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ORIGINAL ARTICLE

Percutaneous Ventricular Restoration Using the Parachute Device: The Parachute III Pressure-Volume Loop Sub-study

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ABSTRACT

Background: Left ventricular (LV) dilatation and remodeling following acute myocardial infarction increases wall stress, ventricular volumes and leads to heart failure (HF), which is associated with a high mortality. Percutaneous ventricular restoration (pVR) therapy reduces LV volumes leading to a more effective ejection. This study investigated the hemodynamic effects of LV volume reduction from pVR on LV performance and its interaction with the arterial system.

Methods: Ten patients with symptomatic ischemic HF of New York Heart Association (NYHA) classes II to IV with LV antero-apical wall motion abnormalities underwent Parachute implantation. Pressure-volume loops were recorded immediately pre- and post-pVR implantation and at 6-month follow up.

Results: Parachute implantation significantly reduced end-diastolic volume index (from 112 ± 39 mL to 100 ± 41 mL; $p < 0.05$), with a greater relative reduction in end-systolic volume index (from 66 ± 33 mL to 56 ± 32 mL; $p < 0.05$) with an overall 7% increase in ejection fraction (from 38 ± 11 to 46 ± 14%; $p < 0.05$). Furthermore, there was an observed reduction in dyssynchrony index (from 20 ± 4 to 14 ± 6%; $p < 0.05$) and enhanced contractile function (Ees) immediately post-procedure, sustained at 6-months (from 0.92 ± 0.27 mmHg/mL to 1.37 ± 0.52 mmHg/mL, $p < 0.05$).

Conclusion: This present study confirms positive hemodynamic effects of LV volume reduction using the Parachute percutaneous ventricular restoration device. The Parachute device improved synchronous contraction and enhanced ventricular-arterial interaction likely due to LV reverse remodeling.

ARTICLE HISTORY Received 9 May 2017; Accepted 9 May 2017

KEYWORDS Ischemic heart failure; left ventricle remodeling; structural heart

Introduction

Left ventricular (LV) dilatation and remodeling is commonly associated with anterior myocardial infarction (AMI).[1–3] It occurs in about one third of patients and often precipitates progression toward chronic heart failure (CHF).[1,2] Despite advances in standard of care, the onset of CHF leads to poor outcome with high mortality risk.[2,3] An important measure of therapeutic efficacy in post AMI cardiac failure is LV volume reduction and improved geometry, which is an independent predictor of improved clinical outcomes.[4] Percutaneous ventricular restoration (pVR) therapy is a catheter-based approach to partition dyskinetic apical myocardial segments using a PARACHUTE device. Initial studies demonstrated safety and feasibility with improved New York Heart Association (NYHA) functional status, left ventricular volumes and ejection fraction.-[5,6] The mechanisms underlying the benefit is hypothesized to relate to improved contractile efficiency by reducing wasted energy expenditure consumed by normal muscle pumping blood into the dyskinetic apex.[7] Accurate assessment of cardiac performance is critical in CHF to gauge prognosis and assess therapeutic response. The gold standard for assessing cardiac performance and its interaction with the arterial system is pressure-volume (PV) analysis. Simultaneous *in-vivo* pressure-volume measurements with a conductance catheter (CC) placed in the LV allow real-time assessment of the cardiac performance and its interaction with arterial load.[8] Accordingly, the objective of this study was to investigate immediate and mid-term hemodynamic effects of pVR on LV performance and ventricular-arterial interactions via PV analysis in a cohort of patients with aneurysmal apices secondary to myocardial infarction.

Materials and methods

Study design

The PARACHUTE III (PercutAneous Ventricular RestorAtion in Chronic Heart FailUre due to Ischemic HearT DiseasE) PV Loop sub-study was a prospective, single arm study conducted in two centers in Europe. The study was designed to assess the hemodynamic effects of the PARACHUTE device through investigation of immediate changes in LV PV relationships

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during pVR using a CC and to relate these findings to acute hemodynamic changes and 6-month hemodynamic and clinical outcomes.

Patient selection

Participants with symptomatic ischemic heart faliure (HF) of NYHA classes II to IV were included in this study. Participants were between 18 and 79 years of age (inclusive) with LV antero-apical wall motion abnormality (akinesis or dyskinesis) secondary to myocardial infarction; LV ejection fraction between 15% and 40%, and managed with optimal medical therapy for at least 3 months, as determined by the site investigator. Subjects with myocardial ischemia requiring revascularization or cardiac resynchronization therapy (CRT) within 60 days, and those with significant valve disease were excluded from the study. Both 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 Parachute device, the pre-shaped delivery catheter and dilator, and the balloon delivery system that facilitates expansion of the device (Figure 1). The Parachute device is composed of a self-expanding nitinol frame (16 struts; radio-opaque), an ePTFE impermeable membrane, and an atraumatic polymer foot available in four sizes (65, 75, 85 and 95 mm) with two different "foot" heights. The tips of the struts anchor the device on the myocardium and the atraumatic foot provides contact between the LV apex and the device, orientating it toward the LV outflow tract.

As per protocol, subjects were enrolled based on the following criteria: (1) signed informed consent form; (2) baseline evaluation for anatomical suitability and device compatibility performed using echocardiography, multi-slice computed tomography (CT) or cardiac magnetic resonance imaging (Figure 2); and (3) successful placement of a 14F or 16F sheath in the femoral artery and pulmonary artery catheter in the femoral vein. Multi-modality imaging was also used to provide accurate measurements and to exclude LV thrombus and severe calcification. The procedure is described in Figure 3, and was performed under conscious sedation in the catheterization laboratory.[9,10] All subjects were required to receive 12 months of aspirin and anticoagulation with warfarin post–device implant.

Pressure-volume measurements

Simultaneous LV PV measurements were performed immediately prior to and following the Parachute implant and at 6-months post implantation. Hemodynamic measurements obtained before and after Parachute implantation were performed under conscious sedation; hemodynamic measurements at 6-month follow up were performed under local anesthesia. Measurements were performed during steady-state conditions, avoiding excessive arrhythmia from premature beats. Recorded variables were averaged from 10 cardiac cycles to minimize inaccuracies from beat-to-beat variation and change in venous return from respiration; repeat baseline recordings ensured reproducibility of CC measurements.

PV measurements were performed using a 7Fr CC (CD Leycom, Zoetermeer, the Netherlands); this flexible over-the-wire pigtail catheter is introduced into the LV using a super-stiff 0.025" J-wire. The catheter has 12 equally spaced

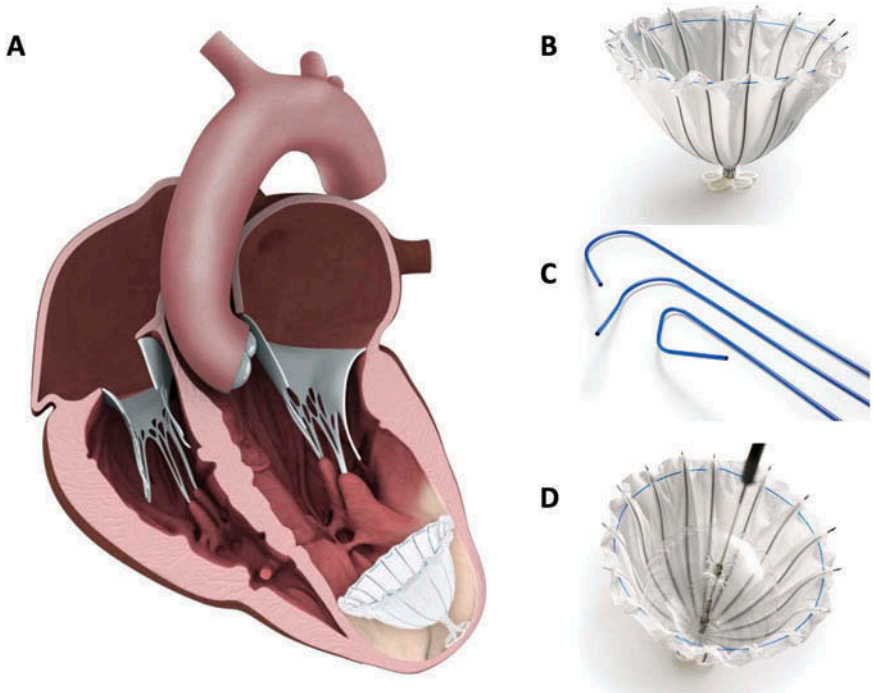

Figure 1. A Parachute device. The left panel demonstrates an illustration of the Parachute device implanted in a dilated left ventricle (A). The right panels demonstrate an open Parachute device (B), various shapes of the delivery catheters (C), and the 20cc balloon delivery system (D).

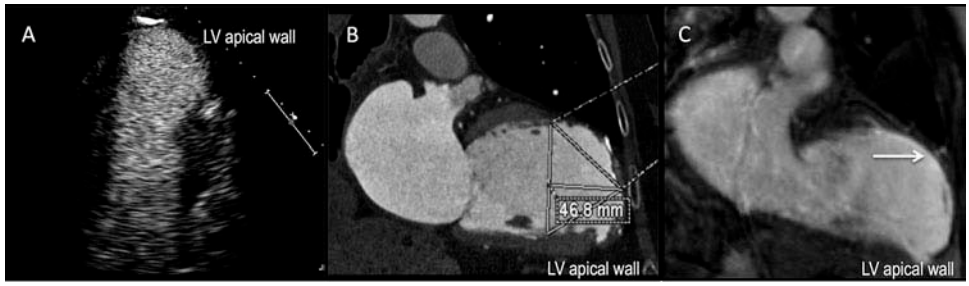

Figure 2. Baseline patient evaluation. Anatomical assessment is performed using echocardiography with contrast to demonstrate aneurysmal apical wall and exclude thrombus (A). Device selection was based on multi-slice computed tomography, which also allowed for identification of pseudochordae or severe calcification, precluding safe deployment (B). Cardiac magnetic resonance imaging with late gadolinium enhancement confirms scarring of the LV apical wall secondary to myocardial infarction, white arrow (C).

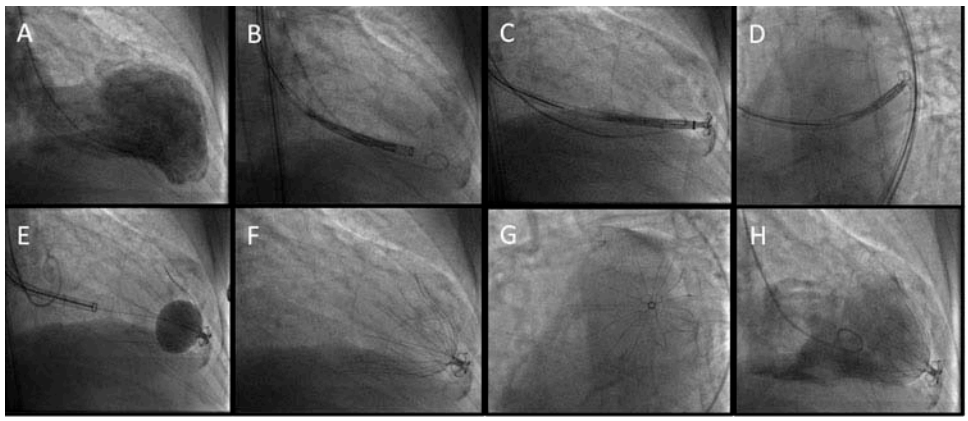

Figure 3. Parachute study procedure. The sequence of parachute implantation in the LV: LV angiography is performed with a pigtail catheter in the LV (A) followed by pre-procedure PV measurements, the delivery catheter is position in the apex (B), the Parachute foot is then exposed and contact is made with the antero-apical wall, confirmed in LAO (C) and RAO (D) views. Device delivery is facilitated by 20 cc balloon expansion (E), retraction of the delivery system, followed by fluoroscopic confirmation of position in LAO (F) and RAO (G) views. LV angiogram confirms partitioning of dyssynchronous myocardium (H) and immediate post-procedure LV PV measurements are performed.

electrodes with a central high fidelity, solid-state pressure sensor and is connected to a PV signal processor (Inca, CD Leycom). The conductance method calculates continuous LV volume tracings by measuring electric conductance between adjacent ventricular blood segments delineated by selected catheter electrodes; this technique has been shown to reflect LV segmental volumes in pre-clinical and clinical studies and has been utilized in the assessment of heart failure device therapies.[11–13] Accurate CC positioning is confirmed by fluoroscopy and on inspection of the segmental PV loop signals. LV volume calibration was performed via right-heart catheterization. A 6Fr single-lumen, balloon tipped Swan-Ganz catheter (Arrow International, PA) was positioned in the pulmonary artery to perform thermodilution and determination of calculated parallel conductance (which was subtracted from the raw CC volume) which was performed by injection of 10 mL boluses of 5% hypertonic saline through the distal port of the Swan-Ganz catheter.[14]

Data analysis

CC data analysis was performed with dedicated data acquisition and analysis software (Conduct NT, version 3.18.1, CD Leycom). End-diastolic and end-systolic volumes (EDV and ESV, respectively) were calculated at the maximum rate of LV pressure rise (dP/dt+) and pressure decay (dP/dt−), stroke volume was calculated as the difference in these volumes. End-diastolic volume index (EDVI) and end-systolic volume index (ESVI) are the ventricular volumes indexed to body surface area reported in mL/m^2. Stroke volume index (SVI) is the stroke volume (EDV − ESV) indexed to body surface area reported in mL/m^2. In addition to instantaneous LV volumes and end-systolic (ESP) and end-diastolic pressures (EDP), this software calculates various parameters related to LV contractility.[15] The slope (Ees) and volume-axis intercept (Vo) of the end-systolic pressure volume relationship (ESPVR) and the parameters of the nonlinear equation describing the end-diastolic pressure volume relationship (EDPVR) (EDP = beta (exp(alpha(V-Vo))-1) were calculated using previously validated single-beat (SB) methods.[16,17] LV stroke work was calculated as the product of peak LV systolic pressure and stroke volume.[13,18] Effective arterial elastance (Ea) was calculated as the ratio of SV to end-systolic pressure (ESP). The Ea:Ees ratio was used to quantify ventricular-arterial coupling. Dyssynchrony index (DS) was calculated as the mean of the segmental dyssynchronies.[19] The latter is quantified as percentage time within the cardiac cycle that a segment is dyssynchronous, defined as segmental change in volume in time (dVseg/d*t*) opposite to the simultaneous change in the total LV volume (dVLV/d*t*) in time. This has

been shown to have a high sensitivity and specificity for dyssynchrony and has been validated with tissue Doppler echocardiography.[20] Pressure-volume area (PVA) was estimated as the sum of stroke work (SW) and elastic potential energy according to the following equation:[21]

$$PVA = SW + \left(\frac{0.5\,x\,ESP^2}{Ees}\right)$$

Efficiency of LV energy transfer, calculated as SW/PVA × 100, is the stroke work expressed as a % of total mechanical energy expenditure. Participant follow up at 6-months was performed with elective admission for repeat invasive hemodynamic assessment. This included clinical follow up and assessment of functional status, transthoracic echocardiography and multi-slice CT. Clinical endpoints were: death, recurrent hospitalization, emergency surgery, NYHA functional class and 6-minute walk test (6-MWT). The hemodynamic endpoints for the PV loop sub-study were a measurable change in LV volumes, assessment of LV Ees, stroke volume and mid-term improvement in ventricular-arterial coupling.

Statistical analysis

Statistical analysis was performed using GraphPad Prism v7.0 (GraphPad Software Inc., CA). Quantitative data are expressed as mean (SD); categorical variables are described as proportions and percentages. Data were assessed for normality of (Gaussian) distribution both graphically and by use of the Shapiro-Wilk test. Statistical comparison of serial hemodynamic measurements (quantitative data) of normal distribution was performed using a repeated measures one-way ANOVA, adjustment for multiple comparisons was performed using the Bonferroni correction to explain significant differences; in the presence of only pre- and post- (absence of 6 months) data, paired t-tests were performed. Categorical data were compared by use of the Fisher exact test. A p-value of 0.05 was considered statistically significant for all tests.

Results

Procedural outcomes

Between December 2013 and May 2015, 11 subjects were enrolled at two sites in Europe: Onze-Lieve-Vrouwziekenhuis, Aalst, Belgium and St. Thomas' Hospital, London, UK. The disposition of enrolled patients is summarized in Figure 4. The implant was not attempted in one of these patients because of anatomical reasons. The other 10 patients underwent successful Parachute implantation. Baseline characteristics are summarized in Table 1. Surgical explant of the Parachute device was performed within 72 hours in two patients for non-optimal positioning of the device; therefore, eight patients were discharged from hospital with the device. One patient had a major vascular complication requiring surgical repair precluding post-implant data collection. Acute hemodynamic data were therefore obtained in seven patients (pre- and post-implant). These seven patients underwent 6-month outpatient clinical follow-up, and a total of six patients underwent 6-month invasive repeat hemodynamic assessment with simultaneous LV PV loop analysis because one patient died from traumatic subdural hematoma during repeat admission prior to catheter laboratory measurements. There were no aortic valve complications.

Hemodynamic and functional outcomes

New York Heart Association functional class distributions at baseline, 6 and 12 months post-procedure are summarized in Figure 5. The median NHYA class remained unchanged (p = 0.5) due to the small sample size; however, symptomatic improvements were evident in 50% of patients, with no change in 37.5% and worsening in 12.5%. Hemodynamic parameters at baseline, post-parachute implant and at 6-month follow-up are summarized in Table 2. Percentage changes of major hemodynamic variables are graphically displayed in Figure 6A.

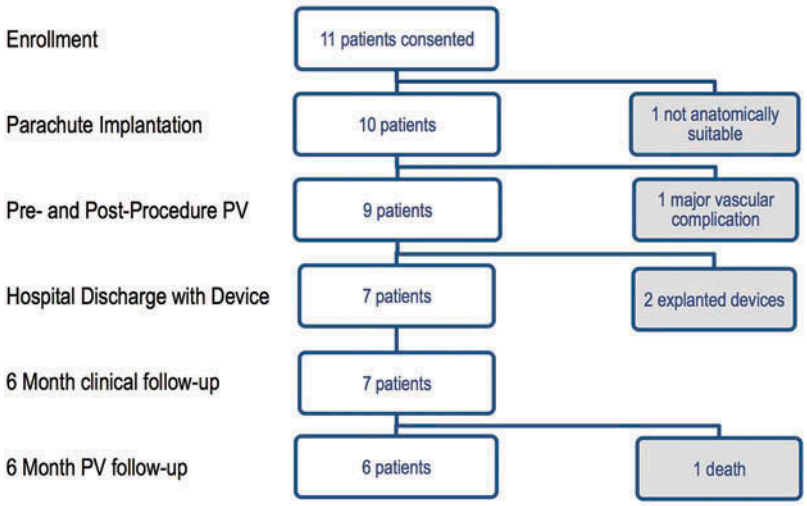

Figure 4. Disposition of patients enrolled. LV PV measurements were performed in nine patients pre- and post-procedure and in six patients pre-, post- and at 6 months.

Table 1. The baseline characteristics of participants in whom Parachute implantations were performed. Data are presented as counts (*n*/*N*) and percentages (%) or as mean ± SD.

Baseline characteristic	Total (*n* = 10)	6-month follow up (*n* = 6)
Device success	8/10 (80%)	6/6 (100%)
Age, years	61.0 ± 10.4	58.8 ± 11.79
Gender, male	9/10 (90%)	5/6 (83%)
Weight, kg	94.0 ± 21.9	97.8 ± 24.6
Height, cm	169.4 ± 10.0	171.8 ± 11.4
BMI kg/m^2	32.3 ± 4.1	32.7 ± 4.5
BSA m^2	2.0 ± 0.1	2.1 ± 0.2
Ischemic heart failure	10/10 (100%)	6/6 (100%)
NYHA II	6/10 (60%)	4/6 (67%)
NYHA III	4/10 (40%)	2/6 (33%)
NYHA IV (ambulatory)	0/10 (0%)	0/6 (0%)
6-MWT, meters	327 ± 131	323 ± 134
Smoking history	8/10 (80%)	5/6 (83%)
History of stroke	1/10 (10%)	1/6 (17%)
History of hypertension	4/10 (40%)	2/6 (33%)
History of diabetes mellitus	4/10 (40%)	1/6 (17%)
History of dyslipidemia	8/10 (80%)	5/6 (83%)
Prior ICD implantation	5/10 (50%)	3/6 (50%)
Prior CRT device	4/10 (40%)	1/6 (17%)
Previous PCI	10/10 (100%)	6/6 (100%)
Previous CABG	1/10 (10%)	0/6 (0%)

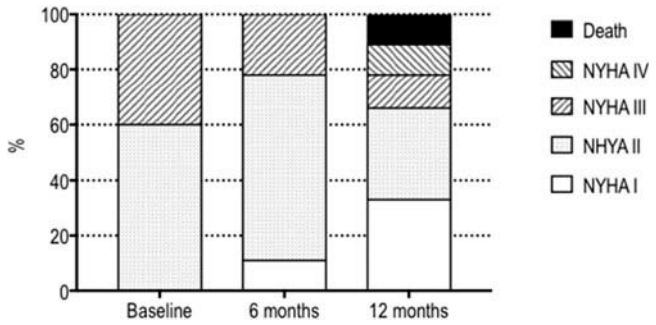

Figure 5. Clinical outcomes of treated subjects, *n* = 10, according to New York Heart Association classes I–IV.

Immediately post-Parachute device implantation, a significant reduction in left ventricular volumes was seen compared to baseline (EDVI mean difference -12mL/m^2, 100±41 versus 112±39mL/m^2, *P*<0.05; ESVI mean difference −10 mL/m^2, 56 ± 32 vs. 66 ± 332 mL/m^2, $p < 0.05$), these were sustained at 6-month hemodynamic follow-up (EDVI mean difference −18 mL/m^2, 94 ± 33 vs. 112 ± 39 mL/m^2, $p < 0.05$; ESVI mean difference −18 mL/m^2, 48 ± 26 vs. 66 ± 33 mL/m^2, $p < 0.05$). This was accompanied by an increase in SVI post device implantation compared to baseline (mean difference 1.0 mL/m^2, 38 ± 11 vs. 37 ± 9 mL/m^2) and at 6 months compared to baseline (mean difference 5 mL; 42 ± 10 vs. 37 ± 9 mL/m^2) but this did not reach significance. However a significant increase in SVI was seen at 6 months compared to post-device implantation (mean difference 4 mL/m^2, 42 ± 10 vs. 38 ± 11 mL/m^2, $p < 0.05$). Compared to baseline there was also an increase in ejection fraction post device implantation (mean difference 4%, 38 ± 11 vs. 42 ± 13%) that reached significance on 6-month hemodynamic follow-up (mean difference 7%; 46 ± 15 vs. 38 ± 11%, $p < 0.05$) (Figure 6A). Left ventricular pressures increased post device implantation compared to baseline (ESP mean difference 5 mmHg, 84 ± 20 vs. 79 ± 17 mmHg), a significant increase was also seen at 6-month hemodynamic follow up compared to post device implantation (ESP mean difference 23 mmHg, 107 ± 12 vs. 84 ± 20 mmHg, $p < 0.05$).

A significant reduction in the ventricular DS was seen immediately post-procedure compared to baseline (mean difference −6%, 14 ± 6 vs. 20 ± 4%, $p < 0.05$) and sustained at 6-month hemodynamic follow-up compared to baseline (mean difference −4%, 16 ± 5 vs. 20 ± 4%). Left ventricular chamber contractility, measured as the ESPVR slope (Ees), increased significantly post device implantation compared to baseline (mean difference 0.2 mmHg/mL, 1.11 ± 0.4 vs. 0.92 ± 0.27 mmHg/mL, $p < 0.05$) and at 6-month follow-up compared to baseline (mean difference 0.5; 1.37 ± 0.52 vs. 0.92 ± 0.27 mmHg/mL, $p < 0.05$). This was accompanied by a significant leftward shift in the Vo intercept of the ESPVR slope both immediately post device implantation compared to baseline (mean difference −17 mL, 46 ± 56 vs. 61 ± 53 mL, $p < 0.05$) and at 6-month hemodynamic follow-up compared to baseline (mean difference −42 mL; 26 ± 37 vs. 61 ± 53 mL, $p < 0.05$).

Compared to baseline, an increase in active relaxation (increased magnitude of maximum derivative of LV pressure decay, dP/dt−) was not seen immediately post-device implantation; however, a significant increase was seen at 6-month follow up compared to baseline (mean difference −271 mmHg/s, −950 ± 177 vs. −675 ± 206 mmHg/s, $p < 0.05$) and at 6-month follow up compared to post-device implantation (mean difference −240 mmHg/s, −950 ± 177 vs. −706 ± 232 mmHg/s, $p < 0.05$). Chamber compliance, representative of passive diastolic function, measured as the beta-coefficient of the EDPVR slope, decreased immediately post procedure (mean difference 0.2, 6.2 ± 0.5 vs. 6.0 ± 0.3,) reaching significance at 6-month follow up when compared to baseline (mean difference 0.3, 6.3 ± 0.5 vs. 6.0 ± 0.3, $p < 0.05$). The alpha coefficient of the EDPVR slope did not change significantly.

The net arterial load, as measured by effective Ea, remained unchanged post parachute implantation. However, an

Table 2. Hemodynamic variables at baseline, immediately post-parachute insertion and at 6-month follow up. Variables are expressed as mean (SD), followed by the mean difference and 95% CI of mean. [a]$p < 0.05$ compared to baseline; [b]$p < 0.05$ compared to baseline and immediate post; [c]Compared to immediate post.

	Baseline ($n = 7$)	Post Parachute ($n = 7$)	6 months Parachute ($n = 6$)	Mean difference (95% CI)		
				Baseline–Post	Baseline–6 months	Post-6 months
HR, bpm	79 (12)	77 (14)	75 (12)	−2 (−7 to 3)	−4 (−18 to 10)	−3 (−18 to 3)
SV, mL	79 (18)	80 (24)	89 (22)[c]	0.4 (−9 to 10)	8 (−4 to 21)	3 (−6 to 12)
SVI, ml/m^2	37 (9)	38 (11)	42 (10)[c]	0.2 (−4 to 5)	4(−2 to 10)	1.4 (−3 to 7)
EF %	38 (11)	42 (13)[a]	46 (14)[a]	4 (1 to 7)	7 (1 to 13)	4.5 (−0.1 to 9.0)
EDV, mL	235 (81)	209 (87)[a]	197 (70)[a]	−25 (−40 to −10)	−43 (−69 to −18)	−24 (−59 to 11)
ESV, mL	139 (69)	117 (67)[a]	100 (55)[a]	−22 (−34 to −9)	−44 (−65 to −22)	−23 (−50 to 3)
EDVI, ml/m^2	112 (39)	100 (41)[a]	94 (33)[a]	−12 (−19 to 5)	−20 (−33 to −6)	−11 (−28 to 5)
ESVI, ml/m^2	66 (33)	56 (32)[a]	48 (26)[a]	−10 (16 to 4)	−21 (−31 to 10)	−11 (−24 to 5)
EDP, mmHg	13 (4)	16 (5)[a]	18 (4)[a]	3 (2 to 4)	4 (1 to 7)	2 (−1 to 5)
ESP, mmHg	79 (17)	84 (20)	107 (12)[b]	5 (−1 to 11)	28 (12 to 43)	25 (5 to 42)
dP/dt−, mmHg/s	−675 (206)	−706 (232)	−950 (177)[b]	−31 (−94 to 32)	−271 (−496 to −47)	−240 (−463 to −17)
Ees SB	0.92 (0.27)	1.11 (0.4)[a]	1.37 (0.52)[a]	0.2 (0.04 to 0.3)	0.5 (0.06 to 0.8)	0.2 (−0.13 to 0.6)
Vo	61 (53)	46 (56)[a]	26 (37)[a]	−17 (−29 to −3)	−42 (−62 to −22)	−8 (−24 to 8)
Beta	6.0 (0.3)	6.2 (0.5)	6.3 (0.5)[a]	0.2 (0 to 0.4)	0.3 (0.05 to 0.5)	0.1 (−0.1 to 0.2)
Alpha ($\times 10^{-13}$)	3.9 (4.1)	10 (15)	6.2 (5.6)	1.7 (−0.1 to 36)	1.2 (−0.1 to 7.5)	5 (−0.2 to 7.5)
SW, mmHg.mL	5699 (1707)	5576 (1865)	7323 (1503)	−123 (−608 to 362)	1526 (−492 to 3545)	1707 (311 to 3103)
PVA mmHg.mL($\times 10^3$)	11.1 (3.3)	10.2 (3.0)	12.4 (2.0)	−0.9 (−1.8 to 0.1)	1 (−1.5 to 3.6)	1929 (128 to 3730)
SW: PVA %	53 (12)	56 (13)	60 (14)[a]	2.6 (−1 to 6)	7 (2 to 11)	4.9 (0 to 10)
DS, %	20 (4)	14 (6)[a]	16 (5)	−6 (−10 to −1)	−4 (−7 to 0.5)	6 (−5 to 7)
Tau, ms	47 (8)	48 (11)	44 (8)	1.5 (−2 to 5)	−3 (−9 to 2)	−4 (−10 to 2)
Ea, mmHg/mL	1.1 (0.6)	1.2 (0.7)	1.3 (0.4)	0.1 (−0.04 to 0.3)	0.2 (−0.2 to 0.5)	0.1 (−0.3 to 0.5)
Ea:Ees	1.2 (0.3)	1.1 (0.3)[a]	0.99 (0.3)	−0.1 (−0.2 to −0.01)	−0.2 (−0.5 to 0.1)	0.2 (−0.3 to 0.1)

Note. SV, stroke volume; SV, stroke volume index; EF, ejection fraction; EDV, end-diastolic volume; ESV, end-systolic volume; EDVI, end-diastolic volume index; ESVI, end-systolic volume index; EDP, end-diastolic pressure; ESP, end-systolic pressure; dP/dt−, LV pressure decay; Ees, end-systolic elastance; SB, single-beat; SW, stroke work; PVA, pressure volume area; DS, dyssynchrony index; Ea, arterial elastance

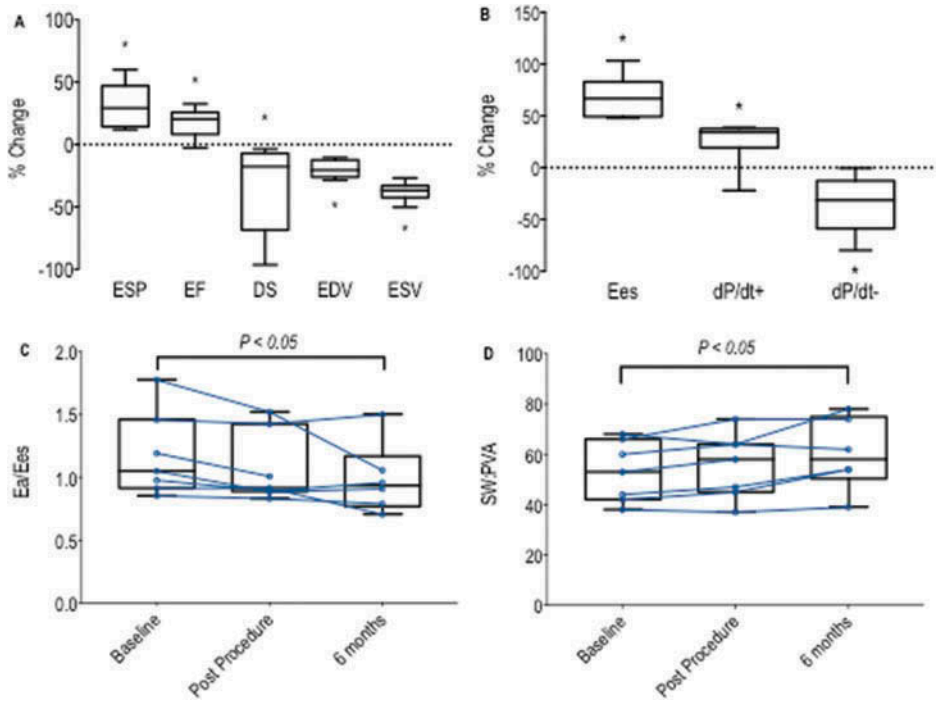

Figure 6. Percentage change in hemodynamic variables: baseline to 6-months post-procedure (A); percentage change in indices of contractility from baseline to 6-months post-procedure (B); change in Ea:Ees at baseline compared to 6-months post-procedure (C); change in SW:PVA expressed as a percentage at baseline compared to 6-months post-procedure (D). Box and whisker plots demonstrate mean with maximum and minimum values; *$p < 0.05$.

improvement in ventricular-arterial coupling immediately post procedure compared to baseline was seen with a reduction in Ea: Ees ratio (mean difference −0.1; 1.1 ± 0.3 vs. 1.2 ± 0.3; $p < 0.05$, Figure 6C). No significant differences were demonstrated in stroke work or pressure volume area; however SW as a % of PVA increased immediately post-procedure compared to baseline (mean difference 2.6%, 56 ± 13 vs. 53 ± 12%), reaching significance at 6 months post implantation compared to baseline (mean difference 7%; 60 ± 14 vs. 53 ± 12%; $p < 0.05$), but not at 6-months compared to immediately post-procedure, Figure 6D.

Pressure-volume loops at baseline and at 6 months follow up are shown in Figure 7 in the six patients. These raw data show that in four of the six patients there is a clear improvement in SV and pressure generation (patients 1–4) and in two of the patients (patients 5 and 6) a leftward shift of the PV loop is demonstrated with little impact on SV or pressure. At baseline, patients 1–4, had an Ea:Ees ratio ≤ 1, whereas patients 5 and 6, in whom there was no demonstrable clinical or hemodynamic benefit had a baseline Ea: Ees ratio >1.

Discussion

The Parachute device partitions and isolates the apical region of the LV from the rest of the chamber. The goal is to exclude infarcted, dyskinetic regions of myocardium to optimize the use of contractile energy produced by remaining myocardium to generate forward cardiac output and blood pressure. Earlier studies of the Parachute device demonstrated safety and feasibility of the device and procedure with improved NYHA functional status and improved survival compared to historical cohorts.[5,6] Device safety and feasibility has been demonstrated to 3 years following the first-in-human studies[10] and in over 100 subjects at 1-year follow up in a real-world setting.[9] In our cohort of patients, although the median NHYA class remained unchanged, symptomatic improvements were evident in 50% of patients, consistent with previous studies.[10,26] The variability in clinical response is likely related to the small sample size and the somewhat variable physiological responses identified in the PV analysis (Figure 7). This in turn could be explained by heterogeneity in baseline hemodynamic phenotype.

Pressure-volume analysis showed that both immediately after and at 6 months following implant, the Parachute device reduced chamber volume, and enhanced pressure generation with a later increase in stroke volume. These were the result of leftward/upward shifts of the ESPVRs and EDPVRs. Along with these, we also saw increased SW/PVA ratio indicating a greater proportion of ventricular work expressed externally suggestive of improved contractility and LV energy transfer as underlying mechanism of improved hemodynamics.

Any procedure, surgical or device-based, that partitions or otherwise excludes a portion of the dysfunctional LV is expected to reduce LV volume and increase ejection fraction. Yet, these immediate effects do not directly reflect the hemodynamic success of the therapy. Rather, it is the impact of the therapy on pump performance indexes such as stroke volume and pressure generation that are clinically important.[22,23] Those effects relate to the procedure's relative effects on the EDPVR and the ESPVR, which in turn are dictated by the mechanical properties (hypo-, a- or dyskinetic) of the excluded portion. Earlier studies of surgical ventricular restoration included patients with different types of apical pathologies and resulted in highly variable effects on stroke volume.[24,25] It is therefore significant that, on average, the shifts in ESPVRs and EDPVRs we observed were associated with increases in pressure generation and increased stroke volumes.

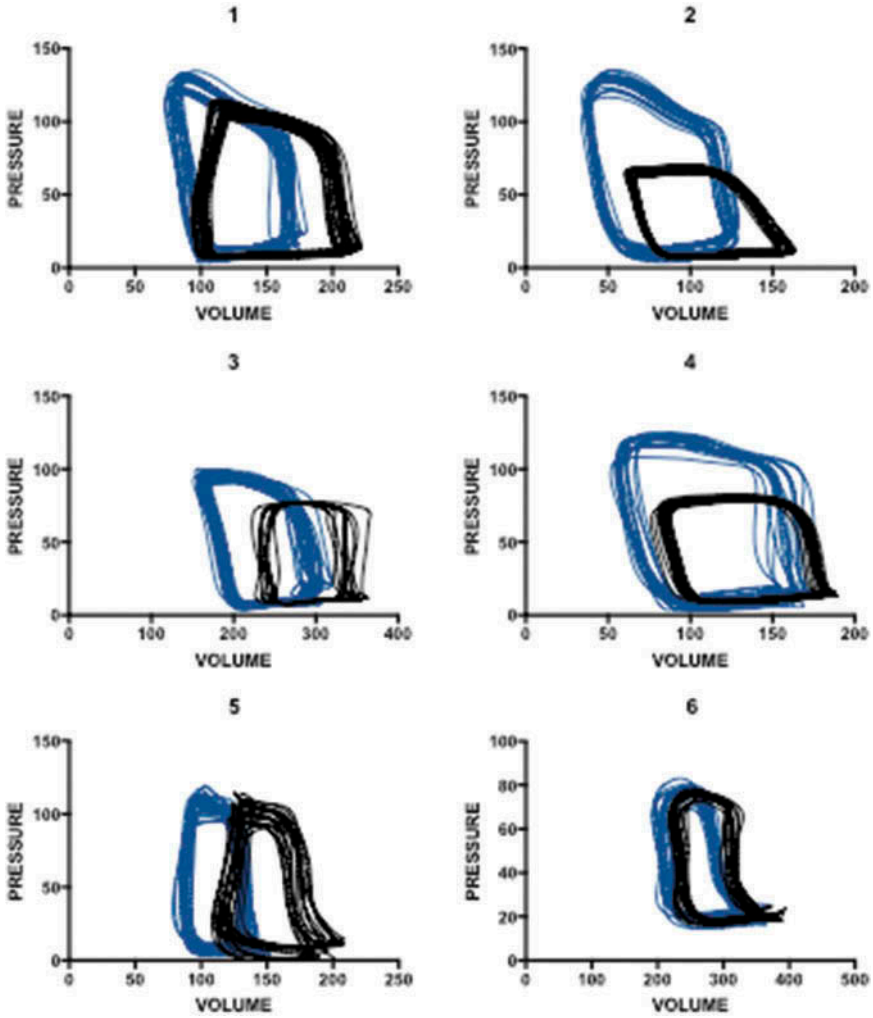

Figure 7. Pressure volume loops in six patients performed prior to implant (black) and 6 months post implant (blue).

Although limited by the small sample size, the continued increase in pressure generation and stroke volume at follow up when compared to the acute hemodynamic change observed following device implantation would be suggestive of reverse remodeling of the ventricle. It is interesting to note, that the hemodynamic and clinical responses were not observed in patients with ventricular-arterial uncoupling, suggesting that in those with either a highly remodeled heart or a disproportionate increase in net arterial load would fail to benefit from this procedure.

Left ventricular dyssynchrony is frequently observed in heart failure and leads to inefficient left ventricular contraction and decreased cardiac output. The segmental signals provided by the CC are able to describe temporal and spatial indices of contractile dyssynchrony that have been described and validated previously.[20] Ventricular dyssynchrony is associated with reductions in SW, SV and systolic dP/dt_{max}.[27–29] Here, we show for the first time that the Parachute device, through partitioning and exclusion of the dyskinetic left ventricular apex, increased synchronicity of contraction, with observed leftward shifts of the PV loop and ESPVR. Furthermore, an improvement in negative dP/dt_{max}, an indication of improved active phase of diastole, may also signify improved synchrony of diastolic relaxation and increased end-systolic pressure.

The STICH trial of surgical ventricular reconstruction (sVR) in patients with ischemic cardiomyopathy, failed to meet its primary endpoint. Several hypotheses have been advanced to explain this failure including the absence of dyskinetic wall motion in 50% of patients and only a modest degree of volume reduction.[14,30–32] However, in patients with similar pre-operative LV dimensions, those who underwent coronary artery bypass grafting (CABG) plus sVR and achieved a post-operative ESVI < 70 mL/m^2 fared better than those who underwent isolated CABG.[33] In this patient cohort there was a reduction of LV end-systolic volume index from an average starting value of 66 mL/m^2 to a value of 48 mL/m^2 at 6 months. The inference from STICH was that patients who failed to reach this ESVI postoperatively due to a very large, highly remodeled heart at baseline or in whom sVR did not otherwise reduce LV volume did not benefit from the procedure. Interestingly, the results of the present study showed similar findings, the subjects who had evidence of ventricular arterial uncoupling at baseline Ea:Ees >1.0 (suggestive of highly remodeled heart) failed to demonstrate a clinical benefit. These findings therefore suggest that a combination of appropriate patient selection with the ability to identify the cohort of patients in whom the procedure may be

futile, consistent device performance, and a less invasive approach with pVR compared to sVR has the potential for beneficial clinical results.

Limitations

This is a mechanistic study limited by the small sample size. Studies involving repeated invasive measurements requiring instrumentation of the LV for mechanistic understanding are, by their nature, relegated to minimum sample sizes and cannot conclusively address overall hemodynamic and clinical outcomes. To the degree that important basic principles have been identified, the need for adding additional patients simply to achieve a certain *p*-value may not be justified. Furthermore, the unblinded, single arm nature of the study poses additional limitations and this study was not designed to demonstrate efficacy and superiority of the device when compared to optimal HF therapies alone. The hemodynamic effects, though on average improved, showed variability in responses suggesting that further refinement of patient selection criteria could result in more uniform hemodynamic improvement.

Conclusions

Although medical therapy remains the mainstay of treatment in CHF, mortality remains significantly high in this cohort.[2,34,35] Other than resynchronization therapy, there are no known percutaneous interventional therapies that aim to restore mechanical synchrony.[18] The present study assessed the immediate and 6-month hemodynamic effects of LV volume reduction using the Parachute percutaneous ventricular restoration device. The Parachute device improved synchrony of contraction and was associated with leftward shifted ESPVRs and EDPVRs that resulted in net improvements in pump function. The ongoing large-scale Parachute IV study will establish the role of this novel therapeutic approach in ischemic heart failure.[36]

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References

1. de Kam PJ, Nicolosi GL, Voors AA, van den Berg MP, et al. Prediction of 6 months left ventricular dilatation after myocardial infarction in relation to cardiac morbidity and mortality. Application of a new dilatation model to GISSI-3 data. *Eur Heart J*. 2002;23:536–542.
2. Chen J, Normand S-LT, Wang Y, Krumholz HM. National and regional trends in heart failure hospitalization and mortality rates for medicare beneficiaries, 1998–2008. *JAMA*. 2011;306:1669–1678.
3. Yancy CW, Jessup M, Bozkurt B, Butler J, et al. 2016 ACC/AHA/HFSA focused update on new pharmacological therapy for heart failure: an update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure. *J Am Coll Cardiol*. 2016. doi:10.1016/j.jacc.2016.05.011
4. Konstam MA, Kramer DG, Patel AR, Maron MS, Udelson JE. Left ventricular remodeling in heart failure: current concepts in clinical significance and assessment. *JACC Cardiovasc Imaging*. 2011;4:98–108.
5. Mazzaferri EL, Gradinac S, Sagic D, Otasevic P, et al. Percutaneous left ventricular partitioning in patients with chronic heart failure and a prior anterior myocardial infarction: results of the PercutAneous Ventricular RestorAtion in Chronic Heart failUre PaTiEnts Trial. *Am Heart J*. 2012;163:812–820.
6. Sagic D, Otasevic P, Sievert H, Elsasser A, et al. Percutaneous implantation of the left ventricular partitioning device for chronic heart failure: a pilot study with 1-year follow-up. *Eur J Heart Fail* 2010:12:600–606.
7. Oliveira GH, Al-Kindi S, Bezerra HG, Costa MA. Left ventricular restoration devices. *J Cardiovasc Transl Res*. 2014;7:282–291.
8. Baan J, van der Velde ET, de Bruin HG, Smeenk GJ, et al. Continuous measurement of left ventricular volume in animals and humans by conductance catheter. *Circulation*. 1984;70:812–823.
9. Thomas M, Nienaber CA, Ince H, Erglis A, et al. Percutaneous ventricular restoration (PVR) therapy using the Parachute device in 100 subjects with ischaemic dilated heart failure: one-year primary endpoint results of PARACHUTE III, a European trial. *EuroIntervention*. 2015;11:710–717.
10. Costa MA, Mazzaferri EL, Sievert H, Abraham WT. Percutaneous ventricular restoration using the parachute device in patients with ischemic heart failure: three-year outcomes of the PARACHUTE first-in-human study. *Circ Heart Fail*. 2014;7:752–758.
11. Burkhoff D, van der Velde E, Kass D, Baan J, et al. Accuracy of volume measurement by conductance catheter in isolated, ejecting canine hearts. *Circulation*. 1985;72:440–447.
12. van der Velde ET, van Dijk AD, Steendijk P, Diethelm L, et al. Left ventricular segmental volume by conductance catheter and Cine-CT. *Eur Heart J*. 1992;13(Suppl.E):15–21.
13. Gaemperli O, Biaggi P, Gugelmann R, Osranek M, et al. Real-time left ventricular pressure-volume loops during percutaneous mitral valve repair with the MitraClip system. *Circulation*. 2013;127:1018–1027.
14. Schreuder JJ, Castiglioni A, Maisano F, Steendijk P, et al. Acute decrease of left ventricular mechanical dyssynchrony and improvement of contractile state and energy efficiency after left ventricular restoration. *J Thorac Cardiovasc Surg*. 2005;129:138–145.
15. Kass DA. Clinical evaluation of left heart function by conductance catheter technique. *Eur Heart J*. 1992;13(Suppl. E):57–64.
16. Klotz S, Hay I, Dickstein ML, Yi G-H, et al. Single-beat estimation of end-diastolic pressure-volume relationship: a novel method with potential for noninvasive application. *Am J Physiol Heart Circ Physiol*. 2006;291:H403–412.
17. Chen C-HH, Fetics B, Nevo E, Rochitte CE, et al. Noninvasive single-beat determination of left ventricular end-systolic elastance in humans. *J Am Coll Cardiol*. 2001;38:2028–2034.
18. Steendijk P, Tulner SA, Bax JJ, Oemrawsingh PV, et al. Hemodynamic effects of long-term cardiac resynchronization therapy: analysis by pressure-volume loops. *Circulation*. 2006;113:1295–1304.
19. Schreuder JJ, Steendijk P, van der Veen FH, Alfieri O, et al. Acute and short-term effects of partial left ventriculectomy in dilated cardiomyopathy: assessment by pressure-volume loops. *J Am Coll Cardiol*. 2000;36:2104–2114.
20. Steendijk P, Tulner SAF, Schreuder JJ, Bax JJ, et al. Quantification of left ventricular mechanical dyssynchrony by conductance catheter in heart failure patients. *AJP: Heart Circ Physiol*. 2004;286:H723–730.
21. Nozawa T, Yasumura Y, Futaki S, Tanaka N, et al. Efficiency of energy transfer from pressure-volume area to external mechanical work increases with contractile state and decreases with afterload in the left ventricle of the anesthetized closed-chest dog. *Circulation*. 1988;77:1116–1124.

22. Artrip JH, Oz MC, Burkhoff D. Left ventricular volume reduction surgery for heart failure: a physiologic perspective. *J Thorac Cardiovasc Surg*. 2001;122:775–782.
23. Burkhoff D, Wechsler AS. Surgical ventricular remodeling: a balancing act on systolic and diastolic properties. *J Thorac Cardiovasc Surg*. 2006;132:459–463.
24. Di Donato M, Fantini F, Toso A, Castelvecchio S, et al. Impact of surgical ventricular reconstruction on stroke volume in patients with ischemic cardiomyopathy. *J Thorac Cardiovasc Surg*. 2010;140:1325–1331. e1–2.
25. Annest LS, Burkhoff D, Jorde UP. Stroke volume alterations in patients undergoing left ventricular reconstructive surgery: a meta-analysis of 3,131 cases. *J Cardiac Failure* 2007;13:S118. doi:10.1007/BF00788534
26. Mazzaferri EL, Jr, et al. Percutaneous left ventricular partitioning in patients with chronic heart failure and a prior anterior myocardial infarction: results of the PercutAneous Ventricular RestorAtion in Chronic Heart failUre PaTiEnts Trial. *Am Heart J*. 2012;163:812–820.e1.
27. Bader H, Garrigue S, Lafitte S, Reuter S, et al. Intra-left ventricular electromechanical asynchrony. A new independent predictor of severe cardiac events in heart failure patients. *J Am Coll Cardiol* 2004;43:248–256.
28. Chakir K, Daya SK, Aiba T, Tunin RS, et al. Mechanisms of enhanced beta-adrenergic reserve from cardiac resynchronization therapy. *Circulation*. 2009;119:1231–1240.
29. Park RC, Little WC, O'Rourke RA. Effect of alteration of left ventricular activation sequence on the left ventricular end-systolic pressure-volume relation in closed-chest dogs. *Circ Res*. 1985;57:706–717.
30. Castelvecchio S, Menicanti L, Donato MD. Surgical ventricular restoration to reverse left ventricular remodeling. *Curr Cardiol Rev*. 2010;6:15–23.
31. Jones RH, Velazquez EJ, Michler RE, Sopko G, et al. Coronary bypass surgery with or without surgical ventricular reconstruction. *N Engl J Med* 2009;360:1705–1717.
32. Witkowski TG, Brinke ten EA, Delgado V, Ng ACT, et al. Surgical ventricular restoration for patients with ischemic heart failure: determinants of two-year survival. *Ann Thorac Surg*. 2011;91:491–498.
33. Michler RE, Rouleau JL, Al-Khalidi HR, Bonow RO, et al. Insights from the STICH trial: change in left ventricular size after coronary artery bypass grafting with and without surgical ventricular reconstruction. *J Thorac Cardiovasc Surg*. 2013;146:1139–1145.e6.
34. Kramer DG, Trikalinos TA, Kent DM, Antonopoulos GV, et al. Quantitative evaluation of drug or device effects on ventricular remodeling as predictors of therapeutic effects on mortality in patients with heart failure and reduced ejection fraction: a meta-analytic approach. *J Am Coll Cardiol* 2010;56:392–406.
35. Packer M. Long-term strategies in the management of heart failure: looking beyond ventricular function and symptoms. *Am J Cardiol*. 1992;69:150G–154G.
36. Costa MA, Pencina M, Nikolic S, Engels T, et al. The PARACHUTE IV trial design and rationale: percutaneous ventricular restoration using the parachute device in patients with ischemic heart failure and dilated left ventricles. *Am Heart J*. 2013;165:531–536.