Improved regional function after autologous bone marrow-derived stem cell transfer in patients with acute myocardial infarction: a randomized, double-blind strain rate imaging study

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Aims
To investigate whether intracoronary transfer of bone marrow progenitor cells (BMPCs) early after reperfusion of an acute myocardial infarction improves regional myocardial function in a randomized double-blind, placebo-controlled strain rate imaging study.

Methods and results
Regional myocardial deformation was measured using velocity-derived strain rate imaging in 67 STEMI patients randomized 1:1 to intracoronary infusion of BMPC (n = 33) or placebo (n = 34). Myocardial segments were grouped into infarct (n = 232), border (n = 250), and remote (n = 526) based on MRI-delayed enhancement and the perfusion territory of the infarct-related vessel.

Four months after revascularization and progenitor cell/placebo transfer, regional myocardial deformation (rate) improved significantly more in the infarct segments of BMPC patients (treatment effect on end-systolic strain: −3.7 ± 1.0%, P = 0.0003; peak-systolic strain rate: −0.20 ± 0.07 s⁻¹, P = 0.0035). These findings were confirmed by a significantly greater improvement of longitudinal mitral valve ring displacement in the infarct walls of BMPC patients (treatment effect: 0.93 mm, P = 0.034).

Conclusion
Intracoronary infusion of BMPC early after reperfusion of a STEMI improves recuperation of regional myocardial function at 4 months’ follow-up. Quantitative assessment of regional systolic function might be more sensitive than global LV ejection fraction for the evaluation of BMPC therapy after STEMI.

Keywords
Stem cell therapy • Regional myocardial function • Strain rate imaging • Acute myocardial infarction
Introduction

Acute myocardial infarction is associated with loss of cardiomyocytes, scar formation, and impaired myocardial function. Despite early reperfusion of the affected myocardium, recuperation of myocardial function is often incomplete. Recently, progenitor cell transfer has been studied as a potential new strategy to enhance functional and structural recovery. Since the first experiments with bone marrow stem cells (BMPCs) in infarcted murine myocardium suggested an improved myocardial function, several experimental and early phase clinical studies have demonstrated the feasibility and safety of intracoronary infusion of autologous bone marrow stem cells in the infarct-related territory. These studies reported an improved ejection fraction and/or wall motion score index (WMSI), which were used as surrogate efficacy endpoints. However, by virtue of their non-randomized design or lack of a double-blind control group, the intrinsic benefit of progenitor cell transfer remains incompletely understood.

The first randomized, placebo-controlled and double-blind study published by our group failed to demonstrate a significant additional benefit on global ejection fraction (LVEF) after early infusion of bone marrow-derived stem cells in the infarct-related territory. Subsequent studies showed either a time-dependent benefit in global ejection fraction or no benefit at all. The reasons for those divergent results are multiple and include differences in cell preparation, imaging modalities, and timing of cell transfer. In addition, LVEF, the load-dependent index of global myocardial performance, may not be the best parameter to evaluate myocardial function recovery. WMSI was recently shown to be an equally powerful predictive factor for all-cause mortality after acute ST-elevation myocardial infarction when compared with LVEF. WMSI has been used before as an endpoint for myocardial function recovery in bone marrow progenitor cell (BMPC) transfer studies. However, the assessment of WMSI is semi-quantitative and operator-dependent. Regional function can be measured more accurately using strain rate imaging, a newer echocardiographic method based on the measurements of myocardial velocities. Strain rate is the velocity of deformation of a myocardial segment, whereas strain is the absolute amount of deformation during a specified time period.

The aim of this study was, therefore, to focus specifically on the effect of the intracoronary transfer of BMPCs on regional myocardial function assessed by ultrasound strain rate imaging.

Methods

Study design and cell transfer

The selection of patients, presenting with a first acute myocardial infarction, more than 2 h after the onset of symptoms, with cumulative ST-segment elevation of ≥6 mm, a successful reperfusion with stent implantation, and a documented significant LV dysfunction has been extensively reported before. Severity of LV dysfunction was documented using either angiography or echocardiography and was defined as involvement of at least three dysfunctional segments in the infarct territory. After informed consent, patients were randomized 1:1 to intracoronary infusion of BMPC or placebo (Control) by the Leuven Coordinating Centre in Clinical Trials, which also created a dedicated database for the independent collection of data from all different labs.

Bone marrow was harvested under local anaesthesia from the iliac crest in all patients within 24 h after the index PCI. BMPCs were isolated using Ficoll density gradient centrifugation and after two washing steps, prepared in a 10 mL suspension containing saline supplemented with 3% autologous serum. The cell suspension or placebo (NaCl 0.9% with 5% autologous serum) was infused in three fractions via an over-the-wire balloon catheter during stop flow conditions (3 min low pressure balloon inflation) 4–6 h after bone marrow harvest.

Standard echocardiography

Standard echocardiographic and myocardial velocity imaging (MVI) data were acquired in all patients at the day of randomization (after PCI and before stem cell injection) and 4 months later using a 2.5 MHz probe on a Vivid 7 ultrasound machine (GE Vingmed, Horten, Norway). The modified Simpson method was used for the determination of LV volumes and global LVEF. Mitral annular ring displacement, a measure of longitudinal ventricular function, was measured from the inferoseptal, anterolateral, inferior, and anterior walls. Conventional Doppler measurements of early and late diastolic transmitral flow, their ratio, the early filling deceleration time, isovolumetric relaxation time, and duration of late diastolic flow, and pulmonary venous curves were made to assess diastolic function. In addition, peak early filling myocardial velocities of the medial and lateral mitral annulus from the apical four-chamber view were acquired to calculate E/E’ for the estimation of LV end-diastolic filling pressures.

From the apical four-chamber view, long- and short-axis dimensions were used to calculate an index of sphericity (LV long-axis length divided by LV short-axis diameter). This parameter allows evaluating global LV geometry, with a decreased sphericity index suggesting a more unfavourable remodelling for the same end-diastolic volume.

To account for differences in afterload, systemic blood pressures were recorded by sphygmomanometry at the start of every ultrasound examination.

Strain rate imaging

MVI data, superimposed on a 2D grey-scale image, were recorded from apical long-axis, two- and four-chamber views. Narrow sector angles were used to obtain a high frame rate (>150 fps). The pulse repetition frequency was adjusted to optimize velocity resolution while avoiding aliasing. Since Doppler velocity measurements are angle-dependent, the individual myocardial walls were aligned with the ultrasound beam. Three consecutive heart cycles were digitally stored in a cine-loop format and transferred to a personal computer with custom-made software (Speqle 4.06, University of Leuven, Belgium) for off-line calculation of peak systolic strain rate and end-systolic strain (Figure 1). This methodology was described before with a relatively low intra- and interobserver variability (11.8–14.4%).

The longitudinal deformation data acquired by ultrasound from 18 myocardial segments were recalculated into 16 segments by averaging the results of the apical anteroseptal and inferoseptal into an apical septal segment and of the anterolateral and inferolateral segment into an apical lateral. This was to be in accordance with the 17-segment consensus model (note: no ultrasound information can be obtained on segment 17, which is the apical cap). A bull’s eye representation of end-systolic longitudinal shortening (or peak-systolic shortening rate) allowed a fast and objective assessment of the location, severity, and extent of regional dysfunction after the infarct and during follow-up (Figure 2).
**Figure 1** Strain rate (upper panel) and strain (lower panel) curves from the basal, mid, and apical segments of an inferoseptal wall at baseline (left) and 4 months’ follow-up (right) in a patient with an anterior infarct. Note that the apical peak-systolic strain rate is close to zero and the positive apical systolic strain curve (arrow) shows that this segment is lengthening during systole. At 4 months’ follow-up, strain rate and strain in the apical segment (arrow) are within normal limits (AVO, aortic valve opening; AVC, aortic valve closure; MVO, mitral valve opening).

**Figure 2** Bull’s eye representation of left ventricular end-systolic strain in a patient with an inferior infarction at baseline and at 4 months’ follow-up. Colour scale represents the percentage of deformation. Negative values (yellow to red colours) indicate shortening, positive values (blue) indicate end-systolic lengthening. Longitudinal function at baseline is severely decreased in the basal inferoseptal, inferior, inferolateral, and mid-inferior segments. After 4 months regional systolic deformation normalized in all segments except for the basal inferior segment (inf, inferior; sept, septum; ant, anterior; lat, lateral).
Magnetic resonance imaging

Cardiac MRI (1.5 T, Intera, Philips, Best, the Netherlands) was performed at day 4 (range 3–5) after the index event. Data were acquired with cardiac-dedicated surface coils and electrocardiographic triggering, and were analysed on an off-line workstation (View Forum, Philips Electronics). MRI late enhancement (LE) images were acquired 10–20 min after the injection of 0.15 mmol/kg gadopentetate dimeglumine with an inversion-recovery gradient-echo sequence from the cardiac short axis, vertical, and horizontal long axis. In the cardiac short-axis direction, the left ventricle was encompassed by contiguous 8 mm thick slices. The transmural extent of LE was visually classified as 0–25%, 26–50%, 51–75%, and 76–100%13 and allocated to the 17-segment model.12

Myocardial segments were divided into three groups according to the results of LE and the individual perfusion territories of the infarct-related arteries (IRAs):13 infarct zone (75–100% LE), border zone (71–74% LE and remaining segments from the perfusion territory of the IRA without LE), or remote myocardium (0% LE, segments not belonging to perfusion territory of IRA).

Statistical analysis

Continuous variables are presented as mean ± SD. All analyses were done using SAS version 8.02. An analysis of covariance (ANCOVA) was used to assess differences between the treatment groups at 4 months, adjusted for baseline values. The ANCOVA included the variable at 4 months as dependent variable and the associated baseline values, and a factor for treatment as covariates. For regional function recovery, we assessed the association between infarct transmurality and treatment with the probability of improved end-systolic strain/peak systolic strain rate in abnormal segments by means of repeated measures ANOVA. The model was adjusted for baseline values and included factors for randomized treatment, region, and the interaction between the two. To account for the correlation between segments (multiple segments per patient used in the analysis), a spatial covariance structure was used assuming an exponential decay with Euclidian distance between segments. All tests were two-sided and assessed at the 5% significance level.

This study was approved by the ethical committee of the University Hospital Gasthuisberg, Leuven, and is registered with clinicaltrials.gov, number NCT00264316.

Results

Patient characteristics and cell transfer

From 67 randomized patients, 33 received BMPC and 34 received placebo. One patient from the BMPC group died from hemorrhagic shock after an intra-abdominal bleeding caused by excessive oral anticoagulation therapy. A total of 66 patients completed the 4-months’ follow-up. Table 1 summarizes the baseline characteristics of the patients included in the study. Overall baseline characteristics were well matched between the groups, although a history of hypertension was more frequent in control patients (14/34 compared to 6/33 BMPC patients). Importantly, blood pressure at admission was similar in both groups. In patients randomized to BMPC, a mixed population of 304 ± 128 x 10^6 nucleated and 172 ± 72 x 10^6 mononuclear cells was reconstituted, phenotypically analysed and infused using an intracoronary delivery catheter as described.6

Standard echocardiography

Left ventricular volume and ejection fraction measured using the modified Simpson’s method increased over time in BMPC and control, but without evidence of a significant treatment effect (Table 2, Figure 3). Similarly, diastolic function variables were not different between BMPC and control patients (Table 2). In contrast, 4 months after the index event, recuperation of mitral valve ring subluxation was more frequent in control patients (14/34 compared to 6/33 BMPC patients). Importantly, blood pressure at admission was similar in both groups.

Table 1 Baseline patient characteristics (n = 67)

<table>
<thead>
<tr>
<th></th>
<th>Control (n = 34)</th>
<th>BMPC (n = 33)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>58 ± 10</td>
<td>55 ± 11</td>
<td>0.17</td>
</tr>
<tr>
<td>Male sex, n</td>
<td>28</td>
<td>27</td>
<td>1.00</td>
</tr>
<tr>
<td>BMI (kg/m^2)</td>
<td>26.8 ± 3.2</td>
<td>26.1 ± 4.1</td>
<td>0.43</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>136 ± 20</td>
<td>134 ± 24</td>
<td>0.67</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>79 ± 14</td>
<td>80 ± 18</td>
<td>0.73</td>
</tr>
<tr>
<td>Infarct-related artery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LCA, n</td>
<td>21 (62)</td>
<td>21 (64)</td>
<td>1.00</td>
</tr>
<tr>
<td>RCA, n</td>
<td>13 (38)</td>
<td>12 (36)</td>
<td>1.00</td>
</tr>
<tr>
<td>Time to PCI, h (median, IQR)</td>
<td>4.1 (3.1–8.3)</td>
<td>3.7 (2.5–7.6)</td>
<td>0.18</td>
</tr>
<tr>
<td>LV ejection fraction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angiography (%)</td>
<td>55 ± 11.6</td>
<td>56 ± 11.8</td>
<td>0.73</td>
</tr>
<tr>
<td>TTE (%)</td>
<td>53 ± 7.8</td>
<td>56 ± 7.1</td>
<td>0.10</td>
</tr>
<tr>
<td>Maximum CK (U/L)</td>
<td>2344 ± 1464</td>
<td>2255 ± 1336</td>
<td>0.82</td>
</tr>
<tr>
<td>Maximum CK-MB (U/L)</td>
<td>198 ± 132</td>
<td>202 ± 115</td>
<td>0.92</td>
</tr>
<tr>
<td>Maximum Troponin I (µg/L)</td>
<td>88 ± 61</td>
<td>79 ± 52</td>
<td>0.63</td>
</tr>
</tbody>
</table>

Values are n (%) or mean ± SD, unless otherwise indicated.

BMI, body-mass index; LCA, left coronary artery; RCA, right coronary artery; TTE, transthoracic echocardiography; CK, serum creatine kinase; CK-MB, cardiac specific isoenzyme.
### Table 2 Standard echocardiography data at baseline and 4 months' follow-up

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>BMPC (n = 32)</th>
<th>4 months</th>
<th>BMPC (n = 32)</th>
<th>Difference</th>
<th>P Treatment effect</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control (n = 34)</td>
<td>Control (n = 34)</td>
<td>Control (n = 34)</td>
<td>BMPC (n = 32)</td>
<td>BMPC (n = 32)</td>
<td>BMPC (n = 32)</td>
</tr>
<tr>
<td>Global LVEF (%)</td>
<td>53.0 ± 7.8</td>
<td>55.7 ± 7.1</td>
<td>57.8 ± 7.4</td>
<td>59.2 ± 7.9</td>
<td>5.0 ± 5.6</td>
<td>3.5 ± 8.3</td>
</tr>
<tr>
<td>LVEDV (mL)</td>
<td>113 ± 26</td>
<td>112 ± 29</td>
<td>138 ± 33</td>
<td>131 ± 39</td>
<td>26 ± 28</td>
<td>20 ± 27</td>
</tr>
<tr>
<td>LVESV (mL)</td>
<td>53 ± 17</td>
<td>50 ± 15</td>
<td>60 ± 20</td>
<td>54 ± 22</td>
<td>7 ± 17</td>
<td>4 ± 19</td>
</tr>
<tr>
<td>Ring displacement (mm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infarct walls (n = 128)*</td>
<td>9.9 ± 3.1</td>
<td>10.6 ± 3.2</td>
<td>12.0 ± 3.0</td>
<td>13.3 ± 2.9</td>
<td>2.0 ± 3.1</td>
<td>2.7 ± 2.5</td>
</tr>
<tr>
<td>Remote walls (n = 124)*</td>
<td>11.5 ± 3.1</td>
<td>12.1 ± 3.4</td>
<td>13.1 ± 3.4</td>
<td>14.4 ± 3.2</td>
<td>1.7 ± 2.5</td>
<td>2.3 ± 3.1</td>
</tr>
<tr>
<td>E (m/s)</td>
<td>0.62 ± 0.13</td>
<td>0.64 ± 0.15</td>
<td>0.72 ± 0.15</td>
<td>0.72 ± 0.15</td>
<td>0.09 ± 0.15</td>
<td>0.07 ± 0.17</td>
</tr>
<tr>
<td>A (m/s)</td>
<td>0.65 ± 0.14</td>
<td>0.62 ± 0.12</td>
<td>0.66 ± 0.17</td>
<td>0.61 ± 0.13</td>
<td>0.01 ± 0.17</td>
<td>0.01 ± 0.08</td>
</tr>
<tr>
<td>Dt (ms)</td>
<td>166 ± 43</td>
<td>163 ± 41</td>
<td>206 ± 41</td>
<td>195 ± 36</td>
<td>39 ± 42</td>
<td>32 ± 54</td>
</tr>
<tr>
<td>Duration A (ms)</td>
<td>128 ± 17</td>
<td>125 ± 16</td>
<td>135 ± 19</td>
<td>137 ± 23</td>
<td>7 ± 19</td>
<td>12 ± 24</td>
</tr>
<tr>
<td>IVRT (ms)</td>
<td>114 ± 17</td>
<td>107 ± 20</td>
<td>114 ± 13</td>
<td>112 ± 16</td>
<td>0 ± 18</td>
<td>5 ± 18</td>
</tr>
<tr>
<td>PV S (m/s)</td>
<td>0.57 ± 0.15</td>
<td>0.54 ± 0.13</td>
<td>0.64 ± 0.14</td>
<td>0.65 ± 0.13</td>
<td>0.06 ± 0.16</td>
<td>0.10 ± 0.14</td>
</tr>
<tr>
<td>PV D (m/s)</td>
<td>0.43 ± 0.12</td>
<td>0.40 ± 0.12</td>
<td>0.51 ± 0.14</td>
<td>0.50 ± 0.11</td>
<td>0.08 ± 0.12</td>
<td>0.10 ± 0.14</td>
</tr>
<tr>
<td>PV R (m/s)</td>
<td>0.28 ± 0.05</td>
<td>0.28 ± 0.05</td>
<td>0.30 ± 0.08</td>
<td>0.28 ± 0.04</td>
<td>0.00 ± 0.06</td>
<td>0.01 ± 0.07</td>
</tr>
<tr>
<td>Duration PV R (ms)</td>
<td>132 ± 14</td>
<td>127 ± 18</td>
<td>142 ± 23</td>
<td>138 ± 23</td>
<td>12 ± 24</td>
<td>9 ± 22</td>
</tr>
<tr>
<td>E' (m/s)</td>
<td>0.052 ± 0.012</td>
<td>0.062 ± 0.022</td>
<td>0.059 ± 0.017</td>
<td>0.067 ± 0.017</td>
<td>0.0062 ± 0.015</td>
<td>0.0063 ± 0.015</td>
</tr>
<tr>
<td>E/E'</td>
<td>12.6 ± 3.9</td>
<td>11.1 ± 3.4</td>
<td>13.3 ± 5.5</td>
<td>11.0 ± 2.7</td>
<td>0.7 ± 4.1</td>
<td>−0.3 ± 3.8</td>
</tr>
<tr>
<td>Sphericity index</td>
<td>1.72 ± 0.19</td>
<td>1.71 ± 0.23</td>
<td>1.60 ± 0.22</td>
<td>1.68 ± 0.26</td>
<td>−0.12 ± 0.24</td>
<td>−0.03 ± 0.24</td>
</tr>
</tbody>
</table>

Values are mean ± SD.
LVEF, left ventricular ejection fraction; LVEDV, end-diastolic volume; LVESV, end-systolic volume; E, left ventricular early diastolic filling; A, late diastolic filling; Dt, early filling deceleration time; IVRT, isovolumetric relaxation time; PV S, systolic component pulmonary vein flow; PV D, diastolic component; PV R, atrial reversal pulmonary vein flow; E', early filling septal ring velocity.

*Based on the presence of MRI late enhancement (in 63 patients).
displacement in the infarcted walls (defined by the presence of at least one segment of LE, \( n = 128 \)) was significantly higher in patients treated with BMPC (treatment effect \( 0.93 \pm 0.43 \) mm, \( P = 0.034 \), Figure 4). Recuperation of mitral valve ring displacement in the BMPC-treated group was less prominent in remote regions (defined by the absence of LE, \( n = 124 \), treatment effect \( 0.87 \pm 0.46 \) mm, \( P = 0.063 \), Table 2).

### Strain rate imaging

Ultrasound strain rate imaging data from 66 patients was obtained at baseline and at 4 months’ follow-up. Since baseline MRI-delayed enhancement data were available from 63 patients (two claustrophobia and one cochlear implant), and segments were matched between ultrasound and MRI using the consensus model, a total of 1008 (63 \( \times \) 16) segments were included in the analysis.

At baseline, end-systolic strain and peak-systolic strain rate differed significantly between infarct (\( n = 232 \)), border zone (\( n = 250 \)), and remote segments (\( n = 526 \)), irrespective of treatment assignment. After 4 months, end-systolic strain in the segments with a transmural infarct improved significantly more in the BMPC than in the control groups (\( -8.2 \pm 7.2 \) vs. \( -4.7 \pm 8.3 \% \), treatment effect \( -3.7 \pm 1.0 \% \), \( P = 0.0003 \), Figure 5). Consistently with this observation, peak-systolic strain rate also improved significantly more in the transmural infarct segments 4 months after BMPC infusion (\( -0.32 \pm 0.82 \) vs. \( -0.22 \pm 0.78 \) s\(^{-1} \), treatment effect \( -0.10 \pm 0.07 \) s\(^{-1} \), \( P = 0.0035 \)).
In this study, strain rate imaging allowed us to quantify the extent of regional dysfunction early after PCI and before cell/placebo transfer and to evaluate functional recovery over time in BMPC and control patients. We observed that regional deformation improved significantly more in infarcted segments after BMPC transfer. This improved regional deformation can be the result of a change in three factors: improved intrinsic myocardial function, a decrease in loading (volume or pressure), and/or an increase in elasticity.

Intrinsic myocardial function

The mechanisms of action and homing of BMPC infused into infarcted myocardium remain unclear: transdifferentiation into cardiomyocytes, cell fusion, neovascularisation, and paracrine effects have all been proposed.

Transdifferentiation of BMPC into mature cardiomyocytes that are fully (electrically and mechanically) coupled with residual viable myocardium would improve intrinsic myocardial function. Although suggested in earlier experimental studies,\(^2\) it was refuted in subsequent reports,\(^{18,19}\) and is unlikely present in the clinical setting.

Cell fusion of BMPC with existing cardiomyocytes could prevent apoptotic cell death and increase intrinsic myocardial function,\(^{19}\) but this mechanism has not yet been identified in humans.\(^{20}\)

Capillary density in infarcted territory was increased after transendocardial injection of BMPC.\(^{21}\) Moreover, mobilization of endothelial progenitor cells and BMPC could stimulate neovascularization in response to tissue ischaemia.\(^{22,23}\) Interestingly, invasive flow measurements suggested an improved microcirculation after intracoronary progenitor cell transfer in AMI.\(^{24}\) In our blinded randomized study, we did not see a supplemental increase in segmental blood flow using \(^{11}\)C-acetate PET after BMPC in the infarct or peri-infarct territory. In contrast, we observed in this territory a significant increase in metabolism in patients suffering from large (>20% of LV mass by MRI LE) infarcts after BMPC.\(^6\) Possibly, small inaccuracies in segmentation or insufficient sensitivity of \(^{11}\)C-acetate PET to detect subtle but relevant changes in regional myocardial blood flow may account for these varying clinical results.

Paracrine effects (protection against apoptotic cell death, stimulation of angiogenesis, and recruitment of cardiac specific progenitor cells) might indirectly improve intrinsic myocardial function.
This is supported by the observation that only a small fraction (1.3–2.6%) of infused unselected BMPC remain in the infarct territory. To what extent cardiac specific progenitor cells can mediate such repair in the remote, peri-infarct, and infarct zone of an acute myocardial infarct remains to be determined.

**Improved myocardial deformation and loading conditions**

As regional deformation parameters are load dependent, a decrease of loading could contribute to improved regional deformation after BMPC therapy. At baseline, blood pressures were similar in both groups. However, 4 months after the index event, patients treated with BMPC had a lower systolic blood pressure compared to controls, although all patients were receiving similar state-of-the-art post-infarction medical treatment. The reason for this and its impact on the improvement of regional function in patients treated with BMPC remain unclear and warrant future studies. LVED volumes and sphericity indices were similar in both groups before and after cell transfer, suggesting a similar preload.

**Improved myocardial deformation and elasticity**

Increased influx of activated white blood cells and macrophages or a better preservation of microvascular flow might enhance infarct healing and resolution of tissue oedema after infusion of BMPC. A recent study in rats showed that the injection of human mesenchymal stem cells in an infarct area reduced fibrosis and increased myocardial compliance. Interestingly, the significant reduction in infarct size, a secondary endpoint of our study, might decrease myocardial stiffness and result in an increased elasticity. The net result could be an improvement in regional myocardial deformation for the same intrinsic myocardial function.

**Global function**

In contrast, MRI measurements of global LVEF failed to demonstrate a significant improvement of global myocardial function beyond that obtained by current state-of-the-art therapy of acute myocardial infarction. Combination of early mechanical reperfusion, adjunctive medical therapy, stringent secondary prevention, and early cardiac rehabilitation improves mortality and morbidity after acute myocardial infarction. However, Ottervanger et al. demonstrated in study of 600 patients that the mean absolute increase in ejection fraction 6 months after mechanical reperfusion of an acute myocardial infarct reached only 2.5% (from 43.7 ± 11.3 to 46.3 ± 11.5%, P < 0.01), which is similar to the values observed in our control population, measured by MRI. Because measurement of global ejection fraction by any technique is associated with a considerable inter- and intra-observer variability (5–10% for MRI), larger trials may be necessary to demonstrate a possible benefit of intracoronary cell transfer on LVEF. Of note, two larger randomized trials recently published, applied BMPC considerably later after the infarct (3–8 days) and demonstrated either no improvement in ejection fraction as assessed with MRI at 6 months (ASTAMI, 100 patients) or a significant 2.5% increase as assessed with LV angiography at 4 months (repair-AMI, 204 patients).

**Limitations**

Distribution of segments into infarct, border, and remote was based on MRI-delayed enhancement and the individual coronary anatomy. It is known that up to two-thirds of dysfunctional segments after myocardial infarction might reflect stunned, hibernating, or partial thickness infarction. The current segmentation, therefore, may underestimate the number of peri-infarct (border) segments.

Since it is crucial to align the scanned myocardial wall carefully with the ultrasound beam in order not to underestimate myocardial velocities, the ultrasound probe might be positioned a small distance away from the true myocardial apex. Since MRI does not have this limitation, apical segmentation might differ slightly between the two techniques. No segments were excluded because of technical reasons.

Although intra- and interobserver variability of velocity-based strain and strain rate measurements are not neglectable, they were relatively small compared to the regional deformation differences observed in STEMI patients.

**Conclusion**

BMPCs transfer early after reperfusion of an acute myocardial infarction significantly improved regional myocardial function recovery in the infarct territory at 4 months’ follow-up as measured using strain rate imaging. Quantitative assessment of regional systolic function is, therefore, a valuable and sensitive tool to evaluate BMPC therapy after acute myocardial infarction. Whether this improved regional systolic function persists over time and translates into more favourable LV remodelling and improved clinical outcome remains to be (and will be) investigated.

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**References**


