Percutaneous Ventricular Restoration Therapy Using the Parachute Device in Chinese Patients with Ischemic Heart Failure: Three-Month Primary End-point Results of PARACHUTE China Study

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Abstract

Background: The primary cause of ischemic heart failure (HF) is myocardial infarction (MI) resulting in left ventricle (LV) wall motion abnormality secondary to ventricular remodeling. A prospective, nonrandomized study conducted in China was designed to assess safety and efficacy of the percutaneous ventricular restoration therapy using Parachute device (CardioKinetix, Inc., CA, USA) in ischemic HF patients as a result of LV remodeling after anterior wall MI.

Methods: Thirty-one patients with New York Heart Association (NYHA) Class II, III ischemic HF, ejection fraction between 15% and 40%, and dilated akinetic or dyskinetic anterior-apical wall without the need to be revascularized were enrolled from seven sites in China from October to December 2014. The Parachute device was implanted through femoral artery. All patients received low-dose aspirin and anticoagulation with warfarin for at least 12 months postdevice implantation. The primary end-point was the assessment of efficacy as measured by the reduction in LV end-systolic volume index (LVESVI) against baseline LVESVI at 3 months postdevice implantation, determined by the echocardiography and measured by echocardiography core laboratory. Quality of life was assessed using EQ-5D and visual analog scale (VAS). For quantitative data comparison, paired *t*-test (normality data) and signed-rank test (abnormality data) were used; application of signed-rank test was for the ranked data comparison.

Results: A change in LVESVI as measured by echocardiography from the preimplant baseline to 3-month postdevice implantation revealed a statistically significant reduction from 77.5 ± 20.0 ml/m^2 to 53.1 ± 17.0 ml/m^2 ($P < 0.0001$). The trial met its primary end-point. Of the 31 patients, the procedural success was 96.8%. Overall, NYHA HF class assessment results showed an improvement of more than half a class at 3 months ($P < 0.001$). Quality of life assessed by the VAS value increased 11.5 points ($P < 0.01$), demonstrating improvement at 3 months.

Conclusion: The favorable outcomes observed in the high-risk patients provide reassuring safety and efficacy data to support adoption of this technology as a therapeutic option for ischemic HF patients.

Trial Registration: ClinicalTrials.gov, NCT02240940; https://clinicaltrials.gov/ct2/show/NCT02240940.

Key words: Ischemic Heart Failure; Left Ventricle Remodeling; Percutaneous Ventricular Restoration; Structural Heart

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Introduction

During the past decade, the number of hospitalizations for acute myocardial infarctions (MIs) has risen drastically in China. Between 2001 and 2011, estimated national rates of hospital admission for ST-segment elevation myocardial infarction (STEMI) increased (3.7/100,000 in 2001, 8.1/100,000 in 2006, 15.8/100,000 in 2011; $P < 0.0001$).[1] The primary cause for ischemic heart failure (HF) is myocardial damage, resulting in left ventricle (LV) wall motion abnormality secondary to an MI.[2,3] If left untreated, LV remodeling will continue hindering the viable muscle fibers and reducing the LV's ability to contract, which has been well-characterized.[3] The remodeling cycle will continue causing further decline in the patient's health status as the symptoms of HF increase rapidly. Once hospitalized for HF, the overall one-year mortality remains unacceptably high at 32% in spite of modern pharmacological and mechanical approaches.[4]

The concept of percutaneous ventricular restoration (PVR) of the LV is based on the premise that a dedicated partitioning, compliant device delivered through a catheter-based approach may achieve LV volume reduction, geometric reconfiguration, and synchronized wall motion to achieve a more effective ejection while minimizing the risk of a surgical approach.[5]

Methods

Study design

The Percutaneous Ventricular Restoration in Chronic Heart Failure due to Ischemic Heart Disease (PARACHUTE) China study was a prospective, nonrandomized, observational study conducted in seven medical centers in China designed to assess safety and efficacy of the Parachute device. Following implantation of the device, clinical and echocardiographic follow-up was performed at 3 months. An additional protocol was developed with additional follow-up visits at 6 months and 1 year.

Subject selection

The study included patients of symptomatic ischemic HF with New York Heart Association (NYHA) Class II, III, or nonhospitalized IV before enrollment. The patients were at least 18 years of age with LV wall motion abnormalities (anteroapical akinesis or dyskinesis) secondary to MI, an LV ejection fraction (EF) between 15% and 40% determined by the echocardiography and measured by echocardiography core laboratory (core lab). All patients were managed with stable doses of standard HF medical therapy. Patients with myocardial ischemia who underwent revascularization or cardiac resynchronization therapy within 60 days of enrollment and those with significant valvular (tricuspid, mitral, or aortic) stenosis or regurgitation >2+ were excluded from the study. Device sizing and anatomical approval were granted by the central computed tomography (CT)/magnetic resonance imaging (MRI) core lab. All sites obtained approval from the Ethics Committee before the study commencement and written informed consent was obtained for all patients at the appropriate time before involvement in the study.

Study device and procedure

The Parachute system (CardioKinetix, Inc., CA, USA) includes the device, a delivery system with a balloon that facilitates the expansion of the device, and a preshaped delivery catheter and dilator. The Parachute device is comprised a self-expanding nitinol frame, an expanded polytetrafluoroethylene impermeable membrane, and an atraumatic polymer foot, which has eight sizes (65, 75, 85, and 95 mm in diameter, each offered in two "foot" heights). The distal atraumatic foot is radiopaque and provides a contact point on the LV apical wall. The contact point is selected to orient the device with a vector toward the outflow tract.

The procedure was performed in a catheterization laboratory with the patients usually under conscious sedation. Device size selection was based on multi-slice CT, which also allowed identification of any LV apical thrombus, pseudochorda, or severe calcification, which could have precluded safe deployment. All patients received low-dose aspirin and anticoagulation with warfarin for at least 12 months postdevice implant.

Data collection and oversight

All study-related data were collected on standardized case report forms. Study-mandated echocardiograms were sent to an Independent Core Laboratory (Yale Cardiovascular Research Group, Yale University, School of Medicine, New Haven, CT, USA). All study-mandated CTs or MRIs were sent to an Independent Core Laboratory (University Hospitals Case Medical Center Cardiovascular Imaging Core Laboratories, Cleveland, OH, USA). Data management was performed by an independent contract research organization (Peking University Clinical Research Institute). On-site monitoring was performed on 100% of the data.

Study end-points

The primary end-point of the PARACHUTE China study was the assessment of efficacy as measured by the reduction in left ventricle end-systolic volume index (LVESVI) against baseline LVESVI at 3 months postdevice implantation. The functional LV volume was used in the follow-up echocardiographic variables. The functional volume was defined as total LV volume minus the partitioned volume by the Parachute device. The secondary end-points consisted of procedure- or device-related major adverse cardiovascular event (MACE), improvement in NYHA class at 3 months compared to baseline, improvement in quality of life using EQ-5D and visual analog scale (VAS) at 3 months compared to baseline, improvement in 6 min walk test at 3 months compared to baseline, technical success measured by success in releasing the implant, and combined clinical and technical success measured by success in releasing the implant without serious adverse events, additional interventional surgeries, embolisms, or technical failure. Where MACE is defined as

death from any cause, MI is defined as needing for elective or urgent cardiac or thoracic aortic surgery or needing for the use of device or device surgery with a catheter as the basis of interventional therapy, or renal failure requiring dialysis.

Statistical design and statistical analysis

The sample size of the trial was based upon an estimated change in LVESVI of 14 ± 14 ml/m^2 from prior European and United States data. In addition, the following criteria were used to determine the sample size: two-tailed, $\alpha = 0.05$, and power ≥90%, $\beta = 0.10$. Considering dropout and potential echo quality for analysis, the sample size was determined to be thirty patients.

The primary end-point and secondary safety end-point analyses would be performed on the intention-to-treat (ITT) population and who had been discharged from the hospital after being treated with the study device. The MACE and other safety end-point analysis would be performed on the safety data set. Separate analyses for the effectiveness end-points would be performed on the as-treated population. Baseline characteristics were summarized using mean ± standard deviation (SD) for continuous variables and counts and percentages for categorical variables. For quantitative data comparison paired *t*-test (normality data) and signed-rank test (abnormality data) were used; application of signed-rank test was for the ranked data comparison. All statistical tests were performed using two-sided test; $P \leq 0.05$ was considered statistically significant. All analyses were performed using SAS version 9.3 (SAS, Cary, NC, USA).

Results

Subject population

Between October 2014 and December 2014, 31 patients were enrolled into the study [Table 1]. There were no major protocol inclusion and exclusion violations for the study.

Table 1: Baseline characteristics of Parachute-treated patients (*n* = 31)

Characteristics	Value
Age (years), mean ± SD	57.1 ± 10.4
Gender (male), *n* (%)	29 (93.6)
BMI (kg/m^2), mean ± SD	25.0 ± 2.2
Smoking history, *n* (%)	20 (64.5)
Ischemic etiology, *n* (%)	31 (100.0)
History of hypertension, *n* (%)	20 (64.5)
History of diabetes, *n* (%)	9 (29.0)
Prior ICD implantation, *n* (%)	0 (0)
Prior pacemaker, *n* (%)	1 (3.2)
Prior PCI, *n* (%)	28 (90.3)
Prior CABG surgery, *n* (%)	0 (0)
NYHA Class III, *n* (%)	2 (6.4)
NYHA Class II, *n* (%)	29 (93.6)

BMI: Body mass index; ICD: Implantable cardioverter-defibrillator; CRT: Cardiac resynchronization therapy; PCI: Percutaneous coronary intervention; CABG: Coronary artery bypass grafting; NYHA: New York Heart Association; SD: Standard deviation.

Baseline characteristics

While all of the patients must have had a diagnosis of NYHA Class II, III, or IV before enrollment to be included in the study, 94% were Class II and 6% were Class III at time of their baseline assessment. Ischemic heart disease was present in all patients with more than 90% having their left anterior descending artery MI within 12 months of enrollment. Most patients were male (94%) and 90% had a prior percutaneous coronary intervention. Baseline medication usage for this population was aspirin (94%), clopidogrel (61%), ACEi (39%), ARB (32%), beta-blockers (84%), and diuretic (29%) along with no change at the 3-month follow-up.

Procedural outcomes and complications

All four diameters (65, 75, 85, and 95 mm) of the Parachute were implanted in 35%, 26%, 16%, and 23% of patients, respectively. Of the 31 ITT patients, the procedural success was 96.8%. In one patient, the device was explanted before discharge due to nonoptimal positioning of a device resulting in a successful surgical removal. Only one major vascular complication was noted and that was a groin hematoma at the femoral access site. There were no procedure complications from the following categories: life-threatening or disabling bleeding events due to an overt source of bleeding requiring more than units of blood, aortic valves requiring surgical repair, LV perforations, arrhythmic, or stroke events.

Primary end-point

The primary end-point was the reduction in mean LVESVI at 3 months postdevice implantation compared with baseline LVESVI. The baseline LVESVI was 77.5 ± 20.0 ml/m^2. At 3 months postdevice implantation, the average LVESVI was 53.1 ± 17.0 ml/m^2, yielding a mean reduction of 24.3 ml/m^2 (95% confidence interval: −28.870–−19.800) and an associated $P < 0.0001$; therefore, the primary end-point of the study was successfully met. Furthermore, the systolic function, including EF, fractional shortening, etc., was also improved. A complete table of hemodynamic variables is shown in Table 2.

Safety outcomes (major adverse cardiovascular event)

The primary safety end-point (MACE) at 3 months was 3% measured by procedural or device related MACE. The single device-related MACE was an acute procedural surgical removal of an implant due to nonoptimal position preventing the device from anchoring in the appropriate location in the LV. There was one nondevice- or nonprocedure-related hemorrhagic stroke resulting in death. The stroke developed more than a month after the procedure probably due to warfarin anticoagulation. All MACE outcomes are shown in Table 3.

Functional outcomes

As an end-point analysis, the change in exercise tolerance as measured by 6-min walk distance from the preimplant baseline through 3 months was not statistically significant. The baseline distance was 479.9 ± 81.4 m. At 3 months, the

Table 2: Hemodynamic outcomes for Parachute-treated patients at 3 months

Items	*n*	Baseline	3 months	Statistics value	*P*
Heart rate (beats/min)	30	66.6 ± 10.2	69.8 ± 12.3	92.50*	0.03
Blood pressure (mmHg)					
Systolic	30	121.6 ± 17.0	126.4 ± 14.2	2.30	0.03
Diastolic	30	74.3 ± 10.8	73.8 ± 11.8	−0.36	0.72
LV volume (ml/m^2)					
ESVi	30†	77.5 ± 20.0	53.1 ± 17.0	−10.97	<0.001
EDVi	30†	110.8 ± 26.1	82.1 ± 21.3	−9.59	<0.001
Systolic function					
Ejection fraction (%)	30	30.0 ± 5.4	35.8 ± 6.8	5.19	<0.001
Fractional shortening (%)	29	18.3 ± 5.7	22.8 ± 7.2	2.78	0.01
Contractility index (mmHg·m^{-2}·ml^{-1})	28	1.5 ± 0.4	2.4 ± 0.9	7.79	<0.001
Stroke work/EDVi (mmHg)	28	29.2 ± 5.5	35.9 ± 8.8	4.40	<0.001
Wall motion severity index	30	2.6 ± 0.2	2.0 ± 0.3	−9.29	<0.001
Diastolic function					
LAVi (ml/m^2)	28	32.3 ± 8.4	32.7 ± 8.3	0.96	0.047

*Value used the signed-rank test, the others used paired *t*-test; †The functional LV volume is used in the follow-up echo variables. The functional volume is defined as total LV volume minus the partitioned volume by the Parachute device. The missing values of LV volume estimates used the closest one last observation carried forward estimation method. EDVi: End-diastolic volume index; ESVi: End-systolic volume index; LAVi: Left atrial volume index; LV: Left ventricle.

distance was 487.7 ± 101.6 m ($P = 0.27$). NYHA HF class assessment results for the treated population are shown in Table 4. Overall, there was an improvement of more than half a class ($P < 0.001$) at 3 months seen in the treated subject population.

Quality of life was assessed using EQ-5D and VAS. At 3 months, the VAS value increased 11.5 points ($P < 0.01$) demonstrating an improvement of quality of life. In addition, a trend in an increased ability to conduct daily activities ($P = 0.13$) and a trend in patients feeling less anxious and depressed ($P = 0.13$) were observed.

Discussion

The PARACHUTE China study met the primary end-point. A change in LVESVI as measured by echocardiography significantly reduced from the preimplant baseline to 3 months (77.5 ± 20.0 ml/m^2 vs. 53.1 ± 17.0 ml/m^2, $P < 0.0001$). The systolic function was also improved. The percentage of success was very high. Only one device-related MACE was an acute procedural surgical removal of an implant due to malposition. NYHA HF class assessment and quality of life were also improved. The exercise tolerance as measured by 6-min walk distance was not significantly changed statistically from the preimplant baseline through 3 months. However, the sample size was not powered for assessing the exercise tolerance. Due to the variability in the data, a sample size of approximately 60 patients would be needed to show statistical significance whereas only 25 patients in this study completed both the baseline and 3-month test. In addition, it was found that three patients with a significant decrease in distance compared to baseline had overexerted themselves on the day of the follow-up visit.

While the PARACHUTE China trial was the first in the series of Parachute device trials to include mainly NYHA II patients, there were similar baseline anatomical characteristics such as EF and end diastolic volume across all trials. However, there was one major difference that should be noted which is the time from the MI to the HF symptoms. The average duration in the previously reported data from Europe and the United States was approximately

Table 3: MACE in population (*n* = 31), *n* (%)

Events	Cases
MACE	2 (6.4)
Noncardiac death	1 (3.2)
Cardiac death	0 (0)
Myocardial infarction	0 (0)
Stroke	1 (3.2)
Elective or emergent cardiac surgery	1 (3.2)
Erosion of device thru LV	0 (0)
Cardiac tamponade	0 (0)
Endocarditis or device infection	0 (0)
Device migration or embolization	0 (0)
Placement of mechanical support	0 (0)
Transplant	0 (0)
Vascular procedure complication	1 (3.2)
Groin hematoma	1 (3.2)

MACE: Major adverse cardiovascular event; LV: Left ventricle.

Table 4: Changes of NYHA classes from baseline to 3 months

NYHA heart failure class	Baseline (*n* = 31)	3 months (*n* = 30)	Statistics value	*P*
Class I, *n* (%)	0 (0)	18 (60.0)	105.00	<0.001
Class II, *n* (%)	29 (93.6)	12 (40.0)		
Class III, *n* (%)	2 (6.4)	0 (0)		
Class IV, *n* (%)	0 (0)	0 (0)		

NYHA: New York Heart Association.

6 years. The average duration in the Parachute China trial was approximately 1 year. One could make the case that treating earlier in the LV remodeling process provides more viable tissue that compliments the mechanistic theory of the PARACHUTE which is to reduce volume, thereby reducing wall stress in the upper chamber of the LV, and to synchronize wall motion during systolic contraction by replacing the eccentric wall motion in the apical region with a more compliant device. The benefits of reducing wall stress and synchronizing apical wall motion throughout the cardiac cycle allow for improved cardiac output and reduced filling pressure. One key observation in the hemodynamic response of the Chinese patients versus previously published Parachute data is the much greater improvement in systolic function, specifically EF and end systolic volume index.[5,6] A likely theory may be that the Chinese patients were treated earlier in the progression of HF (i.e., NYHA II) whereby the basal and mid LV function responded better to a reduction in wall stress and improvement in synchronized contraction.

The PARACHUTE China study confirms the safety and effectiveness of PVR, to treat patients with ischemic HF and akinetic or dyskinetic anterior-apical wall. The outcomes observed in patients treated with the Parachute device not only met the study objectives but also are consistent with previous data reported from Europe and the United States.

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

In conclusion, the favorable outcomes observed in this high-risk population provide reassuring safety and efficacy data to support adoption of this technology as a therapeutic option for ischemic HF patients.

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Conflicts of interest

There are no conflicts of interest.

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