The process of left ventricular (LV) dilatation and remodeling after myocardial infarction has been well documented in experimental and clinical investigations. Progressive LV dilatation or remodeling post–myocardial infarction occurred in 33% of patients enrolled in the GISSI-3 trial (The third Gruppo Italiano per lo Studio della Sopravvivenza nell’Infarto Miocardico; n=13679). Advances in the treatment of myocardial infarction may have reduced the incidence of LV dilation post–myocardial infarction, but once heart failure (HF) develops, the overall 1-year mortality percentage remains unacceptably high at 32% in spite of modern pharmacological and mechanical approaches. Therapeutic efficacy depends, albeit not exclusively, on improvements in LV volumes and geometry. LV end-systolic and end-diastolic volumes are surrogate measures of LV remodeling and have been shown to be independent clinical predictors of outcomes in HF patients. The treatment goal for this group of patients is to reduce LV volume thereby reducing wall stress and reshape the LV to improve flow dynamics.

Background—Left ventricle remodeling after anterior wall myocardial infarction leads to increased left ventricle volumes, myocardial stress, and ultimately heart failure (HF). Treatment options are limited for these high-risk HF patients. A study was conducted to assess safety and feasibility of a percutaneous ventricular restoration therapy using the Parachute device in subjects with HF because of a cardiac ischemic event.

Methods and Results—Thirty-nine subjects with New York Heart Association class II to IV ischemic HF, ejection fraction between 15% and 40%, and dilated akinetic or dyskinetic anterior-apical wall without the need to be revascularized were enrolled in a prospective, nonrandomized, multicenter investigation testing percutaneous ventricular restoration using the Parachute device. The safety primary end point was defined as successful procedure without device-related major adverse cardiac events during 6 months. Clinical and echocardiographic outcomes were obtained at 6, 12, 24, and 36 months post-treatment. Echocardiographic and end point data were adjudicated independently. Of the 39 subjects enrolled, device implantation was attempted in 34 and successful in 31 patients. Twenty-three subjects reached 3 years post-treatment with the device implanted. New York Heart Association symptom class was improved or maintained in 85% of subjects. Left ventricle end-diastolic volume index and end-systolic volume index were reduced from 128.4±22.1 and 94.9±22.3 mL/m² preimplant to 115.2±23.1 and 87.3±18.7 mL/m² at 3-year follow-up (end-diastolic volume index, \(P=0.0056\); end-systolic volume index, \(P=0.4719\)). The cumulative incidence of HF hospitalization or death was 16.1%, 32.3%, and 38.7% at 12, 24, and 36 months, respectively. By 3-year follow-up, 2 (6.5%) of 31 patients with successful implant had died from cardiac reasons, with no cardiac deaths occurring past 6 months post-treatment.

Conclusions—The first series of ischemic HF patients treated with percutaneous ventricular restoration using the Parachute device demonstrates feasibility and safety of the device ≤3 years post-treatment.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifiers: NCT00573560 (US patients) and NCT01286116 (EU patients). (Circ Heart Fail, 2014;7:752-758.)

Key Words: heart failure • myocardial infarction • ventricular remodeling

The concept of percutaneous ventricular restoration (PVR) of the LV is based on the premise that a dedicated partitioning device delivered via a catheter-based approach may achieve LV volume reduction and geometric reconfiguration while minimizing the risk of a more invasive method. The Parachute
device was designed with a conical nitinol frame covered with fluoropolymer (expanded polytetrafluoroethylene, ePTFE) membrane that can be compressed into a delivery catheter and deployed into the LV apex to partition off akinetic or dyskinetic myocardium (Figure 1). Three-year echocardiographic and clinical outcomes of the first series of ischemic HF subjects treated with PVR using the Parachute device are presented in this article.

Methods

Study Design
The PercutAneous Ventricular RestorAtion in Chronic Heart FailUre due to Ischemic Heart DiseasE (PARACHUTE) first-in-human study was a prospective, single-arm study conducted in 10 medical centers in the United States and Europe. The study was designed to assess the safety and feasibility of the Parachute device. After implantation of the device, clinical and echocardiographic follow-up was performed at 6 months and annually up to 3 years.

Patient Selection
The study included subjects with symptomatic ischemic HF of the New York Heart Association classes II to IV. The subjects had to be ≤18 years of age with LV wall motion abnormalities (anteroapical akinesia or dyskinesis) secondary to myocardial infarction, an LV ejection fraction between 15% and 40%, and managed with stable doses of standard HF medical therapy for ≤3 months. Subjects with myocardial ischemia requiring revascularization <60 days, those with revascularization or cardiac resynchronization therapy <60 days, and those with significant valve disease were excluded from the study. All sites obtained approval from an institutional review board or ethics committee before study commencement, and written informed consent was obtained from all subjects at the appropriate time before involvement in the study.

Study Device and Procedure
The Parachute system includes the device (Parachute), a delivery system, a balloon that facilitates expansion of the device, and a pre-shaped delivery catheter and dilator (Figure 1). The Parachute device is comprised of a self-expanding nitinol frame, an ePTFE impermeable membrane, and an atraumatic polymer foot. The nitinol frame has a conical shape with 16 struts. At the time of this investigation, the device had 2 sizes (75 and 85 mm). The tip of each strut ends in a 2-mm anchor. The anchors engage the myocardium and help stabilize the device. The distal atraumatic foot is radio-opaque and provides a contact point between the LV apex and the Parachute device in addition to facilitating visualization to ensure proper placement.

The procedure (Figure 2) is performed in a catheterization laboratory, and subjects are under conscious sedation. Per protocol, subjects were considered enrolled if they signed a consent form, underwent a baseline evaluation, and had a successful placement of a 14F or 16F sheath in the femoral artery. Device size selection was initially based on echocardiography assessment of the LV midcavity at the intended site of device anchoring. After the first 15 cases, multislice computed tomography was implemented to provide accurate measurements and rule out LV apical thrombus and severe calcification, which would preclude safe deployment of the device. The LV was accessed via femoral approach using a conventional pig-tail wire. A stiff 0.035-inch wire was positioned in the LV for support. The preshaped catheter was then placed near the LV apex. The Parachute device was advanced through the sheath guided by fluoroscopy until the foot was exposed. The delivery system was then advanced until the foot was in contact with the LV apex. Proper position was confirmed by fluoroscopy or transesophageal echocardiography. The device was deployed by retracting the delivery catheter, exposing the device frame. Self-expansion of the Parachute device was facilitated by inflating a low-pressure, low-profile balloon.
contrast-filled 6-mL balloon with a nominal diameter of 24 mm until the anchors were fully expanded and in contact with the LV wall. The device remained attached to the delivery system after deployment, and contrast LV angiography was performed to confirm correct positioning before releasing the device. After device release, a final LV angiography was performed, all catheters were removed, and, when appropriate, the femoral access sheath was removed. All subjects were required to receive 12 months of aspirin and 6 months of clopidogrel post–device implant. It was also recommended that subjects be placed on anticoagulation with warfarin for 3 months post–device implant.

Data Collection and Oversight
All study-related data were collected on standardized case report forms. All protocol-mandated echocardiograms were sent to an independent core laboratory (University of Pennsylvania Medical Center, Philadelphia, PA). Data management was performed by an independent contract research organization, and an independent data safety monitoring board met frequently to oversee the trial and provide recommendations on study progress. An independent clinical events committee adjudicated serious adverse events, cardiac and noncardiac deaths, and HF hospitalizations, and determined the relationship with device and procedure.

Study End Points
The primary safety end point of the PARACHUTE study was defined as the successful delivery and deployment of the device without the occurrence of device-related major adverse cardiac events ≤6 months postprocedure. Major adverse cardiac events were broadly defined and included the occurrence of any of the following: cardiac death, emergent cardiac surgery, erosion of the device through the LV, cardiac tamponade, peripheral embolization (including stroke), new or worsened HF, endocarditis or device infection, device migration or embolization, or placement of a mechanical support device. Worsening HF hospitalization was defined as an unplanned hospitalization that results in at least 1 overnight stay (ie, where the admission date and the discharge date are different) that includes increased signs or symptoms of worsening HF including increased jugular venous pressure and requires the administration or augmentation of intravenous HF therapy (eg, inotropes, diuretics, or vasodilators). Vascular complications were defined using an expanded Valve Academic Research Consortium definition that includes damage of the aortic valve requiring surgery.5 Secondary efficacy end points included serial hemodynamic measurements determined by echocardiography (LV volume indices, ejection fraction, and stroke volume) and functional parameters. A substudy was performed in 10 patients measuring LV end-diastolic pressure at baseline and 6-month follow-up with a Swan-Ganz catheter. To measure functional status and quality of life, subjects underwent a standardized 6-minute walk test and Minnesota Living with Heart Failure quality-of-life assessment at clinic visits up to 1 year post-treatment.

Statistical Analysis
Baseline characteristics were summarized using mean±SD for continuous variables and counts and percentages for categorical variables. Continuous variables assessed over time were evaluated using a linear mixed model with variance components covariance structure, controlling for baseline values and categorical visit. Least square means and SEs were presented for scheduled time points, and P values presented for pairwise comparisons between visits and baseline. Death, stroke, end-stage HF utilization of LV assist device or heart transplant, and HF rehospitalizations were evaluated using Kaplan–Meier analysis. All analyses were performed using SAS version 9.3 (SAS, Cary, NC).

Results
Between October 2005 and June 2009, 39 subjects were enrolled at 10 sites in the United States and Europe. Thirty-one subjects were discharged with the Parachute device and followed up for hemodynamic, functional, and clinical outcomes. The mean follow-up time for this population was 2.6 years. The number of patients who completed 3-year follow-up is shown in Figure 3.

Procedural Outcomes
Of the 39 consented subjects, no attempt to deliver the Parachute device was made in 5 subjects because of anatomic reasons. Three of the 34 treated subjects (Table 1) had the device explanted before discharge because (1) the nitinol frame did not fully expand likely because of the thickness of ePTFE in the first-generation device construct, (2) LV calcification prevented the device from being secured, and (3) unrelated splenic abscess with sepsis resulting in precautionary device removal at day 15 postimplant. Minor vascular complications

<table>
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<th>Table 1. Baseline Characteristics</th>
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<td><strong>Device success</strong></td>
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<td><strong>Prior ICD implantation</strong></td>
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<td><strong>Prior CABG surgery</strong></td>
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Data are presented as either percent or mean±SD for subjects where treatment was attempted. CABG indicates coronary artery bypass grafting; CRT, cardiac resynchronisation therapy; HF, heart failure; ICD, implantable cardioverter defibrillator; LV, left ventricular; and PCI, percutaneous coronary intervention.
related to the femoral access site were noted in 14.7% (4 of 34) of subjects. There were no major vascular complications or aortic valve injuries.

**Hemodynamic and Functional Outcomes**

At 3-year follow-up, echocardiograms were available for 20 of 23 active subjects. Figure 4 shows New York Heart Association class distribution for 3 years postprocedure. Symptomatic improvements were evident in 52% of subjects, with no change in 33% and worsening in 15% of subjects for 3-year follow-up. The Minnesota Living with Heart Failure and 6-minute walk test have been reported previously in the 12-month follow-up report. Complementary data supporting the hemodynamic and functional improvements were collected on a subset of patients. Invasive pressure monitoring data were available in 10 subjects showing a 29% reduction in LV end-diastolic pressure at 6 months postprocedure ($P<0.05$). Available serial echocardiographic data are reported in Tables 2 and 3 and Figures 5 and 6. Improvements in LV volume indices were sustained through the 3-year follow-up. In contrast to other interventions such as neurohormonal antagonists and cardiac resynchronisation therapy, the Parachute device reduction in LV volume occurs immediately post-treatment with no further decrease over time.

**Clinical Outcomes**

The primary safety end point, defined as the successful delivery and deployment of the Parachute device through 6-month follow-up without the occurrence of major adverse cardiac events related to the investigational device, was met by 29 of 34 patients (85.3%). The incidences of clinical adverse events for 12, 24, and 36 months are listed in Table 4. There were no strokes at 1-year follow-up, 1 ischemic stroke at 24-month follow-up, and 1 ischemic and 2 hemorrhagic strokes at 36-month follow-up. No cardiac deaths occurred after 6 months post-treatment, and the overall 3-year incidence of death was 13.9%. Noncardiac deaths occurred in 2 subjects. One death, in relation to lung cancer, occurred at 28 months and the other death, related to cerebral hemorrhage, occurred at 29 months. The 3-year cumulative incidence of HF hospitalization was 33%. The combined measure of death or HF hospitalization was 38.7% (Figure 7).

**Discussion**

The PARACHUTE study introduces a novel approach, namely PVR, to treat subjects with ischemic HF and akinetic or dyskinetic anterior-apical wall. The long-term outcomes observed in this first series of subjects treated with the Parachute device demonstrated the feasibility and safety of PVR. These preliminary results show reduction of LV volumes for ≤3 years postimplant and concomitant improvements in HF symptoms. There were no cardiac deaths past 6 months, and the risk of hospitalization between year 2 and 3 was <5%. In the absence of a control group, these findings should be interpreted cautiously.

Medications such as angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, β-blockers, and aldosterone antagonists remain the cornerstone of HF therapy. Patients with advanced HF and ventricular dyssynchrony are most likely to benefit from simultaneous pacing of both right and left ventricles. In addition, surgical interventions to repair dysfunctional cardiac valves, bypass coronary artery disease, LV assist devices, and ultimately heart transplantation are integral components of modern strategies to improve outcomes of subjects with HF. In spite of these advances in both pharmacological and mechanical therapeutic approaches.
to HF, the overall mortality remains high at 32% in the first year after a HF hospitalization. Five-year mortality from Framingham Heart Study and Hillingdon Heart Failure Study after the onset of HF was 65%. A recent meta-analysis highlighted the critical role of LV end-systolic and end-diastolic volume reduction for the success of pharmacological and mechanical approaches to HF. However, the data reported in this report have to be interpreted with caution because the compiled data did not include mechanical or direct reduction of LV volume, such as produced by PVR therapy. Reduction in LV volumes in subjects with dilated cardiomyopathy has been the target of SVR, with promising results reported by experienced centers. Unfortunately, the ability to surgically reconstruct an elliptical shape of the LV cavity with appropriate degree of volume reduction may vary significantly among operators. Furthermore, the SVR approach is not without operative risk, and it has been associated with malignant ventricular arrhythmias. A recent multicenter trial investigating the role of SVR combined with coronary artery bypass grafting was unable to demonstrate clinical benefits when compared with coronary artery bypass grafting alone. Several hypotheses have been postulated to explain the failure of SVR in STICH (Surgical Treatment for Ischemic Heart Failure), including the fact that 50% of subjects did not have akinetic/dyskinetic wall motion, the study entry criteria were based on ischemic symptoms with 50% of subjects in New York Heart Association class I to II HF, and thus reduction in LV volumes were relatively modest. A recent study using untagged MR images to create patient-specific mathematical LV models before and after SVR provided a mechanistic explanation to the STICH trial results. The authors noted increase in LV sphericity after SVR, which contributes to a depressed Starling relationship and diastolic dysfunction that likely counterbalanced the potential beneficial effects of LV volume reduction.

A percutaneous approach to ventricle restoration may achieve volume reduction with a more reproducible reconfiguration of the conical shape of the LV cavity in a less invasive manner. The Parachute device is the first device designed to achieve this goal.
specifically for PVR to treat subjects who have ischemic cardiomyopathy with akinetic/dyskinetic anterior wall motion and HF symptoms. The device shape was designed to partition the damaged, noncontractile myocardium while creating a new apex and restoring the elliptical shape of the LV cavity in a reproducible manner. The nitinol construct permits contraction of the underlying healthy myocardium. The percutaneous nature of the procedure, which is performed under local anesthesia, may minimize operative risk and avoid suture-related myocardial scar. There are several possible mechanisms by which the implant of the Parachute device may improve cardiac performance and explain these preliminary positive results: (1) reduction of volumes and partition of nonviable myocardium may reduce contractile wall stress; (2) the shape of the device and its nitinol framing may help restore the elliptical shape of the LV cavity and allow systolic torsion, respectively; (3) partition of the scarred anteroseptal wall with a conical shaped nitinol frame covered with ePTFE may improve diastolic compliance. The ongoing, large US pivotal trial, PARACHUTE IV, will examine paired echocardiographic data to further define this response to treatment and to assess the more subtle changes of myocardial performance such as strain analysis, e/E′, and other measures of diastolic function.

Limitations
The study does have limitations given its small sample size and unblinded, single-arm nature. Because of this study design, one cannot rule out potential bias in the adjudication process, and without a control group efficacy, conclusions cannot be made.

Conclusions
The favorable long-term outcomes observed in this high-risk population are certainly not definitive, but provide reassuring safety and feasibility data to support further investigations. The ongoing, large-scale randomized clinical trial in the United States will be critical to validate the present results and establish the role of this novel therapeutic approach for patients with ischemic HF.

Appendix
Sinisa Gradinac, MD, PhD, FETCS; Dragan Sagic, MD; Petar Otasevic, MD; Ayesha K. Hasan, MD, FACC; Thomas L. Goff, MD; Nina Wunderlich, MD; Venita DePuy, PhD;

| Table 4. Cumulative Percentages of Subjects Experiencing Clinical Outcomes by Time Period |
|----------------------------------|-----------------|-----------------|-----------------|
|                                  | 12 mo (n=31)    | 24 mo (n=28)    | 36 mo (n=27)    |
| Mortality, % (n)                 | 6.5% (2)        | 6.5% (2)        | 13.9% (4)       |
| Cardiac mortality, % (n)         | 6.5% (2)        | 6.5% (2)        | 6.5% (2)        |
| Mortality plus HFH, % (n)        | 16.1% (5)       | 32.3% (10)      | 38.7% (12)      |
| HFH, % (n)                       | 12.9% (4)       | 29.7% (9)       | 33.0% (10)      |
| VAD or transplant, % (n)         | 3.5% (1)        | 6.9% (2)        | 13.8% (4)       |
| Stroke, % (n)                    | 0% (0)          | 3.6% (1)        | 15.9% (4)       |

Three subjects did not complete the 12-mo visit (2 deaths, 1 transplant). One subject did not complete the 24-mo visit (1 transplant). Four subjects did not complete the 36-mo time point (2 deaths, 2 VADs). HFH indicates heart failure hospitalization; and VAD, ventricular assist device.

Figure 7. Kaplan-Meier curves for mortality, heart failure hospitalization (HFH), and the combination of HFH and mortality.
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Disclosures

M.A. Costa and W.T. Abraham are paid consultants for CardioKinetics. V. DePuy is a statistician hired by CardioKinetics. S. Gradinac has received stock options as compensation for consulting. The other authors report no conflicts.

References


CLINICAL PERSPECTIVE

Advanced heart failure is a deadly and costly medical condition. Current therapeutic options are limited, and the number of patients with heart failure continues to grow every year. There is a paucity of new therapies being developed to treat heart failure. This report provides seminal data on the potential of a novel therapeutic option, namely percutaneous ventricular restoration using the Parachute device, to improve outcomes among select patients with post–myocardial infarction heart failure. The feasibility and safety of percutaneous ventricular restoration was demonstrated, and ongoing, large randomized clinical trials will define its clinical effectiveness.
Percutaneous Ventricular Restoration Using the Parachute Device in Patients With Ischemic Heart Failure: Three-Year Outcomes of the PARACHUTE First-in-Human Study
Marco A. Costa, Ernest L. Mazzaferri, Jr, Horst Sievert and William T. Abraham

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