± 21.6 (4.0–108.0) 12.0 n = 49
Time to ambulation (d)	1.7 ± 1.2 (0–6.0) 1.0 n = 41
ICU length of stay (d)	2.9 ± 3.0 (1.0–16.0) 2.0 n = 51
Hospital length of stay (d)	8.0 ± 5.0 (3.0–29.0) 6.0 n = 51

SD, Standard deviation; *ICU,* intensive care unit. *Anesthesia time is defined as time from induction of anesthesia to patient consciousness. One patient did not receive an implant, but this patient's anesthesia (147 minutes) and skin to skin (101 minutes) times are included in the table.

Ventricular assist device placement was required in these 3 patients and was accomplished without incident.

Major adverse events (Table 5) included 2 deaths during the initial hospitalization and within 30 days of procedure (overall in-hospital and 30 day mortality was 4%). One patient had significant pulmonary dysfunction and methicillin-resistant *Staphylococcus aureus* pneumonia requiring reintubation. The patient progressed to multisystem organ failure and died on postoperative day 16. Postmortem examination confirmed severe bilateral necrotizing pneumonia and evidence of necrotizing pancreatitis. There was no evidence of device malfunction, nor was the device implicated as the cause of death. The pericardial adhesions to the device were noted to be mild. Pneumonia developed in 1 patient who required reintubation and had a period of hemodynamic instability requiring vasopressors. This progressed to multisystem organ failure, and the patient died on postoperative day 14. Postmortem examination showed evidence of gastrointestinal hemorrhage and bilateral lower lobe consolidation of the lungs. The report did not comment on density of intrapericardial adhesions to the device. These 2 patients had the largest LVEDDs in this series (90 mm and 94 mm, respectively). After the deaths of these 2 patients with large LVEDDs, patients with an LVEDD greater than 85 mm or

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TABLE 5. Adverse events

Adverse event	No. of events	No. of patients
Death*	3	3
Reoperation for bleeding†	1	1
Arrhythmias, bradycardias, and tachycardias	17	14
Laceration	2	2
Pericarditis	1	1
Worsening heart failure‡	11	4
Anemia	3	2
Obtundation/altered mental status	1	1
Phrenic nerve injury	2	2
Stroke/transient ischemic attack	2	1
Dyspnea, shortness of breath	1	1
Pleural effusion	4	3
Pneumothorax	1	1
Respiratory failure/atelectasis/ pneumonia	2	2
Empyema	1	1
Renal insufficiency/failure/ compromise	2	2

*Two deaths occurred in-hospital and within 30 days, and 1 death occurred 8 months after implant. †Bleeding secondary to diaphragmatic source; no intrapericardial bleeding. ‡Three patients have ultimately required ventricular assist devices for worsening heart failure at 4, 8, and 22 months after implantation of the HeartNet device.

an LVEDD index greater than 40 mm were excluded from implantation of the HeartNet device. There were no subsequent early deaths.

Functional parameters showed significant improvement at 6 months in the 6-minute walk test (mean increase 65.7 m, $P = .002$, n = 36) and Minnesota Living with Heart Failure score (mean decrease 15.7 units , $P = .002$, n = 26 (US only) when compared with baseline (Figure 3). The peak volume of oxygen use (n = 35) demonstrated a trend toward improvement but did not reach significance at the 6-month interval. It is known that cardiopulmonary exercise testing is a complex test with many confounding factors, requiring further analysis and study of this result.

Echocardiographic parameters also demonstrated significant improvement at the 6-month interval (n = 39, 39 eligible patients, 100% follow-up) with improvements in LVEDD (mean decrease 3 mm, $P = .038$), end-diastolic volume (mean decrease 25.7 cm^3, $P = .025$), end-systolic volume (mean decrease 23.5 cm^3, $P = .037$), and left ventricular mass (mean decrease 23.1 g, $P = .046$). The trends in NYHA class paralleled the findings of functional and echocardiographic improvement (Figure 4).

Discussion

This report summarizes the current worldwide experience with the Paracor HeartNet device during the Safety and Feasibility trial of this myocardial constraint device. Previous reports have detailed the archetype myocardial constraint device: the Acorn CorCap (Acorn Cardiovascular, St Paul, Minn).[11,17] The Paracor HeartNet device differs from the CorCap device in several important ways. The HeartNet device is delivered via a minimal access left thoracotomy inside the pericardium with the aid of an introducer and delivery system, and adheres to the heart because of small textured areas on the epicardial side of the device. The pericardium remaining intact around the heart has an unknown effect on the long-term progression of the disease process, but may facilitate future cardiac surgery. The HeartNet device currently has

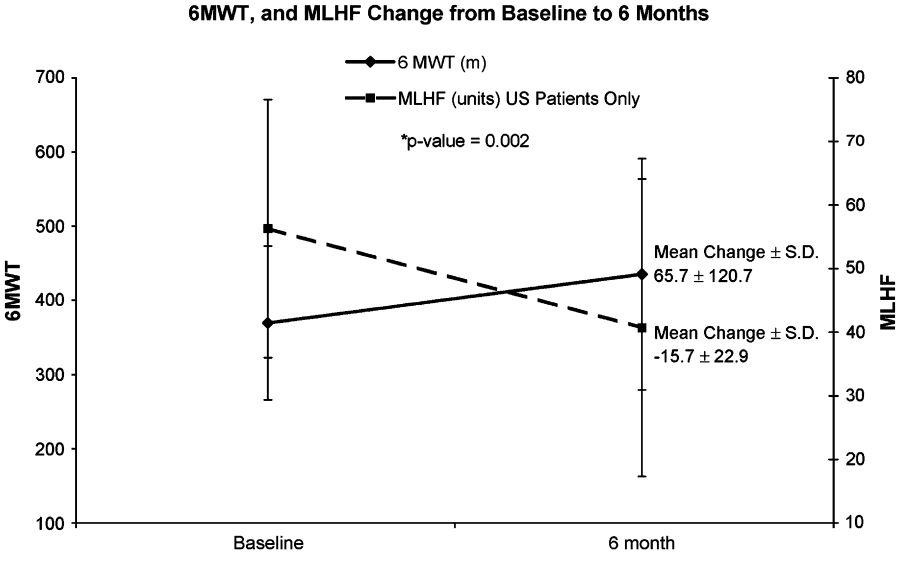

Figure 3. 6MWT and MLHF change from baseline to 6 months. *6MWT,* 6-minute walk test; *MLHF,* Minnesota Living with Heart Failure; *SD,* standard deviation. **P* value for MLHF calculated using Wilcoxon signed-rank test; *t* test was used for all other parameters.

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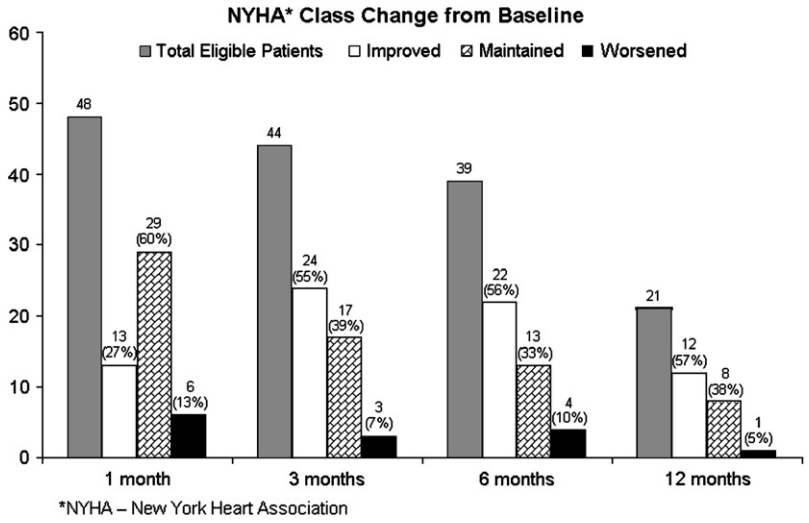

Figure 4. New York Heart Class change from baseline. *NYHA,* New York Heart Association.

16 sizes available and is sized by echo parameters, in theory making the fit consistent over a large size range. This pre-procedure sizing based on objective criteria should allow for reproducible fit to the myocardium and reproducible results. It is also constructed of a nitinol mesh, which is both compliant and elastic. The relatively large compliance range reduces the likelihood of developing a constrictive-type physiology, although the elasticity may provide some positive epicardial pressure that may be beneficial compared with the non-elastic construction of the CorCap device. A recently published ovine study noted that the optimal physiologic restraint level of 3 mm Hg was identified to maximize improvement without an adverse affect on systemic hemodynamics.[18] The nitinol mesh may have an additional benefit of reduced adhesion formation when compared with other materials, although further study will be required. It is known that in the patients who have developed progressive heart failure and required ventricular assist devices (n = 3), the devices were implanted uneventfully. Reports from the implanting surgeons (1 HeartNet investigator, 2 not involved in the study) detailed moderate adhesions over the apex of the left ventricle at the site of the pericardial opening, but otherwise mild adhesions. This may ultimately prove a dramatic advantage to this type of device, because some of these patients inevitably will require either assist devices or cardiac transplantation. Further study of the device will help to better elucidate these advantages over other ventricular restraint devices, such as the CorCap or cardiomyoplasty procedures.

Class IV heart failure and adhesions from previous cardiac operations were considered as exclusions for the initial safety and feasibility trial of the HeartNet device. This may have led to a selection bias of a greater number of nonischemic patients with heart failure. It is unclear at this time what the impact of these exclusions would be on the eventual clinical adaptation of this device. In addition, longer follow-up will be required to determine the effect of device implantation on patients with greater than 2+ mitral regurgitation (n = 8).

This report demonstrates that the HeartNet device can be implanted with a high degree of surgical success (98%) in patients with heart failure and reduction of left ventricular function. The surgical implantation procedure was relatively straightforward with only 2 intraoperative complications and a single patient with significant postoperative bleeding. Major adverse events occurred in the 2 patients with the largest hearts as measured by end-diastolic dimension. This early experience indicates that, as with the CorCap, the patients with the largest end-diastolic dimensions are not optimal candidates for this therapy. In the remaining patients, the postoperative course parallels what might be expected after any thoracotomy in this moderately severe ill patient cohort. Also similar to post-thoracotomy care, adequate preoperative pulmonary evaluation and excellent postoperative pain control seem to be paramount to success. The 6-month paired data suggest a functional and clinical benefit, with a trend toward reverse remodeling, and support the conduct of a randomized controlled pivotal trial (Prospective Evaluation of Elastic Restraint to LESSen the effects of Heart Failure), which has begun enrollment in the United States.

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Discussion

Dr M. Acker *(Philadelphia, Pa)*. I congratulate you on this feasibility study and the honest reporting of all of the complications. What I found most interesting in your talk is actually the slide that compared the compliance of the Paracor device with the CorCap and pericardium and how unbelievably low it is, and yet still I guess the theory is that this amount of push-back on diastolic stress is still enough to have a biological effect. We don't know what that limit is because the Paracor almost seems to have no push-back compared with the other membranes around the heart. I wonder if you would comment on that.

Dr Klodell. Thank you for that excellent question, Dr Acker. I think that is exactly true. It is a very interesting concept to think about. I am sure, as you are aware and I will point out for the audience, in the early March issue of *Circulation* the Brigham group published their results on an ovine model looking at the optimal epicardial pressure that did not result in hemodynamic compromise but did perhaps promote reverse remodeling, which was approximately 3 mm Hg of epicardial pressure in their study, and that is fairly consistent with what the Paracor device provides. So it may be that this is about the right amount of epicardial pressure.

Dr M. Anstadt *(Dayton, Ohio)*. I have a question about the implications on diastolic dysfunction. Clearly, the girdling effect of these passive constraint devices is beneficial for systolic function. If you examine the basic research around constraint devices, both passive and active, there are implications that diastolic function can be impaired, particularly if you look at the right. Now that we have these clinical studies ongoing, what is being done to assess diastolic function after device implantation, particularly in the right ventricle? You mentioned that you can image these hearts echocardiographically, and with new imaging techniques, ventricular inhibited [pacemaker], and so forth, we have a critically important opportunity. Obviously diastolic dysfunction may have contributed to your reported deaths in these larger hearts. Do you think that constraint devices have a negative impact on diastolic function that can significantly exacerbate the underlying diastolic dysfunction of heart failure?

Dr Klodell. It is unknown, as you pointed out right now, what the long-term effects on diastolic dysfunction are going to be. One of the advantages, again, of this device may be the fact that it is more compliant and that it triggers whatever neurohormonal signals there are for the reverse remodeling. Perhaps it will have a beneficial effect, but I hope the Pivotal Trial is going to answer that question.

I think as far as your comment about the 2 deaths, that is an interesting thing to consider, although I believe that the 2 deaths were completely due to patient selection. They were patients who had a preexisting pulmonary dysfunction, and they did have particularly large hearts. Trouble began early, they had to be reintubated, and they spiraled into multisystem organ failure related to their pulmonary dysfunction.

Dr A. Elami *(Jerusalem, Israel)*. I am referring to a letter to the editor published 3 months ago in *The Journal of Thoracic and Cardiovascular Surgery* regarding a similar device, the CorCap. The questions raised in this letter were left open, however, and I would like to raise them again.

I believe everybody in this room is familiar with the echocardiographic appearance of the globally enlarged ventricle in these patients, especially the bulge of the ventricular septum into the right side. Your device does not address the septum at all. What is the mechanism by which you are expecting this device to influence the septum if it is not addressed by the device? This is the first question.

The second question is with regard to the systolic interaction between the device and the heart. We all know that the pressures in the right side of the heart are much lower than in the left side. Now during systole, assuming that the tension of the device is equal and evenly distributed around the heart, why should it prevent the left ventricle from expanding rather than squeeze the lower pressure right ventricle? What is the mechanism of action during systole?

Dr Klodell. As far as addressing the septum, you are absolutely correct, none of the restraint devices, meaning the CorCap or this device, directly address the septum, and again, I think there is a complex interplay between the potential for systolic augmentation by direct epicardial pressure and neurohormonal remodeling that goes on. These devices are being used in patients who have

ongoing clinical deterioration or progressive remodeling without clinical deterioration. It is unknown how to stop that progress, but it is known what the consequences are if those patients' clinical condition continues to progress. It is important to realize the proposed effect of these devices is thought to involve the complex interplay of the neurohormonal signals for reverse remodeling, not direct mechanical effects.

As far as the systolic interaction, again, the epicardial pressure generated by these devices is very low. Even once the device is on, you can very easily slip a finger underneath it, and it is compliant enough that it does not have but 3 or 4 mm of direct pressure on the epicardium. So we have not seen that interplay with the right ventricle to be a problem at this point.

Dr M. Acker. We have to move on. As far as that question goes, this is not a mechanical effect. A mechanical effect is a signal to start a change in the phenotype at a cellular level, and that gives the neurohormonal changes, and this has been shown well by Tony Sabbah. So it is not just the girdling effect. That is how the septum gets better. It is the neurohormonal cascade that is started by this pressure that is exerted during diastole.