

# Administration of Cardiac Stem Cells in Patients With Ischemic Cardiomyopathy: The SCIPIO Trial

## Surgical Aspects and Interim Analysis of Myocardial Function and Viability by Magnetic Resonance

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**Background**—SCIPIO is a first-in-human, phase 1, randomized, open-label trial of autologous c-kit<sup>+</sup> cardiac stem cells (CSCs) in patients with heart failure of ischemic etiology undergoing coronary artery bypass grafting (CABG). In the present study, we report the surgical aspects and interim cardiac magnetic resonance (CMR) results.

**Methods and Results**—A total of 33 patients (20 CSC-treated and 13 control subjects) met final eligibility criteria and were enrolled in SCIPIO. CSCs were isolated from the right atrial appendage harvested and processed during surgery. Harvesting did not affect cardiopulmonary bypass, cross-clamp, or surgical times. In CSC-treated patients, CMR showed a marked increase in both LVEF (from 27.5±1.6% to 35.1±2.4% [ $P=0.004$ , n=8] and 41.2±4.5% [ $P=0.013$ , n=5] at 4 and 12 months after CSC infusion, respectively) and regional EF in the CSC-infused territory. Infarct size (late gadolinium enhancement) decreased after CSC infusion (by manual delineation: -6.9±1.5 g [-22.7%] at 4 months [ $P=0.002$ , n=9] and -9.8±3.5 g [-30.2%] at 12 months [ $P=0.039$ , n=6]). LV nonviable mass decreased even more (-11.9±2.5 g [-49.7%] at 4 months [ $P=0.001$ ] and -14.7±3.9 g [-58.6%] at 12 months [ $P=0.013$ ]), whereas LV viable mass increased (+11.6±5.1 g at 4 months after CSC infusion [ $P=0.055$ ] and +31.5±11.0 g at 12 months [ $P=0.035$ ]).

**Conclusions**—Isolation of CSCs from cardiac tissue obtained in the operating room is feasible and does not alter practices during CABG surgery. CMR shows that CSC infusion produces a striking improvement in both global and regional LV function, a reduction in infarct size, and an increase in viable tissue that persist at least 1 year and are consistent with cardiac regeneration.

**Clinical Trial Registration**—This study is registered with clinicaltrials.gov, trial number NCT00474461. (*Circulation*. 2012;126[suppl 1]:S54–S64.)

**Key Words:** coronary artery bypass ■ heart failure ■ infarction ■ MRI ■ stem cells ■ regeneration

The prevalence of heart failure (HF) in industrialized nations has reached epidemic proportions; in the United States, it is nearly 6 million and continues to rise. Despite notable advances, the prognosis of patients who are hospitalized with HF remains poor, with a 5-year mortality that approaches 50%.<sup>1</sup> Ischemic heart disease, with the attendant loss of myocardium, is considered to be the most common underlying cause of HF.<sup>2–4</sup> Consequently, the concept of regenerating myocardium with stem cell therapy has garnered

increasing attention among investigators within the cardiovascular research community. Most efforts made to date have focused on bone marrow–derived progenitor cells.<sup>5</sup> In the study reported herein, we used a different approach that harnesses stem cells normally found in the heart itself.

Anversa et al<sup>6</sup> were the first to describe the existence of cardiac stem cells (CSCs), a resident population of stem cells in adult mammalian myocardium that is marked by the surface receptor tyrosine kinase c-kit. Numerous preclinical

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studies have demonstrated the efficacy of this cell population in the treatment of HF secondary to myocardial infarction (MI).<sup>6–8</sup> This large body of preclinical evidence motivated us to undertake the first-in-human clinical trial of CSCs.<sup>9</sup> In August 2008, we received approval from the Food and Drug Administration to conduct SCIPIO (Stem Cell Infusion in Patients with Ischemic cardiomyopathy), a phase 1 clinical trial of CSCs. The primary goal of SCIPIO is to investigate the safety and feasibility of using autologous CSCs for the treatment of HF resulting from ischemic heart disease. The secondary goal is to gain initial insights into the effects of CSCs on left ventricular (LV) function, infarct size, and functional status. Since SCIPIO is the first study of CSCs in humans, the results will be important for developing this new form of cell therapy and planning future studies.

An interim analysis of SCIPIO has recently been published, and has shown a significant increase in LV ejection fraction (EF), measured by 3D echocardiography, in functional capacity, assessed by NYHA class, and in quality of life, gauged by the Minnesota Living With Heart Failure Questionnaire.<sup>9</sup> That analysis, however, was limited by the fact that LVEF was not assessed by cardiac magnetic resonance (CMR), which is considered the “gold standard” for measuring LV function and infarct size,<sup>10–14</sup> that infarct size was not measured by semiautomated methods, that viable LV mass was not assessed, and that the surgical aspects of the study were not evaluated.

Since that initial report,<sup>9</sup> we have completed enrollment of control and treated subjects and performed a detailed CMR analysis. Accordingly, we describe here the surgical aspects of the entire cohort of control and treated patients enrolled in SCIPIO. Additionally, we present the interim results of a comprehensive CMR evaluation of global and regional LV function, infarct size, and LV viable tissue.

## Methods

### Initial and Final Enrollment (Before and After Coronary Artery Bypass Grafting)

SCIPIO is a first-in-human, phase 1, randomized, open-label clinical trial designed to explore the effects of autologous c-kit-positive CSCs in patients with ischemic cardiomyopathy. The trial is still ongoing. A full description of the study protocol and inclusion and exclusion criteria has been published<sup>9</sup>; enrollment and exclusions are summarized in Figure 1.

In summary, criteria for inclusion were HF with an LVEF  $\leq 40\%$ , evidence of a previous myocardial infarction (MI), and need for coronary artery bypass grafting (CABG). Final enrollment was based on assessment for eligibility at 2 time points. If a patient met the initial enrollment criteria within 2 weeks of CABG surgery, and agreed to participate, he/she signed an institutional review board-approved informed consent before tissue harvest. The patient was then reevaluated at 4 months after CABG surgery (Figure 1); if the eligibility criteria were met, and the patient agreed to continued participation, the patient was included in the study. An interval of 4 months from surgery to cell therapy was selected because, in many patients with low LVEF, this variable is known to improve spontaneously during the first few months after CABG surgery as a result of resolution of myocardial hibernation and/or stunning<sup>15,16</sup>; since this spontaneous improvement usually occurs within the first 4 months, administering cell therapy after a 4-month interval enabled us to separate the effects of CSCs from those of surgical revascularization.<sup>17–19</sup>

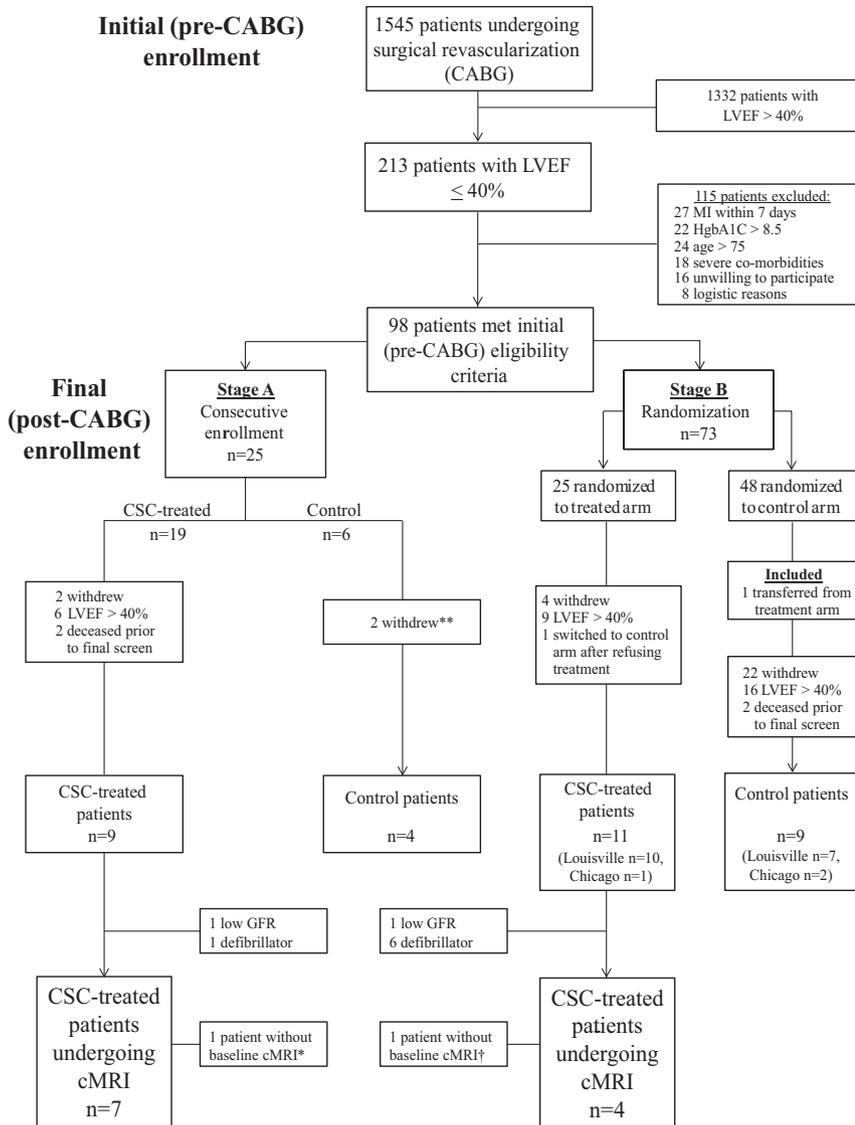
The trial was conducted in 2 sequential stages (Figure 1). Stage A, aimed mainly at assessing feasibility and short-term safety, proceeded with the consecutive enrollment of 9 treated patients followed by 4 control patients. Subsequently, in stage B, an adaptive block randomization scheme was employed as previously described. Using this template, 11 and 9 patients were assigned to final enrollment in the treated and control groups, respectively.<sup>9</sup> Thus, while 98 patients were enrolled based on satisfaction of initial enrollment eligibility (Figure 1), only 33 patients (20 CSC-treated and 13 control patients) met final eligibility criteria and agreed to participate in the study. Data regarding safety herein are reported for all 33 patients, all of whom will be included in the final analysis of data collected at prespecified time points; there have been no patients lost to follow-up. The study protocol was approved by the Institutional Review Board of the participating clinical centers and the trial results were monitored by an independent Data and Safety Monitoring Board.

### Surgical Methods and Cell Production

C-kit-positive cells were isolated and grown from the right atrial appendage. Consequently, only patients undergoing “on-pump” CABG surgery were enrolled in the trial, as the appendage is routinely removed in these cases to allow access for right atrial cannulation. This tissue sample ( $\approx 1$  g) was excised and placed into a sterile specimen cup, which was then passed on to an investigator in the operating room. Using a sterile field (Online Data Supplement Figure 1) and aseptic technique, the investigator transferred the specimen to a sterile Petri dish, where the tissue was immersed in CSC growth medium. The tissue was minced into fine fragments ( $\approx 200$ – $400$   $\mu\text{g}$  each), which were placed into several sterile cryovials (Nalgene Nunc International, Rochester, NY) filled with freezing solution (growth medium and DMSO in a 9:1 ratio). The cryovials were transported on ice to a Good Manufacturing Practice laboratory (Brown Cancer Center, University of Louisville) for storage at  $-80^\circ\text{C}$ . Cryopreservation in a specialized cryovial ensured slow cooling (approximately  $-1^\circ\text{C}$  per hour), thereby preserving cell viability. After  $\approx 80$  hours, the tissue was shipped overnight, via courier, in a freezing container to the core laboratory at the Brigham and Women’s Hospital for dissociation, isolation, and expansion of CSCs. Once allocation to the control group was confirmed, those cell cultures were destroyed in compliance with institutional biohazard handling policies. The methods for expanding CSCs from the atrial tissue have been described previously.<sup>9</sup>

### Preparation for CSC Infusion

At  $\approx 4$  months (range, 3–5 months) after surgery, patients allocated to the treated arm returned for pretreatment evaluation, which included 2D/3D echocardiography and CMR. CMR studies were performed only if renal function was adequate (eGFR  $>40$   $\text{mg/mL}$ ) and if no standard CMR contraindications existed (eg, prior ICD/pacemaker, metal hardware, etc). Decisions regarding which vascular territory should be infused with CSCs were made by a group of investigators that included an interventional cardiologist, a radiologist, a noninvasive cardiologist, and a cardiac surgeon. Infusion territories were denoted by identifying infarcted region(s) using all of the imaging modalities available for each patient. The infusion vessel(s) was chosen based on the anatomic association between the coronary artery and the infarcted region(s). If the territory to be infused was the anterior LV wall (supplied by the left anterior descending artery),  $1 \times 10^6$  CSCs were injected into the graft supplying the left anterior descending artery. For other territories,  $5 \times 10^5$  CSCs were injected into the graft(s) supplying those regions (Online Data Supplement Table 1). If 2 infarcts were identified,  $5 \times 10^5$  cells were infused into each infarcted territory. Regardless of number of infarcts or territories involved, a maximum of  $1 \times 10^6$  CSCs was allowed for each patient. Cells were transported from the Brigham and Women’s Hospital to the University of Louisville; the vial to be injected was prepared by suspending CSCs in Plasmalyte A solution.



**Figure 1.** Screening and enrollment as of November 12, 2011. CABG indicates coronary artery bypass graft surgery; LVEF, left ventricular ejection fraction; CSC, cardiac stem cell. \*Patient excluded from analysis because baseline cMRI was not performed due to newly placed thoracic staples. †Patient excluded from analysis because of refusal to undergo baseline cMRI. \*\*The majority of those who withdrew refused to follow the rigorous testing regimen schedule set forth for all patients regardless of treatment allocation.

## CMR Studies

In patients eligible for CMR, these studies were performed at the University of Louisville using a 1.5-T MR scanner (Espree, Siemens Medical Solutions, Erlangen, Germany). Screening and enrollment of patients for the CMR studies are summarized in Figure 1. After anatomic axes of the heart were determined by scout images, a complete short-axis steady-state free precession (SSFP) cine sequence series covering the whole heart with 10 to 16 contiguous slices was obtained. The methods for acquisition and analysis of CMR images are described in the Online Data Supplement.

## Statistical Analysis

The 33 eligible, evaluable patients were analyzed according to the treatment received (ie, the analysis combined data from both stages of the study and does not follow the intention to treat paradigm for the patient who refused the experimental treatment). The CMR assessments were performed in a blinded fashion. All global and regional data were collected, after which segments treated with CSCs were unblinded for statistical analyses alone. Changes in EF and infarct size over time were assessed using repeated measures ANOVA followed by paired *t* tests. Correlations between two imaging modalities were initially analyzed using Pearson's Correlation. Those with significant correlation ( $P < 0.05$ ) were then further delineated for association using linear regression models. Data are

reported as mean ± SEM. All analyses were performed using SPSS 19.0 (SPSS, Inc, Chicago, IL).

## Results

### Surgical Aspects of SCiPIO

Enrollment in SCiPIO is complete (20 treated and 13 control patients). Of the 20 treated patients, 18 received  $1 \times 10^6$  cells whereas two received  $5 \times 10^5$  cells (Online Data Supplement Table I). Seventy-five percent of the surgical grafts used for cell infusion were venous.

The baseline characteristics of enrolled subjects are summarized in Table 1. Important clinical variables that may affect surgical outcome, such as diabetes, hypertension, body mass index, and serum creatinine, were not statistically different between the treated and control groups. There were no differences in demographic information such as age, race, and sex. Measures of preoperative cardiac status, such as number of diseased coronary vessels, location of infarction, and infarct-related arteries, were similarly distributed between the 2 groups.

**Table 1. Baseline Characteristics**

	Treated (n=20)	Control (n=13)	P
Age	57.6 (1.9)	55.8 (2.5)	0.565
Race			
White	19 (95%)	12 (92%)	0.693
Black	1 (5%)	1 (8%)	
Male sex	18 (90%)	12 (92%)	0.667
Body mass index, kg/m <sup>2</sup>	29.7 (1.0)	27.7 (1.3)	0.210
Diabetes mellitus	5 (25%)	5 (38%)	0.664
Hypertension	17 (85%)	9 (69%)	0.393
Hyperlipidemia	14 (70%)	11 (85%)	0.431
Tobacco use	5 (25%)	6 (46%)	0.270
Positive family history of CAD	9 (45%)	7 (54%)	0.888
Baseline ejection fraction	29.9 (1.7)	29.2 (1.9)	0.796
No. of arteries with stenosis >50%	2.9 (0.1)	2.6 (0.1)	0.187
Infarct artery			
RCA	17 (47%)	10 (43%)	
LAD	15 (42%)	11 (48%)	
LCx	4 (11%)	2 (9%)	
No. of old infarcts	1.8 (0.1)	1.8 (0.2)	0.862
Anterior infarction	15 (42%)	11 (48%)	
Non-anterior infarction	21 (58%)	12 (52%)	
No. of vessels infused	1.7 (0.1)	N/A	N/A
LIMA	8 (24%)	N/A	
Non-LIMA	25 (76%)	N/A	
No. of cells injected			
1 000 000	18 (90%)	N/A	N/A
500 000	2 (10%)	N/A	N/A
Medications			
Aspirin	20 (100%)	12 (92%)	0.826
β-blocker	16 (80%)	12 (92%)	0.641
ACE inhibitors or ARB	14 (70%)	7 (54%)	0.567
Statin	17 (85%)	11 (85%)	0.641
Clopidogrel	7 (35%)	5 (39%)	0.866

CAD indicates coronary artery disease; RCA, right coronary artery; LAD, left anterior descending; LCx, left circumflex; LIMA, left internal mammary artery; N/A, not applicable.

Baseline characteristics of all patients enrolled in the SCIPIO trial. Data are n (%) or mean±SEM.

CABG surgery was performed at the clinical site of enrollment, either in Louisville (University of Louisville or Jewish Hospital) or in Chicago (Advocate Christ Medical Center). The surgical characteristics are summarized in Table 2. In general, this was a population of patients with severe HF. There were no statistically significant differences between control and treated groups with respect to the number of grafts placed and/or in the choice of arterial versus vein grafts. Four patients in each group were found to have significant left main coronary artery disease (stenosis >50%). Intra-aortic balloon pump placement was necessary in five CSC-treated and four control patients (this was done preoperatively in 1 control patient, postoperatively in another

**Table 2. Surgical Characteristics of the Treated and Control Groups**

	Treatment Group (n=20)	Control Group (n=13)	P
Total surgery time, min	211.7 (9.8)	229.8 (12.2)	0.256
Total CPB time, min	86.2 (5.6)	101.5 (7.9)	0.116
Cross-clamp time, min	58.6 (4.7)	61.0 (6.3)	0.755
IABP placed	5 (25%)	4 (31%)	0.971
No. of grafts	2.3 (0.2)	2.7 (0.2)	0.099
Vein grafts	34 (74%)	24 (69%)	0.780
Arterial grafts	12 (26%)	11 (31%)	
Grafts with >50% narrowing 4 mo postop			
Vein grafts	6 (18%)	N/A	N/A
Arterial grafts	0		
STS preoperative risk			
Mortality	2.2 (0.4)	2.7 (0.9)	0.575
Morbidity or mortality	21.1 (2.4)	22.5 (4.2)	0.757
Concomittant valve surgery	1 (5%)	3 (23%)	0.276
Repeat surgery	2 (10%)	0	0.508
Perioperative complication*	2 (10%)	1 (8%)	0.693
Positive sterility test			
Endotoxin†	0	N/A	N/A
Mycoplasma	0	N/A	
Anaerobic culture	0	N/A	
Aerobic culture	0	N/A	

CPB indicates cardiopulmonary bypass; IABP, intra-aortic balloon pump; STS, Society of Thoracic Surgeons; N/A, not applicable.

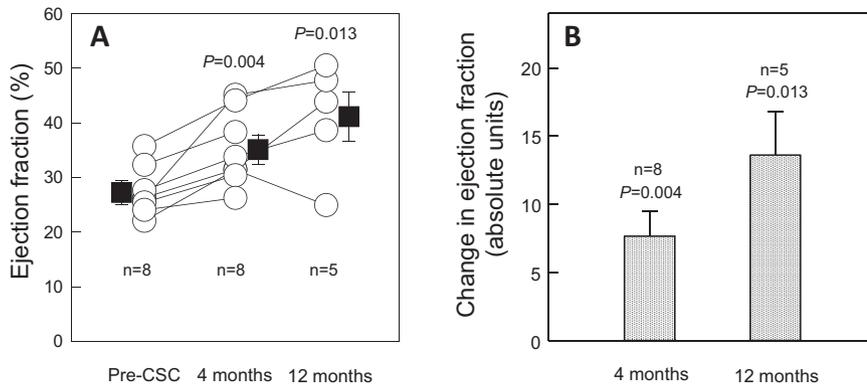
Data are reported as n (%) or mean±SEM.

\*Infected sternal wires and cellulitis at vein harvest site in cardiac stem cell (CSC)-treated patients, persistent sternal pain postoperatively in control patient.

†Sterility testing was performed on the CSC solution at 2 time points before infusion. All testing was negative for microbial contamination.

control, and intraoperatively in the other 7 patients [Table 2]). Preoperative LVEF was similar in the treated and control groups (25.3±1.7% versus 27.8±2.3%, P=0.380). The proportion of patients with preoperative LVEF ≤20% was 35% in the treated group and 31% in the control group. Concomittant valve surgery and number of repeat surgical procedures were similar between groups. As a result of these similarities, the Society of Thoracic Surgeons (STS) risk score for mortality or morbidity was not statistically different between groups (Table 2). Thus, the 2 groups of patients enrolled in SCIPIO were well-balanced with respect to important preoperative predictors of outcome, supporting the concept that the improvement in LV function was due to CSC administration rather than baseline differences.

Average values for incision to closure, cardiopulmonary bypass, and aortic cross-clamp times in the two groups combined (218.8±7.7, 92.2±4.7, and 59.5±3.7 minutes, respectively [Table 2]) were similar to the average times reported for all open-heart surgeries performed at the main surgical center (Jewish Hospital) over the previous 12 months, indicating that intraoperative tissue procurement did not adversely affect standard operating procedure or compro-



**Figure 2.** A, Left ventricular ejection fraction (LVEF) at baseline ( $27.5 \pm 1.6\%$ ), 4 months after cardiac stem cell (CSC) infusion ( $35.1 \pm 2.4\%$ ), and 12 months after CSC infusion ( $41.2 \pm 4.5\%$ ). B, Change in LVEF at 4 months and 12 months after CSC infusion (absolute EF units). Data are mean  $\pm$  SEM.

mise patient safety. There was no microbial contamination of any of the cell cultures, as confirmed by rigorous sterility testing that included aerobic and anaerobic cultures maintained for 14 days and independent assays for both mycoplasma detection and endotoxin levels (Table 2). Mean endotoxin levels for all samples tested were well below the accepted standard ( $<5$  EU/kg). Collectively, these results demonstrate the safety and feasibility of harvesting and preparing tissue in the operating room.

Having completed enrollment, we report here, for the first time, data on the safety of intracoronary CSC infusion in the entire population of 20 treated patients enrolled in SCPIO (our previous report<sup>9</sup> was limited to 16 patients). In this cohort of 20 treated patients, we experienced two complications during CSC infusion into a graft (LIMA dissection repaired with covered stent, and elevated cardiac enzymes after balloon inflation consistent with periprocedural MI). Interestingly, CSC infusion in the treated group offered a unique insight into the condition of the bypass grafts at 4 months after operation; angiograms performed at the time of CSC infusion demonstrated  $>50\%$  stenosis in 18% of vein grafts and none of the arterial grafts (Table 2). Overall, major adverse cardiac event (MACE) rates are similar between treated and control groups (Online Data Supplement Table II).

### CMR Analysis

According to the original protocol, CMR studies were performed only in CSC-treated patients. The selection of the patients with CMR studies is described in Figure 1. Of a total of 20 patients enrolled in the treated arm, nine were not eligible for CMR; among the remaining 11 patients, baseline CMR studies could not be performed in two, one because of recently-placed surgical clips and another because of patient's scheduling conflicts. Consequently, the analysis of CMR data were carried out in the nine treated patients that have baseline and 4-month follow-up images. The baseline characteristics of the patients included in the CMR analysis are described in Online Data Supplement Table III. The average age of the infarcts in this cohort was  $4.1 \pm 1.0$  years.

### EF Analysis

One patient was excluded from the EF analysis because of moderate to severe aortic stenosis. In the remaining eight patients, EF was measured both in the entire left ventricle

(global EF analysis) and in the infarcted regions that received CSC infusion (regional EF analysis).

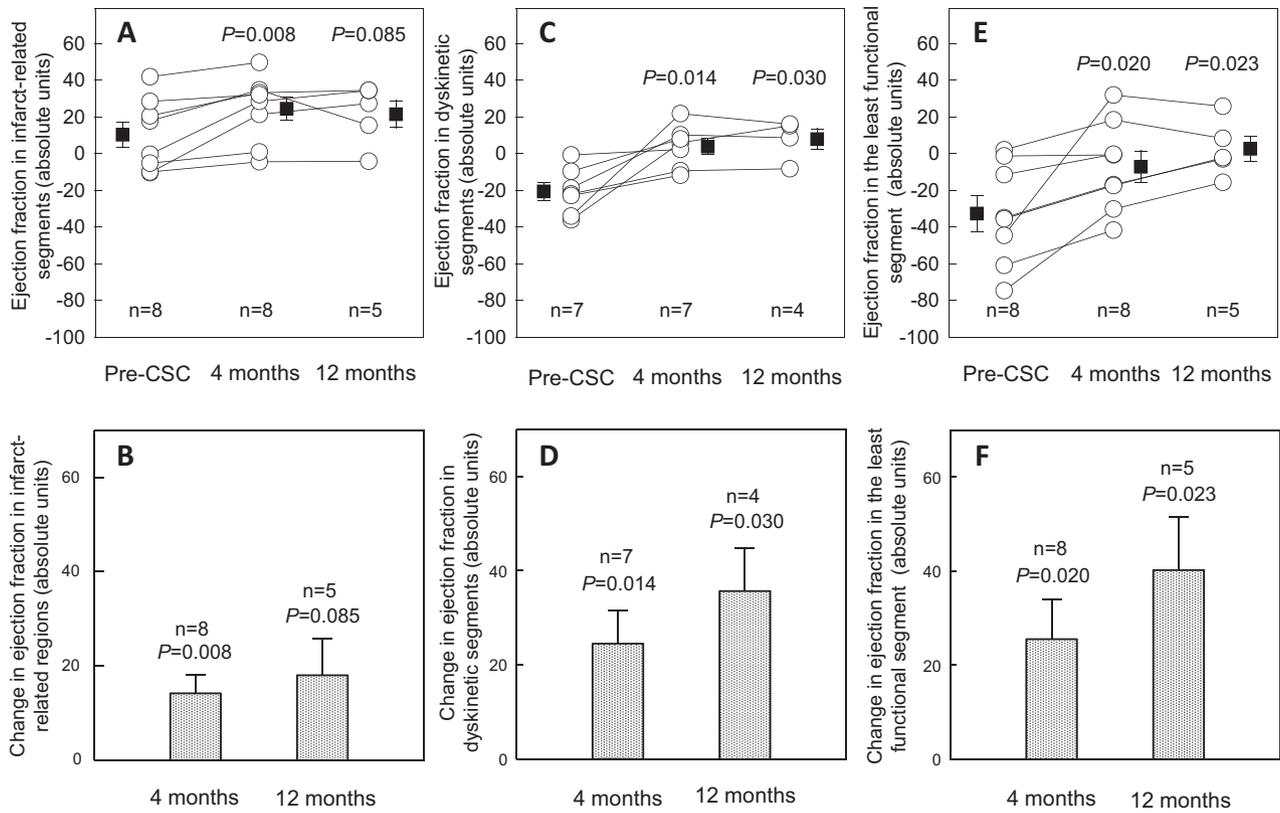
### Global EF Analysis

The mean baseline LVEF in the eight treated patients who were included in the CMR analysis was  $27.5 \pm 1.6\%$  at baseline (4 months after CABG surgery and before CSC infusion), and increased markedly to  $35.1 \pm 2.4\%$  ( $P=0.004$ ,  $n=8$ ) at 4 months and  $41.2 \pm 4.5\%$  ( $P=0.013$ ,  $n=5$ ) at 12 months after CSC infusion (Figure 2). By CMR, the net increase in LVEF was 7.7 EF units at 4 months ( $P=0.004$ ) and 13.6 EF units at 12 months ( $P=0.013$ ). Interestingly, strong correlation between measurements of LVEF by CMR and 3D echocardiography in this patient cohort was noted (Online Data Supplement Figure II).

### Regional EF Analysis

In the infarcted regions that received intracoronary CSCs, regional EF averaged  $10.3 \pm 6.9\%$  at baseline ( $n=8$ ); after CSC infusion, it increased by 14.2 EF units at 4 months ( $P=0.008$ ,  $n=8$ ) and by 17.9 EF units at 12 months ( $P=0.085$ ,  $n=5$ ) (Figure 3 A and 3B). Of the 8 patients with analyzable CMR studies, 7 had dyskinetic segments. The mean regional EF of the dyskinetic segments was  $-20.6 \pm 4.7\%$  at baseline; after CSC infusion, it increased by 24.5 EF units at 4 months ( $P=0.014$ ,  $n=7$ ) and 35.7 absolute EF units at 12 months ( $P=0.030$ ,  $n=4$ ) (Figure 3C and 3D). The mean regional EF of each patient's least functional segment, which was  $-32.7 \pm 9.8\%$  at baseline, increased by 25.6 EF units at 4 months ( $P=0.020$ ,  $n=8$ ) and 40.2 EF units at 12 months ( $P=0.023$ ,  $n=5$ ) (Figure 3E and 3F).

As illustrated in Figure 3, the absolute improvement in regional EF in segments that were dyskinetic (Figure 3D and 3F) was greater than that noted in the entire infarcted regions, which were, on average, hypokinetic (Figure 3B). For example, at 1 year after CSC infusion, the regional EF of the least functional segments in the infarcted region increased by  $40.2 \pm 11.3$  absolute EF units (Figure 3F), more than twice the average increase noted in the entire infarcted region ( $17.9 \pm 7.9$  absolute EF units, Figure 3B). These observations support the concept that the functional benefits of CSCs are inversely related to the baseline functional status of the myocardial region: the lower the baseline function, the greater the improvement afforded by CSC infusion.



**Figure 3.** **A**, Regional EF at baseline and 4 and 12 months after cardiac stem cell (CSC) infusion in the infarct-related regions. **B**, Change in regional EF in the infarct-related regions at 4 and 12 months after CSC infusion (absolute EF units). **C**, Regional EF in the dyskinetic segments of the infarct-related regions at baseline and 4 and 12 months after CSC infusion. **D**, Change in regional EF in the dyskinetic segments of the infarct-related regions at 4 and 12 months after CSC infusion (absolute EF units). **E**, Regional EF in the least functional segment of the infarct-related regions at baseline and 4 and 12 months after CSC infusion. **F**, Change in regional EF in the least functional segment of the infarct-related regions at 4 and 12 months after CSC infusion (absolute EF units). Data are mean±SEM.

**Infarct Analysis**

All of the 9 treated patients who had CMR studies were included in the infarct analysis. An example of CMR images of an infarct before CSC infusion and 4 and 12 months after infusion is shown in Figure 4. Infarct size, measured by manual delineation, averaged 30.4±5.1 g at baseline and decreased to 23.5±3.7 g at 4 months after CSC infusion (P=0.002 n=9) and 22.6±5.5 g at 12 months (P=0.039, n=6), corresponding to a percent reduction of 22.7% and 30.2%, respectively (Figure 5A and 5B). Measurement of infarct size by a semiautomated method (FWHM, which measures “core” infarct size [Online Data Supplement Table IV]) yielded even more striking results: infarct size decreased from 34.9±2.3 g at baseline to 21.6±2.7 g at 4 months (P<0.001, n=9) and 18.7±3.6 g at 12 months (P=0.003, n=6), corresponding to a percent reduction of 38.1% and 44.8%, respectively (Figure 5C and 5D). The most dramatic reductions were noted when we calculated nonviable LV mass (measured by semiautomated methods and defined as areas with delayed enhancement in which the infarct involves ≥50% of the LV wall thickness [Online Data Supplement Table IV]). Nonviable LV mass, which averaged 24.1±3.9 g at baseline, decreased by 50% at 4 months after CSC infusion (to 12.1±3.4 g; P=0.001, n=9) and by 59% at 12 months (to 10.4±3.0 g; P=0.013, n=6) (Figure 6A and 6B). Thus, all 3 parameters used to assess infarct size consistently exhibited a

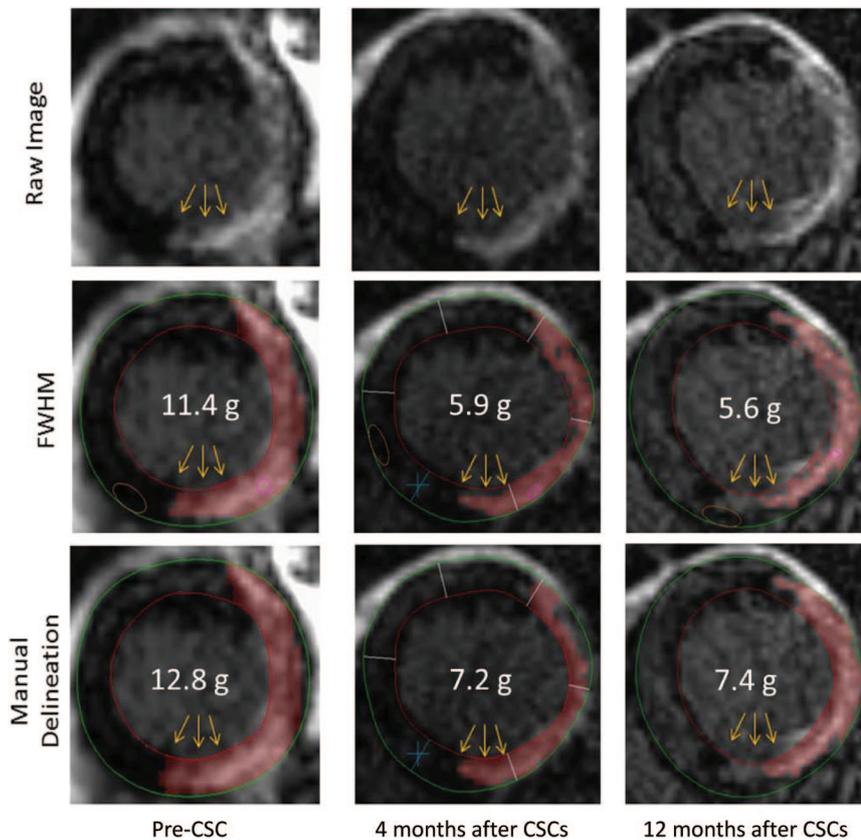
dramatic reduction after administration of CSCs, although the magnitude of the benefit differed depending on the method used.

At the same time, the total viable LV mass increased from 151.0±15.3 g at baseline to 162.6±12.5 g at 4 months (P=0.055) and 177.8±18.8 g at 12 months (P=0.035), corresponding to a percent increase of 7.6% and 21.5%, respectively (Figure 6C and 6D). Based on the decrease in infarct size, and assuming that 90% of the regenerated myocardium is composed by cardiomyocytes and the volume of differentiated myocytes is ≈20 000 μm<sup>3</sup> 20, it can be estimated that ≈294×10<sup>6</sup> and 415×10<sup>6</sup> cardiomyocytes were generated within the scar at 4 and 12 months, respectively.

**Discussion**

As the first trial of CSC therapy in humans, SCIPIO has the potential to open a new avenue in the treatment of patients with ischemic cardiomyopathy and severe HF.<sup>21</sup> This patient population, which is quite large, currently has a poor prognosis and limited options.<sup>22</sup> We have recently reported the interim results of SCIPIO, which indicate that intracoronary infusion of autologous CSCs results in improved LVEF (assessed by 3D echocardiography), functional capacity (assessed by the NYHA class), and quality of life (assessed by the Minnesota Living With Heart Failure Questionnaire).<sup>9</sup> Since that initial report, we have completed patient enroll-

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**Figure 4.** Example of changes in the size of an infarct from baseline (before cardiac stem cell [CSC] infusion) to 4 and 12 months after CSC infusion. The numbers (in white) denote the infarct size (in g) in the slice shown. FWHM indicates “full-width half-maximum” method, which uses all areas with  $>50\%$  of the maximal signal intensity to define the infarcted myocardium. Note the decrease in gadolinium enhancement in the inferolateral wall at 4 months after CSCs, which persisted at 12 months.

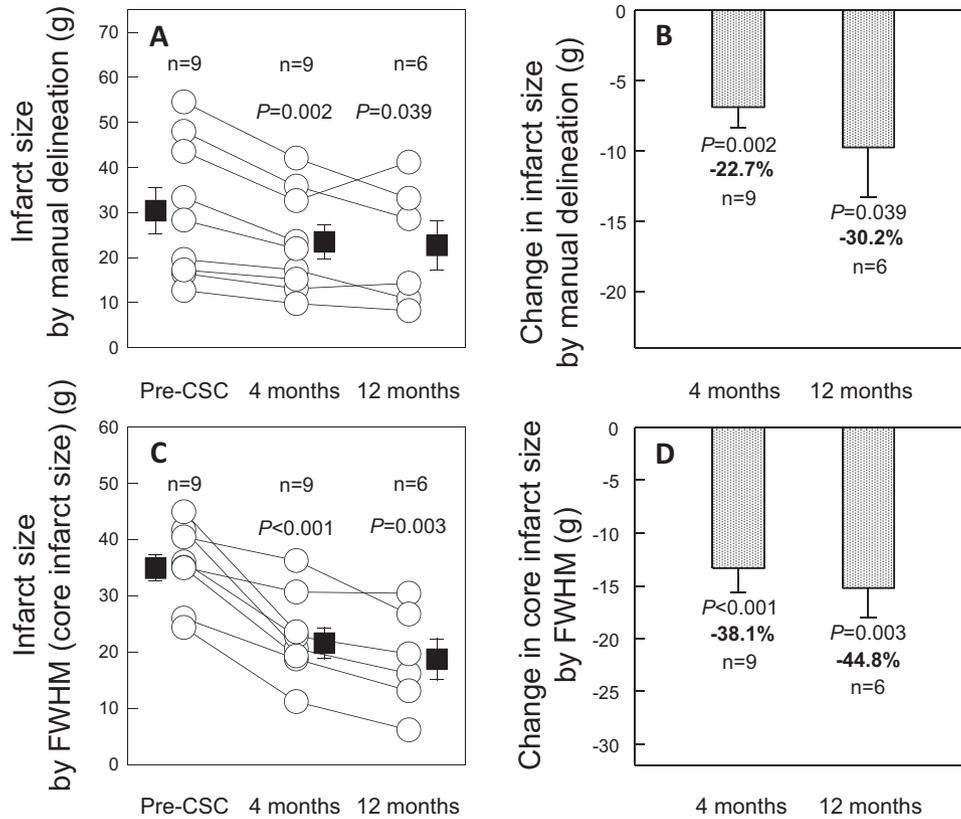
ment and performed further analysis of the CMR studies, which enables us to present herein a complete report of the surgical aspects of SCIPIO and a summary of the CMR data available to date.

Our salient findings can be summarized as follows: (1) harvesting and processing the right atrial appendage in the operating room for subsequent isolation and expansion of CSCs was eminently feasible in all 33 patients enrolled in the study, yielding successful CSC cultures in each case despite the fact that these patients have severe coronary artery disease, severe HF, and multiple comorbidities; (2) this new method for obtaining autologous stem cells did not interfere with standard surgical procedures or with surgical outcomes, and thus appears to be feasible in most patients undergoing CABG; (3) CMR (generally considered the most accurate technique for these analyses<sup>10–14</sup>) demonstrated that intra-coronary infusion of autologous CSCs  $\approx 4$  months after CABG surgery resulted in a striking increase in LVEF (+7.7 EF units) 4 months later and an even greater increase (+13.6 EF units) 12 months later, accompanied by a parallel increase in regional contractile function in the infarcted regions that were infused with CSCs; (4) this improvement in LV function was coupled with a concomitant decrease in infarct size, which was consistently observed with three different CMR methods (reductions at 4 and 12 months after CSC infusion, respectively:  $-22.7\%$  and  $-30.2\%$  by manual delineation,  $-38.1\%$  and  $-44.8\%$  by a semiautomated method [FWHM], and  $-49.7\%$  and  $-58.6\%$  using nonviable mass), and was accompanied by an increase in LV viable mass (+11.6 g at 4 months and +31.5 g at 12 months after CSC infusion),

implying robust regeneration of myocardial tissue. Taken together, these results, obtained with the best methodology currently available (CMR), indicate that administration of autologous CSCs obtained from a surgical specimen is effective in improving LV function and promoting cardiac regeneration in patients with chronic ischemic cardiomyopathy.

Although the improvement in LV function observed herein with CMR is consistent with our previous observations with 3D echocardiography,<sup>9</sup> it must be underscored that the present study provides several important new pieces of information. This is the first analysis of the surgical characteristics of the entire cohort of patients enrolled in SCIPIO (20 treated and 13 control patients). The results show that harvesting and processing right atrial appendages in the operating room did not prolong cardiopulmonary bypass time, aortic cross-clamp time, or total surgical time. CSCs were successfully isolated and expanded from all of the 33 specimens in this cohort, with no microbial contamination in any of the cell cultures. To our knowledge, SCIPIO is the first clinical trial to utilize surgical specimens for the isolation of stem cell populations to be used in the treatment of ischemic HF. Our present results demonstrate that this method for obtaining CSCs is safe and feasible in virtually all patients, and thus is applicable on a widespread basis.

This manuscript is the first analysis of the effects of CSC infusion on LVEF measured by CMR. The results show a striking improvement at 4 months, which persisted and became even more pronounced at 12 months (Figure 2). LVEF would not be expected to improve spontaneously in these patients, who have LV scars  $\approx 4$  years old and severe



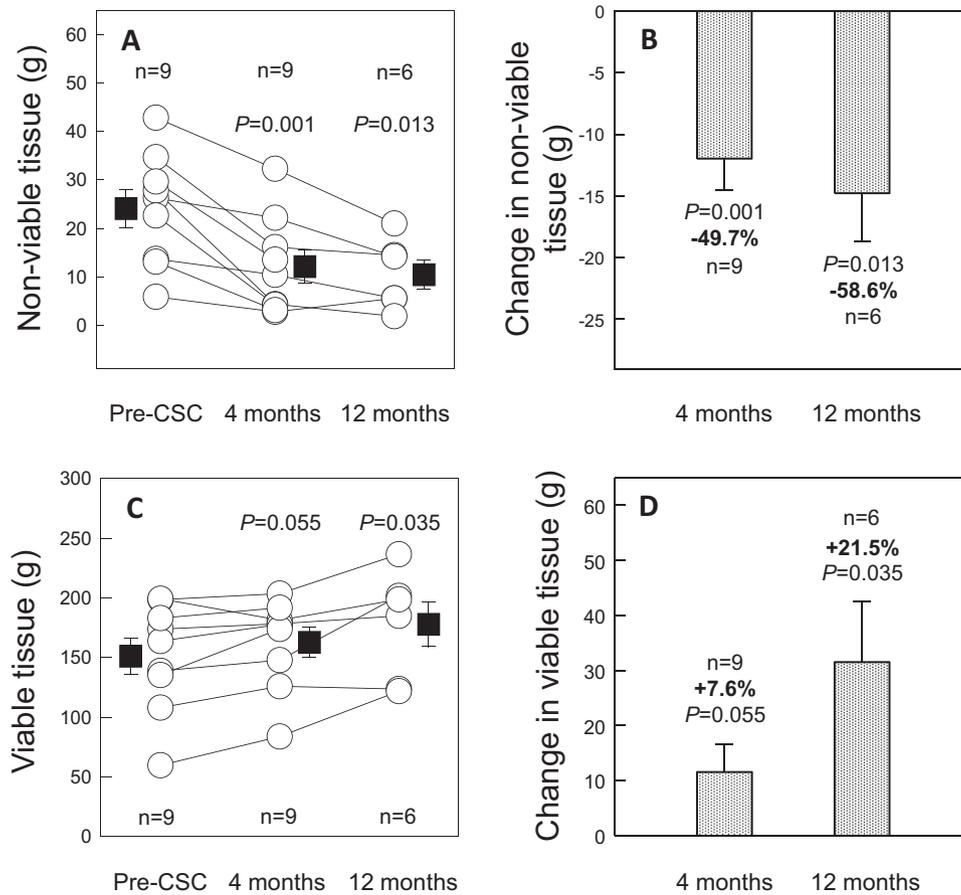
**Figure 5.** A, Infarct size (in g) at 4 and 12 months after cardiac stem cell (CSC) infusion measured by manual delineation. B, Reduction in infarct size at 4 and 12 months after CSC infusion measured by manual delineation. C, “Core” infarct size (in g) at 4 and 12 months after CSC infusion measured by the full-width half-maximum (FWHM) method. D, Reduction in core infarct size at 4 and 12 months after CSC infusion measured by the FWHM method. Data are mean±SEM.

HF (Online Data Supplement Table III). Indeed, a previous CMR study in this patient population (ischemic cardiomyopathy) has demonstrated that in nonviable regions (defined as in the present study) there was no improvement in function after coronary revascularization.<sup>23</sup> We also found an excellent correlation between measurements of LVEF by 3-D echocardiography and CMR (Online Data Supplement Figure II)—a finding that is important because many patients with chronic ischemic cardiomyopathy are not eligible for CMR studies.

In our previous report,<sup>9</sup> we provided CMR measurements of wall thickening in the entire left ventricle (in 6 patients at 4 months) but did not assess regional function; here, we have expanded this analysis greatly by providing measurements of regional EF in the territories infused with CSCs, in a larger patient cohort (8 patients at 4 months and 5 patients at 12 months), and also separately in dyskinetic segments (Figure 3). Our data demonstrate a marked improvement in the function of the infarcted regions that were treated with CSCs (Figure 3), which is consistent with our data on regression of infarction (*vide infra*). We further demonstrate that the beneficial effects of CSCs were more pronounced in the LV segments that exhibited the greatest degree of contractile dysfunction (Figure 3)—a finding that is important for the selection of patients for CSC therapy as well as for the design of future trials.

Compared with our previous report<sup>9</sup> in which we measured infarct size only by manual delineation in 7 patients at 4

months and 6 patients at 12 months, here we present a much more comprehensive analysis of infarct size and viability. Rather than relying on one method, as is frequently done, we used three CMR methods: (1) manual delineation of infarct size [which remains the method by which most semiautomated methods are compared<sup>24,25,26</sup>(Figure 5A and 5B)], (2) the FWHM method to measure core infarct size (Figure 5C and 5D) (a newer semiautomated methodology that appears to be extremely promising<sup>24</sup>), and (3) a semiautomated method to measure nonviable tissue mass (Figure 6). All three methods demonstrated a consistent and robust reduction in infarcted tissue at 4 months that persisted or became even more pronounced at 12 months (Figures 5 and 6). The reduction, however, was more dramatic using the measurements of core infarct (−45% at 12 months) and nonviable mass (−59% at 12 months) than manual delineation (−30% at 12 months). By employing three separate approaches, we sought to strengthen the association of infarct regression with CSC therapy, particularly because controversies regarding infarct measurements by CMR have become more prevalent<sup>27</sup> as several semiautomated methods have been recently described. The concordance of the three methods in demonstrating a decrease in infarcted tissue bolsters the robustness of the conclusions. The differences among the methods in the magnitude of infarct size reduction (Figures 5 and 6) are interesting in and of themselves, as they point to the need to standardize infarct size measurements by CMR in the future.



**Figure 6.** Changes in viable and nonviable left ventricular (LV) mass (defined as segments with infarcts involving <50% or >50% of the LV wall thickness, respectively). **A**, Nonviable mass (in g) at 4 and 12 months after cardiac stem cell (CSC) infusion. **B**, Reduction in nonviable mass (in g) at 4 and 12 months after CSC infusion. **C**, Viable mass (in g) at 4 and 12 months after CSC infusion. **D**, Increase in viable mass (in g) at 4 and 12 months after CSC infusion. Data are mean  $\pm$  SEM.

Regardless of its exact magnitude, the finding of infarct regression is conceptually important. Since the infarcts in the patients undergoing CMR studies were, on average,  $\approx$ 4 years old (Online Data Supplement Table III), and since old myocardial scars are stable and do not shrink over time,<sup>28</sup> the decrease in infarct (scar) size and the replacement of scar with viable myocardium (Figure 6) indicate myocardial regeneration. CABG is insufficient to account for our findings; indeed, previous studies have shown no benefit with revascularization (either reduction in infarct size or improvement in function) when infarcts involving >50% of the LV wall thickness (such as those present in our patients) were noted with CMR delayed enhancement.<sup>13,23</sup> In fact, to our knowledge, no previous investigation has demonstrated a decrease in the size of an old infarct after coronary revascularization. In contrast, in SCIPIO the nonviable mass decreased strikingly (by 50% at 4 months after CSCs and by 59% at 12 months [Figure 6A and 6B]), a finding that cannot be explained by the natural history of the disease or by revascularization. This notion is also supported by studies of bone marrow cell infusion in the setting of an old MI, in which patients enrolled in the control arm did not exhibit any significant changes in either LV function or infarct size over time.<sup>29–31</sup> Even in the setting of acute MI and subsequent revascularization, little or no change in myocardial function

or scar size was found at 2 months after revascularization<sup>32</sup> and global LV function was reported to remain similar from 5 days to 1 year after MI.<sup>33</sup>

In addition to showing a decrease in infarct size, this is the first report to show that administration of CSCs results in an increase in viable tissue at 4 and 12 months (Figure 6C and 6D). We applied known morphometric parameters<sup>20</sup> to estimate the number of new myocytes that had to be formed to account for the observed replacement of scar with viable tissue. Using, conservatively, the smallest of our 3 measures of infarct regression (Figures 5 and 6), that is, that obtained by manual delineation, we calculated that  $294 \times 10^6$  and  $415 \times 10^6$  cardiomyocytes were generated within the scar at 4 and 12 months, respectively. Our estimates of regeneration are consistent with previous observations in animal models of MI, in which the injection of human CSCs resulted in a similar recovery of cardiac muscle mass.<sup>34,35</sup>

An interesting finding was that the magnitude of functional improvement was greater in regions where the infarcts had greater transmural (Online Data Supplement Figure III). Also, we found that the functional improvement was greater in dyskinetic segments than in the entire infarcted region (+24 and +36 EF units at 4 and 12 months, respectively, versus +14 and +18 EF units in the entire infarct-related region; Figure 3A through 3D), and that the segment with the

greatest level of dysfunction exhibited the greatest improvement after CSC infusion (+26 and +40 EF units at 4 and 12 months, respectively; Figure 3E and 3F). These findings indicate that the functional improvement effected by CSCs is greatest in the regions that have the greatest level of baseline dysfunction—a concept that had not been appreciated before and will be important in the design of future trials of stem cell therapy. Conceptually, our results are consistent with those of the REPAIR-AMI MRI substudy, in which patients with more profound ventricular dysfunction received a significant benefit from administration of bone marrow mononuclear cells<sup>36</sup>; however, this is the first report that the improvement in regional function affected by stem cells is greatest in the segments with greatest baseline dysfunction.

In summary, the results presented herein demonstrate the safety and feasibility of isolating and expanding CSCs from cardiac tissue obtained during CABG surgery, a new method for procuring stem cells for the treatment of ischemic cardiomyopathy. Using CMR (the current “gold standard”), we demonstrate that CSCs obtained with this method effect a striking improvement in global and regional LV function, concomitant with a profound decrease in infarct size and an increase in viable tissue, indicative of cardiac regeneration. This new method for CSC procurement and therapy is potentially applicable to most patients undergoing CABG surgery and appears to be remarkably efficacious. Larger studies of CSCs isolated and expanded from surgical specimens are, therefore, warranted.

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### Disclosures

P.A. is a member of Autologous.

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## Administration of Cardiac Stem Cells in Patients With Ischemic Cardiomyopathy: The SCPIO Trial: Surgical Aspects and Interim Analysis of Myocardial Function and Viability by Magnetic Resonance

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