

Infarct Remodeling After Intracoronary Progenitor Cell Treatment in Patients With Acute Myocardial Infarction (TOPCARE-AMI)

Mechanistic Insights From Serial Contrast-Enhanced Magnetic Resonance Imaging

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Background—Experimental and initial clinical studies suggest that transplantation of circulating blood– (CPC) or bone marrow–derived (BMC) progenitor cells may beneficially affect postinfarction remodeling processes after acute myocardial infarction (AMI). To relate functional characteristics of the infused cells to quantitative measures of outcome at 4-month follow-up, we performed serial contrast-enhanced MRI and assessed the migratory capacity of the transplanted progenitor cells immediately before intracoronary infusion.

Methods and Results—In 28 patients with reperfused AMI receiving either BMCs or CPCs into the infarct artery 4.7±1.7 days after AMI, serial contrast-enhanced MRI performed initially and after 4 months revealed a significant increase in global ejection fraction (from 44±10% to 49±10%; $P=0.003$), a decrease in end-systolic volume (from 69±26 to 60±28 mL; $P=0.003$), and unchanged end-diastolic volumes (122±34 versus 117±37 mL; $P=NS$). Infarct size, measured as late enhancement (LE) volume, decreased significantly, from 46±32 to 37±28 mL ($P<0.05$). There was a significant correlation between the reduction in LE volume and global ejection fraction improvement. The migratory capacity of transplanted cells as assessed ex vivo toward a gradient of vascular endothelial growth factor for CPCs and stromal cell derived factor-1 for BMCs was closely correlated with the reduction of LE volume. By multivariate analysis, migratory capacity remained the most important independent predictor of infarct remodeling.

Conclusions—Analysis of serial contrast-enhanced MRI suggests that intracoronary infusion of adult progenitor cells in patients with AMI beneficially affects postinfarction remodeling processes. The migratory capacity of the infused cells is a major determinant of infarct remodeling, disclosing a causal effect of progenitor cell therapy on regeneration enhancement. (*Circulation*. 2003;108:●●●-●●●.)

Key Words: cells ■ myocardial infarction ■ magnetic resonance imaging ■ remodeling

Myocardial salvage is the hallmark of successful reperfusion therapy, which has significantly reduced early mortality rates and improved prognosis in patients with acute myocardial infarction (AMI).¹ However, postinfarction heart failure resulting from ventricular remodeling processes remains a major challenge.² Recent experimental and initial clinical studies suggested that either intravenous infusion or intramyocardial injection of bone marrow–derived (BMC) or circulating blood–derived (CPC) progenitor cells may contribute to the regeneration of infarcted myocardium and enhance neovascularization of ischemic myocardium, resulting in sustained improvement of cardiac function.^{3–12} In our

previously published Transplantation of Progenitor Cells and Regeneration Enhancement in Acute Myocardial Infarction (TOPCARE-AMI) pilot trial,¹² we demonstrated that intracoronary infusion of progenitor cells is associated not only with increased perfusion indices of infarcted segments but also with significant improvements in global and regional contractility and beneficial effects on postinfarction remodeling processes in patients with AMI. However, whether intracoronary infusion of progenitor cells contributes causally to the observed improvement in function remains enigmatic.

Contrast-enhanced MRI not only allows for a comprehensive quantitative analysis of the structural and functional

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consequences of myocardial injury but also is capable of distinguishing between reversible and irreversible dysfunction after AMI.^{13–16} Thus, we performed serial contrast-enhanced MRI and assessed the migratory capacity of the transplanted progenitor cells immediately before intracoronary infusion into the infarct artery to relate functional characteristics of the transplanted progenitor cells to quantitative measures of outcome at 4-month follow-up.

Methods

Patients

Patients between 18 and 75 years of age were eligible for inclusion into the study if they had a first acute ST-elevation myocardial infarction that was treated acutely by coronary stenting with GP IIb/IIIa blockade. Exclusion criteria were the presence of cardiogenic shock (defined as systolic blood pressure <80 mm Hg requiring intravenous pressors or intra-aortic balloon counterpulsation); major bleeding requiring blood transfusion after acute reperfusion treatment; a history of leukopenia, thrombocytopenia, or hepatic or renal dysfunction; evidence of malignant diseases; or unwillingness to participate. The ethics review board of the Hospital of the Johann Wolfgang Goethe University of Frankfurt, Germany, approved the protocol, and the study was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from each patient. The angiographic, echocardiographic, PET, and coronary flow reserve data of 14 of the 28 patients have been reported previously.¹²

Study Protocol

The study protocol has been described previously.¹² In brief, patients were randomly assigned to receive intracoronary infusion of either BMCs or CPCs 4 days after AMI. In patients receiving BMCs, 50 mL of bone marrow aspirate was obtained in the morning of the day of cell transplantation. In patients receiving CPCs, 250 mL of venous blood was collected immediately after random assignment (24 hours after the AMI); mononuclear cells were purified and cultured *ex vivo* for 3 days and then reinfused into the infarct artery as described.^{12,17–19} Cells were infused via an over-the-wire balloon catheter advanced into the stent previously implanted during the acute reperfusion procedure and inflated with low pressure to completely block blood flow for 3 minutes to allow for adhesion and potential transmigration of the infused cells through the endothelium. This maneuver was repeated 3 times to accommodate infusion of the total 10-mL progenitor cell suspension, interrupted by 3 minutes of reflow by deflating the balloon to minimize extensive ischemia. After completion of intracoronary cell transplantation, coronary angiography was repeated to ascertain vessel patency and unimpeded flow of contrast material.

Characterization of Infused Cells

The BMC suspension consisted of heterogeneous cell populations including hematopoietic progenitor cells, which were determined by fluorescence-activated cell sorter analysis using directly conjugated antibodies against anti-human CD34 (FITC; Becton Dickinson), anti-CD45 (Becton Dickinson), and CD133 (Miltenyi Biotech). Overall, a mean of $5.5 \pm 2.8 \times 10^6$ CD34/CD45-positive cells and $0.7 \pm 0.4 \times 10^6$ CD133-positive cells (in $238 \pm 79 \times 10^6$ mononuclear cells) were infused per patient. More than 90% of the CPC suspension (injected cells, mean $13 \pm 12 \times 10^6$) show endothelial characteristics, as demonstrated by Dil-acetylated LDL uptake and lectin binding and the expression of typical endothelial marker proteins, including vascular endothelial growth factor receptor (VEGFR2) (KDR) (Relia Tech), endoglin (CD105) (NeoMarkers), von Willebrand factor (Oncogene), and platelet endothelial cell adhesion molecule-1 (PECAM-1/CD31) (Dianova).^{12,17–19}

Assessment of Migratory Capacity of Transplanted Progenitor Cells

Immediately before intracoronary cell infusion, a sample of progenitor cells was resuspended in 500 μ L endothelial basal medium (Cell Systems) and counted, and 2×10^4 CPCs or 1×10^6 BMCs were placed in the upper chamber of a modified Boyden chamber. Then, the chamber was placed in a 24-well culture dish containing endothelial basal medium and either 50 ng/mL VEGF for measuring migratory capacity of circulating CPCs or 100 ng/mL SDF-1 for measuring migratory capacity of BMCs. After 24 hours of incubation at 37°C, the lower side of the filter was washed with PBS and fixed with 2% paraformaldehyde. For quantification, cell nuclei were stained with DAPI and were counted manually in 5 random microscopic fields by a blinded investigator.^{19,20} Migrating BMCs were pelleted by centrifugation and were manually counted.

Magnetic Resonance Imaging

Cardiac MRI (1.5-T system; Magnetom Sonata, Siemens Medical Solutions) was performed 9 ± 4 days after myocardial infarction as well as 4 months after progenitor cell therapy. All images were acquired by use of a phased-array body surface coil with 4 to 12 elements during breath-holds (maximum, 12 seconds) and were ECG triggered. Cine images with a slice thickness of 8 mm were acquired throughout the entire left ventricle (LV) by use of contiguous 2D True-FISP (true fast imaging in steady-state precession) sequences. The typical in-plane resolution was 2.2×1.3 mm².

After intravenous application of Gd-DTPA (0.2 mmol/kg body wt), “late enhancement” (LE) imaging was performed with a delay time of 15 minutes. Contiguous inversion recovery 2D Turboflash (turbo fast low-angle shot) or 2D True-FISP sequences using an individually optimized inversion time of 170 to 280 ms were acquired. Again, the slice thickness was 8 mm; the in-plane resolution varied between 1.7×1.4 and 1.4×1.4 mm².

Data Analysis

Two patients with flow-limiting restenosis of the stented lesion in the infarct artery at follow-up angiography at 4 months were excluded from the analysis.

With the ARGUS software, LV function (ejection fraction, EF), end-systolic and end-diastolic volumes, LV mass normalized to body weight, and the volumes of the regions revealing LE were calculated from both examinations. In addition, regional EF was assessed by the same method restricted to slices with late hyperenhancement. Moreover, images were analyzed by use of a 17-segment model as recently proposed by the American Heart Association.²¹ Segmental wall thickening was assessed semiquantitatively and judged visually to be either normal (2), hypokinetic (1), or akinetic (0) by 2 independent investigators (M.B.B., N.D.A.) blinded to the type of cells infused. The number of normokinetic, hypokinetic, and akinetic segments per patient was calculated and the wall motion score defined as the number of hypokinetic and akinetic segments per patient. Segmental functional recovery was defined as an increase from hypokinetic to normokinetic or an increase from akinetic to hypokinetic or normokinetic. Segmental LE extent was scored according to the following classification: 0%, >0 to $\leq 25\%$, >25 to $\leq 50\%$, >50 to $\leq 75\%$, and >75% of either volume extent or transmural extent. Furthermore, the amount of dysfunctional but viable segments (LE extent $\leq 25\%$) per patient was assessed.¹¹

Statistical Analysis

Continuous variables are presented as mean \pm SD. Categorical variables were compared by the χ^2 test or Fisher's exact test. Statistical comparisons between initial and follow-up data were performed in a nonparametric fashion using the paired-sign test. Linear nonparametric correlation was calculated by the Spearman correlation. Multivariate analysis was performed using the linear regression model. Statistical significance was assumed if $P < 0.05$. All statistical analysis was performed with SPSS software (version 11.0, SPSS Inc).

TABLE 1. Demographic, Clinical, and Angiographic Characteristics of the Study Population

	n=26
Age, y	51±9
Male sex, %	88
BMI, kg/m ²	27±5
Hypertension, %	54
Hypertlipidemia, %	62
Diabetes, %	19
Smoking, %	65
Pack-y	29±18
Family history of CHD, %	35
CAD, 1-/2-/3-vessel disease, %	20/6/0
History of CAD, %	0
Infarct territory (anterior/inferior), %	50/50
Infarct-related vessel, %	
LAD	50
LCx	15
RCA	35
Time to revascularization, mean/median, h	23±30/13
Creatine kinase max, U/L	1381±1686
Creatine kinase-MB max, U/L	121±96
Type of progenitor cells: BMC/CPC, %	54/46
Time to MRI, d	9±4
Medication on discharge	
Aspirin, %	100
Clopidogrel, %	100
ACE inhibitor, %	96
β-Blocker, %	100
Statin, %	100

BMI indicates body mass index; CHD, coronary heart disease; CAD, coronary artery disease; LAD, left anterior descending coronary artery; LCx, left circumflex artery; and RCA, right coronary artery.

Results

The demographic, clinical, and angiographic data of the study population are summarized in Table 1. In all patients except 1 who experienced side effects from ACE-inhibitor therapy, aspirin, clopidogrel, statins, and β-blockers and ACE-inhibitor therapy were initiated during the hospitalization for AMI and continued until the 4-month follow-up examination.

Global LV Function

Figure 1 illustrates the data for the assessment of global LV function at the time of progenitor cell transplantation and at 4-month follow-up. Global LV EF increased significantly, from 44.1±9.9% (mean±SD) to 48.9±9.8% (Figure 1A), and end-systolic LV volume decreased significantly, from 69.4±25.5 to 59.5±28.1 mL (Figure 1C), whereas end-diastolic LV volume remained unchanged (121.6±33.7 versus 116.9±36.7 mL; Figure 1B). LV mass decreased slightly but significantly, from 84.6±15.6 to 78.6±15.1 g/m²; $P=0.04$; Figure 1D).

Regional LV Function

As illustrated in Figure 2, regional LV function was significantly improved at 4-month follow-up. Importantly, the number of akinetic segments per patient was reduced profoundly, from 2.7±1.9 at the time of cell therapy to 1.2±1.6 at 4-month follow-up ($P<0.001$), whereas the number of normokinetic segments increased significantly, from 9.9±2.9 to 12.3±2.8 ($P<0.001$).

Infarct Size and Functional Improvement

Infarct size as measured by the volume of LE varied within the patient population. Of the 23 patients with hyperenhancement on the scan at the time of cell therapy, 22 had hyperenhancement on the scan at 4-month follow-up, and all 22 had hyperenhancement in the same territories on both scans. Most importantly, LE volume decreased significantly, by ≈20%, from 46±32 mL at the time of cell therapy to 37±28 mL ($P<0.05$) at 4-month follow-up. Regional LV EF in slices with hyperenhancement increased significantly, from 43.2±11.4% to 47.6±11.5% ($P<0.005$). There was a close correlation between changes in global EF and regional EF within LE segments ($r=0.8$; $P<0.001$).

LE volume at the time of cell therapy did not correlate with future improvement in either global EF ($r=0.24$; $P=0.23$) or regional EF in slices with hyperenhancement ($r=0.16$; $P=0.47$). In contrast, however, as illustrated in Figure 3, there was a significant correlation between the reduction in LE volume and the improvement in global EF (Figure 3A) and in wall thickening (Figure 3B) 4 months after progenitor cell therapy.

Figure 4 shows the percentage of improved segments at 4-month follow-up as a function of LE at the time of cell therapy. Although initially dysfunctional segments without any infarction demonstrated the highest incidence of improvement at follow-up, neither the extent (Figure 4A) nor the transmural (Figure 4B) of hyperenhancement predicted future functional recovery. For example, 48 of 65 segments (74%) without any infarction on the scan at the time of cell therapy improved on the scan at 4-month follow-up, but recovery rates were essentially identical, with 50% for >0% to ≤25% transmural of LE, 47% for transmural of LE >25% to ≤50%, 43% for transmural of LE >50% to ≤75%, and 46% for LE transmural >75%. Thus, almost 50% of dysfunctional segments with varying transmural of infarction improved regardless of the initial extent of LE transmural. Finally, although the extent of regional contractile dysfunction was significantly associated with the extent of LE initially ($r=0.54$; $P<0.005$) and at 4-month follow-up ($r=0.49$; $P=0.01$), the extent of LE at the time of cell therapy did not predict functional improvement of regional contractile function at 4-month follow-up ($r=-0.098$, $P=0.633$).

Table 2 summarizes the univariate predictors for global improvement in contractile function. The only statistically significant predictive variable was change in LE volume, whereas neither the initial LE volume nor the initially determined dysfunctional but viable region by MRI predicted the change in global LV EF at 4-month follow-up. As reported in our initial report,¹² there was no difference between CPCs and BMCs with respect to improvement of global LV function.

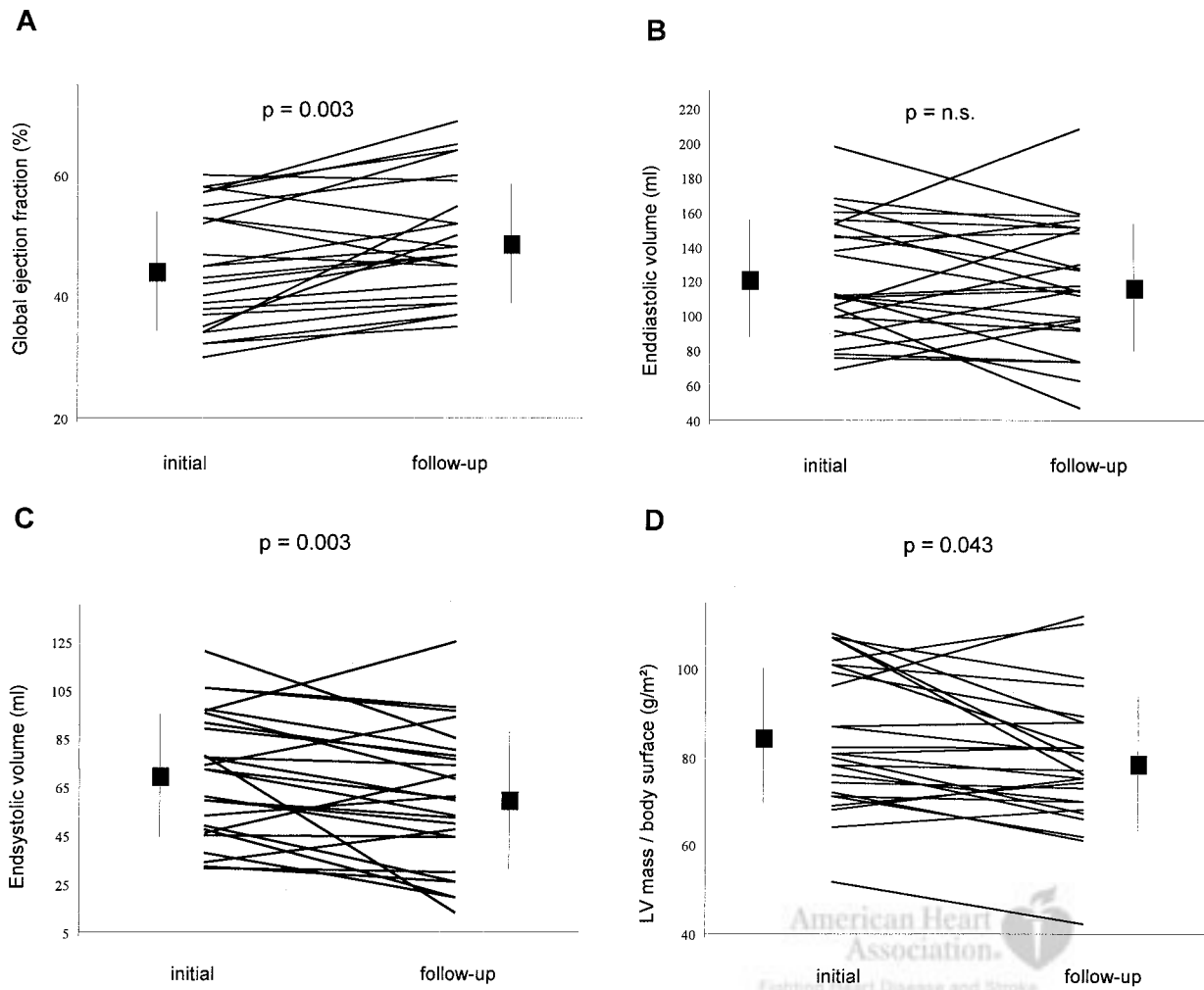


Figure 1. Comparison of initial and follow-up global EF (A), end-systolic volume (B), end-diastolic volume (C), and LV mass normalized for body surface (D). Error bars indicate mean \pm SD.

Number and Migratory Capacity of Transplanted Progenitor Cells and Infarct Remodeling

The absolute number of the infused progenitor cells did not correlate with improved global or regional LV function or with infarct size reduction when total cell numbers or subpopulations were used, eg, CD34/CD45- or CD34/CD133-positive cells (global EF: CPCs, $r=0.18$, $P=0.6$; BMCs, $r=-0.16$, $P=0.6$; infarct size: CPCs, $r=-0.16$, $P=0.6$; BMCs, $r=-0.004$, $P=1.00$). No significant differences were detected in functional improvement when cell numbers were dichotomized (data not shown).

The migratory capacity of the infused progenitor cells was assessed in 15 of the 26 patients. The VEGF-induced migratory capacity of CPCs ranged from 0.8 to 56 cells/high-power field ($n=11$; median, 11 cells/high-power field), and the SDF-1-induced migratory capacity of BMCs ranged from 13.5 to 102 ($n=4$; median, 51.5 cells/high-power field). Because different stimuli were used to assess migration of CPCs and BMCs, we dichotomized the migratory capacity. As illustrated in Figure 5, there was a close relation between migratory capacity and reduction of LE volume. Despite similar values of LE

volume at baseline, the absolute reduction in LE was significantly greater in patients receiving cells with high migratory capacity than in those receiving cells with low migratory capacity (-12.5 ± 16 versus 9 ± 17 mL; $P<0.05$). Similar differences were also detected when only patients receiving CPCs were stratified ($P<0.05$).

To identify independent predictors of infarct remodeling after intracoronary progenitor cell infusion into the infarct artery in patients with AMI, we performed a multivariate analysis including all parameters that were statistically significant or approached statistical significance by univariate analysis or that are known to influence infarct size. As demonstrated in Table 3, the migratory capacity of the transplanted progenitor cells remained the strongest statistically significant independent predictor of infarct size reduction as measured by reduction of LE volume. The only other independent predictor was the baseline EF, whereas neither initial infarct size nor age, sex, or time to revascularization remained independent predictors. Thus, the migratory capacity of infused cells is a major independent determinant of infarct remodeling after progenitor cell therapy in patients with AMI.

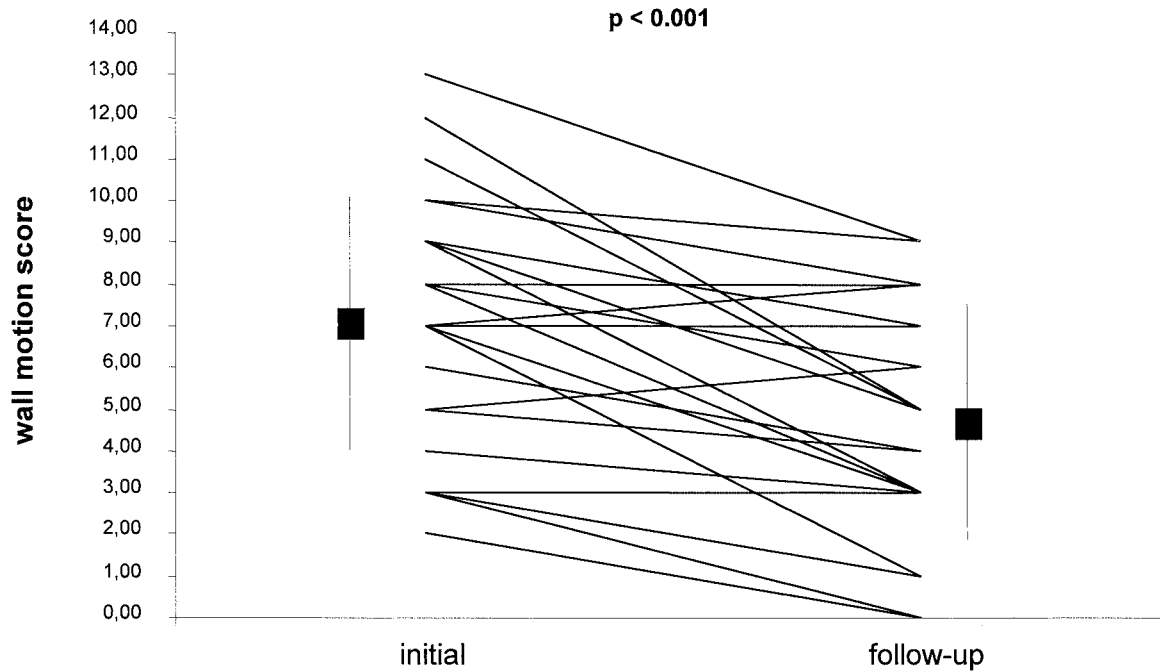


Figure 2. Wall motion score initially after cell therapy and at 4-month follow-up.

Discussion

The results of the present study extend our previously reported observation¹² that transplantation of adult progenitor cells is associated with significant beneficial effects on LV remodeling processes in patients with AMI. Serial contrast-enhanced MRI provided novel and unique insights into potential mechanisms involved in the observed functional improvement: Cell therapy was associated with a significant reduction in infarct size as measured by the volume of LE at 4-month follow-up, the reduction of LE volume correlated directly with the improvement of global LV EF, and both global and regional contractile recovery were independent of the initial LE volume.

Most importantly, however, the present study demonstrates that the functional capacity of the transplanted progenitor cells is a major independent determinant of subsequent infarct remodeling after intracoronary cell transplantation. Interestingly, the functional activity of the cells as assessed by their migratory activity was more informative than the cell num-

ber. This may be because the cell numbers infused were within a rather narrow range (75% of the patients received 4 to 18×10^6 CPCs or 150 to 300×10^6 BMCs). However, it is more likely that the functional activity at least in part can override differences in cell numbers. Taken together, these data for the first time suggest a causal relation between progenitor cell therapy and LV regeneration enhancement in patients with AMI.

In our initial report of the first 20 patients included in the TOPCARE-AMI trial,¹² we demonstrated that transplantation of adult progenitor cells was associated with a significant improvement in global LV EF and reduced end-systolic volumes as assessed by LV angiography. The present study now corroborates these findings by using a more robust and accurate method of assessing LV function, namely, MRI. Especially in the presence of a distorted LV geometry caused by previous myocardial infarction, MRI provides more reliable data because of its ability for 3D visualization of the LV cavity and LV wall. The only available study systematically

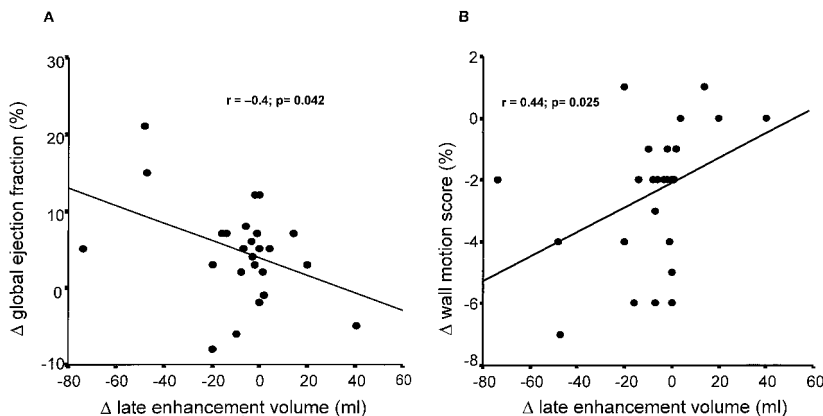


Figure 3. Correlation between changes in global EF (A) and wall motion score (B) and changes in LE volume (n=26).

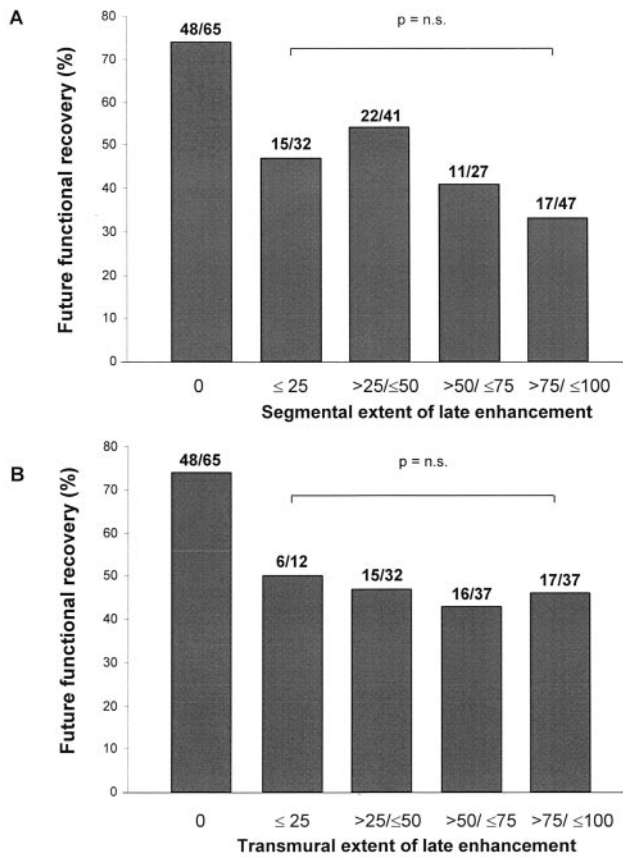


Figure 4. Percentage of improved segments as a function of regional LE extent and transmurality.

investigating LV remodeling by serial MRI at 5 days and 6 months after AMI treated either with percutaneous coronary intervention or thrombolysis revealed a significant increase in both end-systolic and end-diastolic LV volumes, with essentially unchanged LV EF.²² Thus, preservation of LV EF occurred at the expense of increased LV volumes, indicating postinfarction remodeling processes. In contrast, in the present study, LV EF increased significantly but end-systolic LV volume decreased and end-diastolic volume remained unchanged over time, suggesting a beneficial effect of progenitor cell transplantation on LV remodeling processes.

Previous experimental studies suggested that the improvement in ventricular function after experimentally induced

TABLE 2. Univariate Analysis of Global EF Improvement

	Δ EF, <i>r</i>	<i>P</i>
Age, y	0.003	NS
Sex, M/F	0.07	NS
Creatine kinase-MB max	-0.157	NS
Time infarct to MRI	-0.129	NS
Time MRI to cell therapy	0.095	NS
Infarct territory (anterior/inferior)	0.25	NS
Type of progenitor cells: BMC/CPC	0.29	NS
Initial LE volume	0.24	NS
Dysfunctional but viable (MRI)	0.22	NS
Reduction of LE volume	-0.4	0.04

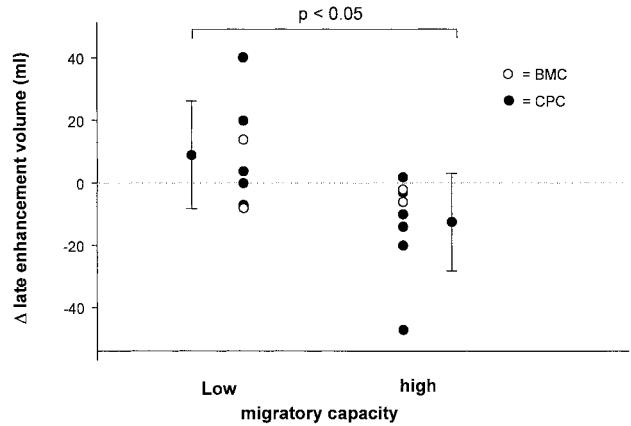


Figure 5. Migratory capacity of transplanted progenitor cells (dichotomized into high and low by use of median values) and infarct remodeling as measured by reduction in LE volume (n=15).

myocardial infarction is a result of stimulated neoangiogenesis preventing late myocardial remodeling through enhanced myocardial blood flow, rescue of hibernating myocardium, reduction of myocardial fibrosis, and decreased apoptosis of hypertrophied myocytes in the peri-infarct region.^{4,5,23,24} In addition, Orlic et al³ reported that intramyocardial injection of BMCs led to regeneration of significant amounts of contracting myocardium, suggesting that the de novo generation of myocardium may contribute to amelioration of the outcome of myocardial infarction after local delivery of adult progenitor cells. Indeed, we have recently demonstrated that CPCs retain the capability to transdifferentiate into functional cardiac myocytes.²⁵

However, prerequisite for the success of cell therapy is the homing and, thus, engraftment of transplanted cells into the target area, especially if an intravascular route of administration is chosen. Therefore, we reasoned that the migratory capacity of adult progenitor cells toward their physiological chemoattractant might reflect their homing capacity into the infarcted area. Both VEGF and SDF-1 are profoundly up-regulated in hypoxic tissue,²⁶⁻²⁹ suggesting that VEGF and SDF-1 may constitute homing signals to recruit circulating progenitor cells to enhance endogenous repair mechanisms after critical ischemia. The results of the present study now demonstrate that the migratory capacity of transplanted progenitor cells is an independent predictor of infarct remodeling as measured by MRI-determined LE volume. Taken together,

TABLE 3. Multivariate Analysis of Independent Predictors of Infarct Remodeling as Measured by Reduction in LE Volume

	Δ LE Volume Standardized Coefficient β	<i>P</i>
Sex	0.09	NS
Age	-0.11	NS
Time to revascularization	0.48	NS
Baseline EF	-0.53	0.01
Baseline LE volume	0.28	NS
Low/high migration	-0.738	0.004

the improvement in local contractile function associated with a reduction in infarct size being independently determined by the functional capacity of infused progenitor cells to migrate toward their physiological chemoattractants discloses a causal relationship between transplantation of progenitor cells and regeneration enhancement in patients with AMI.

Obviously, the present clinical study cannot disclose the cellular mechanisms associated with the improved LV contractile function after progenitor cell therapy. However, the results of the present study demonstrate that the intracoronary infusion of adult progenitor cells is associated with a profound reduction of infarct size, as measured by the volume of MRI-determined LE. This reduction in MRI-determined infarct size directly correlated with improved global and regional contractile LV function, suggesting that local contractile functional recovery is indeed beneficially affected by the infusion of progenitor cells into the infarct artery. Whereas previous studies have firmly established that the magnitude of long-term functional recovery is inversely related to the extent and transmural extent of hyperenhancement,^{14,15} local contractile recovery was entirely independent of both the initial extent and transmural extent of irreversibly injured myocardium in our patients treated with intracoronary progenitor cell infusion. Instead, infarct remodeling as measured by the reduction in LE volume was independently predicted by the migratory capacity of the infused progenitor cells. These data indicate that cell therapy may beneficially modify the healing process of myocardial infarction. Given that the improvement of global LV function was predominantly a result of an improved contractility in LV slices with evidence for LE initially, the effects of progenitor cell therapy on postinfarction LV remodeling indeed appear to include rescue of "irreversibly" dysfunctional myocardium early after AMI. However, whether this novel form of regeneration enhancement therapy associated with augmented myocardial salvage will translate into sustained improvement in LV function and prognosis after AMI awaits the results of larger-scale randomized trials.

Acknowledgments

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