Restoration of left ventricular synchronous contraction after acute myocardial infarction by stem cell therapy: new insights into the therapeutic implication of stem cell therapy for acute myocardial infarction


Heart 2008;94:995-1001; originally published online 1 Nov 2007; doi:10.1136/hrt.2007.124701

Updated information and services can be found at:
http://heart.bmj.com/cgi/content/full/94/8/995

These include:

References
This article cites 25 articles, 16 of which can be accessed free at:
http://heart.bmj.com/cgi/content/full/94/8/995#BIBL

3 online articles that cite this article can be accessed at:
http://heart.bmj.com/cgi/content/full/94/8/995#otherarticles

Rapid responses
You can respond to this article at:
http://heart.bmj.com/cgi/eletter-submit/94/8/995

Email alerting service
Receive free email alerts when new articles cite this article - sign up in the box at the top right corner of the article

Topic collections
Articles on similar topics can be found in the following collections

- Drugs: cardiovascular system (9992 articles)
- Echocardiography (1470 articles)
- Acute coronary syndromes (1276 articles)
- Clinical diagnostic tests (9110 articles)

Notes

To order reprints of this article go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to Heart go to:
http://journals.bmj.com/subscriptions/
Restoration of left ventricular synchronous contraction after acute myocardial infarction by stem cell therapy: new insights into the therapeutic implication of stem cell therapy for acute myocardial infarction


ABSTRACT

Objective: To evaluate the effects of stem cell therapy on restoration of the left ventricular (LV) synchronous contraction in patients with acute myocardial infarction (AMI).

Methods: 40 patients with AMI who underwent successful coronary revascularisation were randomly allocated to the cell infusion or the control group. Evaluations were performed with echocardiographic tissue synchronisation imaging to determine LV dysynchrony and with cardiac magnetic resonance imaging to estimate LV ejection fraction (LVEF) at baseline and at 6 months. To quantify the severity of systolic LV dyssynchrony, the standard deviations of time to peak systolic velocity of the 12 LV segments (Ts-SD) were calculated.

Results: At 6 months, greater improvements of Ts-SD (ΔTs-SD: −45.0 (40.2) vs 5.0 (39.9) ms, p<0.001) and LVEF (ΔLVEF: 6.8% (9.1%) vs −0.2% (6.9%), p = 0.015) relative to the corresponding baseline values were observed in the cell infusion group than in the control group. By multivariate analysis, ΔTs-SD and baseline LVEF emerged as the independent determinants of LVEF improvement and cell infusion, and baseline Ts-SD as the determinant of ΔTs-SD improvement. Maximal exercise capacity measured by symptom-limited treadmill testing correlated well with Ts-SD but not with LVEF at 6 months of follow-up.

Conclusion: Stem cell therapy had a favourable effect on the restoration of LV synchronous contraction in patients with AMI.

An accumulated body of evidence suggests that synchronous contraction of the heart is one of the most important factors in maintaining cardiac output or stroke volume in concert with adequate heart rate, preload and afterload.1 Cardiac resynchronisation therapy has been recently developed and has been shown to guide simultaneous left ventricular (LV) contraction and consequently to improve haemodynamic status, exercise performance and prognosis in selected patients.2 3 Recently, the beneficial effect of peripheral blood-derived stem cell treatment on recovery of the LV systolic performance in myocardial infarction has been well demonstrated.4 5 6 Despite the favourable effect of stem cell therapy on LV systolic function, no data are available regarding the role of stem cell therapy in improving LV synchronous contraction in patients with acute myocardial infarction (AMI).

Therefore, we sought to evaluate, in this prospective clinical study using novel echocardiographic tissue synchronisation imaging technique,6 (1) whether stem cell therapy can lead to a recoordination of LV systolic contraction and, if so, (2) whether LV systolic function and exercise capacity might benefit from improved LV harmonious contraction.

METHODS

Patient population
To establish a normal range for the index of LV synchronicity, we consecutively recruited 129 healthy normal volunteers (86 males, 46 (SD 12; range 19–69) years). The volunteers had no previous medical history and had normal physical and laboratory examinations including electrocardiography, echocardiography and either treadmill test or coronary computed tomographic angiography.

We have previously reported a 6-month follow-up.4 We started the tissue synchronisation imaging study in the middle of enrolment for MAGIC Cell-3-DES trial and continued after completion of enrolment for this trial. In addition to 18 AMI patients from the MAGIC Cell-3-DES trial, 22 patients who were randomised and treated under the same protocol were enrolled for this tissue synchronisation imaging study. Thus, a total of 40 AMI patients were randomised into either the cell infusion or the control group.

Patients with successful drug-eluting stent (DES) implantation in the culprit lesion after AMI were eligible for this study. In addition to the exclusion criteria of the MAGIC Cell-3-DES trial,6 patients with atrial fibrillation or with an implanted pacemaker were also excluded in the current study.

Study protocol
The study was performed using the MAGIC Cell-3-DES trial protocol and details have been previously described.5 Briefly, patients were randomly allocated to either the cell infusion or the control group. Cardiac magnetic resonance imaging (MRI), transthoracic echocardiography and treadmill...
testing were performed at baseline after DES implantation and at the 6-month follow-up. For patients assigned to the cell infusion group, granulocyte-colony-stimulating factor (G-CSF, Dong-A Pharmaceutical, Seoul, Korea) was administered daily subcutaneously for a consecutive 3 days at 10 μg/kg body weight to mobilise stem cells, and then the mobilised stem cells were collected using a Cobe spectra apheresis system (Cobe BCT Inc, Lakewood, CO, USA) using the mononuclear cell collection method. The infusion doses were 1–2×10⁶ mononuclear cells per patient, guaranteeing a minimum target cell dose of 7×10⁶ CD34+ cells. Stem cells collected were selectively infused into the coronary artery supplying infarcted myocardium via an over-the-wire coronary balloon catheter (fig 1).

The study protocol was approved by the institutional review board of Seoul National University Hospital. Written informed consent was obtained from all patients after an in-depth explanation of the procedure and the study risks.

**Echocardiographic data acquisition and analysis**

Transthoracic echocardiography was conducted using a commercially available device (Vivid 7, GE Medical System, Horten, Norway) at baseline and 6-month follow-up. After standard echocardiographic examination, Doppler tissue imaging (DTI) mode was activated in apical four-chamber, two-chamber and long-axis views. Great care was taken to get the highest possible frame rate with sector width and depth optimised. Three consecutive heart beats were digitally saved in a cineloop format by two independent echocardiographers for later offline analysis with a dedicated software package (EchoPac 5.0.1, GE Medical System). Offline analyses were performed by another echocardiographer, who is not involved in image acquisition or patients’ clinical follow-up and who did not know patients’ clinical data.

This tissue synchronisation imaging (TSI) algorithm automatically detects peak positive systolic velocity within a pre-specified time interval, and displays activation differences in time to peak positive systolic velocity (Ts) between myocardial segments through colour-coding directly superimposed on two-dimensional images, which ranges from green (earliest arrival at peak systolic velocity), yellow, orange to red (latest arrival at peak systolic velocity). For the measurement of Ts values, the onset of a QRS signal on the electrocardiogram was used as a reference point. In TSI mode, we could easily obtain the Ts values of myocardial segments by simply placing a 6-mm diameter region of interest in the middle of the segment concerned. To estimate LV systolic dyssynchrony, we employed the six-basal and six-mid-segmental model in the LV (total 12 LV segments). After the procurement of the Ts values of 12 LV myocardial segments, Ts standard deviation (Ts-SD) was automatically calculated. We adopted Ts-SD of the 12 LV segments as a surrogate index for LV synchronicity because Ts-SD obtained using either conventional DTI or TSI tools was found to be the most reliable index of LV synchronicity— that is, the greater the value of Ts-SD, the more severe the systolic dysynchrony. The average Ts-SD values from three consecutive heart beats were taken for analysis. In addition, the global peak systolic myocardial velocity of LV (S’) was calculated from mean peak systolic velocities from six-basal segments as a representative marker for the LV inotropic state. ΔTs-SD was defined as the Ts-SD at 6-month follow-up minus Ts-SD at baseline.

Inter-observer and intra-observer variabilities for Ts-SD measurements were determined by analysing 10 randomly selected patients by two independent blinded observers. Data were analysed by least-squares-fit linear regression analysis using standard-error-of-estimate (SEE).

**Cardiac magnetic resonance imaging**

Cardiac MRI (Sonata 1.5T, Siemens, Erlangen, Germany) was performed at baseline and at 6 months. Short axis cine images with a slice thickness of 8 mm and a gap of 2 mm, were acquired throughout the entire LV using contiguous two-dimensional steady state precession sequences. Using ARGUS software (Siemens, Erlangen, Germany), LV volumes and LV ejection fraction (LVEF) were calculated by a blinded observer.

---

**Acute coronary syndromes**

![Figure 1](https://example.com/image1)

**Figure 1** Study protocol. MRI, magnetic resonance imaging; TDI, tissue Doppler imaging; G-CSF, granulocyte-colony-stimulating factor.

---

**Figure 2** Comparisons of changes in left ventricular ejection fraction (LVEF) or Ts-SD changes (ΔTs-SD) between the control and cell infusion groups. (A) In the cell infusion group, LVEF improvements were significantly greater than in the control group. (B) The cell infusion group showed a remarkable reduction in ΔTs-SD compared to the control group, indicating a better improvement in left ventricular synchronous contraction in the cell infusion group.
ΔLVEF was defined as LVEF at 6-month follow-up minus LVEF at baseline.

**Treadmill exercise test**

Patients underwent a maximum symptom-limited treadmill testing using the modified Bruce protocol at 1 week and 6 months after revascularisation. All anti-anginal medication was continued. The end points of this test included angina pectoris, fatigue, dyspnoea and a significant decrease in blood pressure of more than 10 mm Hg. The achievement of a maximal age-related heart rate was not a reason for termination. Exercise capacity was measured using metabolic equivalents (METs), an estimate based on treadmill speed and grade.

**Statistical analysis**

All values are expressed as means (SD) or as percentages. To compare parametric variables at baseline and at 6-month follow-up, we used the paired t test or Wilcoxon signed rank sum test as appropriate. Comparisons of the continuous variables between the cell infusions and control groups were performed using the independent t test, whereas Fisher’s exact test was used for categorical variables. Pearson’s correlation analysis was employed to compare the relation between ΔTs-SD and ΔLVEF after the 6-month follow-up and the relation between Ts-SD and exercise duration at the 6-month follow-up. Multivariate backward stepwise logistic regression analyses were undertaken to identify independent determinants of ΔLVEF and ΔTs-SD. All statistical analyses were performed with SPSS 12.0 (SPSS Inc, Chicago, IL, USA), and p values of <0.05 were taken to indicate statistical significance.

**RESULTS**

**Study population**

Mean Ts-SD obtained from 129 normal subjects was 23.9 (11.2) ms and, hence, a Ts-SD of 46 ms (mean (+2 SD) for normal subjects) was chosen as a cut-off upper limit value to define LV synchronous contraction. Since no significant change in Ts-SD was detected with ageing (p = 0.75), no further correction for age was carried out in the following analyses.

All the patients underwent the apheresis process without immediate complication and were successfully given stem cell infusion, which contains 9.04 (8.04)×10^7 CD34+ cells and completed the follow-up at 6 months. Among them, 35 performed the exercise test, the other five complained of leg pain caused by degenerative arthritis or claudication. Baseline clinical, echocardiographic and cardiac MRI data of the patient cohort are summarised in table 1.

There was a wide range of variation in Ts-SD and LVEF at baseline in both the control and the cell infusion groups, but there were no significant differences between the two groups in terms of baseline characteristics. When a Ts-SD of >46 ms was used to define significant systolic asynchrony, it was found to be present in 15 patients (75%) in the control group and in 17 patients (85%) in the cell infusion group (p = 0.70), indicative of the presence of LV dyssynchrony in a large proportion of the patients. Again, baseline characteristics were similar between patients with (responders) and those without (non-responders) an improvement in LV dyssynchrony except for the presence of a higher proportion of patients with cell infusion treatment in the responders group (table 1).

**Improvement of Ts-SD and LV systolic function by stem cell therapy**

At the 6-month follow-up, LVEF increment from baseline was significantly higher in the cell infusion group, compared to the control group (ΔLVEF: 6.8% (9.1%) vs 0.2% (6.9%), p = 0.015) (fig 2). Ts-SD values were markedly improved at the 6-month follow-up than at baseline in the cell infusion group (108.0 (50.1) ms vs 65.0 (54.9) ms, p<0.001), but not in the control group (98.2 (52.8) ms vs 105.2 (50.1) ms, p = 0.59) (table 2), implying that ΔTs-SD improvement was greater in the cell infusion group than in the control group (−45.0 (40.2) ms vs 5.0 (39.9) ms, p<0.001) (fig 2). ΔTs-SD exhibited a significant correlation with ΔLVEF in the entire population (r = −0.43, p = 0.005) (fig 3). Changes in S’ were comparable between the two groups (−0.35 (1.31) cm/s in the cell infusion group vs −0.20 (0.89) cm/s in the control group, p = 0.13), indicating no significant difference between the two groups in terms of the alteration in LV contractility.

Inter-observer and intra-observer variability of Ts-SD measurements showed excellent agreements (inter-observer correlation: r = 0.97, SEE = 12.3, p<0.001 and intra-observer correlation: r = 0.99, SEE = 8.1, p<0.001).

**Determinants of LV systolic function and LV synchronicity improvements**

To elucidate independent determinants of LVEF improvement, we performed multivariate analysis and included age, gender, the group factor (control vs cell infusion), medications used, hypertension, diabetes, changes of infarct volume, baseline LVEF, baseline LV end-systolic volume, baseline Ts-SD, baseline QRS duration, ΔS’ and ΔTs-SD as independent variables (no change (ΔLVEF <5%) or an aggravation of LVEF were coded as 0 and an LVEF improvement (ΔLVEF ≥5%) as 1). ΔTs-SD and baseline LVEF were emerging variables identified as independent determinants for LVEF improvement (table 3).

To identify determinants of LV dyssynchrony improvement, we again performed multivariate analysis. The dependent variable was ΔTs-SD (no change or aggravation of Ts-SD (ΔTs-SD =0) was coded as 0 and Ts-SD improvement (ΔTs-SD <0) as 1). Independent variables were age, gender, the group factor, medications used, hypertension, diabetes, changes of infarct volume, baseline LVEF, baseline LV end-systolic volume, baseline Ts-SD, baseline QRS duration, ΔS’ and ΔLVEF. The determinants of ΔTs-SD improvement were baseline Ts-SD and...
the group factor—that is, the performance of cell therapy (Table 3).

Correlation between LV synchronicity and exercise capacity
Maximal exercise capacity in the control group did not improve significantly at the 6-month follow-up, whereas exercise capacity showed a significant improvement in the cell infusion group (Table 2).

We also found that exercise capacity at the 6-month follow-up was significantly correlated with Ts-SD (r = 0.61, p = 0.007). But, LVEF failed to show a significant correlation with maximum exercise capacity (p = 0.59).

There were no deaths, new MI, hospitalisation due to angina or heart failure or revascularisation during 6-month follow-up in either groups.

**DISCUSSION**
This study, for the first time, demonstrates that stem cell therapy improved LV dyssynchrony in systole after AMI, as

---

### Table 1 Baseline clinical, echocardiographic, and cardiac magnetic resonance imaging (MRI) data according to either the presence or absence of cell infusion therapy or the response of Ts-SD after 6-month follow-up

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Control</th>
<th>Cell infusion</th>
<th>p Value</th>
<th>Responders*</th>
<th>Non-responders*</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>20</td>
<td>20</td>
<td>0.90</td>
<td>24</td>
<td>16</td>
<td>0.66</td>
</tr>
<tr>
<td>Age (years)</td>
<td>57.1 (11.9)</td>
<td>56.6 (13.1)</td>
<td>1.0</td>
<td>20 (83)</td>
<td>13 (81)</td>
<td>1.0</td>
</tr>
<tr>
<td>Male (%)</td>
<td>16 (80)</td>
<td>17 (85)</td>
<td>0.11</td>
<td>13 (54)</td>
<td>6 (38)</td>
<td>0.30</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>7 (35)</td>
<td>12 (60)</td>
<td>0.49</td>
<td>7 (30)</td>
<td>5 (31)</td>
<td>0.89</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>7 (35)</td>
<td>5 (25)</td>
<td>0.58</td>
<td>93.0 (17.2)</td>
<td>96.5 (22.3)</td>
<td>0.70</td>
</tr>
<tr>
<td>Primary reperfusion, n (%)</td>
<td>13 (65)</td>
<td>10 (50)</td>
<td>0.34</td>
<td>15 (62)</td>
<td>8 (50)</td>
<td>0.43</td>
</tr>
<tr>
<td>Extent (1-vessel: 2-vessel, 3-vessel disease)</td>
<td>11:9</td>
<td>11:9</td>
<td>1.0</td>
<td>13:11 (54)</td>
<td>9:7 (30)</td>
<td>0.90</td>
</tr>
<tr>
<td>Infarct related artery (LAD:LCX:RCA)</td>
<td>8:2:10</td>
<td>13:3:4</td>
<td>0.28</td>
<td>25.3 (15.5)</td>
<td>31.7 (20.3)</td>
<td>0.12</td>
</tr>
<tr>
<td>LVESV (ml)*</td>
<td>65.5 (36.5)</td>
<td>64.7 (22.0)</td>
<td>0.93</td>
<td>62.9 (22.0)</td>
<td>68.5 (39.2)</td>
<td>0.56</td>
</tr>
<tr>
<td>LV EDV (ml)*</td>
<td>134.6 (32.6)</td>
<td>134.7 (32.4)</td>
<td>0.99</td>
<td>131.5 (30.7)</td>
<td>139.3 (34.5)</td>
<td>0.46</td>
</tr>
<tr>
<td>LV EF (%)*</td>
<td>53.2 (15.7)</td>
<td>52.6 (9.1)</td>
<td>0.89</td>
<td>52.7 (11.0)</td>
<td>53.3 (15.2)</td>
<td>0.70</td>
</tr>
<tr>
<td>Infarct volume (ml)*</td>
<td>25.3 (15.5)</td>
<td>31.7 (20.3)</td>
<td>0.28</td>
<td>28.1 (16.9)</td>
<td>28.9 (20.1)</td>
<td>0.89</td>
</tr>
<tr>
<td>E (m/s)</td>
<td>0.74 (0.21)</td>
<td>0.67 (0.16)</td>
<td>0.22</td>
<td>0.72 (0.18)</td>
<td>0.68 (0.20)</td>
<td>0.54</td>
</tr>
<tr>
<td>A (m/s)</td>
<td>0.71 (0.19)</td>
<td>0.64 (0.20)</td>
<td>0.30</td>
<td>0.66 (0.18)</td>
<td>0.70 (0.21)</td>
<td>0.62</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>1.12 (0.49)</td>
<td>1.11 (0.41)</td>
<td>0.94</td>
<td>1.15 (0.40)</td>
<td>1.08 (0.54)</td>
<td>0.64</td>
</tr>
<tr>
<td>DT (ms)</td>
<td>194.28 (53.01)</td>
<td>180.85 (38.24)</td>
<td>0.36</td>
<td>177.87 (41.63)</td>
<td>206.23 (47.73)</td>
<td>0.10</td>
</tr>
<tr>
<td>S‘ (cm/s)</td>
<td>5.45 (1.89)</td>
<td>5.26 (1.40)</td>
<td>0.72</td>
<td>5.47 (1.47)</td>
<td>5.19 (1.92)</td>
<td>0.61</td>
</tr>
<tr>
<td>Ts-SD</td>
<td>98.20 (52.83)</td>
<td>108.00 (50.11)</td>
<td>0.55</td>
<td>113.50 (47.25)</td>
<td>87.50 (54.08)</td>
<td>0.12</td>
</tr>
<tr>
<td>S‘</td>
<td>5.5 (1.9)</td>
<td>5.1 (1.4)</td>
<td>0.25</td>
<td>5.26 (1.40)</td>
<td>5.19 (1.92)</td>
<td>0.70</td>
</tr>
<tr>
<td>Infarct volume (ml)*</td>
<td>25.3 (15.5)</td>
<td>31.7 (20.3)</td>
<td>0.28</td>
<td>28.1 (16.9)</td>
<td>28.9 (20.1)</td>
<td>0.89</td>
</tr>
<tr>
<td>Medications used, n (%)</td>
<td>0 (0%)</td>
<td>20 (100%)</td>
<td>&lt;0.001</td>
<td>17 (71%)</td>
<td>3 (19%)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

LV, left ventricular; ESV, end-systolic volume; EDV, end-diastolic volume; EF, ejection fraction; DT, deceleration time of E wave; S‘, mean peak systolic myocardial velocity; Ts-SD, standard deviation of the time to peak myocardial velocities; ACEIs, angiotensin converting enzyme inhibitors; ARBs, angiotensin receptor blockers.

*Responders were defined as patients with (Ts-SD at 6 months - Ts-SD at baseline) <0 and non-responders as those with ΔTs-SD >0.

*Measured by cardiac magnetic resonance imaging.

---

### Table 2 Morphological and functional parameters at baseline and follow-up

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Control</th>
<th>Cell infusion</th>
<th>p Value</th>
<th>Cell infusion</th>
<th>Cell infusion</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV EF (%)*</td>
<td>53.2 (15.7)</td>
<td>53.4 (12.6)</td>
<td>0.88</td>
<td>52.6 (8.1)</td>
<td>59.4 (10.6)</td>
<td>0.004</td>
</tr>
<tr>
<td>LV ESV (ml)*</td>
<td>65.5 (36.5)</td>
<td>69.8 (37.3)</td>
<td>0.20</td>
<td>64.7 (22.0)</td>
<td>61.6 (31.7)</td>
<td>0.56</td>
</tr>
<tr>
<td>LV EDV (ml)*</td>
<td>134.6 (32.6)</td>
<td>142.4 (38.5)</td>
<td>0.12</td>
<td>134.7 (32.4)</td>
<td>145.0 (38.0)</td>
<td>0.12</td>
</tr>
<tr>
<td>LV stroke volume (ml)*</td>
<td>69.0 (13.6)</td>
<td>72.5 (12.2)</td>
<td>0.24</td>
<td>70.0 (17.6)</td>
<td>83.3 (15.6)</td>
<td>0.005</td>
</tr>
<tr>
<td>Infarct volume (ml)*</td>
<td>25.3 (15.5)</td>
<td>21.9 (9.9)</td>
<td>0.079</td>
<td>31.4 (20.8)</td>
<td>23.6 (16.5)</td>
<td>0.008</td>
</tr>
<tr>
<td>Ts-SD</td>
<td>98.2 (52.8)</td>
<td>103.2 (50.1)</td>
<td>0.59</td>
<td>108.0 (50.1)</td>
<td>63.0 (54.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>S‘ (cm/s)</td>
<td>5.5 (1.9)</td>
<td>5.1 (1.4)</td>
<td>0.25</td>
<td>5.26 (1.40)</td>
<td>5.19 (1.92)</td>
<td>0.70</td>
</tr>
<tr>
<td>QRS duration (ms)</td>
<td>93.0 (17.2)</td>
<td>93.0 (13.4)</td>
<td>1.0</td>
<td>96.5 (22.3)</td>
<td>98.5 (20.3)</td>
<td>0.32</td>
</tr>
<tr>
<td>Maximal exercise capacity (METs)</td>
<td>9.3 (2.5)</td>
<td>9.8 (3.5)</td>
<td>0.35</td>
<td>8.8 (2.8)</td>
<td>10.1 (2.4)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

*Responders were defined as patients with (Ts-SD at 6 months - Ts-SD at baseline) <0 and non-responders as those with ΔTs-SD >0.

*Measured by cardiac magnetic resonance imaging.

LV, left ventricular; ESV, end-systolic volume; EDV, end-diastolic volume; EF, ejection fraction; Ts-SD, standard deviation of the time to peak myocardial velocities; S‘, mean peak systolic myocardial velocity.
is an reliable and powerful index that embraces the information of all the 12 LV segments, and thus Ts-SD seems to be a more useful surrogate for LV dyssynchrony in patients with ischaemic cardiomyopathy. This concept was evidently supported by the earlier study by Yu et al, where Ts-SD is the single reliable index for LV dyssynchrony in ischaemic cardiomyopathy.

**Restoration of LV synchronous contraction—a plausible mechanism of LVEF improvement with stem cell therapy**

Stem cell therapy was reported to be effective in numerous clinical trials with diverse stem cell collection and delivery protocol.6 16–18 Schachinger et al reported improved LV systolic function in their randomised double-blind trial using intracoronary infusion of bone marrow-derived progenitor cells and Ince et al reported favourable results using peripheral stem cells by a mobilisation method with G-CSF.7 Most of them reported the improvement of LV systolic performance as shown by LVEF improvement and the mechanism of this phenomenon has been under discussion.

Although angiogenesis and myocardial regeneration have been suggested to account for improved cardiac systolic function by stem cell therapy,19 arguments were raised because only small numbers of stem cells could be observed in the long-term follow-up animal studies. Thus, direct myogenesis and angiogenesis were regarded as insufficient in explaining the functional improvements associated with stem cell therapy.20 In these respects, the paracrine effects of transplanted stem cells were newly proposed as a reason for the improvements observed in clinical and preclinical studies,22 though this is mainly supported by circumstantial evidence. Additionally we do not have adequate methodology to evaluate myocardial regeneration and angiogenesis in a clinical setting. Only surrogate markers such as changes in infarct volume, myocardial perfusion score and global peak systolic myocardial velocity were used to evaluate the underlying mechanism of stem cell therapy. In fact, the underlying mechanism of this has not been clearly elucidated till now.

In the present study, we proposed changes of LV synchrony as a novel clinical parameter to explain the mechanism of stem cell therapy. We clearly demonstrated improvement of LV

**Table 3 Determinants for the improvement of the left ventricular ejection fraction or synchronicity**

<table>
<thead>
<tr>
<th>Independent factors</th>
<th>Exponential coefficient (β)</th>
<th>Wald statistics</th>
<th>p Value</th>
<th>95% CI</th>
<th>Independent factors</th>
<th>Exponential coefficient (β)</th>
<th>Wald statistics</th>
<th>p Value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.961</td>
<td>1.425</td>
<td>0.233</td>
<td>0.899 to 1.026</td>
<td>Age</td>
<td>1.025</td>
<td>1.512</td>
<td>0.219</td>
<td>0.985 to 1.067</td>
</tr>
<tr>
<td>Gender</td>
<td>1.029</td>
<td>&lt;0.001</td>
<td>0.988</td>
<td>0.222 to 47.496</td>
<td>Gender</td>
<td>5.124</td>
<td>1.737</td>
<td>0.188</td>
<td>0.451 to 58.189</td>
</tr>
<tr>
<td>DM</td>
<td>2.693</td>
<td>0.877</td>
<td>0.349</td>
<td>0.339 to 21.410</td>
<td>DM</td>
<td>1.365</td>
<td>0.103</td>
<td>0.748</td>
<td>0.205 to 9.091</td>
</tr>
<tr>
<td>HT</td>
<td>0.686</td>
<td>0.146</td>
<td>0.702</td>
<td>0.0830 to 5.342</td>
<td>HT</td>
<td>1.263</td>
<td>0.055</td>
<td>0.814</td>
<td>0.181 to 8.832</td>
</tr>
<tr>
<td>ACEI or ARB</td>
<td>7.128</td>
<td>3.221</td>
<td>0.703</td>
<td>0.834 to 60.888</td>
<td>ACEI or ARB</td>
<td>0.689</td>
<td>0.057</td>
<td>0.811</td>
<td>0.032 to 14.745</td>
</tr>
<tr>
<td>β-blocker</td>
<td>0.124</td>
<td>3.346</td>
<td>0.067</td>
<td>0.013 to 1.161</td>
<td>β-blocker</td>
<td>1.342</td>
<td>0.054</td>
<td>0.817</td>
<td>0.111 to 16.167</td>
</tr>
<tr>
<td>QRS duration</td>
<td>1.023</td>
<td>0.820</td>
<td>0.365</td>
<td>0.970 to 1.088</td>
<td>QRS duration</td>
<td>0.991</td>
<td>0.136</td>
<td>0.712</td>
<td>0.945 to 1.039</td>
</tr>
<tr>
<td>LV EF (baseline)</td>
<td>1.012</td>
<td>0.041</td>
<td>0.840</td>
<td>0.903 to 1.134</td>
<td>LV EF (baseline)</td>
<td>0.977</td>
<td>5.912</td>
<td>0.015</td>
<td>0.959 to 0.996</td>
</tr>
<tr>
<td>LV ESV (baseline)</td>
<td>0.978</td>
<td>1.273</td>
<td>0.259</td>
<td>0.940 to 1.017</td>
<td>LV ESV (baseline)</td>
<td>0.990</td>
<td>0.795</td>
<td>0.373</td>
<td>0.968 to 1.012</td>
</tr>
<tr>
<td>Δ infarct volume</td>
<td>1.041</td>
<td>0.536</td>
<td>0.464</td>
<td>0.935 to 1.159</td>
<td>Δ infarct volume</td>
<td>0.929</td>
<td>2.998</td>
<td>0.083</td>
<td>0.854 to 1.010</td>
</tr>
<tr>
<td>Δ LV EF</td>
<td>1.094</td>
<td>1.353</td>
<td>0.245</td>
<td>0.940 to 1.273</td>
<td>Δ LV EF</td>
<td>0.982</td>
<td>3.930</td>
<td>0.074</td>
<td>0.965 to 0.999</td>
</tr>
<tr>
<td>Δ S’</td>
<td>1.199</td>
<td>0.148</td>
<td>0.701</td>
<td>0.476 to 3.019</td>
<td>Δ S’</td>
<td>1.458</td>
<td>0.479</td>
<td>0.489</td>
<td>0.501 to 4.238</td>
</tr>
<tr>
<td>Group factor (control vs infusion)</td>
<td>0.052</td>
<td>9.341</td>
<td>0.002</td>
<td>0.008 to 0.346</td>
<td>Group factor (control vs infusion)</td>
<td>0.927</td>
<td>0.336</td>
<td>0.076 to 2.410</td>
<td></td>
</tr>
</tbody>
</table>

DM, diabetes mellitus; HT, hypertension; ACEIs, angiotensin converting enzyme inhibitors; ARBs, angiotensin receptor blockers; LV, left ventricular; EF, ejection fraction; ESV, end-systolic volume; S’, mean peak systolic myocardial velocity; Ts-SD, standard deviation of the time to peak myocardial velocities.

**Table 3** Determinants for the improvement of the left ventricular ejection fraction or synchronicity

**Figure 4** Correlation between the degree of LV dyssynchrony and exercise capacity at 6-month follow-up. Ts-SD measured 6 months after cell infusion showed a good correlation with maximum exercise capacity in all study subjects (r = −0.54, p = 0.001).
synchrony after stem cell therapy as well as the close association between this improvement and LVEF enhancement. Of note, on multivariate analysis, LVEF improvement by stem cell therapy is independently related to a re-coordination of LV contraction as well as baseline LVEF rather than with augmented contractility of the LV myocardium evaluated by \( S' \). Although reductions in infarct volume were more prominent in the cell infusion group, infarct size did not play a vital part in altering the LVEF determinant or LV dyssynchrony, as demonstrated by multivariate analysis.

In hearts with asynchronous contraction, myocardial segments contracting earlier might add an additional burden to late-contracting myocardial segments beyond the preload naturally provided and, thus, cause substantial energy wastage during their contraction to overcome the increased preload, which could influence the contractility of late-contracting myocardium in view of the classic Frank-Starling mechanism locally operated.\(^2\) \(^2\) Moreover, asynchronous LV activation was shown to be associated with changes in regional myocardial blood flow and regional metabolism.\(^2\) Based on these previous observations, we can easily understand that asynchronous LV contraction could have a deleterious impact on the progression of underlying LV dysfunction, irrespective of its aetiology and consequently patients' prognosis. The alleviation of abnormally increased myocardial preload may have favourable repercussions on the recovery of regional myocardial function, which would in turn lead to LV reverse remodelling\(^2\) and LV systolic functional improvement. Accordingly, stem cell therapy, through LV resynchronisation, is likely to be a clinically relevant adjunctive therapy that enhances outcomes of patients with MI and LV dyssynchrony beyond that acquired by revascularisation.

**Figure 5** A representative example of tissue synchronisation imaging in the apical four-chamber, two-chamber and three-chamber views in a patient with AMI, who was assigned to the cell infusion group. Upper panel (A) represents images obtained at baseline. Red colours, indicating myocardial segments contracting in a dyssynchronous fashion, were superimposed on mid-anterolateral, anterior and apical walls. After 6 months of follow-up, the extent of the red coloured areas was remarkably diminished, as shown in lower panel (B), indicative of a significant improvement in left ventricular synchronicity with stem cell therapy.

**Restoration of LV dyssynchrony and exercise capacity**

Restoration of LV synchronicity with biventricular pacing improved symptoms and the functional capacities of patients with heart failure.\(^2\) In this study, the exercise capacity of patients in the cell infusion group improved at the 6-month follow-up, and Ts-SD, a surrogate index of LV synchronicity, but not LVEF, displayed a good correlation with maximal exercise capacity 6 months after stem cell therapy. This phenomenon suggests that the restoration of LV synchrony obtained by stem cell therapy is largely responsible for functional improvements in patients treated by stem cell therapy.

**Study limitations**

We cannot provide prognostic data owing to the relatively short follow-up period. However, earlier reports have suggested that restoring LV mechanical synchronicity mitigates patients' morbidity and mortality.\(^13\) \(^25\) Long-term follow-up results to show that the restored LV dyssynchrony after stem cell therapy led to a better prognosis are expected to be available in the near future. In addition, efforts to identify baseline clinical or echocardiographic parameters predictive of LV synchrony improvements after stem cell therapy are probably worthwhile, although the present study failed in this respect.

**CONCLUSIONS**

Treatment with peripheral blood stem cells mobilised by G-CSF offers a unique opportunity to restore LV synchronous contraction, which may be one of the underlying mechanisms for the improvement in LVEF and exercise capacity by stem cell therapy in patients with AMI. The hypothesis that the
restoration of LV synchronicity after stem cell therapy may improve patients’ long-term survival need to be clarified in future studies.

Acknowledgements: This study was approved by the institutional review board of Seoul National University Hospital.

Funding: This study was supported by a grant from the National Research Laboratory for Cardiovascular Stem Cell (HSK) and Innovative Research Institute for Cell Therapy (HJK, HSK).

Competing interests: None.

REFERENCES


