Safety and Feasibility of Autologous Myoblast Transplantation in Patients With Ischemic Cardiomyopathy
Four-Year Follow-Up

Nabil Dib, MD, MSc; Robert E. Michler, MD; Francis D. Pagani, MD, PhD; Susan Wright, BS, RN; Dean J. Kereiakes, MD; Rose Lengerich, RN; Philip Binkley, MD; Diane Buchele, BSN, CNOR; Inder Anand, MD, DPhil; Cory Swingen, MS; Marcelo F. Di Carli, MD; James D. Thomas, MD; Wael A. Jaber, MD; Shaun R. Opie, PhD; Ann Campbell, BSN, RN; Patrick McCarthy, MD; Michael Yeager, RN; Vasken Dilsizian, MD; Bartley P. Griffith, MD; Ronald Korn, MD, PhD; Steven K. Kreuger, MD; Marwan Ghazoul, MD; W. Robb MacLellan, MD; Gregg Fonarow, MD; Howard J. Eisen, MD; Jonathan Dinsmore, PhD; Edward Diethrich, MD

Background—Successful autologous skeletal myoblast transplantation into infarcted myocardium in a variety of animal models has demonstrated improvement in cardiac function. We evaluated the safety and feasibility of transplanting autologous myoblasts into infarcted myocardium of patients undergoing concurrent coronary artery bypass grafting (CABG) or left ventricular assist device (LVAD) implantation. In addition, we sought to gain preliminary information on graft survival and any associated changes in cardiac function.

Methods and Results—Thirty patients with a history of ischemic cardiomyopathy participated in a phase I, nonrandomized, multicenter pilot study of autologous skeletal myoblast transplantation concurrent with CABG or LVAD implantation. Twenty-four patients with a history of previous myocardial infarction and a left ventricular ejection fraction <40% were enrolled in the CABG arm. In a second arm, 6 patients underwent LVAD implantation as a bridge to heart transplantation, and patients donated their explanted native hearts for testing at the time of heart transplantation. Myoblasts were successfully transplanted in all patients without any acute injection-related complications or significant long-term, unexpected adverse events. Follow-up positron emission tomography scans showed new areas of glucose uptake within the infarct scar in CABG patients. Echocardiography measured an average change in left ventricular ejection fraction from 28% to 35% at 1 year and of 36% at 2 years. Histological evaluation in 4 of 6 patients who underwent heart transplantation documented survival and engraftment of the skeletal myoblasts within the infarcted myocardium.

Conclusions—These results demonstrate the survival, feasibility, and safety of autologous myoblast transplantation and suggest that this modality offers a potential therapeutic treatment for end-stage heart disease. (Circulation. 2005;112: 1748-1755.)

Key Words: myocardial infarction ■ cells ■ transplantation ■ trials ■ heart failure

Heart disease remains a leading cause of morbidity and mortality despite continuing advances in various treatment options. With best medical therapy, there is still a significant subset of patients who become refractory or respond suboptimally. The impact of heart disease spans all ethnic groups and has profound economic consequences.1,2 Acute myocardial infarction (AMI) results in an immediate loss of heart muscle, but there is further deterioration in left ventricular (LV) function, and in ∼20% of patients, significant dilatation of the LV (GUSTO I) continues to occur long after the initial event. The decline in heart function and dilatation of the ventricle after MI result in heart failure that is an inexorable process, leading eventually to congestive heart failure and death. Cardiac muscle lacks any significant capacity to regenerate once injured3-5; however, recent results have shown that there may be regenerative cells in the heart...
that someday could be manipulated to effect repair.3–6 Unfortunately, the potential for cardiac self-repair is still theoretical. In contrast with cardiac muscle, skeletal muscle has the capacity for self-repair because of a resident population of proliferative muscle cells, or myoblasts.7 Skeletal myoblasts, once activated, divide and then fuse to form new muscle fibers that may restore lost functionality.8

Preclinical data from a variety of animal studies have demonstrated the capacity for skeletal myoblasts to engrat, form myotubes, and enhance cardiac function after transplantation into infarcted myocardium.9–12 More recently, preliminary human studies focusing on patients with ischemic heart disease have demonstrated successful myoblast transplantation into the postinfarction scar.13–17

Described herein are studies undertaken to test the survival, safety, and feasibility of transplanting autologous myoblasts derived from skeletal muscle into and around a scarred area of the myocardium. This was done in subjects after MI with LV dysfunction. The transplantation of autologous myoblasts was performed during coronary artery bypass graft surgery (CABG) or LV-assist device (LVAD) implantation as a bridge to heart transplantation.

Methods

Study Design and Patient Eligibility

Several phase 1 studies were conducted, and all were prospective, nonblinded, multicenter clinical trials that enrolled a total of 30 patients. Feasibility and safety of myoblast transplantation were assessed in 24 patients who were candidates for elective CABG. Feasibility, safety, and engraftment were evaluated in 6 patients who were candidates for LVAD as a bridge to heart transplantation. Eligibility criteria for the CABG group included previous MI and LV ejection fraction (LVEF) <30% (CABG00-2, 12 patients) or <40% (I IAM02-3, 12 patients). Patients who required LV aneurysmectomy were included only in CABG00-2. For the IAM02-3 study, all patients had irreversible scar as demonstrated by positron emission tomography (PET) and magnetic resonance imaging (MRI) as entrance criteria. Eligibility criteria for the LVAD arm included patients undergoing LVAD as a bridge to heart transplantation and who were willing to donate their heart after explantation for histological examination. Excluded were patients with skeletal muscle disease, active malignancy, recent history of alcohol or drug abuse, pregnancy, or active infection. All studies were conducted in accordance with Good Clinical Practices, were regulated by the US Food and Drug Administration under an investigational new drug (IND) package with automatic edge detection. Segmentation accuracy was verified and edited when necessary by hand, and standard structural and functional parameters were assessed by using accepted formulas. The following MRI measurements were made: LV end-diastolic and end-systolic volumes and diameters; LVEF; and delayed gadolinium enhancement was performed with a pulse sequence for 3D, rapid, T1-weighted imaging. Imaging of delayed hyperenhancement (viability imaging). Imaging of delayed hyperenhancement was performed with a pulse sequence for 3D, rapid, T1-weighted imaging. A contrast agent dosage of 0.2 mmol/kg was used, with an inversion time of 200 ms as a starting value.

[18F]FDG PET Scanning

A 15- to 20-minute transmission scan was acquired for correction of photon attenuation. Regional myocardial glucose utilization was evaluated with FDG and PET. Studies were acquired in the glucose-loaded state. All measurements of glucose levels and insulin doses were recorded in the PET imaging transmittal form and in the patient’s chart. Ten to 15 mCi of FDG was injected intravenously, and after 45 to 60 minutes (to allow for metabolic trapping of FDG in the myocardium), images were acquired for 25 minutes. The PET images were reconstructed at each participating site with use of a Hanning filter with a 0.30 cycles/pixel cutoff frequency. Recono-
structured data were transferred to the Nuclear Core Laboratory for analysis.

**Myoblast Procurement and Culturing**

Depending on the cell dose to be administered, a skeletal muscle biopsy sample of 2 to 5 g was obtained from each patient 3 to 5 weeks before the scheduled surgery. The muscle specimens were immediately placed in a resealable container filled with transport medium, packed in an insulated shipping container with sufficient gel ice packs to maintain temperature between −2°C and 7°C, and shipped to the cell processing facility (GenVec, Inc, Charlestown, Mass). During processing, connective tissue was removed from each specimen, and the rest of the muscle tissue was minced into a slurry. The slurry underwent several cycles of enzymatic digestion at 37°C with trypsin/EDTA (0.5 mg/mL trypsin, 0.53 mmol/L EDTA; Gibco-BRL) and collagenase (0.5 mg/mL; Gibco-BRL) to release satellite cells. Skeletal myoblasts were cultured according to a modified Ham’s method. The satellite cells were plated and grown in myoblast basal growth medium (SkBM, Clonetics), which contained 15% to 20% fetal bovine serum (HyClone), recombinant human epidermal growth factor (10 ng/mL), and dexamethasone (3.9 µg/mL). To prevent myotube formation during the culturing process, cell densities were maintained throughout the process at <80% confluence. Myoblasts were expanded for 11 to 13 doublings, harvested, and cryopreserved before transplantation. Myoblasts were thawed, washed, and resuspended in transplantation medium at 1 to 1.60 × 10^8 cells/mL, loaded into 1-mL tuberculin syringes, chilled to 4°C, and shipped on ice to the clinical center for transplantation. At the time of transplantation, cells were warmed to room temperature and were ready for injection.

**Myoblast Transplantation**

At the time of surgery, the cultured myoblasts were injected into the epicardial surface of the infarcted area according to an escalating-dose regimen. All patients underwent CABG or LVAD implantation concurrent with myoblast transplantation. In the CABG group, 12 patients were divided into 4 escalating-dose groups (3 patients per group) of 1, 3, 10, and 30 × 10^7 cells, and 12 patients received a fixed dose of 3 × 10^6 cells. The cell dose for LVAD patients was 3 × 10^6 cells, except for 1 patient, who received only 2.2 × 10^6 cells. Myoblasts were injected into and around the area of infarction from the epicardial surface over a period of 15 seconds, in the same area and within 30 minutes of the start of surgery. Adverse Events

A total of 30 patients were enrolled in the study and underwent myoblast cell transplantation concurrent with CABG or LVAD. Baseline demographics of CABG patients are presented in Table 1. Twenty-four patients with a mean age of 55.2 years (range, 34 to 76) were enrolled in the CABG arm. Patients received an average of 2.7 bypass grafts, 22 of 24 had left internal mammary grafts, and 3 patients had an LV aneurysmectomy procedure. Six patients (mean age, 56 years; range, 43 to 65) underwent LVAD implantation as a bridge to heart transplantation. Fourteen patients in the CABG group showed nonsustained ventricular tachycardia on baseline Holter monitoring, which persisted in only 7 patients on follow-up Holter monitoring after CABG and cell transplantation.

**Cell Culturing**

There were no serious complications related to biopsy sample procurement; however, all patients experienced mild discomfort and 1 patient had a small hematoma. The myoblast cultures were maintained for 11 to 13 population doublings, with an average doubling time of 24 hours. Analysis of the cultures before transplantation by phase-contrast microscopy showed only single cells and no evidence of fused, multinucleated myotubes. There was no bacterial or fungal contamination as determined by USP sterility and Mycoplasma testing. In all but 1 case that required early surgery, growth of the number of target cells was achieved. Purity of the myoblast preparation, based on anti-CD56 monoclonal antibody staining and fluorescence-activated cell-sorting analysis, ranged from 42% to 98% (mean, 79%). Trypan blue viability testing of the injected cells at the time of transplantation ranged from 85% to 98% (mean, 92%).
procedure was clinically well tolerated, and the myoblasts were delivered successfully. No deaths or arrhythmias occurred during surgery or injection of the cells. Minimal bleeding from the injection sites was seen on occasion. Four deaths occurred during the follow-up period: 3 in the LVAD group and 1 in the CABG group. None of them were deemed related to the myoblasts or cell transplantation procedure.

In the CABG group, 3 patients in each escalating-dose group received 1, 3, 10, and 30 x 10^5 cells/mL, and an additional 12 patients received 5 x 10^6 cells; in the LVAD group, 5 patients received 3 x 10^6 and 1 patient received 2.2 x 10^6 cells. As of March 4, 2005, postprocedure follow-up for safety on all CABG patients extends to 45 months (minimum, 11; mean, 27; median, 24) and in the LVAD group extends to 33 months (minimum 5 days; mean, 9 months; median, 4 months). Importantly, there was no mortality and no evidence of infection related to cells at any time after transplantation, as determined by fever or elevated leukocyte counts.

One patient who received a dose of 10^8 cells experienced nonsustained ventricular tachycardia 7 days after surgery. The patient was hospitalized and angiography was performed. Two areas of stenosis, 70% and 60%, were found in the left internal mammary artery system. All other recently placed grafts were fully patent. For the remaining 3 patients, 1 received an ICD for asymptomatic, nonsustained ventricular tachycardia recorded from a Holter monitor performed 15 days after treatment (part of the standard study follow-up), and the other 2 received ICDs for arrhythmias but could not be confirmed by device interrogation. Follow-up evaluation revealed proper functioning of the device. Although we cannot exclude the possibility that ICD firing was related to myoblast engraftment, alterations in his medical management were made, and no further events were reported. These events were considered by an independent safety monitor to be unrelated to cell transplantation.

An additional serious adverse event occurred when a patient who received 3 x 10^8 cells experienced nonsustained ventricular tachycardia during week-1 Holter monitoring. A review of Holter monitoring records described multiple episodes of arrhythmia, including wide-complex tachycardia consistent with ventricular tachycardia, intraventricular junctional rhythm, and bigeminy. All episodes were asymptomatic and similar to baseline Holter monitor reports. The patient was hospitalized for observation and electrophysiology consultation. Mildly decreased left systolic function was noted, and an automatic ICD was recommended if the patient was found to be inducible. The patient underwent electrophysiology study that revealed normal sinoatrial node function, mildly abnormal atrioventricular node function, and no inducible, sustained ventricular tachycardia. Digoxin was discontinued, and carvedilol was increased gradually to a final dose of 12.5 mg BID with no further episodes of chest pain, shortness of breath, palpitations, or edema.

For the IIAM02-3, 4 patients received implantation of automatic ICDs and there was 1 patient death: Two received an ICD before the 1-month time point, and 2 received an ICD before the 6-month time point. Because of automatic ICD placement, these patients are no longer evaluable by MRI but are being followed up with all other protocol-specified measures. For 1 patient, the automatic ICD implantation was not deemed a serious adverse event because the device was implanted prophylactically, based on a positive T-wave alternans test result. The implantation did not prolong the patient’s hospitalization, and there have been no firings to date. For the remaining 3 patients, 1 received an ICD for asymptomatic, nonsustained ventricular tachycardia recorded from a Holter monitor performed 15 days after treatment (part of the standard study follow-up), and the other 2 received ICDs not for arrhythmias but because of a continued LVEF <30%. There have been no firings of the ICDs in any of those patients.

One death occurred in the IIAM02-3 study. Twelve days after CABG, subject C.E.E. experienced a suspected AMI, with complaints of severe indigestion, chest pain, and shortness of breath. Autopsy report indicated a large, organizing thrombus in the vein graft to the distal right coronary artery system. All other recently placed grafts were fully patent.

Three deaths occurred in the LVAD implantation group. One death, due to LVAD infection and sepsis, occurred 68 days after the procedure. Autopsy revealed obvious purulence in the driveshaft tract and around the LVAD itself. The other death occurred on the fifth postoperative day due to compli-
cations of acute right cerebral infarct and thrombus of the LVAD device, causing cardiac and respiratory failure. The third death occurred at 33 months while the patient was waiting for a heart transplant. The data safety monitor reviewed all available information on these deaths and considered them both unrelated to the myoblasts or implantation procedure. Although arrhythmias were noted in the LVAD group (Table 2), they are common and expected for this procedure.

Feasibility

Feasibility was determined by 3 criteria: first, the ability to culture sufficient numbers of myoblasts for transplantation; second, the ability to deliver myoblasts into the region of myocardial infarct; and third, the ability to demonstrate engraftment. Five patients underwent LVAD explantation. Histological evaluation was performed on 6 patients in total, 3 patients after heart transplantation and 3 patients after death, at 5 days, 2 months, 3 months, 5 months, 6 months, and 33 months after injection, respectively. Trichrome staining of cross sections of damaged myocardium that had received transplant injections clearly demonstrated engraftment of striated myotubes containing multiple nuclei developing within the fibrotic tissue, with no evidence of lymphocyte infiltration (see Pagani et al12). There was no evidence of myoblast migration into normal myocardium. Immunostaining with the MY-32 antibody (a skeletal muscle–reactive anti-myosin that does not stain cardiac muscle) confirmed myoblast engraftment. Verification of engrafted myofibers was visualized in all LVAD recipients, except the first patient who received only \(2.2 \times 10^6\) cells and a patient who remained alive for 33 months and received a second LVAD.

Functional Assessment

PET scanning, which was optional in CABG00-2, was performed in 7 of 12 patients enrolled in CABG00-2 at baseline and at the 6-month follow-up. Evidence of cell viability in the region of myocardial scar after myoblast transplantation was seen in 3 of those patients. For 2 patients who received \(3 \times 10^7\) cells, the PET scan showed no improvement. One of 3 scanned patients who received \(10^6\) cells and the 2 of 2 patient scanned who received \(3 \times 10^6\) cells showed an increase in FDG uptake in the transplanted zone (data not shown). All 12 patients in the IIAM02-3 group who received \(3 \times 10^8\) cells had baseline PETs performed, and 11 of those patients underwent follow-up scans at 6 months: The first patient in this study died 12 days after CABG because of an apparent AMI resulting from an occluded bypass graft. Two of 11 patients showed significant improvement from baseline to 6 months, with the remainder showing no change. A PET scan from 1 of the 2 patients showing PET improvement is shown in Figure 1.

In addition to PET scanning, MRI delayed-hyperenhancement scans were performed on patients in study IIAM02-3 who received \(3 \times 10^8\) cells. Scans were performed at baseline, 6 months’, and 12 months’ follow-up. Three of 12 patients were ineligible for follow-up scans because of either an automatic ICD (n=2) or death (n=1). A significant change in hyperenhancement was seen in 1 of the 9 patients at follow-up. A 17-segment polar map for hyperenhancement is shown in Figure 2. This shows a significant increase
in the area of tissue viability, and the area corresponds to the same area shown in Figure 1 that shows increased glucose metabolism by PET.

Individual LVEFs for each patient and their corresponding cell doses are shown in Table 3. The New York Heart Association classification at baseline was 2.1; 1.4 at 12 months (change, −0.7, \( P=0.004 \) by ANOVA); 1.5 at 18 months (change, −0.6, \( P=0.03 \), by ANOVA); and 1.7 at 24 months (change, −0.5, \( P=0.18 \), by ANOVA), with too few patients to reach statistical significance (Table 3). The mean baseline LVEF, measured by echocardiography, for the CABG patients was 28% at baseline; 35% at 12 months' follow up (change, +7%, \( P=0.02 \), by ANOVA); 37% at 18 months (change, +9%, \( P=0.008 \) by ANOVA); and 36% at 24 months (change, +8%, \( P=0.01 \) by ANOVA). The average LV systolic volumes decreased from an average of 129 mL at baseline to 104 mL at 12 months (\( P=0.01 \) by paired \( t \) test), to 98 mL at 18 months (\( P=0.02 \) by paired \( t \) test), and to 96 mL at 24 months (\( P=0.04 \) by paired \( t \) test). The average end-diastolic volumes decreased from an average 187 to 156 mL at 12 months (\( P=0.02 \) by paired \( t \) test), to 166 mL at 18 months (\( P=0.08 \) by paired \( t \) test), and to 146 mL at 24 months (\( P=0.006 \) by paired \( t \) test). A comparison of ventricular dimensions measured by MRI in 9 of the 12 patients in IIAM02-3 with that observed in all patients by echocardiography revealed similar dimensions.

Only 9 patients could be followed up after CABG by MRI because of 1 patient death and ICD placement in 2 patients. Data for changes in ventricular dimensions from MRI are

---

**Figure 2.** MRI hyperenhancement viability measure: 17-segment bull’s-eye representation of gadolinium-hyperenhancement MRI scan for CABG patient at baseline and at 6-month follow-up. Color coding represents the amount of gadolinium exclusion. Upper end of the scale (blue) means high uptake, and lower end of the scale (red) means complete exclusion. Comparison of baseline with 6 months shows a significant decrease in the area of dye uptake in this patient. Abbreviations are as defined in the legend to Figure 1 and text.

### Table 3. Baseline and Follow-Up Measures of LVEFs and Ventricular Volumes Measured by Echocardiography and MRI With Statistical Analysis for Changes From Baseline at Various Time Points

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>3 mo</th>
<th>6 mo</th>
<th>12 mo</th>
<th>18 mo</th>
<th>24 mo</th>
<th>( P ) for Change at 3 mo</th>
<th>( P ) for Change at 6 mo</th>
<th>( P ) for Change at 12 mo</th>
<th>( P ) for Change at 18 mo</th>
<th>( P ) for Change at 24 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>NYHA</td>
<td>2.1±0.8</td>
<td>...</td>
<td>...</td>
<td>1.4±0.5</td>
<td>1.5±0.7</td>
<td>1.7±0.7</td>
<td>...</td>
<td>...</td>
<td>( P=0.004 )</td>
<td>0.04</td>
<td>0.2</td>
</tr>
<tr>
<td>( n )</td>
<td>24</td>
<td>...</td>
<td>...</td>
<td>17</td>
<td>12</td>
<td>9</td>
<td>...</td>
<td>...</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Echo EF</td>
<td>28±9%</td>
<td>...</td>
<td>...</td>
<td>35±8%</td>
<td>37±12%</td>
<td>36±11%</td>
<td>...</td>
<td>...</td>
<td>( P=0.02 )</td>
<td>0.008</td>
<td>0.01</td>
</tr>
<tr>
<td>( n )</td>
<td>24</td>
<td>...</td>
<td>...</td>
<td>17</td>
<td>13</td>
<td>11</td>
<td>...</td>
<td>...</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Echo EDV</td>
<td>187±60</td>
<td>...</td>
<td>...</td>
<td>156±47</td>
<td>166±70</td>
<td>146±64</td>
<td>...</td>
<td>...</td>
<td>( P=0.02 )</td>
<td>0.08</td>
<td>0.006</td>
</tr>
<tr>
<td>( n )</td>
<td>18</td>
<td>...</td>
<td>...</td>
<td>14</td>
<td>8</td>
<td>9</td>
<td>...</td>
<td>...</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Echo ESV</td>
<td>129±50</td>
<td>...</td>
<td>...</td>
<td>104±48</td>
<td>98±53</td>
<td>96±48</td>
<td>...</td>
<td>...</td>
<td>( P=0.01 )</td>
<td>0.02</td>
<td>0.04</td>
</tr>
<tr>
<td>( n )</td>
<td>18</td>
<td>...</td>
<td>...</td>
<td>13</td>
<td>8</td>
<td>10</td>
<td>...</td>
<td>...</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>MRI EDV</td>
<td>250±89</td>
<td>213±64</td>
<td>221±73</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>0.03</td>
<td>0.05</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>( n )</td>
<td>9</td>
<td>9</td>
<td>8</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>NA</td>
<td>NA</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>MRI ESV</td>
<td>180±96</td>
<td>156±83</td>
<td>153±90</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>0.02</td>
<td>0.02</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
</tbody>
</table>

NYHA indicates New York Heart Association; EDV, end-diastolic volume; ESV, end-systolic volume; and NA, not applicable.
shown in Table 3. Statistically significant changes were observed as early as 3 months after CABG and were maintained at 6 months.

Discussion
The main findings of this study can be summarized as follows: (1) Epicardial transplantation of autologous skeletal myoblasts is feasible and safe, in that there were no deaths directly related to transplantation and no infections or allergic reactions resulting from the procedure or the myoblast preparation. (2) Myoblast transplantation in combination with bypass surgery was accompanied by an increase in LVEF, an increase in tissue viability (PET scanning and gadolinium MRI delayed hyperenhancement), and a reduction in ventricular systolic and diastolic volumes (echocardiography and MRI), further verifying the safety of the procedure. However, changes may be related only to benefits of the CABG, and further studies are needed to assess any improvements related to the cells per se. The most serious adverse event that the safety monitoring board determined could have been possibly related to cell transplantation was nonsustained ventricular arrhythmias. Histology confirmed myoblast survival, myofiber formation, and engraftment. This occurred in only 3 of 24 CABG patients and was effectively treated with medications and an ICD. Previous experience with autologous myoblast transplantation noted the occurrence of ventricular arrhythmias in 4 of 10 patients between postoperative days 9 and 22.13,14 However, the data presented herein and recent data from a multicenter myoblast transplantation study being performed in France and other countries indicate that the 4 of 10 patients with arrhythmia represented an anomalously high incidence because of small sample size. The current multicenter European trial has shown 6 of 17 patients with post-CABG arrhythmias (Dr Menasche, personal communication, March 8, 2005). Coupled with the 3 of 24 patients shown here, the cumulative experience indicates that the post-CABG arrhythmia rate ranges from 10% to 15%, the expected rate for patients undergoing CABG or LVAD appears to be safe and technically feasible. Most important, no increased risk for arrhythmia was detected. Histology confirmed myoblast survival, myofiber formation, and engraftment. Furthermore, we conclude that additional clinical trials are warranted to explore the impact of this and other cell-dosage regimens on regional as well as global ventricular function. Consideration should be given to clinical trials in the absence of CABG as well as with increasing dosage regimens and with a control group.

Acknowledgments
The authors thank the entire GenVec staff in the Charlestown location for the production and quality release of patients’ myoblasts and to the clinical staff for all their efforts in the successful initiation and completion of these clinical trials. We thank Dr Neal Salomon for his assistance in patient qualification and data safety monitoring. We also thank Sheila Ulrich for administrative support.

Disclosures
This study was sponsored by GenVec, Inc, Charlestown, Mass, which is developing myoblasts as a commercial product. Dr Anand has received a research grant from and has served as a consultant to GenVec. Dr Dinsmore is employed by GenVec. Dr Di Carli has received grants from Bracco Diagnostics and BMS Medical Imaging and served on the speakers’ bureaus of and/or received honoraria from GE Healthcare, Fujisawa USA, and BMS Medical Imaging. Dr MacLellan has received research grants from the American Heart Association and National Institutes of Health.

References H1439–H1445.
10. Taylor DA, Atkins BZ, Hunspeegs P, Jones TR, Reedy MC, Hutcheson KA, Glower DD, Kraus WE. Regenerating functional myocardium:


Safety and Feasibility of Autologous Myoblast Transplantation in Patients With Ischemic Cardiomyopathy: Four-Year Follow-Up


_Circulation_. 2005;112:1748-1755
doi: 10.1161/CIRCULATIONAHA.105.547810

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2005 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/112/12/1748

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org//subscriptions/