Procedural Safety and Predictors of Acute Outcome of Intracoronary Administration of Progenitor Cells in 775 Consecutive Procedures Performed for Acute Myocardial Infarction or Chronic Heart Failure

Salvatore De Rosa, MD, PhD; Florian H. Seeeger, MD; Jörg Honold, MD; Ulrich Fischer-Rasokat, MD; Ralf Lehmann, MD; Stephan Fichtlscherer, MD; Volker Schächinger, MD; Stefanie Dimmel, PhD; Andreas M. Zeiher, MD; Birgit Assmus, MD

Background—Cell-based therapies are a promising option in patients with acute myocardial infarction or chronic heart failure (CHF). However, administration of cells requires intracoronary or intracardiac instrumentation, which is potentially associated with periprocedural risks. Therefore, we analyzed periprocedural complications and 30-day outcome in 775 consecutive procedures of intracoronary administration of progenitor cells using the stop-flow technique.

Methods and Results—Indications for cell administration were acute myocardial infarction (n=126) and CHF of ischemic (n=562) or nonischemic (n=87) etiology. Vessel injury was observed in a total of 9 procedures (1.2%) and could be promptly managed by additional progenitor cell injection (PCI) in all but 1 case. No procedural deaths were observed. A periprocedural increase in troponin T was observed in 3.2% of the CHF procedures, in which no concomitant PCI was performed and troponin levels were not elevated before the procedure. Independent significant predictors of troponin T increase were higher New York Heart Association (NYHA) class (NYHA I versus NYHA IV; \( P = 0.01 \); NYHA I versus III; \( P = 0.19 \); NYHA I versus II; \( P = 0.55 \)), presence of elevated troponin T before the procedure (\( P < 0.01 \)), and peripheral occlusive disease (\( P = 0.04 \)). At 30 days, there were 4 deaths (0.5%), 1 stroke (0.13%), 8 acute myocardial infarctions (1%), and 5 hospitalizations for exacerbation of heart failure (0.64%).

Conclusions—Intracoronary infusion of progenitor cells can be performed with adequate safety in patients with acute myocardial infarction or CHF, because the safety profile was similar to what is usually expected from a coronary angiogram in the present cohort.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00962364, NCT00284713, and NCT00289822. (Circ Cardiovasc Interv. 2013;6:00-00.)

Key Words: outcome stem cells ■ procedural safety ■ stop-flow technique

Experimental studies have demonstrated that application of circulating or bone marrow–derived progenitor cells may improve neovascularization of ischemic tissue and reduce fibrosis in myocardial infarction (MI) models. Several randomized clinical trials tested the effects of intracoronary administration of bone marrow–derived mononuclear cells (BM-MNC) in patients with acute or chronic myocardial ischemia. Although not all trials report beneficial effects on left ventricular contractile function, recent meta-analyses of MI trials suggest a beneficial effect of intracoronary infusion of autologous BM-MNC on contractile recovery of left ventricular function.

However, intracoronary BM-MNC infusion requires intracoronary instrumentation, which might be associated with potential procedural risks. It is well-established that even in elective uncomplicated cardiac or coronary procedures, almost one-third of patients experience some increase in troponin and, if this increase is relevant, it was shown to be associated with increased rates of major adverse clinical events.

Given the ongoing debate on the potential clinical benefit of intracoronary BM-MNC administration, we assessed the procedural safety of intracoronary administration of progenitor cells with the stop-flow technique in 775 consecutive procedures performed at a single center.

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From the Division of Cardiology, Department of Medicine III, Goethe University Frankfurt, Germany (S.D.R., F.H.S., J.H., U.F.-R., R.L., S.F., A.M.Z., B.A.); Division of Cardiology, Klinikum Fulda, Germany (V.S.); and Institute for Cardiovascular Regeneration, Center of Molecular Medicine, Goethe University Frankfurt, Germany (S.D.).

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Correspondence to Andreas M. Zeiher, MD, Division of Cardiology, Department of Medicine III, Goethe University Frankfurt, Theodor Stern Kai 7-60590 Frankfurt, Germany. E-mail zeiher@em.uni-frankfurt.de

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WHAT IS KNOWN
- Cell-based therapies have demonstrated promising results after intracoronary administration in patients with acute or chronic ischemia.
- Intracoronary instrumentation is associated with a procedural risk of coronary injury.

WHAT THE STUDY ADDS
- Intracoronary administration of bone marrow-derived cells with the stop-flow technique is as safe as a coronary angiogram in patients with acute myocardial infarction or chronic heart failure.
- Specific care has to be taken when infusing cells via the stop-flow technique into coronary bypass grafts.

Methods

Patient Cohort
Between January 2001 and April 2010, a total of 775 consecutive procedures for intracoronary administration of progenitor cells with the stop-flow technique were performed at a single center, the Goethe University in Frankfurt, Germany.

Indications for cell administration were acute myocardial infarction (AMI: n=126) and chronic heart failure (CHF) of ischemic etiology (ICM: n=562) or CHF of nonischemic etiology (DCM: n=87), as reported in Table 1. The patients were recruited into the controlled clinical trials TOPCARE-AMI, TOPCARE-CHD, TOPCARE-DCM,11–13 and into an ongoing registry assessing the clinical effect of intracoronary infusion of BM-MNC in patients with AMI and CHF (www.clinicaltrials.gov numbers NCT00962364, NCT00284713, and NCT00289822). Patients receiving intracoronary treatment within ongoing randomized trials are not included in the current analysis.

Exclusion criteria were the presence of acutely decompensated heart failure with a New York Heart Association class of IV, a history of severe chronic diseases or cancer, or unwillingness to participate. The Ethics Review Board of the Goethe University in Frankfurt, Germany, approved the protocols, and written informed consent was obtained from all patients.

Preparation and Administration of Progenitor Cells
In 637 procedures, bone marrow aspirate (50 mL) was obtained from the iliac crest under local anesthesia during the morning of the cell administration day. BM-MNCs were isolated by density gradient centrifugation, as previously reported.11 Alternatively, in 138 patients, circulating progenitor cells were isolated from 300 mL peripheral blood by density gradient centrifugation.11 Before intracoronary administration, cell preparations were checked to fulfill the release criteria presented in Table 1.

Table 1. Baseline Characteristics of the Study Cohort

<table>
<thead>
<tr>
<th></th>
<th>AMI (n=126)</th>
<th>ICM (n=562)</th>
<th>DCM (n=87)</th>
<th>P* Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y; mean±SD</td>
<td>54±11</td>
<td>62±11</td>
<td>57±14</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sex, male/female; n</td>
<td>118/22</td>
<td>496/67</td>
<td>66/21</td>
<td>0.008</td>
</tr>
<tr>
<td>Heart rate, bpm; mean±SD</td>
<td>67±10</td>
<td>68±12</td>
<td>74±12</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systolic BP, mm Hg; mean±SD</td>
<td>102±21</td>
<td>116±24</td>
<td>111±21</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>26</td>
<td>32</td>
<td>18</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>58</td>
<td>70</td>
<td>54</td>
<td>0.001</td>
</tr>
<tr>
<td>Hypercholesterolemia, %</td>
<td>51</td>
<td>82</td>
<td>53</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Smoking, %</td>
<td>75</td>
<td>71</td>
<td>46</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Family history of CAD, %</td>
<td>42</td>
<td>51</td>
<td>49</td>
<td>0.161</td>
</tr>
<tr>
<td>PAOD, %</td>
<td>4</td>
<td>12</td>
<td>3</td>
<td>0.002</td>
</tr>
<tr>
<td>Time from last MI to study therapy, mean±SD (median)</td>
<td>3±1 d</td>
<td>92±90 (60) mo</td>
<td>NA</td>
<td>&lt;0.001†</td>
</tr>
<tr>
<td>Mitral regurgitation (c/moderate)</td>
<td>0%</td>
<td>8%</td>
<td>21%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Creatinine, mg/dL; median (IQR)</td>
<td>0.9 (0.8–1.0)</td>
<td>1.1 (0.9–1.1)</td>
<td>1.1 (1.0–1.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NT-proBNP, pg/mL; median (IQR)</td>
<td>748 (418–1244)</td>
<td>841 (360–2337)</td>
<td>1537 (808–3276)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Troponin T, ng/dL; median (IQR)</td>
<td>1.73 (0.82–3.06)</td>
<td>0.01 (0.01–0.01)</td>
<td>0.01 (0.01–0.01)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Antiplatelet therapy, %</td>
<td>100</td>
<td>95.3</td>
<td>81.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Oral Anticoagulant tx, %</td>
<td>6.5</td>
<td>33.5</td>
<td>57.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ACEI or ATRB, %</td>
<td>99.2</td>
<td>94.8</td>
<td>92</td>
<td>0.037</td>
</tr>
<tr>
<td>β-Blocker, %</td>
<td>98.4</td>
<td>93.4</td>
<td>94</td>
<td>0.091</td>
</tr>
<tr>
<td>Diuretic (any), %</td>
<td>41.9</td>
<td>85.1</td>
<td>93.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Statin, %</td>
<td>95.2</td>
<td>91.6</td>
<td>39.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Aldosterone antagonist, %</td>
<td>17.6</td>
<td>47.5</td>
<td>75.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pacemaker, %</td>
<td>0</td>
<td>9.8</td>
<td>10.3</td>
<td>0.001</td>
</tr>
<tr>
<td>ICD, %</td>
<td>2.4</td>
<td>26.9</td>
<td>48.3</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

ACEI indicates angiotensin converting-enzyme inhibitor; AMI, acute myocardial infarction; ATRB, angiotensin receptor antagonist; BP, blood pressure; CAD, coronary artery disease; DCM, chronic heart failure of nonischemic etiology; ICD, implantable cardioverter-defibrillator; ICM, chronic heart failure of ischemic etiology; IQR, interquartile range (25%–75%); NA, not available; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; and PAOD, peripheral arterial occlusive disease.

*Comparisons among the 3 groups were performed by means of 1-way ANOVA for normally distributed variables and by means of the Kruskal–Wallis test for non-normally distributed variables. For discrete variables, the Pearson χ² was calculated.

†Given the lack of the DCM group for this variable, a Mann–Whitney U test was used to compare between the 2 groups.
For intracorony cell administration, arterial puncture was followed by the administration of 5000 to 7500 IU heparin. An over-the-wire balloon catheter oversized by 0.5 mm was advanced into the proximal target vessel (Table 2). To allow for adhesion and potential transmigration of the infused cells, the stop-flow-technique was applied. In general, balloons were placed in already-stented segments, if present in the proximal part of the coronary artery, and placement within bifurcations was avoided for safety reasons. In patients with AMI, the balloon was always placed within the stent previously implanted during reperfusion therapy. In patients with ICM or DCM, balloons were, in general, inflated in the most proximal side branch-free segment of the coronary artery supplying the most dyskinetic left ventricular regions. When bypass grafts were used for cell administration, occluding balloons were positioned in the most proximal segment of arterial grafts, whereas special care was undertaken to avoid balloon inflations in severely diseased segments of degenerated venous grafts, and balloons were advanced into the native coronary artery supplied by the venous bypass graft, whenever possible. In patients experiencing severe angina during balloon occlusion for cell infusion, the occlusion was relieved prematurely. After completion of intracorony cell transplantation, coronary angiography was repeated to ascertain vessel patency and unimpeded flow of contrast material.

After the cell administration procedure, all patients received clopidogrel sulfate 75 mg/day for 4 weeks in addition to the ongoing therapy. However, triple therapy including acetyl salicylic acid, clopidogrel, and oral anticoagulation was avoided by interruption of anticoagulation therapy. However, triple therapy including acetyl salicylic acid, clopidogrel, and oral anticoagulation was avoided by interruption of anticoagulation therapy. According to our local ethics committee, patients experiencing severe angina during balloon occlusion for cell infusion, the occlusion was relieved prematurely. After completion of intracorony cell transplantation, coronary angiography was repeated to ascertain vessel patency and unimpeded flow of contrast material.

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Assessment of Procedural Complications and Short-term Follow-up

Procedural data were collected by study nurses during the procedure and reviewed by an independent interventional cardiologist. Troponin T levels were prospectively measured (enzyme-linked immunosorbent assay; Boehringer Mannheim) before and 24 hours after the cell administration procedure in the central laboratory of our hospital. For patients from the TOPCARE-AMI trial, serial assessment of creatine kinase (CK) and CK-MB isoform levels was performed. Therefore, for investigation of the total AMI cohort, we focused on serial assessment of CK-MB isoform levels.

Clinical data, medication, and laboratory data were prospectively collected by study nurses. Follow-up visits were scheduled at 14 days and at 3 to 4 months. All clinical events were adjudicated by means of reviewing medical records by the study physicians.

Statistical Analysis

Continuous variables are presented as mean (±SD), unless otherwise noted. Categorical variables were compared with the use of the χ2 test. One-way ANOVA testing was used for the comparison of approximately normal distributed variables. The Kruskal–Wallis test was used for comparisons across 3 groups for non-normally distributed variables.

Patients were categorized into 2 groups according to peri-procedural changes in troponin T serum levels (troponin T <0.02 ng/mL or ≥0.02 ng/mL). Univariate logistic regression analyses were conducted for studying factors being associated with elevated peri-procedural troponin T. Significant factors from univariate analyses were entered into a multivariate logistic regression model.

Statistical significance was assumed for P<0.05. All statistical analyses were performed with SPSS software (version 20.0, SPSS/IBM, Armonk, New York, NY).

Results

Cohort Characteristics

A total of 775 consecutive procedures for intracoronary cell administration were performed in AMI (n=126) patients (within 7 days after AMI) as well as in chronic ischemic (n=562) or nonischemic (n=87) heart failure. The baseline characteristics of the patients are summarized in Table 1. As expected, patients with AMI were significantly younger compared with the chronic ischemic heart failure patients. Likewise, patients with ischemic heart failure experienced more comorbidities, and cardiac function was profoundly reduced in patients with CHF, as evidenced by reduced left ventricular ejection fraction and increased levels of N-terminal pro-hormone of brain natriuretic peptide serum levels. All patients received optimal pharmacological treatment.

Of the total 775 procedures, in 638 (82.3%), cells were administered directly into a native coronary artery and in 107 (13.8%) procedures, cell administration was performed through a coronary bypass graft (Table 2; 47 arterial grafts and 60 venous grafts). Finally, in 28 procedures (3.6%) cells were injected into the vessel supplying collateral perfusion of the target area because of chronic occlusion of the vessel perfusing the target region. Target vessel for cell administration was the infarct related artery for all procedures performed for AMI (n=126), whereas for DCM (n=87) or ICM procedures (n=562) cells were administered as shown in Table 2. Mean total time for all 3 balloon occlusions for intracoronary cell application did not show any significant differences between the groups. The maximal pressure for balloon inflation was slightly, but significantly, higher in the AMI group, which most likely reflects the comfort of the operator in performing balloon occlusion within a stent. Elevated troponin T levels before cell administration were detected in 15.8% of the procedures in CHF.

Procedural Data

Bone marrow puncture, performed under local anesthesia, was well-tolerated. No complications, such as pronounced hematoma formation or bleeding at the bone marrow puncture site, were observed after the procedure. In 1 patient, a minor

<table>
<thead>
<tr>
<th>Table 2. Procedural Characteristics</th>
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<tbody>
<tr>
<td><strong>AMI</strong> (n=126)</td>
</tr>
<tr>
<td>Target vessel</td>
</tr>
<tr>
<td>LAD, %</td>
</tr>
<tr>
<td>LCX, %</td>
</tr>
<tr>
<td>RCA, %</td>
</tr>
<tr>
<td>Bypass, %</td>
</tr>
<tr>
<td>Collaterals, %</td>
</tr>
<tr>
<td>Total occlusion time, min; mean±SD</td>
</tr>
<tr>
<td>Max pressure for balloon dilation, mm Hg; mean±SD</td>
</tr>
<tr>
<td>Balloon inflation within a previously implanted stent, %</td>
</tr>
<tr>
<td>qLVEF, mean±SD; n=101/441/55</td>
</tr>
<tr>
<td>LVEDP, mm Hg; mean±SD</td>
</tr>
</tbody>
</table>

AMI indicates acute myocardial infarction; DCM, chronic heart failure of nonischemic etiology; ICM, chronic heart failure of ischemic etiology; LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; LVEDP, left ventricular end diastolic pressure; qLVEF, left ventricular ejection fraction evaluated by quantitative LV angiography; and RCA, right coronary artery.
transient lower extremity weakness in the nervus peroneus area was observed after generous subcutaneous 0.5% mepiva- 
vacaine infiltration.

Vascular access was the femoral artery for 719 procedures 
and the radial artery for 56 procedures. There were 2 major 
complications (0.2%) related to the access site. One patient
experienced upper thigh hematoma with retroperitoneal effu-
sion after puncture of the superficial right femoral artery, 
which was associated with relevant anemia requiring blood transfu-
sion. Bleeding was successfully stopped by prolonged manual 
compression and resolved without sequelae. Thrombotic 
occlusion of the right radial artery was observed in 1 patient 
several days after a radial access procedure. Successful vessel 
recanalization was performed by means of Fogarty thrombec-
tomy, and long-term patency of the radial artery was achieved.

Clinically indicated concomitant percutaneous coronary 
intervention (PCI) was performed during 152 (19.6%) proce-
dures, either as part of a staged procedure after treatment of 
the culprit lesion in the setting of AMI (19 procedures, 15% 
of AMI patients) or after angiographic evidence of a previ-
ously unknown flow-limiting stenosis in ICM patients (133 
procedures, 24% of ischemic CHF patients, including 12 cell 
application–related coronary complications). PCI of the ves-
sel targeted for cell infusion was performed in 113 (14.4%) 
patients, of whom 15 had lesions treated in nontarget vessels 
as well. In 40 (5.1%) procedures, isolated PCI on a nontar-
get vessel was indicated. Total procedural coronary compli-
cations are shown in Table 3. The 152 concomitant coronary 
revascularization procedures were complicated in 17 cases. In 
detail, the occlusion of a side branch (n=3; 2%) or presence of 
a nonflow-limiting dissection (n=9; 5.9%) could be success-
fully managed by stent implantation. In addition, we observed 
a transient no-reflow phenomenon within a complex PCI pro-
cedure (n=2; 1.3%) and coronary embolism (n=3; 2%), both 
resolving without further treatment. In 1 case of an extensive 
dissection of a severely diseased LAD, antegrade flow could 
not be re-established despite multiple stent implantations.

Intracoronary infusion of cells was associated with 
coronary complications in 11 of 755 procedures (1.9%), 
consisting of 2 flow-limiting dissections (0.3%) with occlu-
sion of either a main epicardial vessel or a side branch, 7 
nonflow-limiting dissections (0.9%), and 2 procedures with 
angiographic evidence of thrombus formation (0.3%; Table 4). 
Whereas the nonflow-limiting dissections and the side 
branch occlusion were all successfully treated by stent 
PCI, the small thrombus resolved without need for adjunctive 
treatment. However, 1 main epicardial vessel remained 
occluded because of extensive dissection, leading to a 
procedure-related non-ST-elevation myocardial infarction 
(NSTEMI). Of note, cell application into a bypass graft was 
associated with a greater procedural risk of 2.8% (3 compli-
cations in 107 grafts) compared with 1.8% (8 complications 
in 455 chronic procedures) when cells were infused into a 
native coronary artery of the ICM cohort (Table 4).

Importantly, all coronary complications were observed in 
patients with acute or chronic ischemic heart disease. No com-
pliation was observed in patients with DCM. No intraproce-
dural deaths occurred.

Relevant cardiac arrhythmias starting during the cell admin-
istration procedure were observed in a total of 5 procedures 
(0.7%). In 1 procedure, atrial flutter was detected before coro-
nary balloon occlusion for cell administration. Two procedures 
were complicated by ventricular fibrillation during ischemia 
induction by balloon occlusion, which was successfully

<table>
<thead>
<tr>
<th>Table 3. Total Procedural Complications (Cell Administration–Related and Concomitant PCI-Related)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMI (n=126)</td>
</tr>
<tr>
<td>Native Vessel (n=455)</td>
</tr>
<tr>
<td>Dissection (nonflow-limiting)</td>
</tr>
<tr>
<td>Main vessel occlusion</td>
</tr>
<tr>
<td>Side branch occlusion</td>
</tr>
<tr>
<td>Thrombus formation/ embolization</td>
</tr>
<tr>
<td>Arrhythmia</td>
</tr>
</tbody>
</table>

AMI indicates acute myocardial infarction; DCM, chronic heart failure of nonischemic etiology; ICM, chronic heart failure of ischemic etiology; and PCI, progenitor cell injection.

<table>
<thead>
<tr>
<th>Table 4. Procedural Complications Related to the Sole Cell Administration Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMI (n=126)</td>
</tr>
<tr>
<td>Native Vessel (n=455)</td>
</tr>
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<td>Dissection (nonflow-limiting)</td>
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<td>Thrombus formation/ embolization</td>
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<td>Arrhythmia</td>
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AMI indicates acute myocardial infarction; DCM, chronic heart failure of nonischemic etiology; and ICM, chronic heart failure of ischemic etiology.
Predictors and Prognostic Significance of Periprocedural Troponin T Elevation in Patients With CHF

Because of the challenge to define a clinically relevant increase in troponin T in patients with recent AMI, we focused on CK evaluation in this group, in which 118 of 126 paired measurements were available. Only in 2 (1.7%) of these patients was there a substantial (>3 × 99th percentile of upper reference limit) increase in CK, but it was without clinical symptoms or new ECG changes indicative of periprocedural MI.

Serial assessment of troponin T serum levels was available in 411 of 562 patients with CHF (63% of total CHF population). Patients with available serial troponin T levels did not significantly differ from those without. An increase of at least 0.02 ng/mL with respect to the value measured before the intracoronary cell administration procedure was observed in a total of 40 procedures. In 21 of these 40 procedures with any periprocedural troponin T increase, troponin T levels were already elevated before the procedure. Of the remaining 19 procedures associated with an increase in troponin T, concomitant coronary revascularization by stent PCI was performed in 10 procedures, whereas in 9 procedures the observed troponin T increase occurred primarily in response to the cell administration procedure (9 of 279 procedures in which no concomitant PCI was performed and for which serial troponin T values were available; Figure).

A periprocedural troponin T increase (≥0.02 ng/mL) was more frequently observed in patients who already presented with elevated troponin T levels before the procedure (32% versus 6%; P<0.001). In addition, left ventricular ejection fraction was significantly lower in procedures associated with periprocedural troponin T increases (31% ± 11% versus 38% ± 11%; P=0.001). Additional univariate predictors of a periprocedural troponin T increase after intracoronary cell administration in CHF were higher New York Heart Association class (median, 3 versus 2; P=0.001), presence of peripheral arterial occlusive disease (26% versus 8%; P=0.001), concomitant coronary intervention (24% versus 6%; P<0.001), and angiographic evidence of coronary artery injury during the procedure (43% versus 9%; P=0.023). Importantly, total duration of balloon occlusion for cell infusion or balloon inflation outside a stented segment were not associated with periprocedural troponin T increases. There was no association with the numbers of injected cells and troponin T increase (circulating progenitor cell: odds ratio, 1.03; P=0.56; BM-MNC: odds ratio, 0.99; P=0.43).

To identify those factors that are independently associated with a periprocedural troponin T increase ≥0.02 ng/mL, we performed a multivariable analysis by using a logistic regression model including univariate significant factors. The multivariable analysis demonstrates that higher New York Heart Association class, concomitant PCI and peripheral arterial occlusive disease, as well as presence of elevated troponin T levels before the procedure remain independently associated with periprocedural troponin T increase (Table 5). The results the patients without concomitant PCI are shown in Table 6, clearly indicating that on multivariable analysis the preprocedural elevation of troponin also was an independent factor being associated with a periprocedural troponin T increase, together with peripheral arterial occlusive disease and higher New York Heart Association class.

Short-Term Outcome at 30 Days

Short-term (30 days) follow-up was available for 771 of 775 procedures. Reason for absence of follow-up data were either unwillingness to be contacted (n=2) or inability to contact the patient after several attempts (n=2). Four deaths (0.5%) occurred within 30 days after the cell administration procedure. One death was observed during the hospital stay because of cardiac arrest after a complex concomitant coronary revascularization procedure including stent PCI of the left main
coronary artery, left anterior descending coronary artery, and right coronary artery. One death occurred after discharge from hospital because of rapidly progressing heart failure of ischemic etiology at 21 days after cell therapy. Another death was observed after a procedure performed in the AMI group, in which the patient experienced reinfarction of the target vessel used for cell administration, but also of a nontarget vessel, at days 3 and 5 after cell therapy, respectively, with subsequent cardiogenic shock and death at day 19 after the procedure. Finally, another death was observed after development of cardiogenic shock attributable to recurrent ventricular tachycardia with degeneration into ventricular fibrillation and several adequate implantable cardioverter-defibrillator shocks, after discharge from hospital at day 10 after intracoronary cell administration for CHF.

In addition, 1 stroke (0.1%) was observed 16 days after the cell administration procedure in a patient with ICM, known occlusion of the right internal carotid artery, and aortic valve stenosis. Moreover, 6 MIs occurred within 30 days (0.8%). In 5 of these 6 events, the culprit vessel of the repeat MI was the cell-treated artery. Of note, 2 of these events occurred in patients with AMI, and 4 events occurred in patients with ICM. In 2 of the 4 procedures in patients with repeat MI after cell therapy for ICM, a periprocedural coronary vascular injury was observed during cell therapy (n=1) or during concomitant PCI (n=1). Similarly, for the 2 procedures performed in the AMI group, periprocedural coronary vascular injury was observed during cell therapy (n=1) or during concomitant PCI (n=1).

Moreover, angiographic reevaluation of patients treated for nonischemic dilated cardiomyopathy did not reveal any luminal narrowing at the site of previous balloon inflation, and none of these patients required any revascularization procedure during further follow-up to 3 years. In patients with ischemic cardiomyopathy who did not require PCI of the target artery used for cell administration or another coronary artery at the time of cell therapy (n=429), a total of 15 patients (3.5%) required clinically indicated PCI of the vessel that had been used for cell application previously, and 15 patients (3.5%) required clinically indicated PCI of a nontarget vessel (not used for cell application) at 4-month follow-up.

Finally, after 5 procedures (0.6%), rehospitalization for heart failure occurred at 16±8 days after the cell administration procedure. Of note, 2 of these patients received cell therapy for AMI and 4 received cell therapy for ICM.

| Table 5. Multivariable Predictors of Periprocedural Troponin T Elevation: All CHF Procedures (n=411) |
|-------------------------------------------------|-------------------------------|------------------|
| OR (95% CI) | P Value |
| NYHA class I vs II | 0.64 (0.14–2.82) | 0.550 |
| NYHA class I vs III | 2.46 (0.65–9.31) | 0.186 |
| NYHA class I vs IV | 12.43 (1.75–88.50) | 0.012 |
| Coronary arterial injury | 0.22 (0.04–1.33) | 0.099 |
| Concomitant PCI | 0.24 (0.11–0.52) | <0.001 |
| Preprocedural troponin T elevation | 0.20 (0.09–0.45) | <0.001 |
| PAOD | 0.38 (0.15–0.94) | 0.035 |

CHF indicates coronary heart failure; CI, confidence interval; NYHA, New York Heart Association; OR, odds ratio; PAOD, peripheral arterial occlusive disease; and PCI, progenitor cell injection.

In 2 of the 4 procedures in patients with repeat MI after cell therapy for ICM, a periprocedural vascular injury was observed during cell therapy (n=1) or during PCI (n=1). Similarly, for the 2 procedures performed in the AMI group, periprocedural vascular injury was observed during cell therapy (n=1) or during PCI (n=1).

Moreover, angiographic reevaluation of patients treated for nonischemic dilated cardiomyopathy did not reveal any luminal narrowing at the site of previous balloon inflation, and none of these patients required any revascularization procedure during further follow-up to 3 years. In patients with ischemic cardiomyopathy who did not require PCI of the target artery used for cell administration or another coronary artery at the time of cell therapy (n=429), a total of 15 patients (3.5%) required clinically indicated PCI of the vessel that had been used for cell application previously, and 15 patients (3.5%) required clinically indicated PCI of a nontarget vessel (not used for cell application) at 4-month follow-up.

Finally, after 5 procedures (0.6%), rehospitalization for heart failure occurred at 16±8 days after the cell administration procedure. Of note, 2 of these patients received cell therapy for AMI and 4 received cell therapy for ICM.

Discussion

The present in-depth analysis evaluating the procedural safety of the stop-flow technique for intracoronary cell administration in a large patient population with AMI and CHF demonstrates that intracoronary cell application can be performed with adequate procedural safety. Thus, our analysis paves the way for further clinical evaluation of this promising strategy to interfere beneficially with adverse left ventricular remodeling processes to improve clinical outcome.

The safety of bone marrow aspiration in our patient cohort treated with ASS, thienopyridines, or anticoagulants is excellent, and is the same as reported for healthy volunteers during bone marrow cell donation.14

In our cohort, the overall complication rate of 1.1% for the sole intracoronary application of autologous BM-MNC or circulating progenitor cell compares favorably with complication rates reported for diagnostic coronary angiography. Moreover, no-reflow or slow-flow was only observed in 4 procedures, of which 3 were accompanied by concomitant PCI. However, cell application into a bypass graft was associated with a higher procedural risk for complications as compared with cell application into a native coronary vessel.

In the literature, procedural complications in the context of coronary procedures in diseased coronary arteries have been reported in 2% to 3% of cases.15,16 Thus, although a low-pressure balloon occlusion (inflation pressure 1–3 atm) for cell infusion is not comparable with balloon angioplasty and stent placement with higher inflation pressures, the total procedural complication rate observed in the present study appears to be rather low. Of note, Gloekler et al17 reported a procedural complication rate of 0.3% after diagnostic coronary balloon occlusion with low inflation pressures (1–3 atm) in subjects without angiographic evidence of coronary artery disease. We did not observe any procedural complication in patients with CHF of nonischemic etiology presenting with angiographically normal coronary arteries. Moreover, using the radial approach as the preferred choice of vascular access allows for intracoronary cell administration to be performed as an outpatient procedure.

In addition, the identical number of repeated revascularization procedures in the cell therapy target vessel and in the vessel not used for cell application argues against a disease acceleration process, but suggests instead that this may reflect disease progression independent from the cell application procedure. This is in line with our previous applications to improve clinical outcome.
report that intracoronary administration of progenitor cells is not associated with higher restenosis rates compared with a control group when quantitative angiographic analysis was applied.\textsuperscript{18}

A different safety aspect of intracoronary infusion of progenitor cells is related to the increase in troponin T serum levels, which was observed in 9 of 279 of the procedures performed in the setting of CHF without concomitant PCI or preprocedural troponin elevation (3.2%). Although it has been reported that 10 minutes of cardiac ischemia is sufficient to obtain measurable levels of troponin I in a porcine model,\textsuperscript{19} we do not think that the performed stop-flow procedure could be responsible for the observed elevation in troponin T. In the present study, a maximum of 3 minutes of vessel occlusion was performed, which was repeated 3 times to complete the cell administration. We could not identify any association between the maximal occlusion time and increases in troponin T. Likewise, there was no association between the number of the infused cells with subsequent troponin elevations.

Obviously, the results of the present study with respect to the very low rate of microvascular obstruction as assessed by slow-flow after cell administration are limited to bone marrow–derived or blood-derived mononuclear cells. In contrast, both mesenchymal stem cells\textsuperscript{20} as well as cardiosphere-derived cells require careful selection of the cell number to be infused into the coronary artery without causing microembolization.

Conclusions

The current single-center analysis demonstrates that intracoronary administration of progenitor cells with the stop-flow technique can be performed with adequate safety in patients with AMI as well as in patients with CHF. At least for patients with AMI, the previously reported safety data within the REPAIR-AMI trial, which were similar to the data reported in the present article, document that this conclusion also can be extended to the use of this technique in a multicenter fashion including 17 different centers.\textsuperscript{7}

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Disclosures

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References


Procedural Safety and Predictors of Acute Outcome of Intracoronary Administration of Progenitor Cells in 775 Consecutive Procedures Performed for Acute Myocardial Infarction or Chronic Heart Failure

Salvatore De Rosa, Florian H. Seeger, Jörg Honold, Ulrich Fischer-Rasokat, Ralf Lehmann, Stephan Fichtlscherer, Volker Schächinger, Stefanie Dimmeler, Andreas M. Zeiher and Birgit Assmus

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Supplemental Material

Supplemental methods

1. Details of cell preparation and release criteria (according to TOPCARE AMI and TOPCARE-CHD)

BM-MNC were isolated by density-gradient centrifugation, as previously reported in detail. Bone marrow aspirate was diluted 1:5 with NaCl 0.9% at room temperature (RT). After obtaining a sample for evaluation of culture sterility, mononuclear cells were isolated by density gradient centrifugation with Ficoll (15ml/30ml of undiluted bone marrow aspirate) at 800g for 20’ (with brake) at RT. After 2 washing steps, cells were filtered through a 100µm Filter and resuspended in 10 mL X vivo-10 medium (Biowhittaker) with 20% of autologous serum as a supplement. Thus, the resulting cell suspension consists of heterogeneous cell populations including hematopoietic progenitor cells, as determined by FACS analysis. A mean of 174.3 ± 110 * 10^6 cells were available for the intracoronary infusion procedure after processing.

Alternatively, in 138 patients, circulating mononuclear proangiogenic cells (CPC) were isolated from 300 ml peripheral blood by density gradient centrifugation and expanded in cell culture dishes 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 6.4x10^5 cells/mm² on 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 final cell preparation was concentrated into a 10 mL suspension and a total of 20.3 ± 14 * 10^6 cells were finally available for intracoronary administration.

Prior to intracoronary administration, the cell preparation was checked to fulfill the release criteria as shown below.
<table>
<thead>
<tr>
<th>Criterium</th>
<th>Standard</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serological Test</td>
<td>Negativity for following tests: HIV-1,2; HBsAg; anti-HCV; anti-Hbc; TPHA</td>
</tr>
<tr>
<td>Total number of cells</td>
<td>cell count ranging 50 - 500 x10^6</td>
</tr>
<tr>
<td>Low red blood cells (RBC) contamination</td>
<td>Haematocrite in cell suspension &lt; 2%</td>
</tr>
<tr>
<td>Cell viability</td>
<td>&gt; 80% viable cells (methods)</td>
</tr>
<tr>
<td>Sterility of cell’s suspension</td>
<td>Every step performed in a closed system</td>
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</tbody>
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