

Intramyocardial Stem Cell Injection in Patients With Ischemic Cardiomyopathy

Functional Recovery and Reverse Remodeling

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Rationale: Transcatheter, intramyocardial injections of bone marrow–derived cell therapy produces reverse remodeling in large animal models of ischemic cardiomyopathy.

Objective: We used cardiac MRI (CMR) in patients with left ventricular (LV) dysfunction related to remote myocardial infarction (MI) to test the hypothesis that bone marrow progenitor cell injection causes functional recovery of scarred myocardium and reverse remodeling.

Methods and Results: Eight patients (aged 57.2 ± 13.3 years) received transcatheter, intramyocardial injection of autologous bone marrow progenitor cells (mononuclear or mesenchymal stem cells) in LV scar and border zone. All patients tolerated the procedure with no serious adverse events. CMR at 1 year demonstrated a decrease in end diastolic volume (208.7 ± 20.4 versus 167.4 ± 7.32 mL; $P=0.03$), a trend toward decreased end systolic volume (142.4 ± 16.5 versus 107.6 ± 7.4 mL; $P=0.06$), decreased infarct size ($P<0.05$), and improved regional LV function by peak Eulerian circumferential strain in the treated infarct zone (-8.1 ± 1.0 versus -11.4 ± 1.3 ; $P=0.04$). Improvements in regional function were evident at 3 months, whereas the changes in chamber dimensions were not significant until 6 months. Improved regional function in the infarct zone strongly correlated with reduction of end diastolic volume ($r^2=0.69$, $P=0.04$) and end systolic volume ($r^2=0.83$, $P=0.01$).

Conclusions: These data suggest that transcatheter, intramyocardial injections of autologous bone marrow progenitor cells improve regional contractility of a chronic myocardial scar, and these changes predict subsequent reverse remodeling. The findings support the potential clinical benefits of this new treatment strategy and ongoing randomized clinical trials. (*Circ Res.* 2011;108:792-796.)

Key Words: heart failure ■ bone marrow ■ stem cells ■ reverse remodeling

In a series of detailed preclinical porcine studies, we have demonstrated that transcatheter, intramyocardial injection of bone marrow–derived progenitor cells to chronically scarred myocardium is safe and improves left ventricular (LV) regional function, reduces scar size, and creates reverse remodeling.¹ A therapy that leads to reverse remodeling in chronically scarred human hearts would be precedent-setting and predicted to have favorable clinical benefits for patients. Using various imaging modalities, a growing number of clinical trials of intramyocardial bone marrow cell injections

in patients with chronic ischemic heart failure have shown improved regional function; however, these improvements in regional contractility have only translated to modest global functional changes.^{2,3} Furthermore, the relationship of improved regional contractility and reverse remodeling has not been investigated. Here, we tested the hypothesis that intramyocardial injection of bone marrow–derived stem cells into humans with chronically scarred myocardium causes functional restoration followed by reverse remodeling. The data here derive from the phase I pilot of the Transendocar-

Original received February 12, 2011; revision received February 16, 2011; accepted February 21, 2011. In January 2011, the average time from submission to first decision for all original research papers submitted to *Circulation Research* was 13.3 days.

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From the Interdisciplinary Stem Cell Institute (A.R.W., D.L.V., I.M., A.W.H., J.M.H.); Department of Medicine (B.T., G.A.L., J.P.Z., A.W.H., J.M.H.), Cardiovascular Division; Department of Surgery (A.R.W.); and Department of Radiology (P.M.P., J.F.), University of Miami Miller School of Medicine, FL; BioCardia Inc (P.A., D.R.), San Carlos, CA; and The EMMES Corporation (A.M.M.), Rockville, MD.

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DOI: 10.1161/CIRCRESAHA.111.242610

dial Autologous Cells in Ischemic Heart Failure (TAC-HFT) (clinicaltrials.gov identifier NCT00768066) study of catheter-based intramyocardial injections of autologous bone marrow progenitor cells in patients with LV dysfunction secondary to remote myocardial infarction.⁴

Methods

Eight patients with a diagnosis of ischemic cardiomyopathy underwent bone marrow aspiration from the iliac crest followed by transcatheter injection (Helical Infusion Catheter; BioCardia, San Carlos, CA) of autologous bone marrow progenitor cells (mononuclear cells, $n=4$; or mesenchymal stem cells, $n=4$). Cardiac MRI (CMR) phenotyping of structure and function was conducted at baseline, 3 and 6 months, and 1 year after cell therapy. Written informed consent was obtained from all patients on this Institutional Review Board–approved protocol.

An expanded Methods section is available in the Online Data Supplement at <http://circres.ahajournals.org>.

Results

Eight patients (aged 57.2 ± 13.3 years; all male with remote myocardial infarction [MI] [68.8 ± 21.4 months, range 4 months to 11 years]) underwent transcatheter injection of bone marrow progenitor cells. No patient experienced a serious adverse event (Online Data Supplement).

Cine CMR demonstrated a decrease in end diastolic volume (EDV) ($P=0.033$) and a trend toward decreased end systolic volume (ESV) ($P=0.058$) (Figure 1 and Online Figure II). Reductions in chamber volumes were significant at 6 and 12 months compared with baseline for ESV ($P=0.022$ and $P=0.023$, respectively) and EDV ($P=0.009$ and $P=0.014$, respectively). Ejection fraction (EF) and LV mass did not change ($P=NS$). A strong correlation between the changes in EDV and ESV ($r^2=0.87$, $P=0.002$) demonstrates parallel decreases in chamber volumes. MI size evaluated by delayed myocardial hyperenhancement decreased by $18.3 \pm 8.3\%$ ($P<0.05$; Figure 1D and Online Figure I).

Peak Eulerian circumferential strain (Ecc), a measure of regional contractility calculated from tagged CMR images, showed improved regional function of the infarct zone (IZ)

Non-standard Abbreviations and Acronyms

CMR	cardiac MRI
Ecc	Eulerian circumferential strain
EDV	end diastolic volume
EF	ejection fraction
ESV	end systolic volume
IZ	infarct zone
LV	left ventricular
MI	myocardial infarction

($P=0.039$) that restored function to the level of the border zone (Figures 1 and 2). The IZ improvements were evident as early as 3 months and persisted at 6 and 12 months compared with baseline ($P=0.02$, $P=0.013$, and $P=0.029$, respectively), and strongly correlated with the changes in EDV ($r^2=0.69$, $P=0.04$) and ESV ($r^2=0.83$, $P=0.01$) (Figure 2). Regional function in border and remote zones did not change ($P=NS$).

Discussion

Here, we show that transcatheter, intramyocardial injection of autologous bone marrow preparations in patients with chronic ischemic cardiomyopathy is well-tolerated and produces functional recovery in scarred myocardium and reverse remodeling of the LV chamber. Importantly, the functional recovery is evident at 3 months following injection and precedes reverse remodeling. Because all patients had documented MI and were previously revascularized, these findings support myocardial regeneration and mirror the phenotype observed in porcine models of chronic ischemic cardiomyopathy.¹⁻⁵

The present findings have several major implications. First, we have established that bone marrow–derived cell therapy clearly can enable reverse remodeling of dilated hearts, a phenotypic change that would be expected to have positive

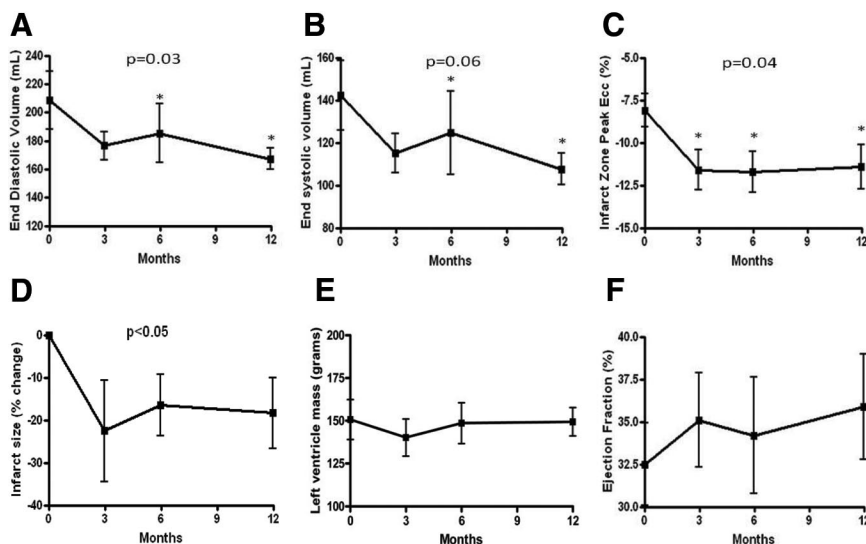


Figure 1. CMR changes after bone marrow progenitor cell injections. A and B, Cine changes in EDV (A) and ESV (B) show reverse remodeling occurred at 6 months and continued through 1 year. Peak Ecc of tagged tissue images demonstrates improved regional function of the treated IZ (C). Improved IZ contractility (more negative Ecc indicates greater circumferential contractility) occurred by 3 months following cell injection and persisted at 6 and 12 months. D shows reduced delayed enhancement infarct size as a percentage of LV mass. E and F, LV mass (E) or EF (F) are unchanged. * $P<0.05$ for difference between time after injection and baseline in the repeated-measures ANOVA.

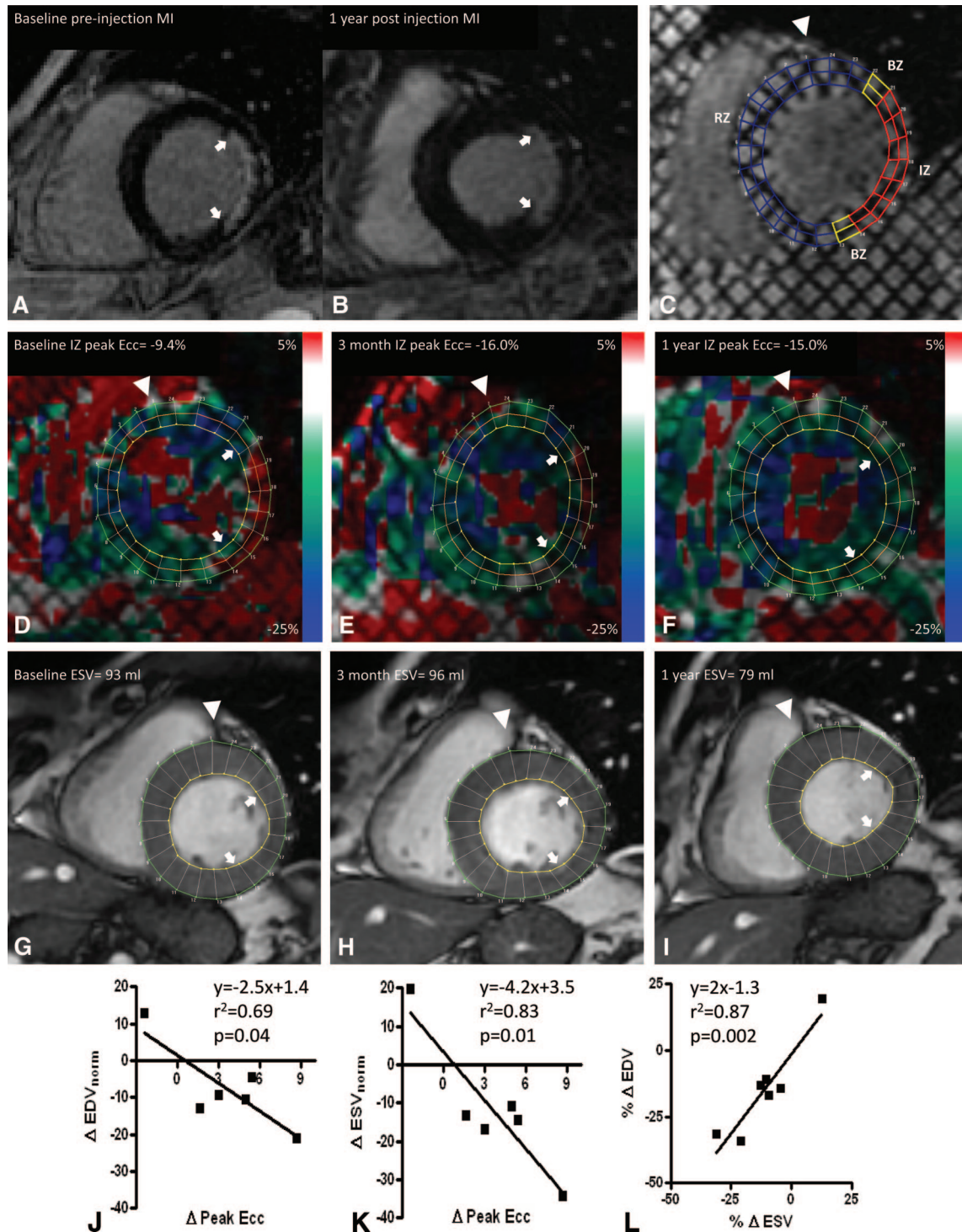


Figure 2. Autologous bone marrow progenitor cell injections increase regional function and precede reverse remodeling. A through I depict a patient injected with bone marrow progenitor cells. **A**, Baseline lateral wall infarct in delayed enhancement CMR (white arrows). **B**, One year postinjection infarct. **C**, Infarct mapped to corresponding segmented tagged CMR image with IZ defined by the presence of enhancing myocardium, neighboring myocardium as border zone (BZ), and normal myocardium as remote zone (RZ) (first segment of each map correlated by right ventricle insertion point; white arrowhead). Tagged harmonic phase CMR strain maps show significantly depressed regional function by peak Ecc at baseline in IZ (white arrows) (**D**). Red/white indicates weak contractility (more positive Ecc) and green/blue indicates vigorous contractility (more negative Ecc) in harmonic phase strain maps. **E and F**, At 3 months after cell injection, the IZ contractility has improved (less red/white, more green/blue) (**E**) and by 12 months is contracting similar to the border zone (mostly green/blue) (**F**). **G through I**, ESV remains relatively stable between baseline (**G**) and 3 months (**H**); however, at 1 year, reverse remodeling is present (**I**). **J and K**, Changes in peak Ecc of the IZ had a strong correlation with the changes in EDV (**J**) and ESV (**K**) at 12 months compared with baseline (difference in peak Ecc between baseline and 1 year versus difference in normalized EDV and ESV, respectively). **L**, Decreases in EDV and ESV strongly correlate with each other, indicating parallel decreases in chamber sizes contributes to unchanging EF after bone marrow stem cell injections.

clinical implications. Second, the reverse remodeling caused substantial parallel declines in systolic and diastolic volumes, so that an EF increase was obscured; accordingly, this strongly suggests that EF is not a good primary end point for assessing responses to cell therapy in dilated hearts and that chamber size, MI size, or regional function is more likely to reflect a favorable outcome. Finally, these data strongly indicate that a high-resolution imaging tool such as MRI, capable of detecting the latter outcomes, is necessary for trials of cardiac regeneration.

Although there is enormous enthusiasm for the possibility of repair of ischemic cardiomyopathy with cell-based therapy, mechanisms and manifestations of this strategy remain highly controversial. To address this, we phenotyped patients using cardiac MRI, which is recognized as the “reference standard” for quantitative assessment of LV function and has been shown to be the most accurate and reproducible imaging modality to assess global and regional LV function.^{6,7} Regional functional improvements (peak Ecc) of the infarct territory were calculated by harmonic phase MRI, arguably the most accurate noninvasive analytic imaging modality to measure regional strain.^{8,9}

The early improvements in regional contractility of a treated infarct predicted later reverse remodeling. Regional strain of the infarct territory improved as early as 3 months following cell injection, which persisted at 6 months and 1 year (Figure 1). The reduction in chamber volumes was not evident until 6 months, and the correlation with improved regional strain was not apparent until 6 months and continued at 1 year (Figure 2). This suggests that the first manifestation of bone marrow cell therapy on the heart is improved regional function that later contributes to reverse remodeling. As a corollary to this finding, infarct size was reduced by 3 months after treatment.

Preclinical studies of bone marrow cell therapy for ischemic heart disease have demonstrated improved EF, but this has not translated to early phase studies in humans. We show a strong parallel decrease in both EDV and ESV ($r^2=0.87$, $P=0.002$) 12 months after treatment. Indeed, this finding strongly suggests that EF may not be a good outcome measure for studies of cell therapy for remodeled ventricles. Importantly, both LV size and infarct size are important clinical indicators of outcome in patients with ischemic cardiomyopathy,¹⁰ and the results here highlight a highly adaptive response to cell therapy, even in the absence of a net increase in EF.

This study lacks the power to determine superiority between mesenchymal stem cells or whole bone marrow and does not have a placebo comparison group. Although only 4 patients had longitudinal assessment of scar size (attributable to artifact distortion in delayed enhancement images due to the presence of implantable cardioverter defibrillators in some patients), MI size was reduced in each of these subjects. Each of these limitations will be definitively addressed in the ongoing TAC-HFT and POSEIDON trials, which together will treat 90 patients in placebo-controlled, blinded fashion.

In conclusion, MRI provides a unique opportunity to image the in vivo structural and functional changes after bone marrow stem cell therapy for the heart. Our data

suggest human autologous bone marrow progenitor cells increase regional contractility of injected myocardial scar tissue within 3 months of treatment, and these functional changes are associated with later reverse remodeling. These findings strongly support ongoing clinical investigation of cell-based therapy for cardiomyopathy and support the use of regional function and chamber size as important end points.

Sources of Funding

This study was supported by the University of Miami Interdisciplinary Stem Cell Institute and BioCardia Inc. J.M.H. is also funded by NIH grant U54-HL081028.

Disclosures

Authors who are employees of BioCardia Inc are identified as such. All authors reviewed and approved the analysis and manuscript. The University of Miami supervised the management of the study, and EMMES Corporation was responsible for data collection, site monitoring, and analyses.

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Novelty and Significance

What Is Known?

- Catheter-based bone marrow progenitor cell injections improve cardiac function and reduce scar burden in large animal models of ischemic cardiomyopathy.
- Using various imaging modalities, early human studies of bone marrow progenitor cell therapy for ischemic cardiomyopathy have shown improved regional function.

What New Information Does This Article Contribute?

- Durable reverse remodeling results from cell-based therapy for healed myocardial infarction/chronic ischemic cardiomyopathy.
- Intramyocardial injections of bone marrow progenitor cells to infarct and border zones of humans with ischemic cardiomyopathy improve regional function of the scar within 3 months of therapy, and this improved regional function predicts subsequent reductions in left ventricular chamber volumes.

- End points for cell-based therapy should focus on chamber dimensions and regional function using reliable and reproducible imaging modalities, such as cardiac MRI.

Early clinical trials have shown the capacity of intramyocardial injections of bone marrow–derived progenitor cells to improve regional function with modest improvements in ejection fraction. We used cardiac MRI to phenotype the in vivo changes of the left ventricle following catheter-based intramyocardial injections of bone marrow progenitor cells. We show improved regional function of scarred myocardium within 3 months of therapy, and this predicts later reverse remodeling. For the first time, we show that this therapy can improve diastolic volumes and parallel decreases in both end systolic and end diastolic volume contribute to the lack of overall improvements in ejection fraction.

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SUPPLEMENTAL METHODS:

Study Design and Patient Selection

Details of the study design and justification have been previously reported.¹ Briefly, eight patients with a diagnosis of ischemic cardiomyopathy were enrolled between October 2008 and June 2009 to document the feasibility and procedural safety of intramyocardial injections of autologous bone marrow progenitor cells via the Helical Infusion Catheter (BioCardia, San Carlos, CA) after remote MI. Data was collected over one year after cell transplantation to assess safety, clinical outcomes, and conduct detailed cardiac structure and function phenotyping using cardiac magnetic resonance imaging (CMR). Patients were eligible if they had chronic ischemic left ventricular dysfunction (LVEF 20-50%) secondary to a previous MI and were on maximal medical therapy for heart failure. Patients were documented to have chronic myocardial scars by CMR, and in all cases were fully revascularized in the infarct related territory by documented cardiac catheterization prior to enrollment. Computed tomography (CT) of the chest, abdomen, and pelvis was obtained and patients excluded if an occult malignancy was identified. Written informed consent was obtained from all patients on this University of Miami Institutional Review Board (IRB) approved protocol.

Harvest, Processing, and Delivery of Bone Marrow Cells

All patients underwent a bone marrow aspiration (BMA) from the iliac crest. Bone marrow aspirate was immediately transported to the University of Miami Good Manufacturing Practice cell lab. Bone marrow mononuclear cells were isolated using Ficoll density gradient centrifugation. The cells were then washed and prepared for infusion. Cells were suspended in 2.5ml of phosphate buffered saline for the first 4 patients and 5ml for the subsequent 4 patients. Patients who were assigned to the bone marrow mononuclear cell arm (n=4) were injected approximately 4-hours following BMA. In the patients allocated to the bone marrow mesenchymal stem cell arm (n=4), the MSCs were isolated from the bone marrow mononuclear cells based on plastic adherence and expanded in culture. After approximately 4-5 weeks in culture, sufficient quantities of MSCs were available and injected into the patients.

The bone marrow cells were delivered to the myocardium by transendocardial injections using the BioCardia Helical Infusion Catheter during cardiac catheterization. Right anterior oblique (RAO) and left anterior oblique (LAO) ventriculograms were obtained with biplane angiography. End-diastolic endocardial border contours were traced over the ventriculograms. Using the previously acquired CMR delayed hyperenhancement images and the wall motion abnormalities on the ventriculograms, an akinetic infarct zone (IZ) and hypokinetic border zone (BZ) were marked. The suspension of bone marrow progenitor cells was divided into 10 syringes of 0.25ml for the first 4 patients and 0.5ml aliquots for the next 4 patients. The ventriculogram tracings were used to guide the Helical Infusion Catheter to the IZ and BZ, where the corkscrew tip of the catheter was inserted. A small injection of iodinated contrast was injected via the side port of the catheter to confirm engagement with the myocardium. The syringes containing the cells were injected followed by a dwell time to prevent washout of cells. This was repeated in 10 areas of the IZ and BZ.

Safety Assessment

The primary outcome of the study was to assess the safety of transendocardial administration of bone marrow mononuclear and mesenchymal stem cells as determined by the incidence of treatment emergent serious adverse events (TE-SAE) defined as the composite of death, non-fatal myocardial infarction (MI) stroke, hospitalization for worsening heart failure, cardiac perforation, pericardial tamponade, ventricular arrhythmias lasting > 15 seconds or with hemodynamic compromise, or atrial fibrillation one-month post-catheterization. Secondary outcomes assessed clinical, laboratory and CMR endpoints, as discussed below. All patients were admitted to the hospital following catheterization for a 72-hour observation period. Peri-procedural safety monitoring included echocardiograms to evaluate for pericardial effusion, Holter ECG monitoring, and cardiac enzymes. Pulmonary function testing was performed at baseline and at 12 months. A 12-month whole body CT was compared to the pre-injection CT to assess for ectopic tissue growth.

CMR Analysis

CMR was used to analyze secondary endpoints of structural and functional effects of bone marrow progenitor cell injections on chronic ischemic heart failure. Cine CMR was used to determine global cardiac function² and tagged cine myocardial imaging³ was used to assess regional LV function. Delayed myocardial enhancement with intravenous gadolinium was used to quantify infarct size.⁴ All patients underwent CMR at baseline, 3 months, 6 months, and 1 year after stem cell transplantation; one patient refused his 3 month and 1 year CMR

CMR was performed on a 1.5 T scanner (Signa HDx, GE Healthcare, Waukesha, WI) using an 8-channel body coil with ECG gating and breath-hold acquisitions. Steady-state free precession (SSFP) cine images in short axis planes (8mm slices with 2mm gap, FOV 35-40cm, matrix 256x200, TR/TE 3.7ms/1.6ms) were obtained; fast gradient echo tagged short axis images with grid pattern (8mm slices with 2mm gap, matrix 256x128, TR/TE 6.8ms/3.2ms); and short axis and multiple long axis views of delayed myocardial enhancement imaging acquired 10 minutes following intravenous gadolinium (0.2mmol/kg; Magnevist, Bayer Healthcare, Wayne, NJ) (8mm slices with 2mm gap, matrix 192x160, TR/TE 4.4ms/1.3ms). In patients with ICD devices, fast gradient echo cine images (matrix 192x128, TR/TE 5.1ms/2.8ms) were substituted for the SSFP cine images to limit artifacts. Patients enrolled in this study that had an implantable cardioverter defibrillator (ICD) were imaged in the magnet based on a previously reported protocol.^{5,6} One patient refused his 3 and 12 month CMR scan

CMR analytical software Segment (Medviso AB; Lund, Sweden) was used to calculate LV mass, end-diastolic volume (EDV), end-systolic volume (ESV), and ejection fraction (EF) from short axis cine images. Scar volume and scar size as a percentage of LV mass were calculated from delayed enhancement (DE). At end-diastole and end-systole, epicardial and endocardial contours were drawn in sub-centimeter contiguous slices covering the apex to mitral valve plane to obtain left ventricle EDV, ESV, and LV mass. Global left ventricle EF was calculated as $[(EDV-ESV)/EDV] \times 100\%$. Infarct scar size was determined from the short axis DE images covering the apex to the mitral valve annulus; tissue an intensity signal > 2 standard deviations above reference normal myocardium was identified as scar and calculated as absolute scar volume and scar as a percentage of LV mass. Because of artifact from the ICD, three patients did not have interpretable delayed enhancement scans and were excluded from the DE scar analysis.

Regional function was measured by tagged CMR images using HARP software (Diagnosoft; Cary, NC). Three contiguous short axis tagged images encompassing the scar were selected for analysis. User defined epicardial and endocardial contours were drawn to create a 24-segment mesh for each slice, and eulerian circumferential strain (Ecc) for each segment at each time point of the cardiac cycle was measured. Using the RV insertion as a reference point, corresponding delayed enhancement and tagged images were segmented into infarct zone (IZ), border zone (BZ), remote zone (RZ). The hyperenhanced zone that was the target for intramyocardial stem cell injections was identified as the IZ and both lateral neighboring 15-degree segments defined as the BZ. A 45-degree segment away from the IZ without enhancing myocardium was marked as RZ. The peak Ecc for each zone was calculated by averaging the peak Ecc (more negative is greater contractility) from each individual segments of the specified zone. The same slices and zones were used between all time points. One patient had poor tracking of tagged images due to ICD artifacts and was excluded from this analysis.

Statistical Analysis

Endpoints following stem cell injection were analyzed with a repeated-measures analysis of variance (ANOVA) with terms for time. Least squares mean and standard errors were estimated along with p-value from the F-statistic using PROC MIXED (SAS version 9.2, Cary, NC) assuming compound symmetry covariance structure. All values are presented as means \pm standard error of mean (SEM) unless otherwise noted. Safety data were summarized with the use of descriptive statistics. Linear correlation analyses were applied to the difference in peak Ecc to the changes in EDV and ESV. All tests were 2-sided and a p-value less than 0.05 was considered statistically significant.

SUPPLEMENTAL RESULTS:

Patient Population and Safety Outcomes

Eight patients were enrolled in this study with baseline characteristics summarized in the Online Table I. The mean age was 57.2 ± 13.3 years, all were male, and all patients had suffered a remote MI (68.8 ± 21.4 months, range 4 months to 11 years). All patients tolerated the bone marrow aspiration without complication and all cell products were manufactured to the protocol defined total dose. Six patients received all 10 injections, of which one had clumping of BM-MSCs and received 50 million cells in the required total volume. Due to losses in transfer of final cell product, one patient received 8 injections (160 million cells) and one patient received 9 injections (150 million cells).

No patient experienced a TE-SAE as previously defined. Perforation, MI, and sustained ventricular arrhythmias are potential complications of intramyocardial injection and were not observed in this study. All patients tolerated the stem cell injections with only transient PVCs, similar to guidewire induced PVCs during catheterization. One patient experienced a non-sustained VT on day 4 post-injection, which resulted in placement of an ICD. There were 2 other patients that received prophylactic ICD as recommended by their primary cardiologist and not due to study related complications. Echocardiography showed one case of a trivial pericardial effusion (less than 0.5cm) at 48-hours post injection that resolved without intervention. Post-procedure and monthly Holter-ECG recordings showed all patients (n=8) to

be in normal sinus rhythm and no cases of ventricular fibrillation were documented (n=0). All patients had episodes of asymptomatic, non-sustained ventricular tachycardia within one-month of injection (n=8, range 3-12 beats). As shown in Online Table II, intramyocardial injection caused a small but significant increase in Troponin-I and CPK-MB at 12 hours which, began resolving by 24 hours. These increases in enzymes are likely the result of needle manipulation of myocardium and did not produce clinical symptoms or ST changes on ECG similar to previously documented animal models.⁷ Whole body CT showed no evidence of new ectopic tissue formation in any patient at 12 months. Pulmonary function tests (PFTs) demonstrated no change in forced expiratory volume in 1 second (FEV1) between baseline and 12 months [2.92 ± 0.25 vs. 2.94 ± 0.22 (81.4 vs. 90.1% of predicted value), p=NS]. Our safety data at one year shows a consistent profile with other clinical trials using intramyocardial stem cell injections of autologous bone marrow cells with the Helical Infusion Catheter.⁸

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Online Table I. Patient characteristics

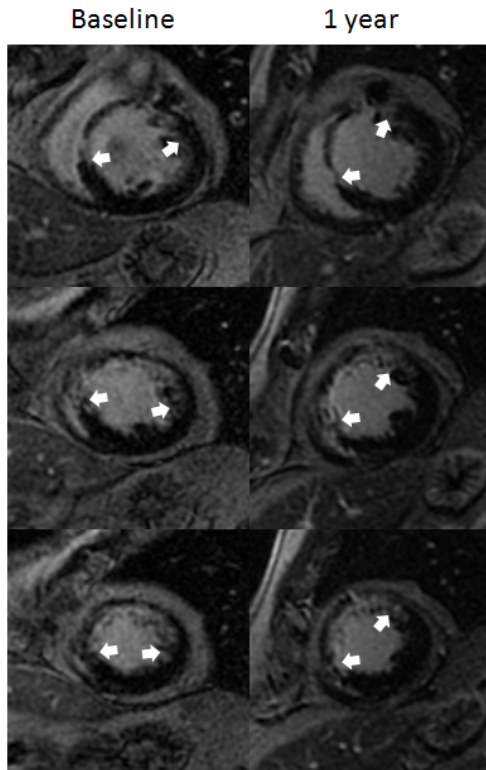
Pt	Age (yrs)	Gender	NYHA Class	HR	BP	History of smoking	DM	Beta blocker	ACE-I or ARB	Previous PCI/CABG*	Age of infarct at injection	Infarct target wall	Bone Marrow Cells (number)
1	65	M	1	51	121/51	N	N	Y	Y	CABG	8 years	Inferior	MNC (100 million)
2	35	M	1	65	108/63	Y	N	Y	Y	PCI	4 months	Anterior/Septum	MSC (100 million)
3	78	M	1	53	141/78	N	N	Y	Y	PCI	9 years	Lateral	MSC (100 million)
4	51	M	2	69	108/74	Y	N	Y	Y	PCI	6 months	Septum	MNC (100 million)
5	65	M	1	60	147/68	Y	N	Y	Y	PCI	11 years	Anterior/Septum	MNC (200 million)
6	45	M	1	71	119/73	N	Y	Y	N	PCI	11 years	Anterior/Septum	MSC (200 million)
7	61	M	3	73	159/85	Y	N	Y	Y	PCI	4 years	Inferior	MSC (200 million)
8	54	M	2	63	101/71	Y	N	Y	Y	PCI	5 months	Anterior	MNC (200 million)

Pt=patient, Age=Age at Injection, M=Male, Y=yes, N=no, NYHA=New York Heart Association Class, HR=heart rate, BP=blood pressure, DM=Diabetes Mellitus, Beta Blocker=On a beta blocker pre-injection, ACE-I=On angiotensin converting enzyme inhibitor or angiotensin receptor blocker (ARB) pre-injection, PCI=percutaneous coronary intervention, CABG=coronary artery bypass grafting, MNC=mononuclear cells, MSC=mesenchymal stem cells. *As per study protocol, all patients underwent coronary revascularization a minimum of 3 months prior to stem cell injection.

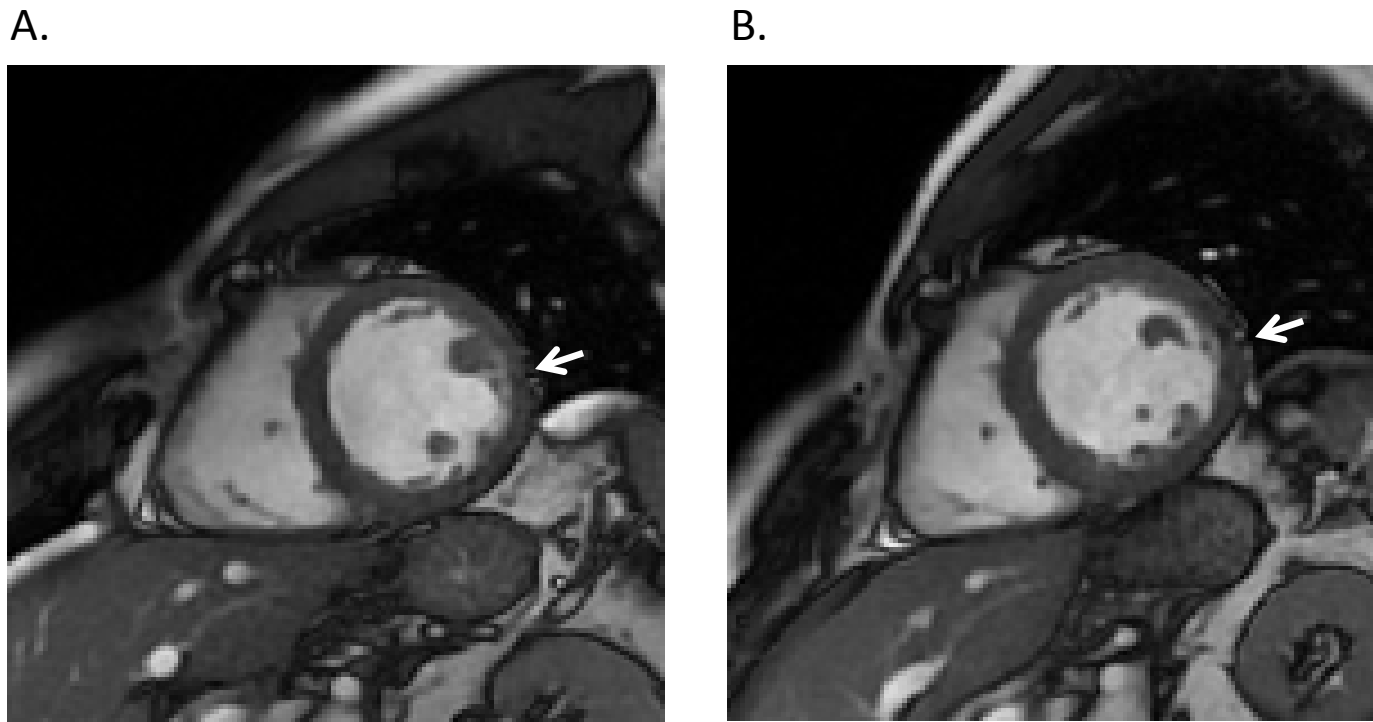
Online Table II. Cardiac enzymes following transendocardial bone marrow injections

Cardiac Enzyme	Time after stem cell injection					p value
	Baseline	12 hr	24 hr	36 hr	48 hr	
Troponin-I (ng/mL)	0.008±0.01	0.85±0.2	0.44±0.2	0.36±0.2	0.32±0.2	0.003
CPK-MB (ng/mL)	3.10±0.8	4.01±1.1	1.88±0.5	1.31±0.3	1.33±0.4	0.002

All values are means ± SEM.



Online Figure I. Example changes in an anterior wall infarct one year after transendocardial bone marrow stem cell injections. Sequential gadolinium delayed-enhancement cardiac MRI short-axis images from base (top) to apex (bottom) of an anterior/septal infarct (between white arrows) at baseline (left) and at one year (right). The EDV decreased from 225.2 to 196.3mL and the ESV decreased from 143.9 to 124.8mL from baseline to 1 year, respectively. A 25% reduction in scar size as a percentage of LV mass was evident at 1 year.



Online Figure II. Short-axis cine cardiac MRI at (A) baseline and (B) 1 year post-injection of bone marrow progenitor cells. This patient had a chronic lateral wall infarct (white arrow) that was treated and showed improved regional contractility at 1 year.