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Background—Experimental studies suggest that transplantation of blood-derived or bone marrow–derived progenitor cells beneficially affects postinfarction remodeling. The safety and feasibility of autologous progenitor cell transplantation in patients with ischemic heart disease is unknown.

Methods and Results—We randomly allocated 20 patients with reperfused acute myocardial infarction (AMI) to receive intracoronary infusion of either bone marrow–derived (n=9) or circulating blood–derived progenitor cells (n=11) into the infarct artery 4.3±1.5 days after AMI. Transplantation of progenitor cells was associated with a significant increase in global left ventricular ejection fraction from 51.6±9.6% to 60.1±8.6% ($P=0.003$), improved regional wall motion in the infarct zone (−1.5±0.2 to −0.5±0.7 SD/chord; $P<0.001$), and profoundly reduced end-systolic left ventricular volumes (56.1±20 mL to 42.2±15.1 mL; $P=0.01$) at 4-month follow-up. In contrast, in a nonrandomized matched reference group, left ventricular ejection fraction only slightly increased from 51±10% to 53.5±7.9%, and end-systolic volumes remained unchanged. Echocardiography revealed a profound enhancement of regional contractile function (wall motion score index 1.4±0.2 at baseline versus 1.19±0.2 at follow-up; $P<0.001$). At 4 months, coronary blood flow reserve was significantly ($P<0.001$) increased in the infarct artery. Quantitative F-18-fluorodeoxyglucose–positron emission tomography analysis revealed a significant ($P<0.01$) increase in myocardial viability in the infarct zone. There were no differences for any measured parameter between blood-derived or bone marrow–derived progenitor cells. No signs of an inflammatory response or malignant arrhythmias were observed.

Conclusions—In patients with AMI, intracoronary infusion of autologous progenitor cells appears to be feasible and safe and may beneficially affect postinfarction remodeling processes. **(*Circulation*. 2002;106:3009-3017.)**

Key Words: myocardial infarction ■ cells ■ remodeling ■ transplantation

Prompt reperfusion of the occluded artery has significantly reduced early mortality rates and improved late clinical outcome in patients with acute myocardial infarction.[1] However, despite rapid restoration of blood flow, postinfarction heart failure remains a major challenge. Postinfarction heart failure results from ventricular remodeling processes characterized by progressive expansion of the infarct area and dilation of the left ventricular (LV) cavity.[2] The major goal to reverse LV remodeling would be the enhancement of regeneration of cardiac myocytes as well as the stimulation of neovascularization within the infarct area. Experimental studies suggested that bone marrow–derived or blood-derived progenitor cells may contribute to the regeneration of infarcted myocardium[3] and enhance neovascularization of ischemic myocardium.[4–6] Indeed, either intravenous infusion or intramyocardial injection of adult progenitor cells resulted in sustained improvement of cardiac function after experimentally induced myocardial infarction.[4–7] Therefore, we investigated the feasibility, safety, and initial clinical outcome of intracoronary infusion of autologous progenitor cells in patients with acute myocardial infarction (AMI).

Methods

Patients

The study was initiated in October 2001 to recruit 20 patients in each treatment group. Because of the experimental nature of the treatment, the study protocol called for an interim analysis of the outcome data after the first 20 patients completed their 4-month follow-up examination. The data reported in this study consist of the results of the first 20 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

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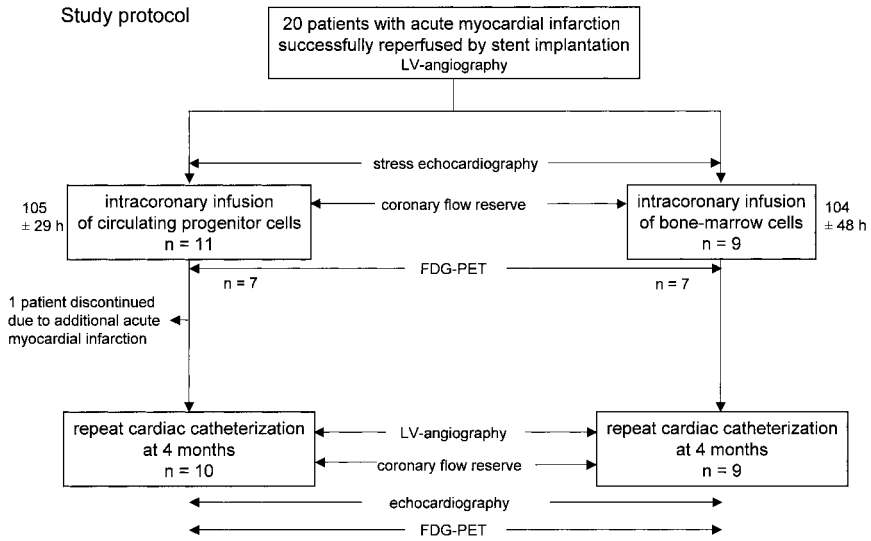

Figure 1. Flow chart outlining the study protocol.

infarction, which was acutely treated by coronary stenting with GPIIb/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 for 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.

As an internal reference group reflecting the standard of care provided at our institution, we selected 11 patients matched for ejection fraction, infarct localization, and infarct size with our study population, in whom acute reperfusion therapy was performed by stent implantation and paired LV angiograms were available acutely and at 4 month follow-up.

Study Protocol

Twenty-four hours after AMI, the patients were randomly assigned to receive either bone marrow–derived or blood-derived progenitor cells (see Figure 1). Since preparation of blood-derived progenitor cells required 3 days of ex vivo culturing (see below), patients were scheduled to receive intracoronary infusion of progenitor cells 4 days after AMI. In patients receiving bone marrow–derived progenitor cells, bone marrow aspirates were obtained in the morning of the day of cell transplantation. In patients receiving blood-derived progenitor cells, 250 mL of venous blood was collected immediately after random assignment (24 hours after the AMI); mononuclear cells were purified and ex vivo cultured for 3 days and then reinfused into the infarct artery.

Catheterization Procedure for Progenitor Cell Transplantation

A mean of 4.3±1.5 days after the AMI an over-the-wire balloon catheter oversized by 0.5 mm was advanced into the stent previously implanted during the acute reperfusion procedure. To allow for adhesion and potential transmigration of the infused cells through the endothelium, the balloon was inflated with low pressure to completely block blood flow for 3 minutes, while 3.3 mL of the progenitor cell suspension was infused distally to the occluding balloon through the central port of the balloon catheter. 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.

Preparation of Progenitor Cells

Circulating blood–derived progenitor cells (CPCs) were expanded ex vivo out of 250 mL venous blood mainly as previously described.[5,8–11] Mononuclear cells were suspended in X vivo-15 medium (Biowhittaker) supplemented with 1 ng/mL carrier-free human recombinant VEGF (R&D), 0.1 μmol/L atorvastatin (provided by Pfizer), and 20% human serum drawn from each individual patient. Cells were seeded at a density of 6.4×10^5 cells/mm^2 at fibronectin-coated dishes (Roche). After 3 days of cultivation, cells were detached with 0.5 mmol/L EDTA, washed twice and resuspended in a final volume of 10 mL X vivo-10 medium. The resulting cell suspension contains a heterogeneous population of progenitor cells. More than 90% of the cells show endothelial characteristics, as demonstrated by Dil-acetylated LDL uptake and lectin binding and the expression of typical endothelial marker proteins including VEGFR2 (KDR) (ReliaTech), endoglin (CD105) (NeoMarkers), von Willebrand factor (Oncogene), platelet endothelial cell adhesion molecule-1 (PECAM-1/CD31) (Dianova), (Figure 2, A and B), and VE-Cadherin or CD146 (data not shown).

Bone marrow–derived mononuclear cells (BMCs) were isolated by density gradient centrifugation. After 2 washing steps, cells were resuspended in 10 mL X vivo-10 medium (Biowhittaker). The cell suspension consists of heterogeneous cell populations including hematopoietic progenitor cells, which were determined by FACS analysis, using directly conjugated antibodies against anti-human CD34 (FITC; Becton Dickinson), anti-CD45 (Becton Dickinson), and CD133 (Miltenyi Biotech) (Figure 2, C and D), but also other cell types (eg, side population cells, stroma cells, and so forth). Overall, a mean value of $7.35\pm7.31\times10^6$ CD34/CD45-positive cells were infused per patient.

LV Angiography

LV angiograms were obtained according to standard acquisition guidelines. LV ejection fraction and volumes were calculated with the use of the area-length method,[12] and regional wall motion was determined with use of the centerline chord method.[13]

Measurement of Coronary Flow Reserve

Immediately before the intracoronary infusion of the progenitor cells, coronary flow reserve was measured in the infarct vessel as well as in a noninfarct reference vessel with the use of an intracoronary Doppler wire and 2.4 mg/min adenosine infused through the guiding catheter, as previously described.[14]

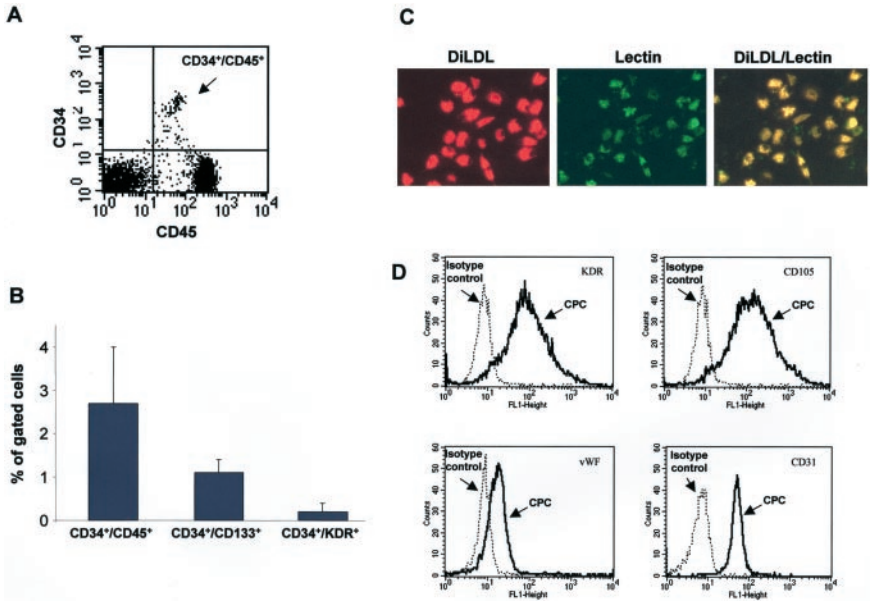

Figure 2. Characteristics of BMCs (A and B) and CPCs (C and D). A and B, Representative FACS analysis and quantification of BMCs. Data are mean±SEM (n=8). C, Cultivated CPCs were incubated with Dil-acetylated LDL (red fluorescence) and stained with lectin (green fluorescence). Representative image is shown. D, FACS analysis of CPCs with antibodies directed against KDR (upper left), CD105 (upper right), von Willebrand Factor (lower left), and CD31 (lower right). Representative pictures are shown.

Stress Echocardiography

At the day of cell transplantation, dobutamine stress echocardiography for the assessment of viable myocardium was carried out before cardiac catheterization as previously described.[15,16] In brief, dobutamine was infused at doses of 5, 10, 20, 30, and 40 μg/kg per minute in 3-minute stages. Two-dimensional echocardiography with a phased-array electronic ultrasound system (System V, Vingmed) was performed in the 4 standard views (parasternal long-axis and short-axis views and apical 4- and 2-chamber views) and 12-lead ECG and blood pressure were continuously recorded.

Regional LV wall motion analysis was performed as described by the Committee on Standards of the American Society of Echocardiography,[16] dividing the left ventricle into 16 segments and scoring wall motion as 1=normal, 2=hypokinesis, 3=akinesis, and 4=dyskinesis for each segment. Contractile reserve was defined as an improvement of ≥1 in the wall motion score between the baseline images and the dobutamine low-dose stage (10 μg/kg per minute). The wall motion score index (WMSI) was calculated as the sum of the scores of the segments divided by the number of the segments evaluated.

F-18-Fluorodeoxyglucose–Positron Emission Tomography

The day after progenitor cell therapy, F-18-fluorodeoxyglucose–positron emission tomography (FDG-PET) was performed with a whole-body PET scanner (ECAT EXACT 47, Siemens CTI). Patients received a single dose of 250 mg acipimox orally 2 hours before administration of FDG.[17,18] Diabetic patients underwent hyperinsulinemic euglycemic clamping as described previously.[18] Nondiabetic patients were given a 50-g oral glucose loading.[19] At the time of decrease of glucose level, FDG was administered, and 45 minutes after administration of FDG, acquisition was started. Standardized quantitative analysis was performed with FDG-PET bullseye views and calculating the mean signal intensity in the respective areas supplied by the 3 major coronary arteries (see Figure 3, C and D).

Data Collection and Follow-Up Examination

Clinical data, medication, and safety laboratory data were prospectively collected, and follow-up visits were performed after 2 weeks, 2 months, and 4 months. Specific attention was paid to any potential signs or symptoms of arrhythmia during follow-up.

Four months after progenitor cell therapy, cardiac catheterization was repeated to measure coronary flow reserve in both the reference and the infarct artery at identical sites as during the initial examination, and left ventriculography was performed with identical projections according to standard acquisition guidelines. Coronary angiograms were analyzed for the presence of collateral filling of the infarct-related artery according to the Rentrop classification scheme.[20] Resting echocardiography as well as FDG-PET were also repeated after 4 months.

Statistical Analysis

Continuous variables are presented as mean±SD. Categoric variables were compared with the use of the χ^2 or Fisher's exact test. Statistical comparisons within the treatment groups were made by paired Student's *t* test if data were distributed normally; otherwise, comparisons were made by the nonparametric Wilcoxon 2-sample test. Comparisons between groups were performed with Bonferroni-corrected ANOVA testing. Statistical significance was assumed at a value of $P<0.05$. All statistical analysis was performed with SPSS (Version 9.0, SPSS Inc).

Results

The demographic, clinical, and angiographic characterization of the study population and the reference group are reported in Table 1. There were no significant differences in any of the baseline parameters between patients receiving blood-derived progenitor cells compared with bone marrow–derived progenitor cells. The intracoronary progenitor cell transplantation procedure did not affect leukocyte blood count or C-reactive protein serum levels, indicating the lack of an inflammatory response (Table 1). Likewise, troponin T serum levels, which were obviously still elevated in these patients 4 days after the AMI, further decreased 24 hours after cell transplantation, indicating that the procedure itself did not incur further ischemic damage (Table 1).

One patient (No. 19), in whom progenitor cell therapy was performed in the right coronary artery for inferior myocardial infarction, had an additional anterior wall infarction 3 days after cell therapy, which was successfully treated by immediate recanalization of the left anterior descending coronary artery. It was discovered afterward that this patient has genetically determined severe anti–thrombin III deficiency. This patient was excluded from follow-up analysis.

In all patients, aspirin, clopidogrel, statin, β-blocker, and ACE inhibitor therapy were initiated during the hospitaliza-

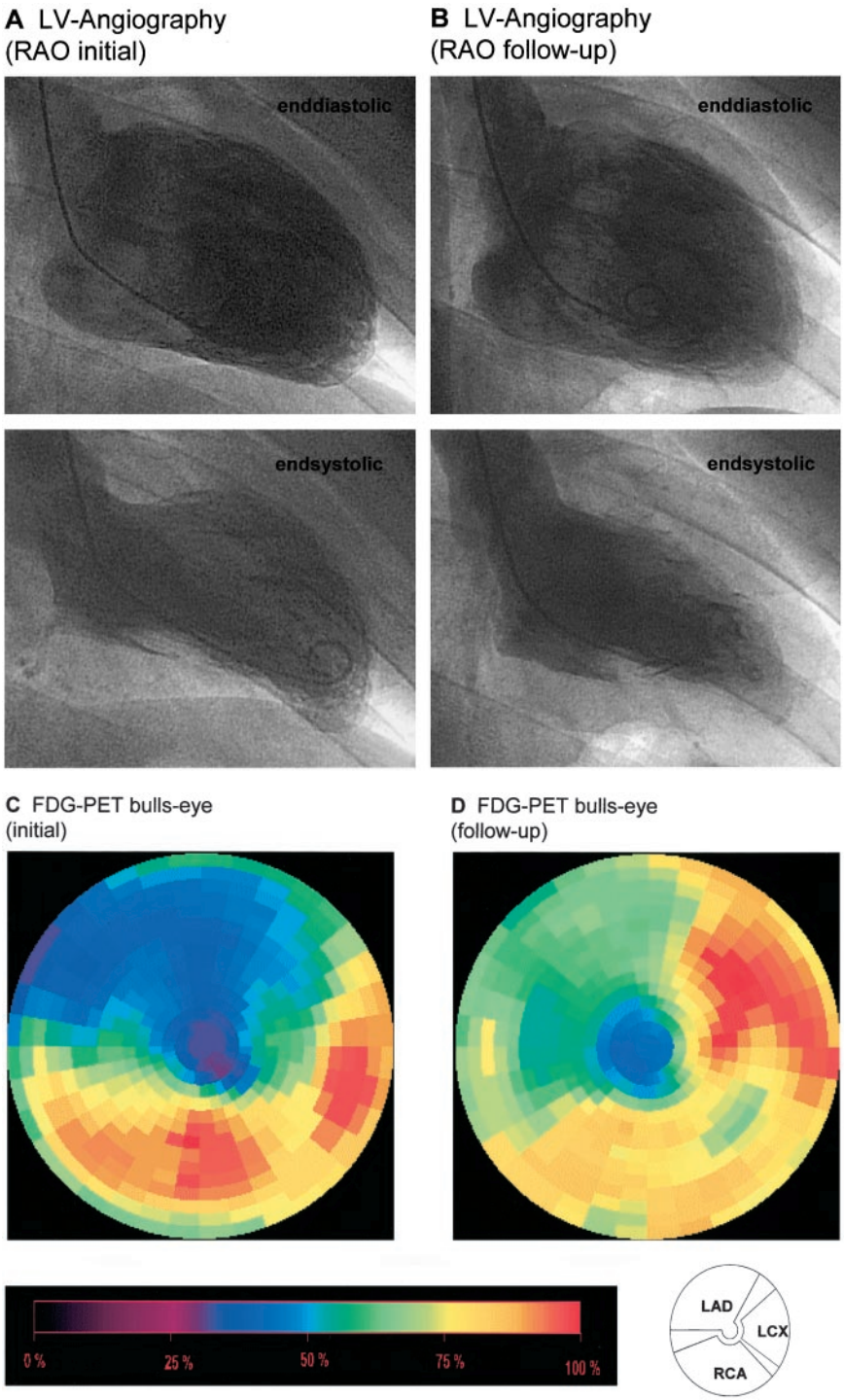

Figure 3. LV angiography before CPC therapy (left panel, A) and at 4-month follow-up (right panel, B). C and D, Corresponding FDG-PET bulls-eye views of the left ventricle of the patient; LV angiography is illustrated in A and B. LAD indicates left anterior descending artery; LCX, left circumflex artery; and RCA, right coronary artery.

tion for AMI and continued until the 4-month follow-up examination. There were no deaths, and none of the patients had any malignant arrhythmias during follow-up. At 4-month follow-up examination, no patient had any clinical findings suggestive of heart failure. Five of 19 patients had restenosis of the stented lesion in the infarct artery.

LV Function by Angiography

Figure 3, A and B, illustrates LV function as assessed by cineventriculography at the time of AMI and at 4-month follow-up in a patient receiving blood-derived progenitor cells. Table 2 summarizes the measurements derived from cineventriculography for the entire study population. There was a significant increase in global LV ejection fraction and regional wall motion in the infarct zone from baseline to follow-up. Moreover, LV end-systolic volume was significantly smaller at 4-month follow-up. Detailed analysis of regional wall motion revealed the most prominent improvement in the border zones adjacent to the central infarct zone (see Table 2).

Improvements in global and regional LV function did not significantly differ between patients receiving bone marrow–derived progenitor cells compared with patients receiving blood-

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

	Circulating Progenitor Cell Group* (n=10)	Bone Marrow Cell Group (n=9)	Control Group (n=11)	*P*
Age, y	52±10	55±8	55±11	NS
Male sex, %	80	89	82	NS
BMI, kg/m	29±4	26±3	ND	NS
Hypertension, %	30	56	55	NS
Hyperlipidemia, %	50	78	82	NS
Diabetes, %	20	22	0	NS
Smoking, %	50	78	82	NS
Pack-years	32±24	37±27	25±15	NS
Family history of CHD (5)	40	33	36	NS
CAD (1-/2-/3-vessel disease)	7/3/0	7/1/1	7/2/2	NS
History of CAD, %	0	0	0	NS
Infarct territory (anterior/inferior), %	30/70	56/44	55/45	NS
Infarct-related vessel, %				NS
LAD	31	60	45	
LCX	23	0	10	
RCA	46	40	45	
Time to revascularization: mean/median, h	21±37/4	25±29/15	16±27/15	NS
Primary therapy PTCA and stent/thrombolysis, n	9/1	6/3	10/1	NS
TIMI III flow after reperfusion, n	9	8	ND	NS
Ejection fraction (visually estimated)	42±9	42±8	40±8	NS
CPR during AMI, n	0	2	1	NS
Creatine kinase max, U/L	906±629	666±666†	813±644†	NS
Creatine kinase MB max, U/L	99±37	98±76†	121±102†	NS
Medication on discharge:				
Aspirin, %	100	100	91	NS
Clopidogrel, %	100	100	100	NS
ACE inhibitor, %	100	100	91	NS
β-Blocker, %	100	100	100	NS
Statin, %	100	100	91	NS
Time stent to cell therapy, h	105±29	104±48	...	NS
No. of injected cells, Mio.	10±7	245±72	...	NS
Before cell therapy:				
White blood cell count, /nL	12±3.5	13±3.6	...	NS
C-reactive protein, mg/dL	3.3±2.7	4.0±2.8	...	NS
Troponin T, ng/mL	2.8±1.2	2.1±1.5	...	NS
24 h after cell therapy				
White blood cell count, /nL	9±2.2	10±2.3	...	NS
C-reactive protein, mg/dL	3.8±3.2	3.9±2.5	...	NS
Troponin T, ng/mL	1.7±1.0	1.5±0.6	...	NS

BMI indicates body mass index; CHD, coronary heart disease; CAD, coronary artery disease; LAD, left anterior descending artery; LCX, left coronary artery; RCA, right coronary artery; CPR, cardiopulmonary resuscitation.

*One patient (No. 19) was excluded because of reinfarction 3 days after cell therapy.

†Without patients with CPR.

derived progenitor cells. In patients receiving CPCs, global LV ejection fraction increased from 51.3±11% to 59.5±9% and regional wall motion in the infarct zone increased from −1.5±0.3 to −0.6±0.6 SD/chord, whereas end-systolic volumes decreased from 56.9±17.6 to 48.9±14.2 mL. Corresponding values for the BMCs were 51.9±9% to 60.7±9% for global LV ejection fraction, −1.6±0.2 to −0.4±0.8 SD/chord for regional wall motion in the infarct zone, and 55.2±24 mL to 34.9±13 mL for end-systolic volumes (all NS versus corresponding data in CPCs).

Although only 3 female patients were included in the study, separate analysis did not disclose any trend toward a potential differential response of female versus male patients.

TABLE 2. LV Function Assessed by Analysis of LV Angiography in the Cell Therapy Group

	Baseline (n=19)	Follow-Up (n=19)	P
Ejection fraction, %	51.6±9.6	60.1±8.6	0.003
End-diastolic volume, mL	117.2±35.1	105.2±29.9	0.199
End-systolic volume, mL	56.1±20.0	42.2±15.1	0.011
Regional wall motion, SD/chord			
Infarct	−1.5±0.2	−0.5±0.7	<0.001
Infarct center	−1.5±0.5	−0.8±0.5	<0.001
Infarct border	−1.3±0.4	−0.4±0.6	<0.001

TABLE 3. LV Function Assessed by Analysis of LV Angiography in the Control Group

	Baseline (n=11)	Follow-Up (n=11)	P
Ejection fraction, %	51±10	53.5±7.9	NS
End-diastolic volume, mL	102±23.6	123±50.3	NS
End-systolic volume, mL	50.4±17.5	58.2±32.2	NS

In contrast, in the reference group of patients, who did not receive progenitor cell infusion but otherwise were treated identically, no significant changes were detected (Table 3). Thus, in the reference group, despite similar baseline values, global LV ejection fraction was significantly lower ($P<0.05$) and end-systolic LV volume increased (end-systolic LV volume change +7.8±22.8 mL versus −13.8±21.4 mL in the progenitor cell treated group; $P<0.02$) at 4-month follow-up.

Regional LV Function by Echocardiography

Low-dose dobutamine stress echocardiography performed immediately before progenitor cell infusion 4.2±2.2 days after AMI revealed a reduction in wall motion abnormality, suggesting the presence of viable but dysfunctional myocardium in 12 of the 19 patients. Figure 4 illustrates the WMSI at resting and low-dose dobutamine stress echocardiography at baseline before progenitor cell therapy as well as the WMSI by resting echocardiography at 4-month follow-up. The number of hypo/akinetic segments was 86 at resting baseline echocardiography, 75 at dobutamine stress baseline echocardiography, and 44 at resting follow-up echocardiography ($P<0.05$ versus baseline stress and $P<0.001$ versus baseline resting echocardiography). At follow-up resting echocardiography, regional wall motion had improved in 12 of 19 patients compared with low-dose dobutamine stress echocardiography at baseline. Importantly, 5 of the 7 patients demonstrating lack of dobutamine-responsive contractile enhancement suggesting the presence of irreversibly damaged myocardium before progenitor cell therapy had improved regional wall motion at 4-month follow-up resting echocardiography. No patient demonstrated deterioration of regional wall motion during the follow-up period. As illustrated in Figure 4, there were no significant differences in wall motion score between patients treated with bone marrow–derived compared with blood-derived progenitor cells.

Coronary Flow Reserve

At baseline, coronary flow reserve measured immediately before progenitor cell infusion was significantly reduced in the infarct artery compared with the reference vessel. Figure 5 illustrates the individual coronary flow reserve values in both the infarct artery (Figure 5A) and the reference vessel (Figure 5B) before progenitor cell therapy and at 4-month follow-up. At 4 months after myocardial infarction, coronary flow reserve had significantly increased in both the infarct artery as well as in the reference vessel. However, the increase in coronary flow reserve was significantly ($P<0.05$) larger in the infarct artery, where the progenitor cells were infused, compared with the noninfused reference vessel. In fact, when the 5 patients who had restenosis of the stented lesion in the infarct artery were excluded from the analysis, coronary flow reserve of the infarct artery was completely normalized 4 months after progenitor cell infusion and no longer differed between the infarct artery and the noninfarct reference vessel (Figure 5C). As illustrated in Figure 5, coronary flow reserve data were similar in both groups of patients.

In 2 of 5 restenosis patients, Rentrop class 2 and 3, respectively, collateral filling of the infarct-related artery was observed by angiography at 4-month follow-up. In addition, in one patient without restenosis development, Rentrop class 1 collateral filling was noted at follow-up.

Myocardial Viability by FDG-PET

In 15 of the 19 patients, FDG-PET was performed at baseline the day after progenitor cell infusion and repeated at 4-month follow-up to assess myocardial viability in the infarct area. In

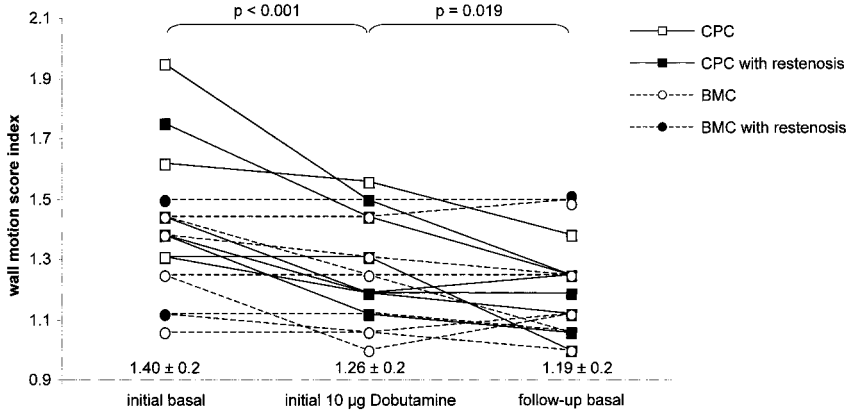

Figure 4. Echocardiographic wall motion score index at rest (initial basal) and during low-dose dobutamine stimulation (initial 10 µg dobutamine) at baseline before progenitor cell therapy and at rest at 4-month follow-up (follow-up basal).

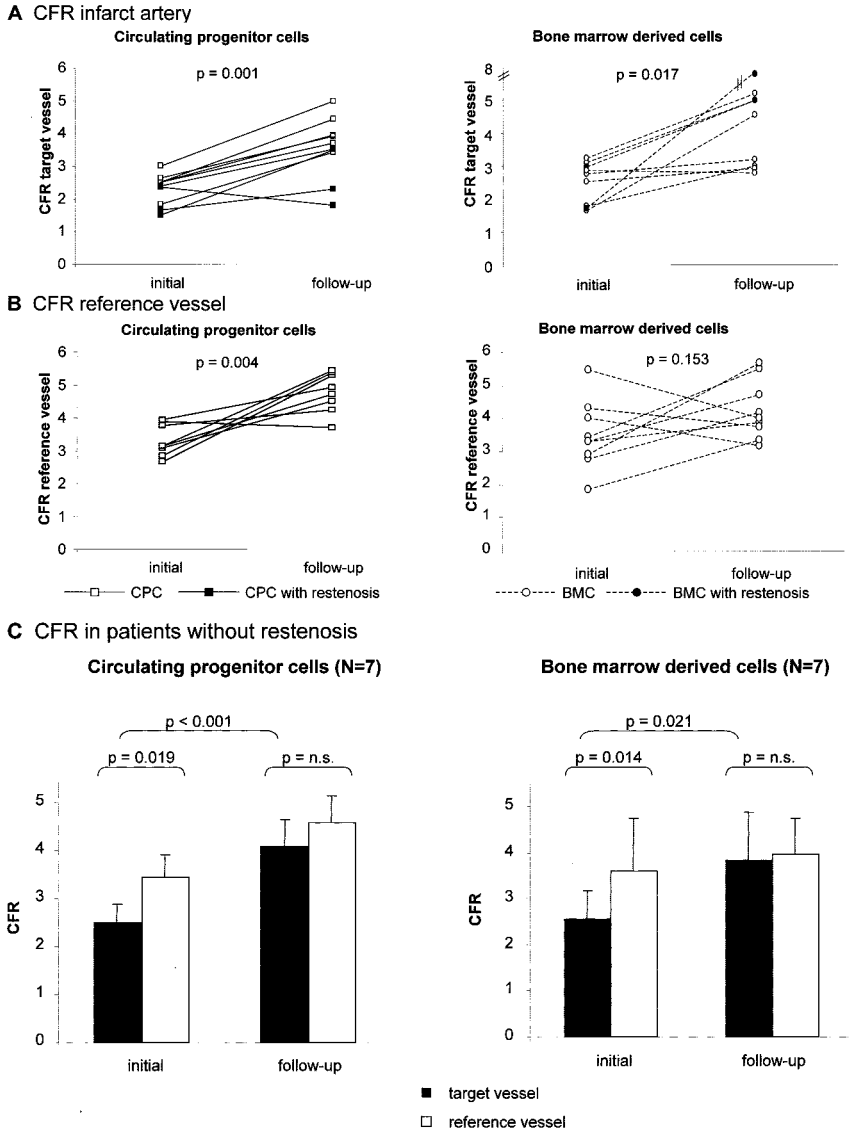

Figure 5. Coronary flow reserve (CFR) in response to 2.4 mg/min adenosine IC in the infarct artery (target vessel, upper panel, A) and in the reference vessel (lower panel, B) immediately before progenitor cell therapy and at 4-month follow-up. Left panels show the results obtained with CPCs; right panel shows patients with BMC therapy. Patients with restenosis are indicated by filled symbols. C, CFR (mean±SD) in patients without restenosis development in the infarct lesion.

one patient, technical limitations prevented the analysis of the baseline FDG-PET scan, leaving a total of 14 paired FDG-PET examinations. Figure 3, C and D, illustrates an example of increased myocardial viability as assessed by FDG-PET scan in a patient treated with blood-derived progenitor cells. For the entire study population, mean tracer uptake in the infarct territory increased significantly ($P<0.01$) from 54.1±12.5% to 62.9±11.0% at 4-month follow-up, whereas no changes in the reference vessel territory were observed (72.4±5% at baseline versus 73.7±7.5% at 4-month follow-up; P=NS) As illustrated in Figure 6, 11 of 14 patients had an increase in tracer uptake by FDG-PET within the infarct territory, suggesting increased myocardial viability in the infarct area. Two of the 3 patients without FDG-PET–derived evidence of improved viability after 4 months had restenosis within the stented lesion. There were again no significant differences between patients receiving blood-derived progenitor cells (n=7) and patients receiving bone marrow–derived progenitor cells (n=7).

Discussion

The results of this pilot trial demonstrate that transplantation of adult progenitor cells by intracoronary infusion is feasible and safe in patients with AMI. In our cohort of patients with AMI optimally treated by coronary stenting for reperfusion, the intracoronary infusion of adult progenitor cells was associated with a significant increase in global LV ejection fraction, a profound improvement in wall motion abnormalities in the infarct area, and a significant reduction in end-systolic LV volumes 4 months after the AMI, suggesting a beneficial effect on postinfarction remodeling processes. The improved LV function was accompanied by complete normalization of coronary flow reserve in the infarct artery and by significant increases in myocardial viability within the infarcted segments as assessed by FDG-PET.

To achieve maximum concentration at the site of ischemic injury, we directly infused progenitor cells into the infarct artery instead of an intravenous administration. Because parenteral harvest and administration of circulating blood-derived progenitor cells is clearly

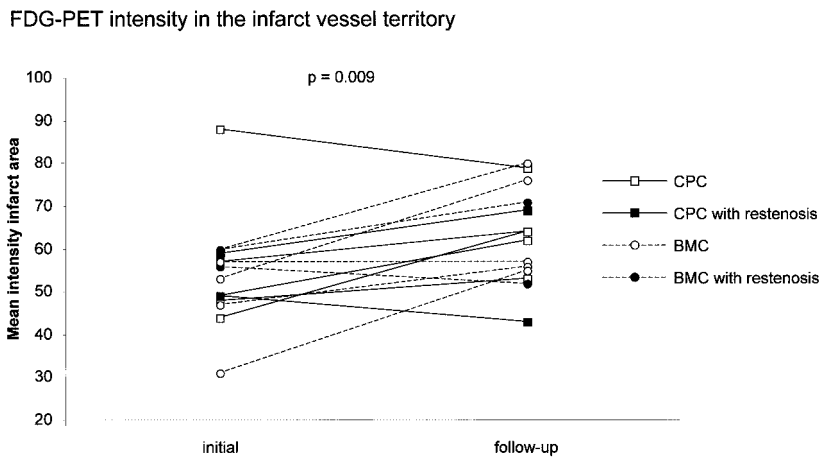

Figure 6. FDG-PET intensity in infarct vessel territory.

less invasive than bone marrow aspiration, we compared the effects of CPCs and BMCs. There is currently uncertainty as to which of the progenitor cell population is most potent to stimulate neovascularization and cardiac regeneration.[21-23] Therefore, we used the entire mononuclear cell population obtained from bone marrow aspiration, which is obviously not a pure progenitor cell population but contains hematopoietic progenitor cells ($\approx 7\times10^6$ CD34-positive cells out of the total number of 245×10^6 infused cells), mesenchymal stem cells, and stromal cells. Alternatively, we expanded circulating progenitor cells ex vivo, which predominantly revealed expression of endothelial marker proteins (see Figure 2) but may also contain contaminating other progenitor cell population(s). The results of our study demonstrate that neither improvement in contractile function nor enhancement of coronary flow reserve were different for the two progenitor cell preparations used in our patients.

Based on the observation that both bone marrow–derived as well as blood-derived CD34-positive progenitor cells enhance neovascularization in ischemic tissue,[4,5,24,25] it was suggested that the improvement in ventricular function after experimentally induced myocardial infarction is due to stimulated neoangiogenesis preventing late myocardial remodeling through enhanced myocardial blood flow, thereby limiting myocyte apoptosis and reducing collagen deposition and scar formation.[4,5] A recent study performed in patients with limb ischemia demonstrated that intramuscular injection into the gastrocnemius of progenitor cells derived from bone marrow essentially in an identical fashion as in the present study resulted in significant improvements in limb perfusion, suggesting that progenitor cells might indeed be suitable for achievement of therapeutic angiogenesis in humans.[26] Most recently, preliminary data also suggested improved myocardial perfusion after intracoronary administration of bone marrow–derived cells in patients after an AMI.[27] The complete normalization of coronary blood flow reserve at 4-month follow-up may suggest that an enhanced neovascularization may have also contributed to the improved LV function observed in the present study. In general, vessels supplying an area of myocardial infarction exhibit an impairment of coronary flow reserve compared with noninfarct reference vessels in the same patient.[28] Thus, the infusion of progenitor cells into the infarct artery may have enhanced neovascularization leading to a reduction in LV dilation and preservation of contractile performance through rescue of hibernating myocardium, reduction of myocardial fibrosis, and decreased apoptosis of hypertrophied myocytes in the peri-infarct region. Indeed, the significant decrease in LV end-systolic volumes 4 months after progenitor cell infusion may indicate a beneficial effect on postinfarction LV remodeling. In addition, Orlic and coworkers[3] reported that intramyocardial injection of bone marrow–derived progenitor cells led to regeneration of significant amounts of contracting myocardium, suggesting that locally delivered bone marrow cells can generate de novo myocardium, thereby ameliorating the outcome of myocardial infarction. Since recent data by our group also demonstrated that blood-derived CPCs retain the capability to transdifferentiate into functional cardiac myocytes (personal communication), we cannot exclude that the infusion of CPCs may also lead to regeneration of contracting myocardium after infarction.

Importantly, none of our patients had deterioration of regional wall motion abnormalities or end-systolic LV volume expansion after progenitor cell therapy. In addition, transplantation of progenitor cells did not induce an acute inflammatory response as measured by leukocyte blood count or C-reactive protein serum levels. Likewise, there were no measurable indications for an acute ischemic damage induced by the intracoronary infusion of progenitor cells. Thus, the ex vivo culture and expansion of blood-derived progenitor cells followed by intracoronary reinfusion appears to be safe for clinical application. Moreover, the results of the FDG-PET scans demonstrating increased viability of the infarct area at follow-up examination argues against the hypothetical concerns that transplantation of whole bone marrow–derived mononuclear cell populations may induce the propagation of noncardiac cells within the myocardium and enhance scar formation after myocardial infarction. Finally, none of our patients had malignant arrhythmias, which appears to be a major limitation of injecting skeletal myoblast-derived cells directly into the myocardium.[29] Previous experimental studies by our group and others have demonstrated that intravenously infused progenitor cells preferentially home to the peri-infarct border zone. In line with these observations, in the present study, we observed the most profound improvement in contractile function in the infarct border zone. Thus, transplantation of progenitor cells through intracoronary infusion into the infarct artery may result in homing to and incorporation into areas bordering the infarct zone, thereby avoiding the generation of "islands" of viable cells within the infarct scar region, which

results from directly injecting skeletal myoblast-derived cells into ischemic myocardium and may provide the substrate for electrical instability leading to malignant arrhythmia.

The major limitation of this pilot trial relates to the lack of a randomized control group, which did not receive intracoronary infusion of progenitor cells. It is well known that prompt reperfusion during AMI combined with state-of-the-art medical therapy including ACE inhibitors and β-blocking agents beneficially affects LV remodeling processes after AMI.[30] However, two recently published larger trials using stent implantation for reperfusion treatment strategy in patients with AMI[31,32] reported increases in LV ejection fraction after 6 months in the range of 3% to 4.1%. These numbers compare favorably with the 2.5% increase in LV ejection fraction observed in our reference group. However, these numbers are significantly less compared with the 9% improvement observed in the progenitor cell–treated patients of the present study. Likewise, the reduction in regional wall motion abnormalities as measured by SD/chords was significantly larger in the patients of the present study compared with the data reported from the CADILLAC trial.[31]

Taken together, the results of the present study suggest that intracoronary infusion of progenitor cells in patients with AMI is associated with significant beneficial effects on postinfarction LV remodeling processes, regional contractile function of the infarcted segment, and coronary blood flow reserve in the infarct artery. Further follow-up examination of the patients by echocardiography and FDG-PET imaging after 12 months will define whether the observed beneficial effects will be sustained also during later phases of LV remodeling. However, whether this novel form of regeneration enhancement therapy can improve the immediate and long-term clinical outcome of patients with AMI awaits the results of larger-scale randomized trials.

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