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RESEARCH ARTICLE

Less invasive ventricular reconstruction for ischaemic heart failure

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Aims Surgical ventricular reconstruction to remodel, reshape, and reduce ventricular volume is an effective therapy in selected patients with chronic heart failure (HF) of ischaemic aetiology. The BioVentrix Revivent TC System offers efficacy comparable to conventional surgical ventricular reconstruction and is less invasive utilizing micro-anchor pairs to exclude scarred myocardium on the beating heart. Here, we present 12-months follow-up data of an international multicenter study.

Methods and results Patients were considered eligible for the procedure when they presented with symptomatic HF [New York Heart Association (NYHA) class ≥II], left ventricular (LV) dilatation and dysfunction caused by myocardial infarction, and akinetic and/or dyskinetic transmural scarred myocardium located in the anteroseptal, anterolateral, and/or apical regions. A total of 89 patients were enrolled and 86 patients were successfully treated (97%). At 12 months, a significant improvement in LV ejection fraction (29 ± 8% vs. 34 ± 9%, $P < 0.005$) and a reduction of LV volumes was observed (LV end-systolic and end-diastolic volume index both decreased: 74 ± 28 mL/m^2 vs. 54 ± 23 mL/m^2, $P < 0.001$; and 106 ± 33 mL/m^2 vs. 80 ± 26 mL/m^2, respectively, $P < 0.0001$). Four patients (4.5%) died in hospital and survival at 12 months was 90.6%. At baseline, 59% of HF patients were in NYHA class III compared with 22% at 12-month follow-up. Improvements in quality of life measures (Minnesota Living with Heart Failure Questionnaire 39 vs. 26 points, $P < 0.001$) and 6-min walking test distance (363 m vs. 416 m, $P = <0.001$) were also significant.

Conclusions Treatment with the Revivent TC System in patients with symptomatic HF results in significant and sustained reduction of LV volumes and improvement of LV function, symptoms, and quality of life.

Keywords Volume reduction • Heart failure • Ventricular remodelling • Myocardial infarction • Device intervention

Introduction

Heart failure (HF) is an important global public health problem due to the associated high morbidity, mortality, and cost. It is estimated that 26 million people are living with chronic HF worldwide, and only half of these patients will live beyond 5 years.[1] Ischaemic heart disease is a major cause of HF, and current therapies do not address directly the scar tissue of the adversely remodelled ventricle after myocardial infarction (MI).[2]

Myocardial infarction from occlusion of a coronary artery often results in areas of dyskinetic or akinetic myocardium, causing increased wall stress and subsequent left ventricular (LV) dilatation.

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Following anterior MI, increased LV volume and symptomatic systolic dysfunction occur in approximately 30% of patients despite revascularization.[3] The dilated and scarred area of the LV wall causes chamber geometry to change from elliptical to spherical, which increases myocardial wall stress further, inducing ischaemia, resulting in afterload mismatch and activation of neurohormonal compensation.[4] The degree of LV dilatation has a major impact on the severity of HF symptoms and mortality rates.[5,6] Exclusion of the non-viable or scarred myocardium with a reduction in LV size and conical reshaping of the chamber decreases LV end-systolic and end-diastolic wall stress and myocardial oxygen consumption, with subsequent improvement in LV function and HF symptoms.[7,8]

Surgical ventricular reconstruction (SVR) has shown to be an effective therapy in selected patients with chronic HF of ischaemic aetiology.[3,9–11] However, SVR is a highly invasive surgical procedure that necessitates median sternotomy, cardiopulmonary bypass with cardioplegic myocardial arrest, and ventriculotomy. The BioVentrix Revivent TC System offers potential efficacy comparable to conventional SVR, aiming to exclude non-functioning scarred myocardium, reshape ventricular geometry, and reduce ventricular volume, but is a less invasive procedure performed on the beating heart with the use of titanium anchor pairs. The implantation procedure for the first-generation system requires median sternotomy, but it is performed on the beating heart without cardiopulmonary bypass.[12] The second-generation system utilizes the same implanted anchor pairs but these are deployed through a hybrid approach: on the beating heart, with access to the heart achieved through a combination of a left-lateral mini-thoracotomy in the 4th or 5th intercostal space and via the right internal jugular vein.

This prospective, multicentre, international single-arm study was designed to evaluate the functional effectiveness and safety of the Revivent TC System, offering a less invasive option for volume reduction and reshaping of the remodelled left ventricle after MI.

Material and methods

Study design

Prospective, multicentre, single-arm study designed to evaluate the efficacy and safety of the Revivent TC System for myocardial scar exclusion, reduction of volume and reshaping of the left ventricle in selected patients with ischaemic cardiomyopathy. The delivery system was modified during the study (*Figure 1*). The study was initiated using a delivery system that required implantation through a median sternotomy. Subsequently, the implantation was performed through a hybrid transcatheter and mini-thoracotomy technique. The study protocols were approved by applicable governmental regulatory agencies (registered under ClinicalTrials.org NCT01568164 and NCT01568138) and the ethics committees of each participating institution. All enrolled subjects were required to give informed consent. The study was conducted according to the principles of the Declaration of Helsinki.

The primary efficacy endpoint for the Revivent TC System was a combination of the reduction of LV volume assessed by echocardiographic changes in LV end-systolic (LVESVI) and end-diastolic volume index (LVEDVI) and improvement in LV ejection fraction (LVEF). All echocardiographic measurements were obtained according to a standardized protocol and analysed at an independent core laboratory at the Ohio State University, Columbus, Ohio. Secondary efficacy endpoints were the reduction of HF symptoms and improvement in the patient's clinical status, assessed by New York Heart Association (NYHA) functional class, 6-min walk test (6MWT) distance, and quality of life score measured by the Minnesota Living with Heart Failure Questionnaire (MLHFQ). Additional data included severity and changes of functional mitral regurgitation (MR) and length of hospital and intensive care unit stay. Safety was assessed by the overall rate of serious adverse events. The specified follow-up times were 6 months and 1 year. Data from this study were used to obtain CE Mark certification.

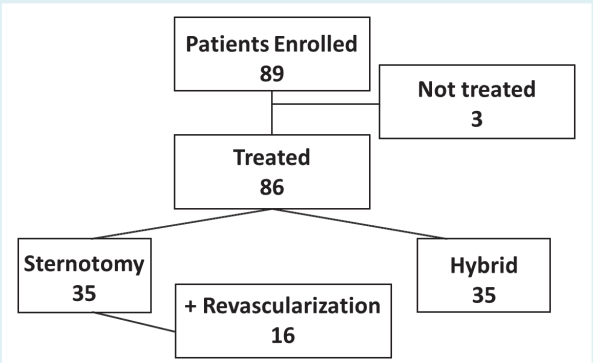

Figure 1 Schematic design of the study. The study was conducted using identical micro-anchor pairs implanted via a sternotomy or hybrid approach. A subgroup of patients implanted via sternotomy were also treated with a planned concomitant coronary revascularization (coronary artery bypass grafting or percutaneous coronary intervention).

An analysis to identify functional responders and non-responders to the less invasive ventricular reconstruction was additionally performed. Conditional of qualifying as a responder is survival up to 12 months of follow-up. A responder is defined as a patient demonstrating an increase in 6MWT distance >32 m between baseline and 12-month follow-up, or (when 6MWT distance was not >32 m) an improvement in quality of life of >14 points between baseline and 12-month follow-up, but only if there was also an improvement in 6MWT distance.[13,14] Additionally (should the aforementioned criteria have not been met), an improvement in NYHA class between baseline and 12-month follow-up of at least one class would also classify a patient as a responder. When the criteria were not met, a patient will be classified as a non-responder.

Patients

Eligible HF patients were ≥18 and ≤80 years old with LV dilatation and dysfunction, caused by MI that occurred at least 90 days prior to study enrolment, and akinetic and/or dyskinetic wall motion located in the anteroseptal, anterolateral, and/or apical regions. Additional criteria include a LVEF >15% and ≤45%, NYHA functional class II–IV, and LVESVI ≥60 mL/m^2 and ≤120 mL/m^2. Imaging studies verified that candidates had sufficient functional remote myocardium (non-infarcted myocardial wall segments), In general three-quarters (or 75%) of remote myocardial segments should be at worst hypokinetic in motion, but preferably exhibit normokinesis. Moreover, the septal scar should be sufficient transmural and suitable for anchor placement. Patients with moderate to severe MR (grade 4) were excluded from

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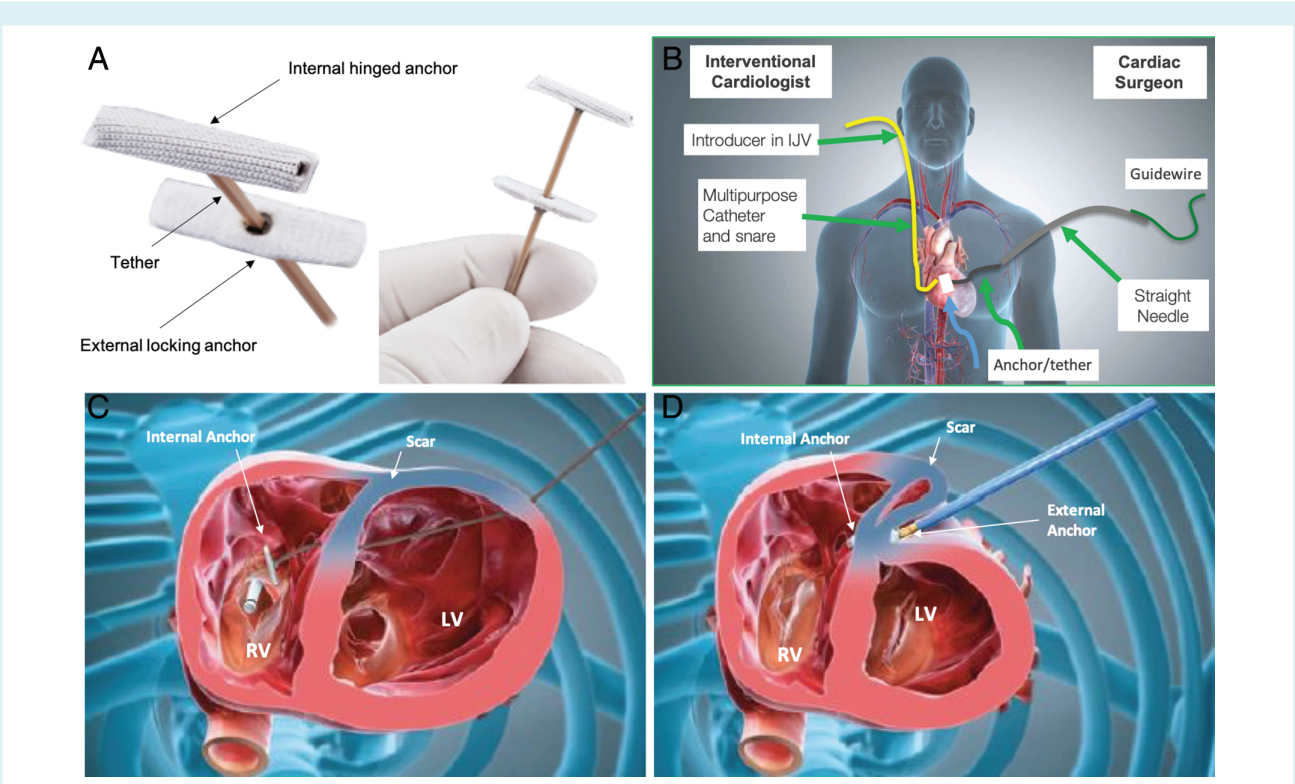

Figure 2 Schematic views of the Revivent TC System anchor with internal hinged and external locking anchor (*A*) and visualization of the hybrid approach *(B)*. Further explanation and corresponding movie can be found in the online supplementary *Video S1*. In the example of left ventricular volume reduction shown in (*C*) and (*D*), the external locking anchor is pushed toward the internal hinged anchor to draw the anterior and the septal walls close, resulting in a significant volume reduction. IJV, internal jugular vein; LV, left ventricle; RV, right ventricle.

this clinical study. A complete listing of the inclusion and exclusion criteria is provided in online supplementary *Table S1*).

Device description and implantation

The implantable components of the Revivent TC System are a series of titanium anchor pairs (23 mm × 4 mm; one internal hinged anchor and one external locking anchor) covered by polyester coating (*Figure 2A)*. The anchor pairs are connected to each other by a tether (1.7 mm × 1.0 mm) made of poly-ether-ether-ketone. The distance between anchors is adjustable and is determined by the location of the sliding locking anchor relative to the fixed hinged anchor. The hinged anchor pivots to facilitate placement through a low-profile introducer, with subsequent rotation to a perpendicular orientation. The sliding locking anchor houses a cam with a reversible locking mechanism, allowing apposition of the two anchors at a continuum of positions. The delivery system comprises of needles, snares, introducers, catheters, and a gauge to control the force at which the anchors are pulled together.

Anteroseptal scarred myocardium is excluded by drawing the locking (epicardial) and hinged (from the right side of septum) anchors together. The fundamental technical manoeuvres for implantation are to place the hinged anchor in the right ventricle, against the septum, and place the locking anchor on the LV epicardium. Then both anchors are drawn toward each other until contact between the two walls is established and apposed along the anchor lengths. The action is repeated along the long axis of the left ventricle until a linear portion of the anterolateral wall is in contact with a corresponding portion of the septum, thus excluding the entire intervening wall segment from the circumference of the chamber. When properly deployed, a discrete portion of the circumference of the LV wall is excluded and the size of the chamber is reduced primarily due to decreased circumference and radius.

The first-generation delivery system required a median sternotomy for direct placement of an internal hinged anchor on the right side of the interventricular septum and a paired locking external locking anchor on the LV epicardium; a tether connected both anchors. Under fluoroscopic guidance, a needle is passed through the LV free wall and across the septum, a guide wire is inserted and the needle removed, and the septal anchor is introduced over the guide wire. A second, locking external locking anchor is fitted onto the tether to allow apposition of the LV free wall at the scar perimeter to the septum. The anchors are fixed in position using a force gauge to limit compression pressure on the anchors and surrounding tissue.

The second-generation hybrid delivery system allows less invasive implantation on the beating heart, utilizing identical anchors, tethers, and implant locations. An outline of the hybrid delivery system is seen in *Figure 2B*. A snare catheter is positioned into the right ventricle via jugular access to capture a wire passed through a needle that is introduced through the anterior wall of the left ventricle and the septum through a small thoracotomy. The snared wire is withdrawn from the jugular vein, and the internal hinged anchor is placed over the wire and advanced to the right side of the interventricular septum. The device is designed to allow removal of the internal hinged anchor

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at any stage of positioning prior to final deployment. The external locking anchor is positioned on the LV anterior wall and the two anchors are connected by the tether. Plication of the affected left ventricle is accomplished by cinching the anchors together through the mini-thoracotomy. Two to three pairs of anchors are usually implanted to achieve sufficient area of scar exclusion and volume reduction (Figure *2C* and *2D*). The length of the septal scar from the base to apex determines the number of anchors implanted.

It is of utmost importance to ensure that the internal hinged anchor is placed in scar with at least 50% transmurality. Because it is difficult to visualize septal scar directly during the procedure, the implanting team must have precise and accurate knowledge of the individual scar morphology from preoperative imaging. Furthermore, tactile feedback when passing the needle and, subsequently, catheters through the scar together with information from intraoperative transoesophageal echocardiography will ensure proper internal hinged anchor placement. An animation of the procedure is provided in the online supplementary *Video S1*.

Warfarin anticoagulation with a target international normalized ratio of 2.0 to 2.5 for 3 months, starting 2 days after the procedure, was recommended for all patients. Thereafter, anticoagulation therapy was at the discretion of the investigator.

Statistical analysis

Categorical variables are expressed as frequencies and percentages. Continuous variables are given as mean ± standard deviation. Pre- and postoperative continuous data of the same patients were compared using the Wilcoxon signed-rank test. Pre- and postoperative categorical data of the same patients were analysed by Pearson's chi-squared test for count data. Adverse event data are presented as the number of patients with the event and the percentage of patients with events. Survival was evaluated using the Kaplan–Meier method and comparisons were made using the log-rank test. Cox proportional hazards regression analysis was performed to identify predictors for survival. Logistic binary regression was used to identify predictors for patients being a responder (or non-responder) to the treatment. Variables with $P < 0.1$ were included in multivariable analysis. For all tests, a P-value of <0.05 was considered statistically significant. Statistics were performed using the R software package (R Core Team 2018, R Foundation for Statistical Computing, Vienna, Austria).

Results

A total of 89 HF patients were enrolled in the study at 22 medical centres in 12 European countries between August 2010 and March 2016. All patients were being treated according to guideline-directed medical therapy at the time of admission to the hospital.[14] Patient demographics, medical history, preoperative medication, and baseline functional status are provided in *Table 1*. All patients had NYHA class II or III symptoms. Baseline 6MWT distance was 345 ± 108 m. Prior percutaneous coronary intervention had been performed in 74% of patients. Successful device implantation was accomplished in 86 of 89 patients (97%). The three patients with unsuccessful implants were considered as not treated and were removed from the study after 30 days (online supplementary *Appendix S1*). Of the 86 patients with a successful device implantation, 51 were treated via sternotomy and 35 were treated using the hybrid approach. Sixteen patients that underwent implantation via sternotomy also had a planned concomitant coronary revascularization procedure (either coronary artery bypass grafting or percutaneous coronary intervention) (*Figure 1*).

Table 1 Preoperative patient characteristics, medications, and clinical and haemodynamic data of all enrolled patients ($n = 89$)

Age, years, mean ± SD	60.4 ± 9.9
Female sex, *n* (%)	17 (20)
BMI, kg/m^2, mean ± SD	28.9 ± 5.7
Diabetes mellitus, *n* (%)	16 (19)
Arterial hypertension, *n* (%)	56 (65)
Hyperlipidaemia, *n* (%)	58 (67)
Creatinine, mg/dL, mean ± SD	1.04 ± 0.32
Ischaemic cardiomyopathy, *n* (%)	86 (100)
Age of infarct, years, mean ± SD	5.5 ± 6.5
Previous PCI, *n* (%)	63 (73)
Previous CVA, *n* (%)	10 (12)
PM, *n* (%)	3 (4)
ICD, *n* (%)	27 (31)
Medication, *n* (%)	
Statin	69 (80)
Beta-blocker	69 (80)
ACE-inhibitor	62 (72)
ARB	10 (12)
Diuretic	60 (70)
Platelet inhibitor(s)	59 (69)
Aldosterone antagonist	60 (70)
Coumadin	17 (20)
Long/short-acting nitrate	16 (19)
Anti-arrhythmic	14 (16)
Clinical data	
NYHA class, *n* (%)	
I	0 (0)
II	35 (41)
III	51 (59)
IV	0 (0)
6-min walk test, m, mean ± SD	345 ± 108
MLHFQ quality of life score (mean)	42

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; CVA, cerebrovascular accident; ICD, implantable cardioverter-defibrillator; MLHFQ, Minnesota Living with Heart Failure Questionnaire; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; PM, pacemaker; SD, standard deviation.

In-hospital mortality and safety data

There were four in-hospital deaths (4.5%), three of which were procedure-related: LV injury ($n = 1$), subendocardial necrosis ($n = 1$), and pulmonary artery injury ($n = 1$). One other death was attributed to bowel perforation. Four late deaths were due to sudden cardiac death ($n = 2$), lung cancer ($n = 1$), and stroke ($n = 1$). Median hospital stay was 14 days (range 5–51 days), and median stay on intensive care unit was 92 h (range 0–1104 h). Patients operated via hybrid approach had a shorter hospital stay (median 12 days, range 5–51 days; $P = 0.01$) than patients who were treated with the sternotomy approach only (median 14 days,

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Table 2 Serious adverse event rates at 12 months grouped by treatment approach

	Sternotomy approach ($n = 51$)	Hybrid approach ($n = 35$)	All ($n = 86$)	*P*-value (difference sternotomy – hybrid approach)
Major adverse events				
Tricuspid valve insufficiency increase	1 (2.0)	4 (11.4)	5 (5.8)	0.0734
Mitral valve insufficiency increase	1 (2.0)	1 (2.9)	1 (1.2)	0.79
Pulmonary valve insufficiency increase	3 (5.9)	0 (0.0)	3 (3.5)	0.15
Ventricular septal defect	1 (2.0)	1 (2.9)	2 (2.3)	0.79
Bleeding	3 (5.9)	4 (11.4)	7 (8.1)	0.36
Renal dysfunction	3 (5.9)	1 (2.9)	4 (4.7)	0.52
Respiratory failure	1 (2.0)	1 (2.9)	2 (2.3)	0.79
Stroke	3 (5.9)	1 (2.9)	4 (4.7)	0.52
Late cardiac arrest	0 (0.0)	2 (5.9)	2 (2.3)	0.09
Minor adverse events				
Atrial fibrillation	1 (1.9)	2 (5.9)	3 (3.5)	0.72
Pleural effusion	3 (5.9)	2 (5.9)	5 (5.8)	0.97
Ventricular arrhythmias	8 (15.7)	4 (11.4)	12 (14.0)	0.58
Low cardiac output	4 (7.8)	1 (2.9)	5 (5.8)	0.34
Pulmonary infection	2 (3.8)	3 (8.6)	5 (5.8)	0.37
Sepsis	4 (7.8)	1 (2.9)	5 (5.8)	0.34

Values are presented as *n* (%).

Table 3 Haemodynamic data and clinical status at baseline and 12 months for the as treated population with matched data

	Baseline	12 months	% Change	*P*-value
LVEF (%) ($n = 64$)	29 ± 8	34 ± 9	16	<0.005
LVESVI (mL/m^2) ($n = 67$)	74 ± 28	54 ± 23	27	<0.001
LVEDVI (mL/m^2) ($n = 67$)	106 ± 33	80 ± 26	24	<0.0001
NYHA class ($n = 77$)	2.6 ± 0.5	1.9 ± 0.8	26	<0.001
6-min walk distance (m) ($n = 46$)	363 ± 92	416 ± 106	21	<0.001
MLHF score ($n = 46$)	39 ± 21	26 ± 22	34	<0.001

Values are presented as mean ± standard deviation.
LVEF, left ventricular ejection fraction; LVEDVI, left ventricular end-diastolic volume index; LVESVI, left ventricular end-systolic volume index; MLHF, Minnesota Living with Heart Failure; NYHA, New York Heart Association.

range 5–43 days). Major and minor adverse events during hospital stay are listed according to implant technique (sternotomy vs. hybrid) and the total number of patients who experienced events for the 'per protocol' population (*Table 2*). Over the 12-month follow-up period, the most frequent observed adverse events were ventricular arrhythmia (14.0%) and bleeding (8.1%). No significant differences were observed regarding both major and minor adverse events between sternotomy and hybrid approach.

Anatomic and functional data

Echocardiographic matched data from all patients treated demonstrated significant LV volume reduction and functional improvement comparing baseline and 12-month follow-up (*Table 3*). Compared with baseline values, mean LVESVI significantly decreased by 27% at 12 months ($P < 0.001$) (*Figure 3A*), and LVEDVI decreased by 24% at 12 months (*Figure 3B*). Mean LVEF was significantly increased by 16% at 12 months ($P < 0.005$) (*Figure 3C*). Evaluating individual changes in LVESVI, all patients demonstrated a significant and sustained reduction in LV volumes (online supplementary *Figure S1*).

Clinical data

Clinical outcomes significantly improved from baseline to 12-month follow-up (*Table 3*). Mean NYHA class improved from 2.6 ± 0.5 to 1.9 ± 0.8 at 12-month follow-up ($P < 0.001$). At baseline, 59% of patients were in NYHA class III compared with 22% at 12 months (*Figure 4A*). Mean 6MWT distance improved by 21% (or 53 m) to 416 m at 12-month follow-up ($P < 0.001$) (*Figure 4B*). Mean MLHFQ score was improved, compared with baseline, by 34% at 12-month follow-up ($P < 0.001$) (*Figure 4C*).

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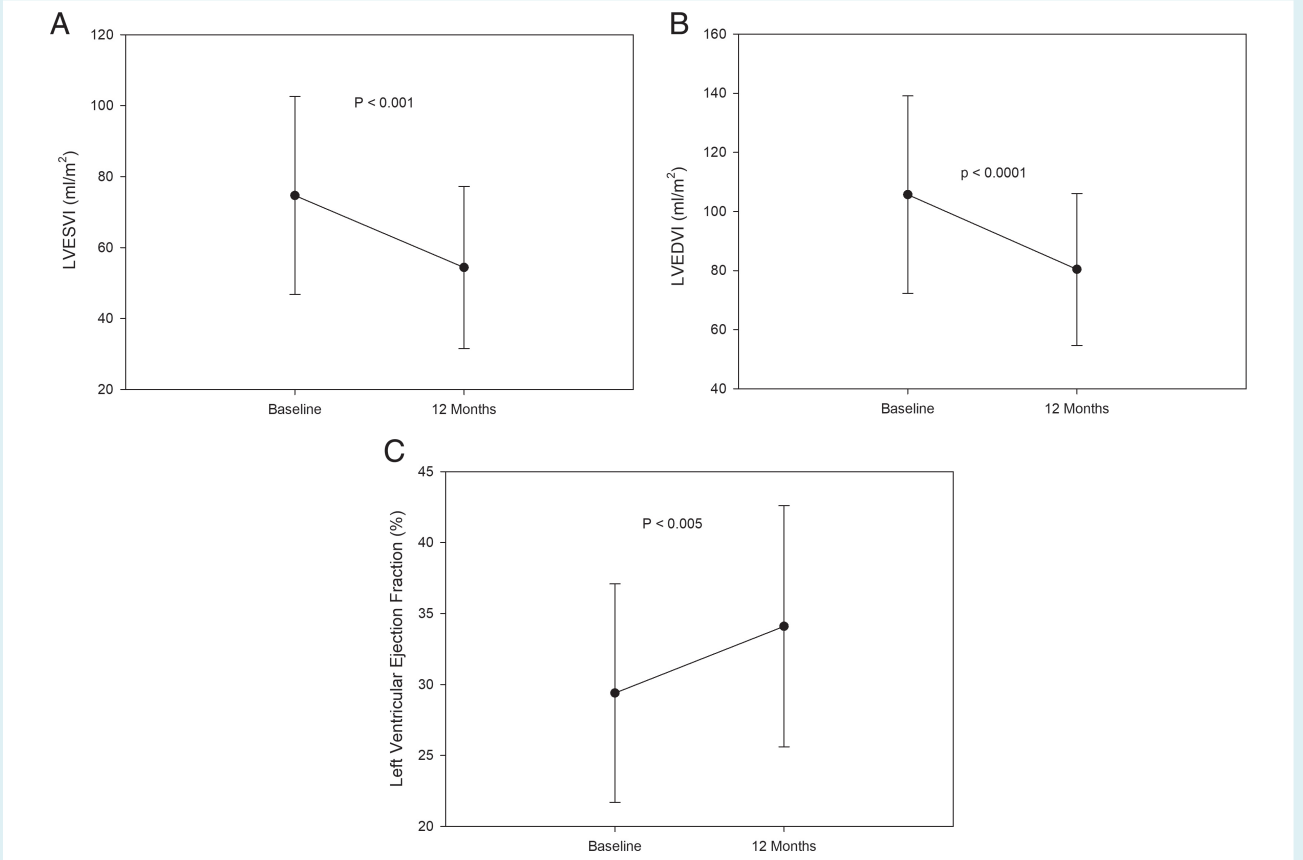

Figure 3 Data plots at baseline and 12-month follow-up for left ventricular end-systolic volume index (LVESVI) (*A*), left ventricular end-diastolic volume index (LVEDVI) (*B*) and left ventricular ejection fraction (*C*).

Mean N-terminal pro-B-type natriuretic peptide levels of matched data showed a decrease of 22% at 12-month follow-up, which was statistically non-significant ($P = 0.37$) (*Table 4*). We observed eight hospital readmissions due to recurrent HF symptoms. One patient was readmitted four times, so out of the 82 surviving patients, five patients experienced one or more readmissions for HF during the 12-month follow-up.

Twelve months after treatment, NYHA class improved regardless of delivery method (sternotomy or hybrid) or adding revascularization. At baseline, 63% (sternotomy), 63% (hybrid), and 44% (adding revascularization) were in NYHA class III–IV compared to 24%, 20% and 20% at 12-month follow-up, respectively.

At baseline, 68 of the 86 patients treated in this study had measurable MR of at least grade 1+, while 19 of the 86 patients enrolled in this study had MR grade 2+ or 3+. Of the 68 patients who entered the study with measurable FMR, the average MR grade was reduced from a mean of 1.12 at baseline to a mean of 0.57 at 6 months and 0.86 at 12 months (*Table 5*).

Survival data

The Kaplan–Meier estimated survival rate was 90.6% at 12 months (*Figure 5*). Univariable Cox proportional hazards regression analysis identified age [hazard ratio 1.11, 95% confidence interval (CI) 1.02–1.21; $P = 0.017$] and smoking (hazard ratio 0.19, 95% CI 0.04–0.78; $P = 0.022$) as significant variables associated with survival. Of note, no haemodynamic variables (i.e. LVEF or LVESVI/LVEDVI) were found significantly associated with survival after the procedure (*Table 6*).

Predictors for responders and non-responders

Univariate logistic binary regression identified hypertension (odds ratio 4.37, 95% CI 1.57–12.9; $P = 0.005$) as significant variable associated with survival. LVESVI showed a tendency towards significance (odds ratio 0.98, 95% CI 0.97–1,00; $P = 0.051$) (*Table 7*). At multivariable logistic regression, no other variable reached statistical significance when hypertension was in the model.

Discussion

Left ventricular remodelling after MI is a complex process that leads to ventricular dilatation, shape alteration, increase in wall stress and a reduction in contractile force of the remote myocardium. This reduction in contractile force is partly based on a decrease in LV torsion, in which the base of the left ventricle rotates in an overall

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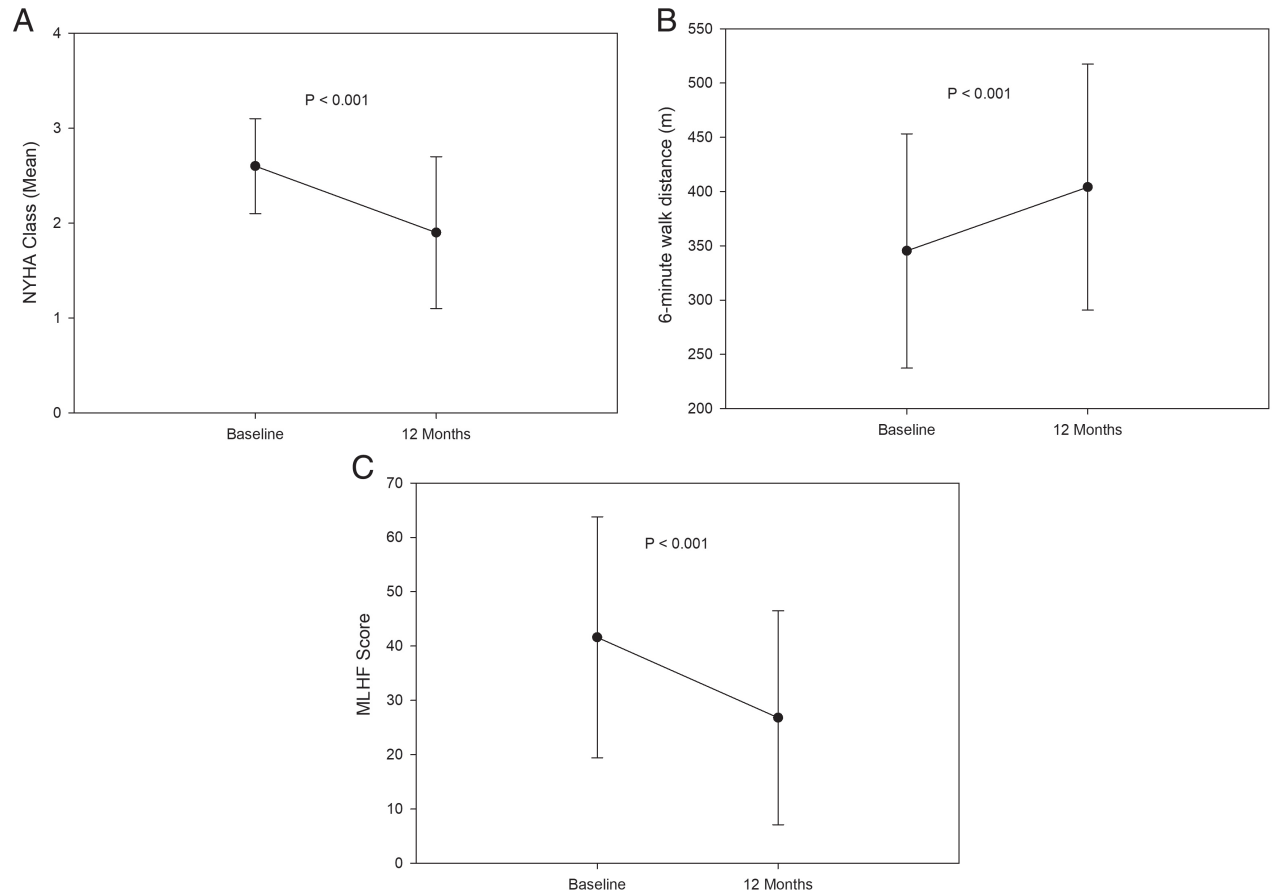

Figure 4 Clinical data for all patients and 12-month follow-up showing results from New York Heart Association (NYHA) class (*A*), 6-min walk test (*B*), and Minnesota Living With Heart Failure Questionnaire (MLHF) (*C*).

Table 4 N-terminal pro-B-type natriuretic peptide levels (pg/mL) at baseline and 12-month follow-up of matched pairs

	Baseline	Follow-up
n	39	39
Mean ± SD	1175.1 ± 1655.2	913.9 ± 1090.4
Min–max	31.5–9042.4	12.8–5291
% Change		22.2%
P-value		0.36577

SD, standard deviation.

Table 5 Functional mitral regurgitation data at baseline, 6-month and 12-month follow-up as measured by transthoracic echocardiography

	Baseline	6 months	12 months
n	82	47	63
Mean ± SD	1.12 ± 0.73	0.57 ± 0.58	0.86 ± 0.64
Min–max	0–3	0–2	0–3
% Change		48.9%	23.7%
t-test		0.0005	0.03
Median	1	1	1
Grade 1	49	23	39
Grade 2	15	2	6
Grade 3	4	0	1
Grade 4	0	0	0

clockwise direction and the apex rotates in a counter-clockwise direction when viewed from apex to base. LV torsion is a critical mechanism of ventricular ejection and filling. The concept of ventricular reconstruction is based on exclusion of scar tissue, volume reduction, reshaping of the distorted chamber and improvement in cardiac function. This improvement is based on a combination of a decrease in wall stress, more optimal myofiber orientation, and recovery of torsional dynamics. The results of this study demonstrate that the Revivent TC System (*Figure 6*) can be used for ventricular reconstruction with acceptable safety using less invasive techniques and that the majority of patients experienced improvement in HF symptoms. The 12-month follow-up data indicate that patients experience sustained improvement in LVEF,

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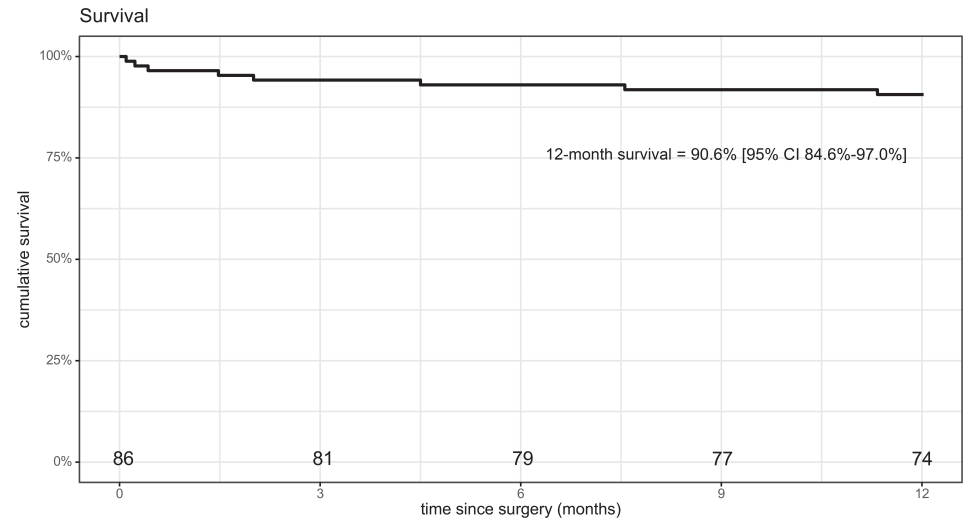

Figure 5 General survival analysis using the Kaplan–Meier survival curve at 12 months ($n = 86$). CI, confidence interval.

6MWT distance and quality of life. The LVESVI and LVEDVI data before and after device implantation demonstrate that a significant and sufficient LV volume reduction is achieved with this device (*Figure 7*). Patients in this study had an improvement in LVEF of 16%, and a reduction in LVESVI of 27%.

Surgical ventricular reconstruction has been applied clinically in a large number of patients during the past two decades.[10,15–18] SVR improves HF symptoms and long-term survival for patients with ischaemic cardiomyopathy.[19] The majority of cases in these studies underwent standard open-heart surgery via sternotomy with cardiopulmonary bypass, cardioplegic myocardial arrest, and ventriculotomy. Concomitant coronary revascularization was performed in most cases, sometimes also in combination with an intervention to the mitral valve for functional or secondary MR. Implantation of the Revivent TC System device does not require cardiopulmonary bypass, cardioplegic arrest, or a ventriculotomy. Implantation was initially performed with sternotomy, followed by the hybrid approach. Both approaches are less invasive compared to standard SVR procedures.

The outcomes and the rate of adverse events during and after implantation of the Revivent TC System appear to be in an acceptable range when compared with SVR. The in-hospital operative mortality of 4.5% in this study is within the range of 3–14% reported in most SVR studies,[8,17,20–22] especially when considering the effects of the early operator's learning curve in this initial experience. Hospital stay could be significantly reduced by using the hybrid approach rather than the initial surgical approach. The observed 12-month survival of 90.6% is also comparable to SVR outcomes.[8,23–25] By comparison, the reported survival from the international Reconstructive Endoventricular Surgery returning Torsion Original Radius Elliptical shape to the left ventricle (RESTORE) registry of 1198 post-anterior infarction SVR cases at 18 months was 89.2%. Improvement in outcomes after implantation of the Revivent TC System should be possible through application of experience gained in selecting candidates and in the technique of implantation. This might also offer an alternative in patients at high risk of perioperative complications or with a frail preoperative condition.

An important element of the Revivent TC System implantation technique is that the anchor pairs are set to a configuration parallel to the long axis of the heart. Each tether and the excluded portion of the scar are taken from the short axis of the heart. With this configuration, virtually all volume reduction decreases the radius of the left ventricle and is not just the result of amputation of an apical aneurysm. Reduction in wall tension, reorientation of myofibers, and improvement in torsional dynamics is, therefore, the most likely explanation for the functional improvement observed in the patients.

The focus of this study was to evaluate both safety and effectiveness of the device system. Clinical outcomes were essentially the same in all groups and were significantly improved through 12 months of follow-up. Both approaches are essentially less invasive compared to conventional SVR, and therapeutic volume reduction was achieved regardless of delivery method. These data compare favourably with the STICH sub-analysis, which established a survival benefit in patients realizing >30% reduction in LVESVI and/or postoperative LVESVI <60 mL/m^2.[11] Another finding from an additional STICH analysis was that patients with smaller ventricles (LVESVI <60 mL/m^2) and better LVEF (≥33%) at echocardiography may have benefited by SVR, while those with larger ventricles (LVESVI >90 mL/m^2) and lower LVEF (≤25%) did worse with SVR.[26] In this study we found weak evidence at univariate analysis that a smaller LVESVI is associated with patients that responded positively to treatment with the Revivent TC system (odds ratio 0.98, 95% CI 0.97–1,00; $P = 0.051$).

Many patients with ischaemic HF also experience (secondary or functional) MR. The presence of functional MR is associated with adverse clinical outcome. Although this therapy does not treat

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Table 6 Univariable Cox proportional hazards regression analysis for predictors of survival

Variable	All (n = 86)	No event (n = 78)	Event (n = 8)	HR (95% CI)	P-value ratio	P-value overall	n
Approach							86
EC (full median sternotomy)	51 (59.3%)	50 (64.1%)	1 (12.5%)	Ref.	Ref.		
TC (hybrid transcatheter)	35 (40.7%)	28 (35.9%)	7 (87.5%)	11.2 [1.38–91.1]	0.024		
Demographic parameters							
Gender							86
Female	17 (19.8%)	15 (19.2%)	2 (25.0%)	Ref.	Ref.		
Male	69 (80.2%)	63 (80.8%)	6 (75.0%)	0.74 [0.15–3.68]	0.716		
Age, years	60.3 ± ± 9.84	59.5 ± 9.66	68.6 ± 7.92	1.11 [1.02–1.21]	0.017	0.017	86
BSA, m^2	2.00 ± 0.23	2.01 ± 0.24	1.90 ± 0.14	0.14 [0.01–3.38]	0.227	0.227	86
BMI, kg/m^2	28.9 ± 5.70	28.9 ± 5.72	28.8 ± 5.79	0.99 [0.88–1.13]	0.918	0.918	86
Diabetes							
No	69 (81.2%)	62 (80.5%)	7 (87.5%)	Ref.	Ref.		
Yes	16 (18.8%)	15 (19.5%)	1 (12.5%)	0.62 [0.08–5.05]	0.656		
Smoking							85
No	22 (25.9%)	17 (22.1%)	5 (62.5%)	Ref.	Ref.		
Yes	63 (74.1%)	60 (77.9%)	3 (37.5%)	0.19 [0.04–0.78]	0.022		
Hypertension							85
No	29 (34.1%)	25 (32.5%)	4 (50.0%)	Ref.	Ref.		
Yes	56 (65.9%)	52 (67.5%)	4 (50.0%)	0.52 [0.13–2.09]	0.359		
Hyperlipidaemia							85
No	27 (31.8%)	25 (32.5%)	2 (25.0%)	Ref.	Ref.		
Yes	58 (68.2%)	52 (67.5%)	6 (75.0%)	1.38 [0.28–6.85]	0.692		
CVA/TIA							85
No	75 (88.2%)	69 (89.6%)	6 (75.0%)	Ref.	Ref.		
Yes	10 (11.8%)	8 (10.4%)	2 (25.0%)	2.55 [0.51–12.6]	0.252		
Arrhythmia							85
No	53 (62.4%)	50 (64.9%)	3 (37.5%)	Ref.	Ref.		
Yes	32 (37.6%)	27 (35.1%)	5 (62.5%)	2.78 [0.66–11.6]	0.162		
Prior PCI							85
No	22 (25.9%)	20 (26.0%)	2 (25.0%)	Ref.	Ref.		
Yes	63 (74.1%)	57 (74.0%)	6 (75.0%)	1.08 [0.22–5.35]	0.926		
Prior ICD							85
No	58 (68.2%)	54 (70.1%)	4 (50.0%)	Ref.	Ref.		
Yes	27 (31.8%)	23 (29.9%)	4 (50.0%)	2.27 [0.57–9.08]	0.246		
Prior PM							68
No	65 (95.6%)	59 (96.7%)	6 (85.7%)	Ref.	Ref.		
Yes	3 (4.41%)	2 (3.28%)	1 (14.3%)	4.85 [0.58–40.4]	0.144		
Functional parameters							
NYHA class							86
II	35 (40.7%)	33 (42.3%)	2 (25.0%)	Ref.	Ref.		
III	51 (59.3%)	45 (57.7%)	6 (75.0%)	2.06 [0.42–10.2]	0.375		
Quality of life (MLHFQ)	41.6 ± 22.2	41.4 ± 21.9	43.1 ± 27.4	1.00 [0.97–1.04]	0.809	0.809	83
6 min walking test distance (m)	345 ± 108	347 ± 106	329 ± 136	1.00 [0.99–1.01]	0.687	0.687	83
NT-proBNP	737 [274–1621]	716 [272–1603]	2156 [2156–2156]	1.00 [1.00–1.00]	0.560	0.560	46
Echocardiographic parameters							
LVEF (%)	61.6 ± 7.77	61.5 ± 7.69	63.2 ± 8.96	1.03 [0.94–1.13]	0.537	0.537	79
LVEDD (mm)	50.0 ± 8.85	49.6 ± 8.71	53.7 ± 10.1	1.05 [0.97–1.13]	0.220	0.220	78
LVESD (mm)	74.7 ± 27.9	73.5 ± 27.0	87.3 ± 35.4	1.02 [0.99–1.04]	0.157	0.157	86
LVESVI (mL/m^2 BSA)	106 ± 33.4	104 ± 32.2	119 ± 43.6	1.01 [0.99–1.03]	0.197	0.197	86
LVEDVI (mL/m^2 BSA)	29.4 ± 7.66	29.6 ± 7.78	27.5 ± 6.60	0.97 [0.88–1.06]	0.476	0.476	86
Functional mitral regurgitation							80
Grade 0	13 (16.2%)	11 (15.1%)	2 (28.6%)	Ref.	Ref.		
Grade 1	49 (61.3%)	46 (63.0%)	3 (42.9%)	0.39 [0.07–2.36]	0.307		
Grade 2	14 (17.5%)	13 (17.8%)	1 (14.3%)	0.47 [0.04–5.20]	0.540		
Grade 3	4 (5.00%)	3 (4.11%)	1 (14.3%)	1.82 [0.16–20.1]	0.626		

BMI, body mass index; BSA, body surface area; CI, confidence interval; CVA, cerebrovascular accident; HR, hazard ratio; ICD, implantable cardioverter-defibrillator; LVEDD, left ventricular end-diastolic dimension; LVEDVI, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic dimension; LVESVI, left ventricular end-systolic volume index; MLHFQ, Minnesota Living with Heart Failure Questionnaire; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; PM, pacemaker; TIA, transient ischaemic attack.

the mitral valve itself, reshaping of the left ventricle is expected to result in reduction in MR in some patients, particularly those with functional MR. Patients with moderate to severe MR (grade 4+) were excluded from this clinical study; however, enrolment of patients with functional MR grade 1+ to 3+ was allowed. At baseline, 68 of the 86 patients treated in this study had measurable MR of at least grade 1+, while 19 of the 86 patients enrolled in this study had MR grade 2+ or 3+. Of the 68 patients who entered the study with measurable functional MR, the average MR grade was reduced from a mean of 1.12 at baseline to a mean

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Table 7 Logistic binary regression (univariable) for predictors for patients being a responder (or non-responder) to the treatment

Variable	Non-responder ($n = 28$)	Responder ($n = 46$)	OR (95% CI)	*P*-value ratio	*P*-value overall	*n*
Approach						74
EC (full median sternotomy)	17 (60.7%)	33 (71.7%)	Ref.	Ref.		
TC (hybrid transcatheter)	11 (39.3%)	13 (28.3%)	0.61 [0.22–1.69]	0.341		
Demographic parameters						
Gender						74
Female	4 (14.3%)	11 (23.9%)	Ref.	Ref.		
Male	24 (85.7%)	35 (76.1%)	0.55 [0.13–1.84]	0.340		
Age, years	60.5 ± 9.68	58.6 ± 9.91	0.98 [0.93–1.03]		0.422	74
BSA, m^2	1.96 ± 0.21	2.04 ± 0.24	4.93 [0.58–42.0]		0.130	74
BMI, kg/m^2	27.8 ± 5.27	29.6 ± 5.72	1.06 [0.97–1.17]		0.168	74
Diabetes						73
No	24 (88.9%)	35 (76.1%)	Ref.	Ref.		
Yes	3 (11.1%)	11 (23.9%)	2.41 [0.65–12.1]	0.196		
Smoking						73
No	7 (25.9%)	9 (19.6%)	Ref.	Ref.		
Yes	20 (74.1%)	37 (80.4%)	1.44 [0.44–4.52]	0.538		
Hypertension						73
No	15 (55.6%)	10 (21.7%)	Ref.	Ref.		
Yes	12 (44.4%)	36 (78.3%)	4.37 [1.57–12.9]	0.005		
Hyperlipidaemia						73
No	12 (44.4%)	11 (23.9%)	Ref.	Ref.		
Yes	15 (55.6%)	35 (76.1%)	2.50 [0.90–7.14]	0.079		
CVA/TIA						73
No	24 (88.9%)	42 (91.3%)	Ref.	Ref.		
Yes	3 (11.1%)	4 (8.70%)	0.76 [0.15–4.41]	0.740		
Arrhythmia						73
No	16 (59.3%)	32 (69.6%)	Ref.	Ref.		
Yes	11 (40.7%)	14 (30.4%)	0.64 [0.23–1.76]	0.385		
Prior PCI						73
No	4 (14.8%)	16 (34.8%)	Ref.	Ref.		
Yes	23 (85.2%)	30 (65.2%)	0.34 [0.08–1.09]	0.069		
Prior ICD						73
No	16 (59.3%)	37 (80.4%)	Ref.	Ref.		
Yes	11 (40.7%)	9 (19.6%)	0.36 [0.12–1.05]	0.061		
Prior PM						57
No	20 (90.9%)	35 (100%)	Ref.	Ref.		
Yes	2 (9.09%)	0 (0.00%)	.[&$$$–]	0.145		
Functional parameters						
NYHA class						74
II	10 (35.7%)	20 (43.5%)	Ref.	Ref.		
III	18 (64.3%)	26 (56.5%)	0.73 [0.27–1.92]	0.524		
Quality of life (MLHFQ)	39.9 ± 22.5	43.0 ± 22.1	1.01 [0.98–1.03]		0.570	72
6 min walking test distance (m)	365 ± 106	332 ± 108	1.00 [0.99–1.00]		0.216	72
NT-proBNP	1318 [366–1753]	601 [251–1442]	1.00 [1.00–1.00]		0.271	45
Echocardiographic parameters						
LVEF (%)	28.3 ± 6.66	30.0 ± 8.55	1.03 [0.97–1.09]		0.345	74
LVEDD (mm)	62.8 ± 7.39	60.2 ± 7.61	0.95 [0.89–1.02]		0.164	69
LVESD (mm)	51.5 ± 7.07	48.1 ± 9.34	0.95 [0.90–1.01]		0.095	68
LVESVI (mL/m^2 BSA)	81.3 ± 27.0	68.4 ± 26.8	0.98 [0.97–1.00]		0.051	74
LVEDVI (mL/m^2 BSA)	112 ± 29.6	99.0 ± 33.8	0.99 [0.97–1.00]		0.089	74
Functional mitral regurgitation					0.914	70
Grade 0	3 (11.1%)	7 (16.3%)	Ref.	Ref.		
Grade 1	19 (70.4%)	26 (60.5%)	0.61 [0.11–2.57]	0.509		
Grade 2	4 (14.8%)	8 (18.6%)	0.87 [0.12–5.68]	0.884		
Grade 3	1 (3.70%)	2 (4.65%)	0.84 [0.05–33.3]	0.909		

BMI, body mass index; BSA, body surface area; CI, confidence interval; CVA, cerebrovascular accident; HR, hazard ratio; ICD, implantable cardioverter-defibrillator; LVEDD, left ventricular end-diastolic dimension; LVEDVI, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic dimension; LVESVI, left ventricular end-systolic volume index; MLHFQ, Minnesota Living with Heart Failure Questionnaire; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; PM, pacemaker; TIA, transient ischaemic attack.

of 0.57 at 6 months and 0.86 at 12 months. Of the 19 patients who entered the study with at least grade 2+ MR, 12 (63%) experienced at least a 1 grade decrease in MR while the other seven patients remained unchanged. Due to reshaping of the left ventricle during and after treatment with the Revivent TC System, a reduction in MR was observed and should be considered as an additional potential benefit in patients who have MR but are not yet in need for mitral valve repair or replacement, or patients who have residual functional MR from previous repair of the mitral valve with ongoing progression of their HF symptoms.

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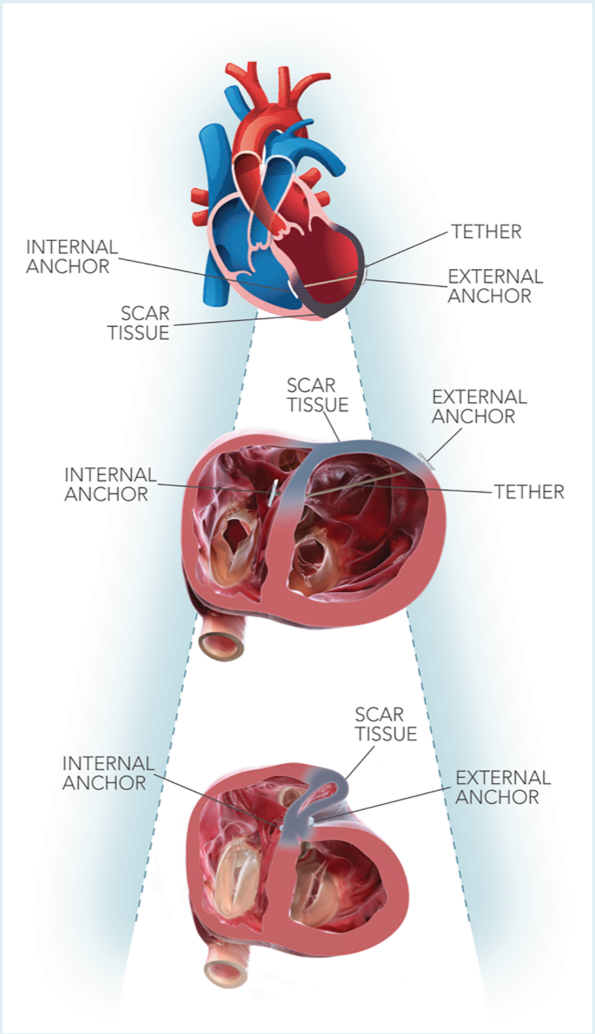

Figure 6 Areas of antero-septal akinetic and/or dyskinetic scarred myocardium are identified with placement of the internal hinged anchor in the right ventricle and placement of the external locking anchor on the epicardial surface, both attached to the tether (top). The anchors and tether are positioned on the leading edge of the scarred myocardium (middle). Once the anchors are drawn together, the scarred myocardium is excluded, and the volume of the left ventricle is reduced (bottom).

Since CE Mark approval of the Revivent TC System in 2016, a registry of clinical data from treated patients has been maintained; publication of the results will be forthcoming. The results of this registry are important as there have been subtle refinements to the system, and experience with implantation has increased considerably.

Limitations

This study is limited by its moderate size in the number of patients treated, the non-randomized, non-controlled trial design and the limited follow-up of 12 months. Furthermore, the number of enrolled patients per centre is relatively low. Possibly, this is more related to the negative result of the STICH trial, than a real shortage of potential patients for this therapy.[27] In addition, patients with previous coronary artery bypass graft were excluded from this study.

Future trials will be randomized against guideline-directed medical therapy or conventional open chest surgery. Patients received the device either through a sternotomy or by mini-thoracotomy and internal jugular vein access and were not independently compared. The focus of these results was the effectiveness of the identical implanted device in both groups, not the delivery method. Nevertheless, both techniques are less invasive compared to conventional SVR, and therapeutic volume reduction was achieved regardless of delivery method. The imaging techniques used by the different centres for LV volume measurement were not uniform; consequently, our analysis was limited to patients that had the same measurement techniques. In future trials, longer follow-up is needed, especially in evaluation of the use in patients with severe HF after large anterior MI. However, in patients with less symptoms (NYHA class I), the use might be discussed to prevent the onset of LV remodelling. In addition, use of a three-dimensional method (magnetic resonance imaging or computed tomography) rather than echocardiography may result in a more accurate assessment of LV remodelling and evaluation of parameters, such as LV strain in remote myocardium to test improvement in deformation.

To further assess the clinical benefit of the Revivent TC System over guideline-directed medical treatment, a randomized controlled trial (Revivent TC versus Guideline Determined Medical Therapy) has been set up and enrolment has started in 2019.

Conclusions

These data indicate that the Revivent TC System can be used as an HF therapy that results in good clinical outcomes. Selection of patients with appropriate anatomic features is a critical aspect for the achievement of durable clinical outcomes. This could be an additional personalized therapy for a specific type of patients with HF after MI with scar tissue in the anteroseptal or apical wall of the left ventricle.[28]

Benefits from LV volume reduction and ventricular reshaping have been demonstrated independent of myocardial revascularization or open chest surgery, using a hybrid approach. The ability to achieve these results without the need for sternotomy or cardiopulmonary bypass is an important advance for the treatment of patients suffering from ischaemic cardiomyopathy HF. This less invasive technique for LV volume reduction demonstrates efficacy and acceptable safety in this moderate sample size of highly selected patients.

Clinical perspective

Surgical SVR following anterior MI to exclude non-functioning myocardium returns the ventricle to a more normal size, thereby improving wall tension and LV function. Historical data have shown that SVR is an effective therapy for HF caused by ischaemic cardiomyopathy. Surgical techniques for SVR involve the use of

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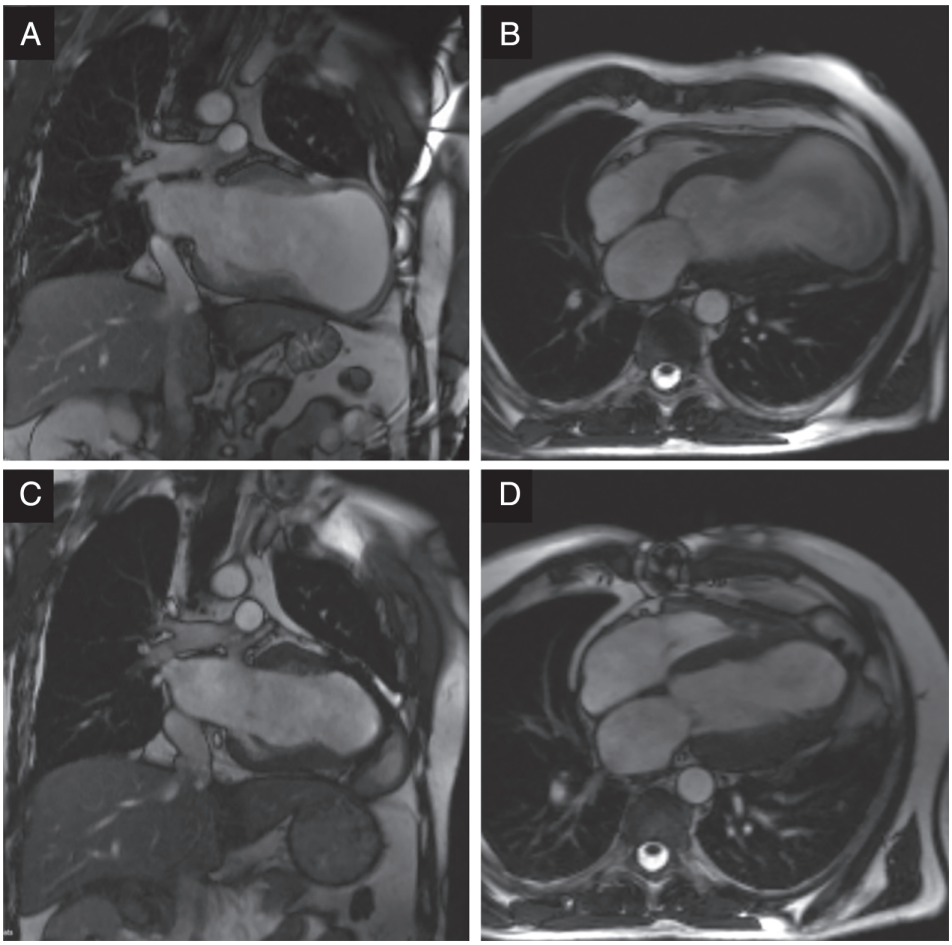

Figure 7 Magnetic resonance images of the heart pre- and post-surgery. On-site images taken before surgery show a large apical aneurysm post-myocardial infarction with increased ventricular volume and thinned wall [two-chamber orientation (*A*); four-chamber orientation (*B*)]. Images taken 6 months after surgery show significant volume reduction and reshaping of the left ventricle [two-chamber orientation (*C*); four-chamber orientation (*D*)].

cardiopulmonary bypass and incisions into the ventricle. The less invasive volume reduction and reshaping of the ventricle using the Revivent TC System has demonstrated its safety and good survival with reduced morbidity and improvement of clinical symptoms and exercise capacity in appropriately selected patients with severe HF.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Appendix S1. Detailed report of the three patients with unsuccessful implants that were not treated and removed from the study after 30 days.

Table S1. Revivent System study inclusion (*A*) and exclusion criteria (*B*).

Figure S1. Individual left ventricular end-systolic volume index change.

Video S1. Animation of the Revivent TC procedure.

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Conflict of interest: P.K. reports consultancy, proctoring and speaker agreements with BioVentrix and Edwards LifeSciences, and speaking fee by LivaNova. S.K. reports consultancy and spear agreements with BioVentrix. The other authors have nothing to disclose.

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References

1. Bui AL, Horwich TB, Fonarow GC. Epidemiology and risk profile of heart failure. *Nat Rev Cardiol* 2011;**8**:30–41.
2. Roth GA, Nguyen G, Forouzanfar MH, Mokdad AH, Naghavi M, Murray CJ. Estimates of global and regional premature cardiovascular mortality in 2025. *Circulation* 2015;**132**:1270–1282.
3. Buckberg G, Athanasuleas C, Conte J. Surgical ventricular restoration for the treatment of heart failure. *Nat Rev Cardiol* 2012;**9**:703–716.
4. Buckberg GD. Ventricular restoration – a surgical approach to reverse ventricular remodeling. *Heart Fail Rev* 2004;**9**:233–239.
5. Hamer AW, Takayama M, Abraham KA, Roche AH, Kerr AR, Williams BF, Ramage MC, White HD. End-systolic volume and long-term survival after coronary artery bypass graft surgery in patients with impaired left ventricular function. *Circulation* 1994;**90**:2899–2904.
6. Axelrad JE, Pinsino A, Trinh PN, Thanataveerat A, Brooks C, Demmer RT, Effner L, Parkis G, Cagliostro B, Han J, Garan AR, Topkara V, Takeda K, Takayama H, Naka Y, Ramirez I, Garcia-Carrasquillo R, Colombo PC, Gonda T, Yuzefpolskaya M. Limited usefulness of endoscopic evaluation in patients with continuous-flow left ventricular assist devices and gastrointestinal bleeding. *J Heart Lung Transplant* 2018;**37**:723–732.
7. Athanasuleas CL, Buckberg GD, Stanley AW, Siler W, Dor V, di Donato M, Menicanti L, Almeida de Oliveira S, Beyersdorf F, Kron IL, Suma H, Kouchoukos NT, Moore W, McCarthy P, Oz MC, Fontan F, Scott ML, Accola KA; RESTORE Group. Surgical ventricular restoration in the treatment of congestive heart failure due to post-infarction ventricular dilation. *J Am Coll Cardiol* 2004;**44**:1439–1445.
8. Di Donato M, Frigiola A, Benhamouda M, Menicanti L. Safety and efficacy of surgical ventricular restoration in unstable patients with recent anterior myocardial infarction. *Circulation* 2004;**110** (11 Suppl 1):II169–II173.
9. Crespo-Leiro MG, Cuenca-Castillo JJ. Surgical treatment of heart failure: heart transplantation and ventricular restoration surgery. *Eur Heart J Suppl* 2006;**8**:E39–E42.
10. Athanasuleas CL, Stanley AW, Buckberg GD, Dor V, di Donato M, Siler W; RESTORE Group. Surgical anterior ventricular endocardial restoration (SAVER) for dilated ischemic cardiomyopathy. *Semin Thorac Cardiovasc Surg* 2001;**13**:448–458.
11. Michler RE, Rouleau JL, Al-Khalidi HR, Bonow RO, Pellikka PA, Pohost GM, Holly TA, Oh JK, Dagenais F, Milano C, Wrobel K, Pirk J, Ali IS, Jones RH, Velazquez EJ, Lee KL, Di Donato M; STICH Trial Investigators. 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.
12. Wechsler AS, Sadowski J, Kapelak B, Bartus K, Kalinauskas G, Rucinskas K, Samalavicius R, Annest L. Durability of epicardial ventricular restoration without ventriculotomy. *Eur J Cardiothorac Surg* 2013;**44**:e189–e192.
13. Shoemaker MJ, Curtis AB, Vangsnes E, Dickinson MG. Clinically meaningful change estimates for the six-minute walk test and daily activity in individuals with chronic heart failure. *Cardiopulm Phys Ther J* 2013;**24**:21–29.
14. Gonzalez-Saenz de Tejada M, Bilbao A, Ansola L, Quirós R, García-Perez L, Navarro G, Escobar A. Responsiveness and minimal clinically important difference of the Minnesota Living with Heart Failure Questionnaire. *Health Qual Life Outcomes* 2019;**17**:36.
15. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, González-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GM, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2016;**18**:891–975.
16. Cooley DA. Endoaneurysmorrhaphy revisited. *Tex Heart Inst J* 1984;**11**: 8–9.
17. Dor V. Left ventricular aneurysms: the endoventricular circular patch plasty. *Semin Thorac Cardiovasc Surg* 1997;**9**:123–130.
18. Athanasuleas CL, Buckberg GD, Stanley AW, Siler W, Dor V, DiDonato M, Menicanti L, de Oliveira SA, Beyersdorf F, Kron IL, Suma H, Kouchoukos NT, Moore W, McCarthy P, Oz MC, Fontan F, Scott ML, Accola KA; RESTORE Group. Surgical ventricular restoration: the RESTORE group experience. *Heart Fail Rev* 2004;**9**:287–297.
19. Broderick JP. The STICH trial: what does it tell us and where do we go from here? *Stroke* 2005;**36**:1619–1620.
20. Di Donato M, Castelvecchio S, Menicanti L. Surgical treatment of ischemic heart failure: the Dor procedure. *Circ J* 2009;**73** Suppl. A:A1–A5.
21. Menicanti L, Castelvecchio S, Ranucci M, Frigiola A, Santambrogio C, de Vincentiis C, Brankovic J, di Donato M. Surgical therapy for ischemic heart failure: single-center experience with surgical anterior ventricular restoration. *J Thorac Cardiovasc Surg* 2007;**134**:433–441.
22. Hwang HY, Kim JS, Cho KR, Kim KB. Surgical anterior ventricular endocardial restoration performed with total arterial revascularization: serial 5-year follow-up. *J Thorac Cardiovasc Surg* 2014;**148**:529–535.
23. Castelvecchio S, Ranucci M, Bandera F, Baryshnikova E, Giacomazzi F, Menicanti L; Surgical and Clinical Outcome Research (SCORE) Group. The additional prognostic value of left atrial volume on the outcome of patients after surgical ventricular reconstruction. *Ann Thorac Surg* 2013;**95**:141–147.
24. Di Donato M, Castelvecchio S, Brankovic J, Santambrogio C, Montericcio V, Menicanti L. Effectiveness of surgical ventricular restoration in patients with dilated ischemic cardiomyopathy and unrepaired mild mitral regurgitation. *J Thorac Cardiovasc Surg* 2007;**134**:1548–1553.
25. O'Neill JO, Starling RC, McCarthy PM, Albert NM, Lytle BW, Navia J, Young JB, Smedira N. The impact of left ventricular reconstruction on survival in patients with ischemic cardiomyopathy. *Eur J Cardiothorac Surg* 2006;**30**: 753–759.
26. Oh JK, Velazquez EJ, Menicanti L, Pohost GM, Bonow RO, Lin G, Hellkamp AS, Ferrazzi P, Wos S, Rao V, Berman D, Bochenek A, Cherniavsky A, Rogowski J, Rouleau JL, Lee KL; STICH Investigators. Influence of baseline left ventricular function on the clinical outcome of surgical ventricular reconstruction in patients with ischaemic cardiomyopathy. *Eur Heart J* 2013;**34**:39–47.
27. Stone GW, Selker HP, Thiele H, Patel MR, Udelson JE, Ohman EM, Maehara A, Eitel I, Granger CB, Jenkins PL, Nichols M, Ben-Yehuda O. Relationship between infarct size and outcomes following primary PCI: patient-level analysis from 10 randomized trials. *J Am Coll Cardiol* 2016;**67**:1674–1683.
28. Ahmad FA, Petrie MC, McMurray JJV, Lang NN. Personalized medicine and hospitalization for heart failure: if we understand it, we may be successful in treating it. *Eur J Heart Fail* 2019;**21**:699–702.

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