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CLINICAL RESEARCH

One-Year Follow-Up of Feasibility and Safety of the First U.S., Randomized, Controlled Study Using 3-Dimensional Guided Catheter-Based Delivery of Autologous Skeletal Myoblasts for Ischemic Cardiomyopathy (CAuSMIC Study)

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Objectives The aim of this study was to test safety and feasibility of myoblast transplantation with the Biosense-NOGA (Diamond Bar, California) 3-dimensional-guided endomyocardial delivery system.

Background Previous Phase-1 trials showed feasibility of epicardial injection of myoblasts. However, catheter-based delivery has several advantages: it can be applied on high-risk patients, the procedure can be repeated, and it is associated with less morbidity and mortality.

Methods Twenty-three subjects, with previous myocardial infarction and heart failure, New York Heart Association (NYHA) functional class II to IV, were enrolled, 11 control and 12 treatment subjects. To assess safety, physical exam, electrocardiogram, continuous rhythm monitoring, quality of life assessments, and heart function were evaluated at baseline and follow-up until 1 year.

Results There was favorable safety: no difference between groups in arrhythmias, and no deaths. Treated subjects showed sustained improvements in NYHA and Minnesota Living with Heart Failure Questionnaire (MLHFQ) compared with control subjects (NYHA, −1.0 point in treatment vs. +0.3 point in control group, $p < 0.0004$; MLHFQ, −14 point in treatment vs. +1 point in the control group, $p = 0.004$). Blinded core laboratory echocardiography evaluations showed sustained reductions in the treatment versus control in end diastolic diameter (−0.03 cm vs. +0.05 cm, $p = 0.07$) and end systolic diameter (−0.05 cm vs. +0.1 cm, $p = 0.07$). Finally, NOGA voltage mapping demonstrated improved voltage measurements (+1.0 mV, $p = 0.008$).

Conclusions This trial of myoblast transplantation via catheter into heart failure patients demonstrated safety and feasibility. Treated patients showed improvement in NYHA, MLHFQ, ventricular viability, and evidence of reverse ventricular remodeling. These data demonstrate positive safety outcomes and warrant initiation of larger phase 2, double-blind, placebo-controlled clinical trials. (J Am Coll Cardiol Intv 2009;2:9–16) © 2009 by the American College of Cardiology Foundation

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Heart failure is an increasingly prevalent health problem in the developing world. Although there are multiple drugs and implantable devices that can treat the symptoms of heart failure, there are no treatment strategies that can halt or reverse the progressive decline of function in heart failure once it has been initiated. Myoblast transplantation is a promising new treatment for patients who suffer from heart failure secondary to previous myocardial infarction (MI) (1,2). The potential use of myoblasts to help repair the damaged myocardium is now being tested (1–10). Preclinical animal studies with myoblasts have shown graft survival after transplantation to ischemic areas of the heart and formation of new contractile tissue that demonstrably improves multiple measures of cardiac function (ventricular volumes, wall motion, ejection fraction, and exercise tolerance) (11–18). Finally, human patient studies have documented a positive safety profile and signs of clinical benefit as well (1,2).

Abbreviations and Acronyms

AMT = autologous myoblast transplantation
CRT = cardiac resynchronization therapy
FDA = Food and Drug Administration
ICD = Implantable cardioverter-defibrillator
ILR = implantable loop recorder
MI = myocardial infarction
MLHFQ = Minnesota Living with Heart Failure Questionnaire
MMT = maximal medical therapy
NYHA = New York Heart Association
SAE = serious adverse event
SPECT = single-photon emission computed tomography
3D = three-dimensional

Although injection of myoblasts to the epicardium during open-heart surgery has been used (1,2,5,7,19), a less invasive means of injecting cells is preferable. Alternative routes of myoblast delivery, such as infusion into the coronary circulation, have been considered experimentally (20) but have not been shown to result in successful grafts like that with direct injections (7,19). The present study seeks to determine whether myoblasts can be safely and effectively delivered to chronic infarcted myocardium with a minimally invasive endovascular transcatheter technique. The chronic infarct scar was first mapped and identified with the commercially available Biosense-NOGA (Diamond Bar, California) electromechanical mapping system combined with fluoroscopic visualization (21). Delivery of myoblasts directly into the endocardial surface of the left ventricle was achieved via the Myostar percutaneous injection catheter. One-year follow-up data from patients receiving injections of autologous myoblasts were used as a basis for determining the safety of the technique.

Methods

Objectives. The primary objective was to evaluate the safety, tolerability, and feasibility of percutaneous endovascular injection of autologous skeletal myoblasts via the Biosense 3-dimensional (3D) Mapping and Injection System in subjects with congestive heart failure. Because myoblasts have not been injected via this approach previously, a dose escalation scheme was used to allow small and then progressively larger doses and numbers of injections to be tested. If there were any complications as dose was increased, the study would have been stopped at the safest allowable dose. The secondary objective was to evaluate changes in myocardial viability (NOGA mapping), quality of life (New York Heart Association [NYHA] and Minnesota Living with Heart Failure Questionnaire [MLHFQ]), and heart function as evaluated by echocardiography

The study was conducted according to Good Clinical Practice under an Investigational New Drug application in compliance with Food and Drug Administration (FDA) regulations, and the protocol was approved by the Arizona Heart Institute (AHI) Institutional Review Board (IRB). All subjects signed IRB-approved patient Informed Consent Forms.

Study design and patient eligibility. This Phase 1, prospectively randomized, dose escalation, open-label, controlled clinical trial was designed to evaluate the safety and feasibility of autologous myoblast transplant (AMT) with the Biosense endomyocardial delivery system. Twenty-three subjects with congestive heart failure (NYHA functional class II to IV) and previous MI were randomized: 11 to control maximal medical therapy (MMT), and 12 to AMT and MMT according to a dose escalation scheme, 3 patients/dose group, receiving 30, 100, 300, or 600 million myoblasts. The optimal dose of cells has been determined through small and large animal studies to be ≤600 million cells (13) and was therefore the maximum dose to be tested.

Inclusion criteria required NYHA functional class II to IV heart failure with previous MI confirmed by nuclear-stress/single-photon emission computed tomography (SPECT) to have resulted in a fixed deficit. Subjects had to be receiving MMT for at least 2 months before treatment and have an ejection fraction ≤40% as measured by SPECT-gated imaging.

Patient exclusion criteria included: skeletal muscle disease; active infection; pregnancy; active malignancy; significant coronary stenosis requiring revascularization within 6 months of enrollment; internal defibrillator implanted within 3 months of participation in the study; cardiac resynchronization therapy (CRT) for <6 months; clinically significant electrocardiographic abnormalities that could interfere with subject safety during the intracardiac mapping and injection procedure; frequent, recurrent, or sustained ventricular tachycardia; significant uncorrected valvular disease; subjects with ventricular wall thickness <5 mm as measured by echocardiography; and left ventricular thrombus.

Patient randomization. Subjects were randomized 1:1 to AMT + MMT (treatment group) or to MMT (control group). The assignment of patients to treatment or control groups was pre-randomized before the trial with a random

block method. The randomization scheme was not revealed to the clinical center to maintain impartiality during the patient recruitment process.

Enrolled patients without an implantable cardioverter-defibrillator (ICD) were required to have an Implantable Loop Recorder (ILR) device (Medtronic REVEAL PLUS Model 9526; Medtronic, Minneapolis, Minnesota) to monitor heart rhythm continuously for the duration of the trial. The ILR is a single-use programmable device containing 2 electrodes for continuous (i.e., looping) recording of a subcutaneous electrocardiogram during arrhythmic events.

Myoblast preparation and transplantation. The procedures for muscle biopsy and processing were performed as previously reported (7,12). Myoblasts were shipped on ice to the clinical center for transplant. At the time of transplant, cells were warmed to room temperature and injected without further manipulation. Viabilities for the cell suspension at the time of transplant were >80% (Fig. 1).

Myoblast purity was measured by reactivity with anti-CD-56 monoclonal Ab, phycoerythrin conjugated (BD Biosciences, Franklin Lakes, New Jersey) with fluorescence activated cell scanning. This antibody selectively stains human myoblasts and not fibroblasts. The ability of myoblasts to fuse into multinucleated myotubes in vitro was also confirmed by seeding 2×10^5 cells/24-well tissue culture plate in growth medium. The following day the growth medium was removed and switched to fusion medium (Dulbecco's minimal essential medium with 0.1% bovine serum albumin and 50 ng/ml insulin-like growth factor; Invitrogen, Carlsbad, California), and cultures were observed 3 days later to assess fusion. Fusion was only used to confirm presence of myoblasts. Cells were not fused before transplant. Sterility tests were conducted on the final product as well as throughout the digestion and expansion procedures.

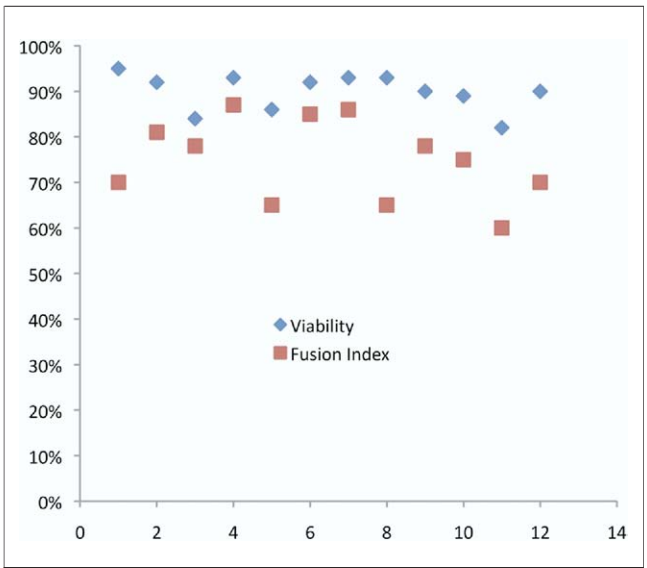

Figure 1. Viability and Fusion Index for Myoblast Preparations for Each Patient

Myoblast samples taken from the final preparation of cells expanded from each patient's biopsy were tested for viability and ability to fuse to form myotubes. The data from those tests are plotted with the fusion index indicated by **red squares** and the viability represented by the **blue diamonds**. Both viability and fusion index are expressed as percent values.

The navigational mapping system, NOGA (Cordis/Biosense Biodelivery Systems), was used for catheter-based, endomyocardial injection. The NOGA system is equipped with electromechanical mapping technology designed for left ventricular guidance, which uses low-intensity magnetic field energy and sensor-tipped catheters to locate positions in 3D space. Coupled with mechanical mapping, this permits construction of a 3D image of the left ventricle, which differentiates among healthy, ischemic, and infarcted myocardium (22). The Myostar injection catheter is a NOGA percutaneous catheter with a deflectable tip and injection needle designed to inject directly into the myocardium. The tip of the injection catheter is equipped with a location sensor and a retractable, hollow 27-gauge needle for fluid delivery. The injection site is indicated on the left ventricular map, allowing for precise distribution of the injections. Local electrical signals are obtained to minimize catheter-tip trauma.

Between 4 and 6 weeks after the muscle biopsy, subjects underwent AMT as in-patient procedures. Subjects received a heparin bolus (5,000 U to maintain activated clotting time values, activated clothing time = 200 to 240 s). Standard procedures for right and left cardiac catheterizations were followed. Beginning and ending times for the whole procedure and times for all intermediary procedures were noted. Coronary angiography was performed. All subjects had left ventriculography in both left anterior oblique and right anterior oblique views. Myoblasts were injected to the myocardium with the Biosense intramyocardial injection catheter. The needle length was set to 60% of the wall thickness in the infarct zone. The injections were made approximately 1 cm apart (as feasible) into the area of infarction at a volume of 0.1 ml (10 million cells/injection) in the 30-million dose group and 0.25 ml (25 million cells/injection) in subsequent dose groups. Each injection was done slowly, made over approximately 20 s. No antiarrhythmic medications or ICD were administered to patients prophylactically.

During AMT, all vital signs were constantly monitored for evidence of serious complications, especially perforation, arrhythmias, bradycardia, or tachycardia. After AMT, subjects were monitored in the catheter laboratory for a minimum of 10 min. Subjects were then admitted to the cardiac care unit where they were closely monitored until discharge. Within approximately 24 h of AMT, subjects underwent a cardiovascular exam and chest X-ray, complete blood cell counts, and comprehensive metabolic panels. Subjects were discharged home approximately 24 h after a

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satisfactory exam. The ILR or pre-existing ICD was interrogated before discharge.

Concomitant therapy. Subjects received MMT for at least 2 months and, if receiving CRT, patients must have been receiving CRT for at least 6 months before randomization. Changes in medication or resynchronization therapy were avoided to allow for comparison of baseline and follow-up evaluations.

Post-procedure evaluation. Follow-up evaluations for control subjects were delayed 1 month from the day of randomization, because the control group did not undergo muscle biopsy. Safety evaluations after the procedure included clinical examination, electrocardiogram, contrast-enhanced echocardiography, ILR/ICD device interrogation, and laboratory tests for the length of the study (12 months). The following schedule was used to evaluate patient changes after either AMT (treatment patients) or randomization (control patients): at 1 week, 1 month, 3 months, 6 months, and 12 months, subjects underwent contrast enhanced echocardiography with all measures evaluated by a core laboratory; 3 months after AMT, subjects underwent left and right heart catheterization as well as NOGA mapping to assess voltage changes (treatment patients only); at baseline, 1, 3, and 6 months, and 1-year, quality of life assessment—MLHFQ and NYHA—were recorded as well.

Statistical analysis. Continuous variables among the groups were compared with a *t* test for 2 samples with equal variance, with a p value of <0.05 considered significant. A paired *t* test was used to compare pre- and post-transplant NOGA voltage maps. For NYHA changes, a Wilcoxon-Mann-Whitney test was used.

Table 1. Baseline Demographic Data for Study Patients

Characteristic	Control Group	Cell Transplant Group	p Value *t* Test
Age (yrs)	62.0	65.1	NS
Gender (%)			
Male	82	91	NS
Female	18	9	NS
NYHA functional class	2.4	2.7	NS*
Minnesota Living with Heart Failure Questionnaire	46.8	46.8	NS
Left ventricular ejection fraction (%)	30	25	NS
Previous myocardial infarction (%)	100	100	NS
Left ventricular end diastolic diameter	6.20	6.41	NS
Left ventricular end systolic diameter	4.89	5.52	NS
Average myocardial infarction age (yrs)	11.3	13.2	NS
Diabetes (%)	27	25	NS
Hyperlipidemia (%)	90	100	NS
Percutaneous coronary intervention (%)	63	75	NS
Coronary artery bypass grafting (%)	72	66	NS
Ventricular arrhythmias (%)	64	67	NS
Atrial arrhythmias (%)	55	42	NS
Implantable cardioverter-defibrillator (%)	82	92	NS
CRT (%)	9†	58	0.01

*Wilcoxon-Mann-Whitney test used to compare baseline New York Heart Association (NYHA) functional class. †One patient in the control group had a cardiac-resynchronization therapy (CRT) device implanted 3 months after entry into the study.

Table 2. Summary of Patients Experiencing Arrhythmic Events at 1 Year

Ventricular Arrhythmias	Control Group	Cell Transplant Group	
		Post-AMT	Pre-AMT During NOGA Mapping
Sustained	1	2	2
Nonsustained	4	4	N/A

AMT = autologous myoblast transplantation.

Results

Baseline demographic data. Between November 2004 and September 2006, 23 subjects were prospectively randomized and treated with AMT (12) or assigned to MMT (11). Baseline demographic data and clinical characteristics were balanced across groups, except 58% of the AMT group and 9% of the control group had CRT (Table 1). There were no deaths in either group.

Myoblast preparations. Myoblasts were successfully grown from each patient biopsy. Myoblast viability was consistently maintained, with average viability of 89 ± 4% (Fig. 1). All myoblast preparations fused readily to form myotubes in vitro, with an average fusion index of 75 ± 9% (Fig. 1).

Safety. All subjects in the AMT group received the planned cell dose and number of injections. All injection procedures were without complications, although 2 study subjects developed sustained ventricular tachycardia before AMT, during NOGA mapping that required direct cardioversion (Table 2).

None of the serious adverse events (SAE), 6 for the control group and 12 for AMT, were considered to be directly related to the myoblasts or the injection procedure. However, 2 SAE did occur during the NOGA mapping before cell transplantation. Table 2 summarizes the arrhythmic events (sustained or nonsustained) for both control and treated subjects. One patient in the control and 2 in the AMT group experienced sustained ventricular tachycardia. One AMT patient had a history of ventricular tachycardia, had an ICD before enrollment, and experienced ventricular tachycardia 9 days after AMT (cell dose 300 million). This event could have been related to the inherent nature of the cardiac dysfunction in this patient or possibly have been related to the myoblasts. The patient received an appropriate electrical shock from the ICD and was successfully converted to sinus rhythm. Amiodarone and procaimide were prescribed and taken by the patient for 3 months. The patient is not receiving any antiarrhythmic medications and has had no further arrhythmias. The second patient experienced ventricular tachycardia at 9 months after treatment

Table 3. NYHA Functional Classification for Patients at Baseline, 3 Months, 6 Months, and 1 Year

NYHA Functional Classification	Baseline	3 Months	6 Months	1 Yr
Myoblast: n = 12	2.7 ± 0.4	1.9 ± 0.5	1.5 ± 0.7	1.7 ± 0.5
p value (Wilcoxon-Mann-Whitney)	NA	<0.016*	<0.0043*	<0.0029*
Control: n = 11	2.4 ± 0.5	2.4 ± 0.5	2.7 ± 0.6	2.8 ± 0.5
p value (Wilcoxon-Mann-Whitney)	NA	<0.97	<0.29	<0.094
p value (Wilcoxon-Mann-Whitney) for the change between myoblast and control groups: n = 23	<0.23	<0.01*	<0.0004*	<0.0004*

*Signifies statistical significance at $p < 0.05$.
NYHA = New York Heart Association.

that triggered ICD firing to terminate the events. There have been no further tachycardias in this patient. The patient in the control group had a ventricular tachycardia at 6 months that was pace terminated.

One subject in each group required percutaneous coronary intervention because of existing coronary stenosis, occurring at 12 months' follow-up for the AMT subject and 6 months' follow-up for the control subject. One patient in the control group had an upgrade of an ICD to CRT at 3 months' follow-up for worsening heart failure symptoms (Table 1). Finally, 1 patient receiving AMT presented at 11 months after treatment with weakness and abdominal pain. Upon examination, the patient had a palpable right lower abdominal and flank mass. Colonoscopy with biopsy revealed the etiology to be a perforated adenocarcinoma. The mass was removed and revealed typical adenocarcinoma morphology. The SAE was deemed not related to AMT.

Heart failure measures. NYHA functional class showed improvement in 10 of 12 subjects at 6 months and 11 of 12 patients at 1 year in AMT, with no patients worsening. The control group showed improvement at 6 months; and at 1 year, 1 subject showed improvement, 4 showed no change, and 6 showed worsening. The improvements in NYHA functional class in AMT were measurable initially at 3 months and also at 6 months and 1 year (Table 3). Control subjects showed little change at 3 months but had worsened at 1 year (Table 3). A comparison between groups for the change in NYHA functional class showed a significant difference between groups beginning at 3 months ($p < 0.01$) that was observed at 6 months and at 1 year ($p < 0.0004$) as well.

Patients also showed similar improvement in MLHFQ (Table 4). The results showed a statistically significant difference ($p = 0.004$, t test) for the change in MLHFQ between the myoblast-treated and control groups at 1 year. There was no significant difference at 3 months ($p = 0.4$, t test), because the control group improved similarly to the myoblast group (Table 4).

Changes in ventricular dimensions. Contrast enhanced echocardiography was used to assess changes in ventricular diameters, systolic and diastolic, in patients (Tables 5 and 6). Data showed a decrease in diastolic diameters from 6.41 ± 0.83 cm at baseline to 6.38 ± 0.83 cm at 1 year in the treated group compared with an increase from 6.20 ± 0.47 cm to 6.30 ± 0.49 cm in the control group ($p = 0.07$). For systolic diameters, there was a decrease from 5.52 ± 0.9 cm to 5.47 ± 0.96 cm in the myoblast group and an increase from 4.89 ± 0.93 cm to 5.09 ± 0.99 cm in the control group ($p = 0.13$). The echocardiography scans were evaluated by the core laboratory and were blinded to patient treatment. Changes in ventricular dimensions were consistent between groups, with the AMT group showing reduced ventricular systolic and diastolic diameters. These changes were first detected at 3 months and were observed at 6 months and 1 year as well. Control patients showed a different course, with both systolic and diastolic diameters increasing from baseline (Tables 5 and 6). Changes were small but consistent across the 2 groups; however, they did

Table 4. MLHFQ Scores for Patients at Baseline, 3 Months, 6 Months, and 1 Year

MLHFQ	Baseline	3 Months	6 Months	1 Yr
Myoblast	47 ± 12	37 ± 20	28 ± 18	33 ± 13
Control	47 ± 21	39 ± 22	47 ± 24	48 ± 15
Number of patients	23	23	23	23
p value (*t* test)	NA	0.4	0.02	0.004

MLHFQ = Minnesota Living with Heart Failure Questionnaire.

Table 5. Blinded Echo Core Lab Measurements of Left Ventricular End-Diastolic Diameter for Patients at Baseline, 3 Months, 6 Months, and 1 Year

Echo Core Lab: Left Ventricular End-Diastolic Diameter	Baseline	3 Months	6 Months	1 Yr
Myoblast	6.41 ± 0.83	6.38 ± 0.78	6.39 ± 0.77	6.38 ± 0.83
Control	6.20 ± 0.47	6.27 ± 0.46	6.37 ± 0.47	6.30 ± 0.49
Number of patients	23	23	23	23
p value (*t* test)	NA	0.13	0.07	0.07

Echo Core Lab = echocardiography core laboratory.

Table 6. Blinded Echo Core Lab Measurements of Left Ventricular End-Systolic Diameter for Patients at Baseline, 3 Months, 6 Months, and 1 Year

Echo Core Lab: Left Ventricular End-Systolic Diameter	Baseline	3 Months	6 Months	1 Yr
Myoblast	5.52 ± 0.90	5.40 ± 0.89	5.41 ± 0.87	5.47 ± 0.96
Control	4.89 ± 0.93	4.99 ± 0.90	5.08 ± 1.0	5.09 ± 0.99
Number of patients	23	23	23	23
p value (*t* test)	NA	0.07	0.06	0.13

Echo Core Lab = echocardiography core laboratory.

not reach statistical significance. Similar changes were measured by SPECT-gated imaging; however, technical failures with the SPECT-scanner precluded analysis of the entire patient group, and these data could not be presented (data not shown).

NOGA mapping. The NOGA mapping was performed at the time of AMT and again at 3 months' follow-up (Figs. 2 and 3). Because this is a Phase I safety study and there are risks associated with the mapping procedure, we did not perform baseline or follow-up maps on control patients. The 3 months' time point was chosen for measurement, because short-term perturbances of the myocardium by the original injection procedure are known to have dissipated (23,24) and enough time has elapsed for the injected myoblasts to have matured after transplant (12,13,24). All patients were successfully treated with the planned dose of cells, requiring from 3 to 24 independent injections to the ventricular endocardial surface. The number of injections varied, depending on the dose group assignment. Figure 2 shows a map (24 injections) representative of the change seen in a majority (9 of 12) of the patients. Figure 3 shows the comparison of NOGA maps for all patients at baseline and at 3 months. There was a statistically significant increase (Fig. 3) in voltage measures, whether comparing the injected segments (5.1 ± 2.9 mV at baseline to 6.1 ± 2.7 mV at 3 months, n = 12, p = 0.008) or the entire ventricle (6.67 ± 3.9 mV at baseline to 7.5 ± 1.5 mV at 3 months, p = 0.005, n = 12).

Discussion

Safety. The purpose of this study was to assess safety and feasibility of using a minimally invasive cardiac transcatheter for AMT to previously infarcted myocardium. Although cardiac catheter devices have been used to inject into ischemic myocardium with normal wall thickness (23), we investigated the feasibility and safety of injecting into a chronic myocardial infarct that can be thin, difficult to penetrate, and potentially easy to perforate. There have been occurrences of ventricular perforation during intramyocardial transcatheter injection (25); therefore, experience with intracardiac injection is critical to reducing complications. Proper training is a key to success in this new area of therapeutic intervention. Muscle biopsy was without incident in all patients. So long as the procedure is performed with the proper controlled environment, there should be no limitations on patient ability to undergo the biopsy. Patient age and health have not been issues for successful biopsy.

We have reported previously (7,24) on 30 patients that received myoblasts via open heart injections and showed survival of the myoblasts in myocardial scar tissue, no evidence for myoblast associated arrhythmias, and significant improvement in ventricular functional measures. Data from the MAGIC (Myoblast Autologous Grafting in Ischemic Cardiomyopathy) multicenter, double-blind, placebo-controlled trial of myoblasts in conjunction with coronary artery bypass graft surgery (97 patients treated) showed similar outcomes (2). Specifically, the MAGIC study showed improvements in ventricular volumes and no arrhythmia risk associated with myoblasts. Although initial open label studies—most notable, 4 of 9 patients in a study by Menasche et al. (6)—suggested a link between myoblasts and arrhythmias, this has not been substantiated in later studies. Furthermore, there are no preclinical data that show causality of arrhythmias by myoblasts (11,13–18,20,24,26–30). Thus, myoblasts and cardiac arrhythmogenesis cannot be linked on the basis of the available data. The

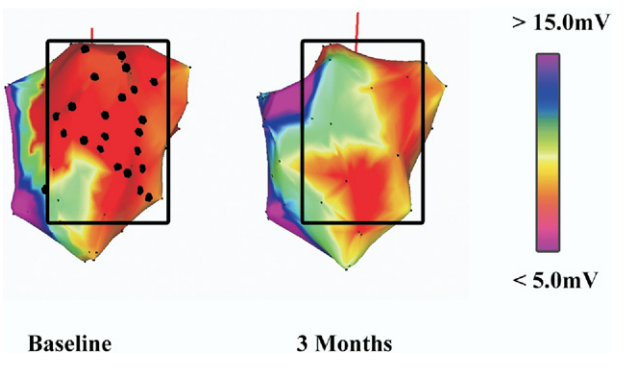

Figure 2. 3D-NOGA Voltage Map Showing Recovery in the Area Injected With Myoblasts

Three-dimensional (3D) NOGA voltage maps are shown at baseline and 3 months after myoblast treatment. The **black dots (boxed area)** in the baseline map identify the sites of myoblast injection. The area **(boxed region)** injected with myoblasts shows recovery of voltage at 3-month follow-up.

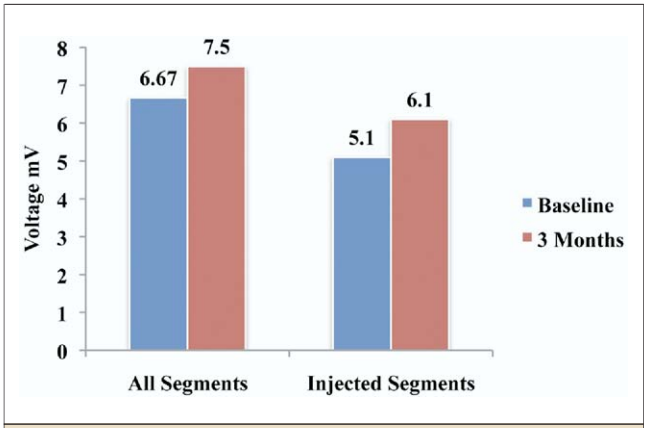

Figure 3. Average Voltage Measurements From NOGA Maps at Baseline and 3-Month Follow-Up

The NOGA voltage maps were performed at baseline and again at 3-month follow-up. The graph shows the average for the 12 myoblast-treated patients, comparing voltages for the entire mapped left ventricle and for the segments injected with myoblasts, n = 12. Statistical analysis was performed with a paired *t* test.

occurrence of arrhythmias observed in some clinical studies then are likely related to the conditions used for myoblast growth, the location or method for injection of myoblasts (25), or the population of myoblasts injected (31). Myoblasts in this study were targeted to the infarct and peri-infarct areas. Because myoblasts do not form electrical connections with surrounding myocardium, restricting cells to the infarct and peri-infarct area should not change the conductance environment; however, if cells were to be delivered to normal myocardium, there could be a disruption to normal conductance that could result in arrhythmia. Therefore, the accurate delivery of cells to infarcted myocardium is likely important for preventing transplant complications.

The results of this trial have demonstrated the safety and feasibility of percutaneous delivery of myoblasts. There were no SAE related to the cells or AMT. There were, however, 2 serious arrhythmic events associated with NOGA endomyocardial mapping. The NOGA mapping catheter is FDA-approved with recognized risks of arrhythmia events inherent to the heart failure population. The added accuracy of AMT to the site of infarcted myocardium is an advantage of NOGA. There are significant concerns associated with 2-dimensional fluoroscopic guided techniques, like poor control over distribution of injection sites, that can result in unintended repeat injections with the potential for local toxicity (25). Ventricular perforation is a risk of any catheter-based transplantation procedure, particularly when injecting into a thinned myocardium that can be 5 to 7 mm (25). For this study, even in challenging patients with severely thinned myocardium, there were no injection-related complications.

Performance outcomes. Patients showed significant improvement in measures of heart failure symptoms. Patients in the AMT group showed statistically significant improvements in both NYHA and MLHFQ at the 6-month and 1-year follow-up (Tables 3 and 4). The changes in NYHA and MLHFQ represent a significant impact on patient quality of life.

Blinded evaluations of echocardiographic data for patients showed consistent but not statistically significant changes in ventricular dimensions for treated versus AMT patients: ventricular dilation was observed in control patients, whereas AMT patients showed a reduction in both left ventricular diastolic and systolic diameters. The core laboratory echocardiographic data provide further support for the safety and feasibility of the approach. Given the nature of this study (variable dose, variable-sized infarcts in patients) and the changes in ventricular dimensions being small, the significance of these observed changes is difficult to determine. There was no attempt to match the cell dose in patients to the size of the infarct. Clearly, lower doses delivered to large infarcts would be suboptimal for effective repair. Future studies will need to be controlled for cell dose and size of infarct to limit this variable. The dosing of cells requires less precision than with other kinds of therapeutics, because cells are subject to feedback mechanisms that limit overgrowth of grafts and allow for growth of cells when delivered in small amounts. The determination of dose is best studied in large animal models, as was performed before commencement of this study (13,28).

Finally, repeat NOGA voltage maps at 3-month follow-up in AMT patients showed increased voltage measures in transplanted areas that were statistically significant, reflecting possible survival of myoblasts. We note that there were increases in both regional and global measures of ventricular conductance. Previous work (7) has shown that myoblast transplants are accompanied by increases in angiogenesis. Therefore, the global improvements in ventricular conductance could be mediated through increased angiogenesis, because local improvements are likely mediated by both myoblast survival and renewed angiogenesis. The patterns of improvements in NOGA maps seen in this study are as would be predicted on the basis of angiogenesis and cell survival mechanisms.

Conclusions

Despite significant advances in treatment of ischemic cardiomyopathy and congestive heart failure, the morbidity and mortality remain high. Remodeling after MI plays an important role in deterioration of left ventricular function. Although many treatments slow the progression of heart failure, none address the underlying mechanism, loss of contractile myocardium. Autologous myoblast transplantation has the capacity to replace lost myocardial contractile cells (5,7) plus arrest and reverse ventricular dilation (11–17). This study demonstrates that myoblasts can be safely and feasibly administered in patients by a transcatheter technique in the hands of a trained investigator. Training will be a key factor in the success of this technique, because not all studies have shown similar freedom from complications as shown here. Larger, randomized, double-blind, placebo controlled and multicenter clinical trials are warranted to further test this therapeutic approach.

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