A Pilot Trial to Assess Potential Effects of Selective Intracoronary Bone Marrow–Derived Progenitor Cell Infusion in Patients With Nonischemic Dilated Cardiomyopathy: Final 1-Year Results of the Transplantation of Progenitor Cells and Functional Regeneration Enhancement Pilot Trial in Patients With Nonischemic Dilated Cardiomyopathy

Ulrich Fischer-Rasokat, Birgit Assmus, Florian H. Seeger, Jörg Honold, David Leistner, Stephan Fichtlscherer, Volker Schächinger, Torsten Tonn, Hans Martin, Stefanie Dimmeler and Andreas M. Zeiher

_Circ Heart Fail_. 2009;2:417-423; originally published online July 29, 2009; doi: 10.1161/CIRCHEARTFAILURE.109.855023

_Circulation: Heart Failure_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Copyright © 2009 American Heart Association, Inc. All rights reserved.

Print ISSN: 1941-3289. Online ISSN: 1941-3297

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circheartfailure.ahajournals.org/content/2/5/417

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation: Heart Failure_ 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: Heart Failure_ is online at:
http://circheartfailure.ahajournals.org/subscriptions/
A Pilot Trial to Assess Potential Effects of Selective Intracoronary Bone Marrow–Derived Progenitor Cell Infusion in Patients With Nonischemic Dilated Cardiomyopathy

Final 1-Year Results of the Transplantation of Progenitor Cells and Functional Regeneration Enhancement Pilot Trial in Patients With Nonischemic Dilated Cardiomyopathy

Ulrich Fischer-Rasokat, MD; Birgit Assmus, MD; Florian H. Seeger, MD; Jörg Honold, MD; David Leistner, MD; Stephan Fichtlscherer, MD; Volker Schächinger, MD; Torsten Tonn, MD; Hans Martin, MD; Stefanie Dimmel, PhD; Andreas M. Zeiher, MD

Background—Intracoronary administration of bone marrow–derived progenitor cells (BMC) was shown to improve coronary microvascular function in ischemic heart disease. Because coronary microvascular dysfunction is implicated in the pathogenesis and prognosis of nonischemic dilated cardiomyopathy (DCM), we investigated the effects of intracoronary BMC administration in patients with DCM.

Methods and Results—Intracoronary infusion of BMC was performed in 33 patients with DCM by using an over-the-wire balloon catheter. Left ventricular contractility at baseline and after 3 months was assessed by analysis of left ventricular angiograms. Coronary hemodynamics were determined by intracoronary Doppler wire measurements. After 3 months, regional wall motion of the target area (contractility from $-1.08\pm0.39$ to $-0.97\pm0.47$ SD/chord, $P=0.029$) and global left ventricular ejection fraction (from $30.2\pm10.9$ to $33.4\pm11.5\%$, $P<0.001$) were improved. Increase of regional contractile function was directly related to the functionality of the infused cells as measured by their colony-forming capacity. Minimal vascular resistance index was significantly reduced in the BMC-treated vessel after 3 months (from $1.53\pm0.63$ to $1.32\pm0.61$ mm Hg · s/cm; $P=0.002$, $n=24$), whereas no changes were observed in the reference vessel (from $1.60\pm0.45$ to $1.49\pm0.45$ mm Hg · s/cm; $P=0.133$, $n=13$). Twelve months after BMC infusion, N-terminal prohormone brain natriuretic peptide (NT-proBNP) serum levels were decreased, suggesting a beneficial effect on left ventricular remodeling processes (from $1610\pm993$ to $1473\pm1147$ pg/mL; $P=0.038$ for logNT-proBNP, $n=26$).

Conclusions—Intracoronary administration of BMC seems to be associated with improvements in cardiac contractile and microvascular function in patients with DCM. Thus, randomized blinded studies are warranted to evaluate potential clinical benefits of intracoronary BMC administration in patients with DCM. (Circ Heart Fail. 2009;2:417-423.)

Key Words: cardiomyopathy ■ cells ■ congestive heart failure ■ myocardial contraction ■ regional blood flow

Severely reduced coronary flow reserve (CFR) and impaired microvascular function have been demonstrated in patients with nonischemic dilated cardiomyopathy (DCM).1,2 The degree of coronary microvascular dysfunction has been shown to be an independent predictor of cardiac events, such as death or further progression of heart failure.3 Recent elegant experimental studies additionally provided convincing evidence for the crucial role of coordinated angiogenesis to prevent the progression from adaptive cardiac hypertrophy to heart failure in the absence of epicardial flow-limiting stenosis.4,5 In fact, inhibition of angiogenesis led to decreased capillary den-
light on the long-known and well-established association between coronary microvascular dysfunction and DCM in the absence of epicardial artery atherosclerosis (for review, see reference 7).

Clinically, therapeutic interventions to improve coronary microvascular dysfunction in the absence of epicardial artery flow-limiting stenoses are very limited.7 However, recent experimental and clinical studies indicated that either intracoronary or intramyocardial administration of bone marrow–derived progenitor cells (BMC) may contribute to increased neovascularization and stimulated angiogenesis in ischemic tissue.8–11 Moreover, 2 recent placebo-controlled clinical trials demonstrated that the administration of either blood- or BMC into the coronary artery supplying both acute as well as chronic myocardial infarction was associated with significant improvements in coronary microvascular function and vascular conductance capacity.12,13 However, it is unknown whether such a treatment strategy may also affect coronary vascular function in patients with DCM.

Therefore, we initiated the Transplantation of Progenitor Cells and Functional Regeneration Enhancement Pilot Trial in Patients with Nonischemic Dilated Cardiomyopathy (TOPCARE-DCM). The primary hypothesis to be tested was whether selective intracoronary infusion of BMC may be associated with measurable improvements in target area contractility in patients with global left ventricular (LV) hypokinesia in the absence of obstructive epicardial coronary artery disease.

Methods

Patients

Thirty-three patients with DCM were recruited in the study. Patients between 18 and 80 years of age were eligible for inclusion in the study, if global left ventricular ejection fraction (LVEF) was <40% and LV end-diastolic diameter was >60 mm, both determined by echocardiography. Moreover, patients had to be in a stable clinical condition within the last 6 months, with a fixed pharmacological therapy. Exclusion criteria were a history of myocardial infarction, a coronary intervention in the past, or a history of other severe chronic diseases or cancer. The ethics review board of the Goethe University in Frankfurt, Germany, approved the protocol; the trial was registered according to the German Drug Law and with clinicaltrials.gov number NCT00284713. The study was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from each patient.

Study Design

This prospective, open-label study consisted of an initial cell therapy and 2 follow-up visits scheduled after 3 and 12 months. Cardiac catheterization was performed initially and after 3 months. The primary end point of the study was the absolute change in regional LV wall motion of the target area as measured by quantitative angiography 3 months after cell administration. Secondary end points included quantitative variables relating to LVEF, LV volumes, CFR, and serum N-terminal prohormone brain natriuretic peptide (NT-proBNP) levels after 12 months.

Preparation of Progenitor Cells

Fifty milliliters of bone marrow aspirate was obtained under local anesthesia in the morning of the cell transplantation day. BMC were isolated by Ficoll density gradient centrifugation as reported previously.14 The number of infused BMC was 259 ± 135 × 10^6. The functional capacity of the infused BMC was determined by measuring their colony-forming unit capacity, as described previously.14

Catheterization Procedure for Progenitor Cell Transplantation

The target vessel used for subselective intracoronary BMC administration was the left anterior descending artery (LAD) in 21 patients and the left circumflex artery in 1 patient, where the LAD could not be selectively wired for advancing the infusion balloon. In additional 11 patients of the TOPCARE-DCM-extended protocol, both the LAD and the left circumflex artery were used for cell administration, each receiving 5 mL of the 10-mL cell suspension. Cells were infused using the stop-flow technique as described.15 After completion of intracoronary cell transplantation, coronary angiography was repeated to ascertain vessel patency and unimpeded flow of contrast material.

LV Angiography

LV angiograms in right and left anterior oblique projections were obtained at the time of the baseline procedure immediately before intracoronary BMC administration and at 3-month follow-up in identical radiographic projections. Quantitative analysis of paired LV angiograms in right anterior oblique projections was performed by the area-length method and by the centerline method with QCA-CMS software (version 6.0, Medis), as described elsewhere.15 The myocardial target region was defined as the LV circumference in right anterior oblique projection supplied by the coronary arteries used for BMC infusion to the distal end of the angiographically visible coronary artery territory. The extent of LV hypokinetic area was defined as percent circumference of hypokinetic chords (% circumference); the severity of LV hypokinesia was defined as the area under the curve given by chords with a contractility <1 SD (area under the curve), contractility of the target area was defined as the mean value of regional standard deviations per analyzed chords (SD/chord).

Magnetic Resonance Imaging

In a subgroup of 9 patients, who did not have implanted defibrillators or pacemakers and who consented to and tolerated the imaging procedure, cardiac MRI (a 1.5-T system; Magnetom Sonata, Siemens Medical Solutions) was performed at baseline and at 3-month follow-up. MRI sequences were analyzed by an experienced investigator as previously reported.16

Measurement of CFR

Paired recordings of Doppler-derived coronary blood flow (CBF) velocities in the target vessel (LAD in all patients) and in the reference vessel (left circumflex artery in 13 of the 24 patients having serial CBF measurements) with sufficient quality for quantitative analysis were obtained in 24 patients, both at baseline and at 3-month follow-up. CBF was assessed using an intracoronary Doppler wire as previously described.17 Basal average peak velocity (APV) was registered after administration of nitroglycerin, and CFR was assessed after induction of maximal blood flow by intracoronary infusion of 2.4 mg/min adenosine, similar to the protocol used by Cox et al.18 Three months after progenitor cell therapy, cardiac catheterization was repeated to measure CFR in both the target and the reference artery at identical sites as during the initial examination.

Parameters of Coronary Flow

Volumetric blood flow at baseline or hyperemic conditions was calculated as 0.125 × Pi × APV (basal or following adenosine infusion) × square of inner lumen diameter of the coronary artery.19 Lumen diameter immediately distal to the Doppler tip was determined by quantitative coronary angiography as previously described.15 Basal and minimal coronary vascular resistance indices were calculated as mean arterial pressure divided by APV measured by the Doppler wire at baseline and during adenosine-induced maximal coronary vasodilatation, respectively. CFR of the target vessel and the reference vessel was computed as the ratio of adenosine-induced APV and APV at baseline.15
**Evaluation of Safety and Feasibility**

Clinical, laboratory, and safety-related data were prospectively collected. Follow-up visits were performed after 3 months (mean time after initial cell therapy, 3.5 ± 1.5 months; median, 3 months) and after 12 months (12.8 ± 1.7 months; median, 12 months). Procedural complications were defined as any new-onset ventricular arrhythmia, visible thrombus formation, distal embolization, or injury of the coronary artery associated with the cell-infusion catheterization procedure. Twenty-four-hour Holter monitoring was performed for each patient at the 12-month follow-up visit. Three patients received a second cell therapy after the 3-month follow-up. However, because follow-up visits in our clinic were continued, safety data, adverse events, and NT-proBNP serum levels at the 12-month follow-up visit of these patients are included into this analysis.

**Measurement of NT-proBNP**

Blood for serum analysis was collected from each patient at the day of cell therapy and at 12-month follow-up, and the serum levels of NT-proBNP in picogram per milliliter were determined using a 1-step enzyme immunoassay (Elecsys 2010, Roche Diagnostics). NT-proBNP values showed a trend to decrease from 81 ± 42 mL/m² of body surface area (BSA) at baseline to 76 ± 38 mL/m² of BSA at 3-month follow-up (P = 0.050), whereas end-diastolic LV volumes remained unchanged (113 ± 45 mL/m² of BSA versus 109 ± 40 mL/m² of BSA; P = 0.288).

In the 9 patients with serial cardiac MRI suitable for quantitative analysis, MRI-derived LVEF increased from 32.3 ± 9.2% to 36.7 ± 9.7% (P = 0.011), end-systolic LV volumes showed a trend to decrease from 90 ± 53 mL/m² to 76 ± 50 mL/m² of BSA (P = 0.066), and end-diastolic LV volumes remained unchanged (127 ± 61 mL/m² at baseline versus 114 ± 56 mL/m² of BSA at follow-up; P = 0.110). Thus, MRI-derived LV functional analysis in a small subset

**Procedural Characteristics**

There were no procedure-related complications during intracoronary instrumentation and BMC administration. In 4 of the 33 patients (12%), troponin T levels increased from below detection limit (<0.01 ng/mL) to 0.02 in 2 patients and to 0.03 and 0.04 ng/mL, respectively, in 2 additional patients 24 hours after BMC administration. Two patients had slightly elevated troponin T levels of 0.02 and 0.07 ng/mL already at baseline before BMC administration. At 3-month angiographic follow-up, none of the patients demonstrated wall irregularities or stenosis at the site of the previous balloon inflation. There was no death, myocardial infarction, or stroke up to 1-year follow-up. Within the 1-year follow-up period, none of the patients revealed ventricular arrhythmias necessitating the implantation of an implantable cardioverter defibrillator, despite extensive 24-hour Holter monitoring.

**Effects of BMC Administration on Quantitative Parameters of LV Function**

Subselective administration of BMC was associated with significantly (P = 0.029) increased contractility of the LV area supplied by the coronary arteries used for BMC administration and, thus, targeted by potential therapeutic effects, as measured by improved wall motion from −1.08 ± 0.39 before cell administration to −0.97 ± 0.47 SD/chord at 3 months angiographically follow-up. In contrast, wall motion did not change in the nontargeted segments of the left ventricle (P = NS, for the chords of the nontargeted area). In parallel with the increase in target area regional wall motion, both the extent of LV hypokinesia (Figure 1A) and the severity of LV hypokinesia (Figure 1B) were significantly reduced. Overall, LVEF increased by an absolute 3.2 ± 4.1 percentage points (Figure 1C), whereas the increase relative to baseline LVEF was 12.8 ± 19.1% (P < 0.001). Patients with a history of active myocarditis (n = 4) did not differ in their changes in LVEF (from 25.5 ± 12.7 to 29.8 ± 15.4%; relative increase 15.4 ± 12.4%) compared with the entire study cohort.

End-systolic LV volumes demonstrated a nonsignificant trend to decrease from 81 ± 42 mL/m² of body surface area (BSA) at baseline to 76 ± 38 mL/m² of BSA at 3-month follow-up (P = 0.050), whereas end-diastolic LV volumes remained unchanged (113 ± 45 mL/m² of BSA versus 109 ± 40 mL/m² of BSA; P = 0.288).

In the 9 patients with serial cardiac MRI suitable for quantitative analysis, MRI-derived LVEF increased from 32.3 ± 9.2% to 36.7 ± 9.7% (P = 0.011), end-systolic LV volumes showed a trend to decrease from 90 ± 53 mL/m² to 76 ± 50 mL/m² of BSA (P = 0.066), and end-diastolic LV volumes remained unchanged (127 ± 61 mL/m² at baseline versus 114 ± 56 mL/m² of BSA at follow-up; P = 0.110). Thus, MRI-derived LV functional analysis in a small subset

**Table. Baseline Characteristics of the Patients**

<table>
<thead>
<tr>
<th>Demographic Characteristics</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>33</td>
</tr>
<tr>
<td>Age, y</td>
<td>56 ± 11</td>
</tr>
<tr>
<td>Female sex, n (%)</td>
<td>8 (24)</td>
</tr>
<tr>
<td>New York Heart Association class I/II/III, n (%)</td>
<td>4 (12)/22 (67)/7 (21)</td>
</tr>
<tr>
<td>Medical history</td>
<td></td>
</tr>
<tr>
<td>Time since first clinical manifestation of heart failure, mo; range (median)</td>
<td>8 to 453 (86)</td>
</tr>
<tr>
<td>Previous myocarditis (mo before cell treatment)</td>
<td>4 (36/70/104/173)</td>
</tr>
<tr>
<td>Pacemaker/implantable cardioverter</td>
<td>4 (12)/13 (39)</td>
</tr>
<tr>
<td>defibrillator, n (%)</td>
<td>32 (97)</td>
</tr>
<tr>
<td>Current medication</td>
<td></td>
</tr>
<tr>
<td>β-blocker, n (%)</td>
<td>32 (97)</td>
</tr>
<tr>
<td>Angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker, n (%)</td>
<td>31 (94)</td>
</tr>
<tr>
<td>Spironolactone, n (%)</td>
<td>26 (79)</td>
</tr>
<tr>
<td>Diuretics, n (%)</td>
<td>33 (100)</td>
</tr>
<tr>
<td>Digoxis, n (%)</td>
<td>21 (64)</td>
</tr>
</tbody>
</table>
of patients without pacemakers/defibrillators corroborated the data obtained by quantitative LV angiographic analysis.

Finally, as illustrated in Figure 2, there was a significant correlation between the number of hematopoietic colonies formed by the BMC used for administration and the absolute decrease in the extent of LV hypokinesia, suggesting a potential relation between the functionality of the infused cells (as measured by their colony-forming unit capacity) and the increase of regional contractile function 3 months after BMC administration. However, there was no correlation between colony-forming unit capacity and changes in global LV function, as measured by LVEF or the number of segments displaying hypokinesia.

Effect of BMC Administration on CBF Parameters
Paired serial assessments of CBF by intracoronary Doppler measurements in the BMC-infused coronary artery were suitable for quantitative analysis in 24 patients, both at baseline and at 3-month follow-up. The rate-pressure product (7942 ± 2238 versus 7481 ± 3550 mm Hg/min; P = 0.331) as well as the coronary artery luminal diameters of the target vessel (2.8 ± 0.7 versus 2.8 ± 0.7 mm; P = 0.864) did not differ between the initial measurement immediately before BMC administration and at 3-month follow-up. At 3-month follow-up, basal CBF in the BMC-treated vessel was unchanged (from 50 ± 20 to 53 ± 24 mL/min, P = 0.549). However, adenosine-induced maximal blood flow showed a trend to increase from 176 ± 84 mL/min before BMC administration to 204 ± 101 mL/min at 3-month follow-up (P = 0.063) in the BMC-treated vessel. Adenosine-induced minimal vascular resistance was significantly reduced in the BMC-treated vessel (1.53 ± 0.63 versus 1.32 ± 0.61 mm Hg · s/cm; P = 0.002, Figure 3). In contrast, in the 13 patients receiving BMC subselectively into the LAD, but not in the left circumflex artery, neither adenosine-induced maximal blood flow (176 ± 87 versus 176 ± 78 mL/min, P = 0.600) nor adenosine-induced minimal vascular resistance (1.60 ± 0.45 versus 1.49 ± 0.45 mm Hg · s/cm; P = 0.133) changed in the untreated reference vessel, whereas basal blood flow slightly, but not significantly, increased (40 ± 20 versus 49 ± 18 mL/min, P = 0.060). However, as illustrated in Figure 3, the individual changes in minimal vascular resistance indices from baseline to 3 months after progenitor cell therapy demonstrated a considerable variability. Moreover, there were no associations between baseline parameters or cell characteristics and changes in coronary hemodynamics. Similarly, changes in coronary hemodynamics did not correlate with changes in regional or global LV function parameters.

Effects of BMC Administration on NT-proBNP Serum Levels as an Objective Marker of Cardiac Function
Analysis of NT-proBNP serum levels 1 year after BMC administration could be performed in 26 patients. Three
patients presented with de novo atrial fibrillation or renal failure at 12-month follow-up, rendering NT-proBNP measurements meaningless, and 4 patients refused blood sampling at 12-month follow-up. NT-proBNP serum levels significantly decreased from $1610 \pm 2994$ before study inclusion to $1473 \pm 1147$ pg/mL ($P = 0.038$ versus baseline for logNT-proBNP) 12 months after progenitor cell administration. The decrease in NT-proBNP serum levels did not correlate with CBF changes or with cell characteristics.

**Discussion**

The results of the current study suggest that, in patients with DCM, the selective intracoronary administration of BMC into 1 of the 3 coronary arteries may be associated with a measurable improvement of regional wall motion of the LV segments targeted by intracoronary cell administration, which seems to translate into an improved global LV pump function at 3 months and an increased overall cardiac performance as measured by reduced NT-proBNP serum levels at 12 months after cell therapy. The improvement in regional contractile function seems to be directly correlated with the functional activity of the infused cells, as measured by their colony-forming capacity. Mechanistically, the administration of bone marrow–derived mononuclear cells seems to be associated with an improvement in maximal vascular conductance capacity of the coronary artery used for cell administration.

The results of this pilot study extend previous observations in patients with acute myocardial infarction$^{19}$ as well as chronic postinfarction heart failure secondary to healed myocardial infarction.$^{20,21}$ In these previous trials, the intracoronary administration of functionally competent BMC into the infarct-related artery was shown not only to increase LV contractile function$^{19–21}$ but also to improve coronary microvascular function$^{12}$ and maximal vascular conductance capacity of the target vessel.$^{12,13}$ A number of experimental studies have demonstrated that cellular therapeutics using various bone marrow- or blood-derived progenitor cells improve neovascularization in ischemic hindlimb or heart models in mice, rats, pigs, and dogs.$^{22–26}$ Mechanistically, transplanted progenitor cells secrete a variety of proangiogenic factors,$^{22,27,28}$ which might contribute to neovascularization and enhance endogenous cardiac repair through paracrine factors.$^{29,30}$ Thus, the neovascularization–mediating effects may not necessarily involve the direct differentiation of transplanted cells into endothelial cells, which is still controversially discussed in humans.$^{31}$ On the basis of convincing experimental evidence that stimulation of coronary microvascular dilator function and angiogenesis is capable to restore cardiac contractile function in models of nonischemic heart failure,$^{5,6}$ we hypothesized that the intracoronary administration of BMC may also improve LV function in patients with DCM, irrespective of potential, yet controversially discussed, effects on cardiomyocyte regeneration.

Mechanistically, the improvement in maximal vascular conductance capacity may have contributed to the increased regional contractile function of the LV segments targeted by intracoronary cell administration. Indeed, in a recent very elegant experimental study, Hare and coworkers$^{24}$ demonstrated that intramyocardial injection of mesenchymal stem cells led to a significant increase in tissue perfusion, which preceded improvements in regional and global LV function. These data suggest that an early effect on tissue perfusion represents an important feature of subsequent functional cardiac regeneration. Disease progression from preserved LV function to progressive impairment of systolic function, ventricular dilation, and overt heart failure has been demonstrated in patients with severely reduced microvascular dilator response.$^{32}$ The increase in vascular conductance capacity after BMC administration observed in the current study may mirror an increase of the cross-sectional area of the targeted vessel, suggesting neovascularization as one potential mechanism of BMC infusion. Thus, it is conceivable that improved microvascular perfusion may have contributed to the increase in cardiac performance in these patients with DCM. However, it should be noted that there was a considerable heterogeneity in individual CBF responses. Moreover, we could not detect any association between changes in coronary hemodynamics and changes in regional wall motion of the targeted LV segments. As disclosed by experimental studies, although sustained increases in tissue perfusion do not seem to be necessary for improved LV function after cell administration, increased blood flow seems to be a critically important feature of functional myocardial regeneration.$^{24}$ In fact, 8 weeks after injection of mesenchymal stem cells into a pig model of acute myocardial infarction, myocardial blood flow was similar in cell injected and control hearts, but both regional and global LV function had significantly improved only in the cell-injected hearts.$^{24}$ Because coronary flow dynamics and LV function were assessed in the current study at a single time point at 3 months after cell administration, it is possible that increases in CBF had not yet translated into the full extent of subsequent functional cardiac regeneration and, therefore, no association between the extent of contractile improvement and increased CBF could be observed. Indeed, the delayed significant reduction in NT-proBNP serum levels at 1 year follow-up observed in the current study suggests that LV remodeling processes continued to occur between 3 and 12 months after cell administration. Thus, additional studies at later time points are required to establish a potential association between changes in CBF and increases in contractile function.

**Limitations**

The most important limitation of this pilot trial is the lack of a randomized control group not receiving cell therapy. As such, we cannot exclude that potential confounders, such as better compliance to medication or more intense medical care, in our patients included in a clinical trial may have affected the results. Although the selective infusion of the cells into a single coronary artery using the noninfused coronary artery as an intrapatient reference vessel in 22 patients, of whom 13 had assessment of coronary flow dynamics, as well as regional analysis of LV function of the segments targeted by the coronary artery used for cell administration does allow for correlating potential effects on LV function with the cell distribution, we cannot exclude that global LV functional parameters and, most importantly, NT-proBNP serum levels as objective markers of global LV...
remodeling have been affected by confounding factors. In addition, we did not use the right coronary artery for cell administration primarily for safety reasons. Thus, we cannot comment on whether therapeutic effects would be increased, when all regions of the left ventricle receive cells. Finally, in the current study, we used the intracoronary route of cell administration. As such, any potential effect of cell therapy requires the extravasation of cells into the myocardial tissue. Previous studies have demonstrated acute cell retention rates in the heart as measured by indium-111 labeling and total body scanning ranging from 1% to 19% of the applied cells after intracoronary administration, with the highest values observed in patients with acute myocardial infarction and lowest values in patients with healed scar tissue >6 years after myocardial infarction.33 Because patients with DCM do not have acute ischemic myocardial injury, the cell retention rate in the current study is anticipated to be in the lower range between 1% and 5% of all applied cells. Given that previous studies have demonstrated significant increases in regional contractile LV function and perfusion by directly injecting bone marrow- or blood-derived progenitor cells into the myocardium,9–11,34,35 it will be important to address the question whether direct intramyocardial cell injection is superior to the intracoronary route of application, specifically in patients with nonischemic heart failure. Similarly, the association between cell functionality and the extent of increase in contractile function observed in the current study may not be relevant, when cells are directly injected into the myocardium. Clearly, any cohort of patients diagnosed with DCM will consist of a variety of different etiologies, including primary and secondary cardiomyopathies.7 Although we excluded patients with clinical and/or biopic evidence of acute myocarditis, there was a considerable heterogeneity in the response of individual patients. However, the number of investigated patients is too small to address any potential difference in the response to intracoronary cell administration with respect to the etiology of the cardiomyopathy.

In summary, the results of this pilot study in patients with DCM may indicate that the intracoronary administration of functionally competent BMC is associated with measurable improvements in contractile function of the targeted LV segments and with a modest reduction in NT-proBNP serum levels. On the basis of the excellent safety profile, the results of this pilot study provide the rationale to design a randomized blinded trial to evaluate potential clinical benefits of intracoronary BMC administration in patients with DCM.

Acknowledgments
We appreciate the enthusiastic support of the staff of our catheterization laboratories and Isabel Geweiker, Beatie Manitz, Heike Wagner, Marga Müller-Ardogan, Stephanie Estel, Tina Rasper, and Tino Röxe.

Sources of Funding
The study was supported by the Deutsche Forschungsgemeinschaft (FOR 501-1:WA146/2-1), the Foundation Leducq Transatlantic Network of Excellence for Cardiac Regeneration, the European Vascular Genomics Network (http://www.evgn.org; contract number LSHM-CT-2003-503254), and Alfred-Krupp-Stiftung (S.D.).

Disclosures
Dr Dimmeler reports being a member of the scientific advisory board of Guidant. Dr Zeiher reports having received consulting fees from Guidant. Drs Dimmeler and Zeiher report that they are cofounders of t2cure, a for-profit company focused on regenerative therapies for cardiovascular disease. They serve as scientific advisors and are shareholders.

References


22. Kinnaird T, Stahlle E, Burnett MS, Lee CW, Bar S, Fuchs S, Epstein SE. Marrow-derived stromal cells express genes encoding a broad spectrum of arteriogenic cytokines and promote in vivo and in vitro arteriogenesis through paracrine mechanisms. *Circ Res*. 2004;94:678–685.


**CLINICAL PERSPECTIVE**

The therapeutic options in patients with heart failure due to nonischemic dilated cardiomyopathy are limited. The current article reports the results of a pilot trial investigating potential effects of intracoronary administration of bone marrow–derived mononuclear cells on regional and global left ventricular function in patients with nonischemic dilated cardiomyopathy. Cell administration was associated with a measurable, but modest, improvement in cardiac contractile function and coronary microvascular function at 3 months. On the basis of the safety profile, the results of this pilot trial provide the rationale to design a randomized blinded trial to evaluate potential clinical benefits of intracoronary cell administration in patients with heart failure due to nonischemic dilated cardiomyopathy.