Chapter 6

The Effect of Intramyocardial Bone Marrow Cell Injection on Left Ventricular Dyssynchrony and Global Strain

Jan van Ramshorst, Douwe E. Atsma, Saskia L.M.A. Beeres, Sjoerd A. Mollema, Nina Ajmone Marsan, Eduard R Holman, Ernst E. van der Wal, Martin J. Schalij, and Jeroen J. Bax

Department of Cardiology, Leiden University Medical Center, Leiden, The Netherlands

Heart. *2009*; 95:119-124

ABSTRACT

Objective: To evaluate the effect of bone marrow cell injection on global strain and left ventricular (LV) dyssynchrony.

Methods: In 15 patients with severe post-infarction heart failure, $93\pm18x10^6$ autologous bone marrow cells were percutaneously injected in the infarction border zone. At baseline and at 3 months, LV ejection fraction (LVEF) (Tc-99m tetrofosmin gated SPECT), LV dyssynchrony (speckle tracking analysis), and echocardiographic global strain (automated function imaging) were assessed. LVEF, LV dyssynchrony and global strain were also assessed in a non-randomized control group comprising 10 patients with history of infarction who developed heart failure and were treated medically.

Results: No peri-procedural complications occurred during bone marrow cell injection. LVEF increased from 23±8% to 27±9% at 3 months (P=0.02). Global strain improved from -7.7±4.7% to -8.5±4.9% at 3 months (P=0.04). In patients with a substantial improvement (>5%) in LVEF after bone marrow cell injection, global strain improved from -8.7±4.6% to -10.6±4.5% (P<0.01). Global strain remained unchanged in patients without a substantial improvement in LVEF (-6.6±4.9% vs. -6.4±4.5%, P=NS). There was a significant relation between the increase in LVEF and the improvement in global strain (r=0.84, P<0.01). In patients with a substantial improvement in LVEF, LV dyssynchrony decreased from 173±64 ms to 116±64 ms (P=0.01). In patients without a substantial improvement in LVEF, LV dyssynchrony remained unchanged (155±67 ms vs. 177±81 ms, P=NS). There was an excellent correlation between the improvement in LVEF and the reduction in LV dyssynchrony (r=-0.77, P<0.01). In the control group, LVEF, global strain and LV dyssynchrony did not improve.

Conclusions: In conclusion, bone marrow cell injection improves LVEF in patients with severe post-infarction heart failure. The improvement in LVEF was related to a reduced LV dyssynchrony and an increased global strain.

INTRODUCTION

Cardiac cell therapy has been proposed as a novel treatment modality for patients with post-infarction heart failure. Various animal model studies reported that bone marrow cell transplantation after myocardial infarction could enhance myocardial contractility.[1-3] In line with these encouraging experimental data, a number of clinical studies suggested that cardiac bone marrow cell transplantation in patients with myocardial infarction may improve left ventricular (LV) function[4-6].

Although this new treatment modality has already been introduced in the clinical setting, the mechanism by which bone marrow cell transplantation improves LV function is only partially understood. It is hypothesized that bone marrow cells may improve myocardial contractility by promoting vascularization and myocyte formation[7]. More recently, Chang and coworkers suggested that bone marrow cell-induced resynchronization of the LV contraction pattern may contribute to the improvement in LV function after bone marrow cell transplantation in patients with myocardial infarction[8].

The aim of the current study was to evaluate the effect of intramyocardial bone marrow cell injection on LV dyssynchrony. Moreover, global strain was assessed before and after cell transplantation and the change in global strain was related to changes in LV ejection fraction (EF). LV dyssynchrony and global strain were evaluated with novel echocardiographic techniques including speckle tracking strain analysis and automated function imaging (AFI) respectively. Changes in LVEF were assessed with gated single photon emission computed tomography (SPECT) imaging.

METHODS

Patients

Bone marrow cell injection was performed in 15 consecutive patients with severe post-infarction heart failure (New York Heart Association (NYHA) class III or IV) despite optimized medical therapy and a LVEF <40% as assessed by Tc-99m tetrofosmin gated SPECT. All patients had a history of myocardial infarction (documented by typical symptoms, elevation of cardiac enzymes, and typical electrocardiographic changes) >12 months before enrolment and a fixed perfusion defect on stress-rest Tc-99m tetrofosmin SPECT.

Patients eligible for percutaneous coronary intervention, coronary artery bypass grafting, valve surgery, surgical LV remodeling or cardiac resynchronization therapy were excluded from the study. For this purpose, coronary angiography, two-dimensional echocardiography and Tc-99m tetrofosmin gated SPECT were performed and reviewed by an independent committee comprising interventional cardiologists and cardiovascular surgeons. Additional exclusion criteria were: a history of malignancy, renal dysfunction (serum creatinine >200 μmol/L), and unexplained hematological or biochemical laboratory abnormalities. The study protocol was approved by the local ethics committee and written informed consent was obtained from all patients.

Apart from the 15 patients receiving bone marrow cell injection, a historical control group was included. The control group consisted of 10 patients with history of infarction and developed severe heart failure who were matched for age, gender and LVEF. The control patients were treated medically.

Study Protocol

Within 2 weeks before bone marrow cell injection, resting Tc-99m tetrofosmin gated SPECT (to assess LV function) and resting two-dimensional echocardiography (to assess LV dyssynchrony and global strain) were performed. At hospital admission for cell injection, an independent physician who was blinded to all other clinical data scored the NYHA functional class and assessed quality-of-life with the use of the Minnesota Living with Heart Failure questionnaire[9].

At 3 months follow-up, NYHA functional class, quality-of-life, and ventricular arrhythmias (24-hour Holter monitoring and device interrogation in patients with an implantable cardioverter defibrillator) were assessed. Tc-99m tetrofosmin gated SPECT and two-dimensional echocardiography were repeated at 3 months follow-up to re-evaluate LV function, LV dyssynchrony, and global strain.

Bone Marrow Aspiration, Isolation of Mononuclear Cells and Cell Injection

Bone marrow was aspirated from the iliac crest under local anesthesia. During mononuclear cell isolation (Ficoll density gradient), non-fluoroscopic LV electromechanical mapping was performed with the NOGA system (Biosense-Webster, Waterloo, Belgium). Areas with unipolar voltage <6.9 mV were considered as the infarcted area[10] if these areas were geographically concordant with the perfusion defect on Tc-99m tetrofosmin SPECT. Autologous bone marrow-derived mononuclear cells injections were targeted

at viable myocardium (unipolar voltage ≥6.9mV) located at the infarction border zone. Before every injection, the catheter was positioned perpendicular to the endocardium with excellent loop stability and the extension of the needle had to induce a premature ventricular contraction. Subsequently, 8-12 intramyocardial injections of approximately 0.2 ml each were delivered in the infarction border zone.

After the procedure, heart rhythm was continuously monitored for 2 days. Laboratory markers of myocardial necrosis were collected at 1, 6, and 24 hours. After bone marrow cell injection, two-dimensional echocardiography was performed to exclude post-procedural pericardial effusion. Routine medical therapy was left unchanged after bone marrow cell injection.

Tc-99m Tetrofosmin SPECT

Electrocardiographic-gated resting images were obtained after intravenous administration of 500 MBq Tc-99m tetrofosmin. Imaging was performed with a triple-head SPECT camera system (GCA 9300/HG, Toshiba Corp, Tokyo, Japan) equipped with low-energy general-purpose collimators. A 20% window was used around the 140-keV energy peak of Tc-99m. Ninety projections were obtained over a 360^0 circular orbit (step and smooth mode, 35 s per projection, imaging time 23 min). Data were stored in a 64x64 matrix. Filtered back projection using a Butterworth filter (cut-off frequency 0.26 cycle/pixel, order 9) was applied to reconstruct the raw scintigraphic data.

The resting Tc-99m tetrofosmin SPECT images were analyzed by 2 independent reviewers, who were blinded to all clinical data (including the time-point of the study). Quantitative assessment of LVEF, LV end-diastolic, and LV end-systolic volumes was performed using previously validated automated software (quantitative gated SPECT, QGS, Cedars-Sinai Medical Center, Los Angeles, California, USA).[11] By estimating and displaying the endo- and epicardial surfaces, the LV end-diastolic and LV end-systolic volumes were calculated and LVEF was derived. A patient was considered to have substantial improvement in LV function after bone marrow cell injection if LVEF increased ≥5%[12].

Echocardiography

Patients were imaged in the left lateral decubitus position, using a commercially available system (Vivid Seven, General Electric-Vingmed, Milwaukee, Wisconsin, USA). Standard images were obtained using a 3.5-MHz transducer, at a depth of 16 cm in the parasternal (short-axis images) and apical (long-axis, 2-, and 4-chamber images) views.

Radial strain was assessed on LV short-axis images at the papillary muscle level, using speckle tracking analysis[13, 14]. With this technique, stable acoustic markers are used to calculate velocity vectors in myocardial movement in the LV. These markers, or speckles, are present on standard ultrasound tissue images and are used to perform off-line analysis of radial strain on digitally stored images. Short-axis images of the LV are automatically subdivided into blocks of 20 to 40 pixels containing stable patterns of speckles. As these speckles are moving together with the myocardium, they can be accurately followed from frame-to-frame. Subsequently, their location throughout the cardiac cycle is tracked by a dedicated software algorithm, using correlation criteria and sum of absolute differences[14]. The generated spatial and temporal data of the speckles are used to derive local two-dimensional tissue velocity vectors. Temporal differences in the mutual distance of neighboring speckles are used to assess myocardial strain. Radial strain is calculated using the change in length of the speckle pattern, compared to the initial length. Myocardial thickening is then represented as positive strain, and myocardial thinning as negative strain.

To assess regional LV strain, a circular region of interest is manually drawn at the endocardial-cavity interface of the mid-LV short-axis view at end-systole. A second larger circle at the epicardial level is automatically created by the speckle-tracking software, such that the region of interest included the entire myocardial wall. The automatically created circle width could be adjusted manually by the operator, depending on the LV wall thickness. The speckle-tracking software automatically tracked the region of interest and calculated radial strain throughout the cardiac cycle, starting at the selected frame at end-systole. Finally, the LV endocardium was automatically divided into 6 standard segments: septal, anteroseptal, anterior, lateral, posterior, and inferior, respectively. From all segments, quality of the obtained signals had to be good (marked green by the software) in order to be able to adequately determine radial strain. From these radial strain data, 6 time-strain curves representing the 6 segments were generated. LV dyssynchrony was assessed by determination of difference in time to peak strain between the earliest activated region and the latest activated region.

Automated function imaging (AFI) was used to assess LV systolic function. This technique is commercially available (General Electrics, Milwaukee, Wisconsin, USA) and calculates the myocardial tissue deformation, using strain tracking from two-dimensional grey scale images. A set of three longitudinal two-dimensional image planes (apical long-axis, 2- and 4-chamber views) was used for AFI analysis. In the selected views, aortic

valve closure timing was marked and three points were anchored inside the myocardial tissue, two placed at the basal segments along the mitral valve annulus and one at the apex. These points triggered the automatic process, in which myocardial motion was analyzed by tracking features ("natural acoustic tags"). The percent of wall lengthening and shortening was displayed for each plane and represented longitudinal strain. The results of all three planes are then summarized in a single bull's-eye view, which presents the analysis for each segment along with a global strain value for the LV.

All echocardiographic measurements were obtained by two independent observers without knowledge of the clinical status of the patient.

Statistical Analysis

Data are expressed as mean±SD. Comparison of continuous data was performed using the paired Student's t-test. Correlations were determined using the Pearson correlation coefficient. All tests were two-sided, with a P-value <0.05 considered significant.

RESULTS

Intramyocardial bone marrow cell injection was performed in 15 patients (mean age 63±9 years, 14 male) with post-infarction heart failure. The control group comprised 10 patients (mean age 62±11 years, 9 men) with a history of infarction who developed heart failure. The 2 groups were matched with respect to baseline characteristics and LVEF (Table 1). The type and dosages of cardiovascular medications remained unchanged during the 3 months follow-up period in all patients.

Procedural Data and Clinical Outcome

Bone marrow cell treated patients received 10.1±1.1 injections of 0.2 ml each in the infarction border zone. With each injection, $9.3\pm1.8\times10^6$ bone marrow-derived mononuclear cells were delivered. Accordingly, the total number of injected bone marrow cells was $93.4\pm14.2\times10^6$ per patient. At the time of cell injection, cell viability was >95% in all patients. The CD34-positive cell fraction was 2.6±1.3%.

Intramyocardial bone marrow cell injection was performed without major peri-procedural complications in all patients. In particular, repetitive laboratory measurements did not reveal evidence of myocardial infarction and two-dimensional echocardiography excluded post-procedural pericardial effusion. Sustained ventricular tachycardias were

not observed during cell injection, hospitalization or during the 3 months follow-up period.

Although 1 bone marrow cell treated patient died from worsening heart failure at 2.5 months follow-up, the mean NYHA class improved from 3.5±0.5 at baseline to 2.7±0.8 at 3 months (P<0.01). Similarly, quality-of-life score in the bone marrow cell group improved from 51±10 at baseline to 38±19 at 3 months follow-up (P=0.02). In control patients, NYHA class remained unchanged (3.4±0.5 at baseline vs. 3.6±0.5 at 3 months, P=NS).

Table 1. Baseline characteristics of the study population.

Characteristic	Bone marrow cell group (n=15)		Control group (n=10)		P-value
Age, yrs	63±9		62±11		NS
Gender (Male)	14/15	(93%)	9/10	(90%)	NS
Cardiovascular risk factors					
Hypertension	10/15	(67%)	5/10	(50%)	NS
Diabetes	7/15	(47%)	6/10	(60%)	NS
Dyslipidemia	13/15	(87%)	7/10	(70%)	NS
Coronary artery disease in family	10/15	(67%)	5/10	(50%)	NS
NYHA class	3.5±0.5		3.4±0.5		NS
Current Medication					
Diuretics	15/15	(100%)	10/10	(100%)	NS
Oral anti-coagulants	15/15	(100%)	10/10	(100%)	NS
Beta-blockers	14/15	(93%)	9/10	(90%)	NS
ACE-inhibitors	14/15	(93%)	8/10	(80%)	NS
Spironolactone	10/15	(67%)	6/10	(60%)	NS
LVEF at baseline (%)	23±8		24±4		NS

ACE = angiotensin converting enzyme; NYHA = New York Heart Association; LVEF = left ventricular ejection fraction

Left Ventricular Function

SPECT imaging in patients receiving bone marrow cell injection revealed that LVEF increased from 23±8% at baseline to 27±9% at 3 months follow-up (P=0.02). Of interest, LVEF improved ≥5% in 7/14 patients. LV end-systolic volume decreased from 230±114 ml at baseline to 219±122 ml at 3 months follow-up (P=0.04), whereas LV end-diastolic volume remained unchanged (291±122 ml vs. 288±134 ml, P=NS).

In control patients, no improvement in parameters of LV systolic function was noted. In particular, LVEF decreased from 24±4% at baseline to 21±4% at 3 months follow-up (P=0.01). LV end-systolic volume tended to increase from 170±66 ml at baseline to 181±70

ml at 3 months (P=NS) and LV end-diastolic volume remained unchanged (224±86 ml vs. 225±82 ml at 3 months, P=NS).

Left Ventricular Dyssynchrony

Patients receiving intramyocardial bone marrow cell injection showed a trend towards a decrease in LV dyssynchrony from 164±72 ms at baseline to 146±77 ms at 3 months follow-up (P=0.10). In patients with a substantial improvement in LVEF (≥5%), however, there was a significant reduction in LV dyssynchrony from 173±64 ms at baseline to 116±64 ms at 3 months (P=0.01) (Figure 1A). On the contrary, LV dyssynchrony remained unchanged in patients without a substantial improvement in LVEF (155±67 ms vs.177±81 ms, P=NS) (Figure 1B). As shown in Figure 1C, there was a good correlation between the improvement in LVEF and the reduction in LV dyssynchrony (r=-0.77, P<0.01). Of interest, LV dyssynchrony decreased in all 7 patients with a substantial improvement in LVEF.

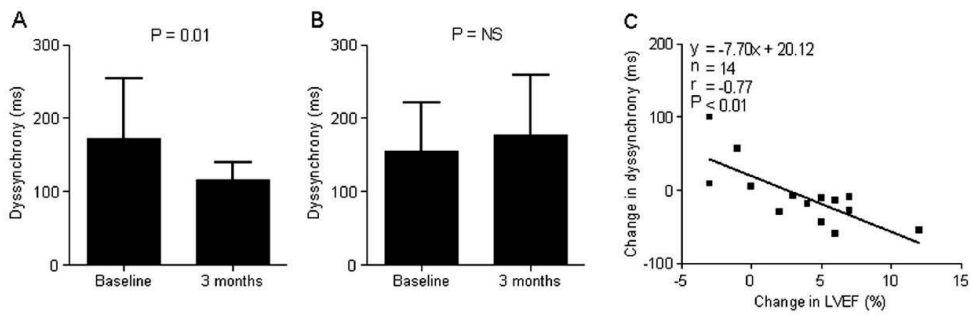


Figure 1. LV dyssynchrony at baseline and at 3 months follow-up as assessed by speckle tracking in patients with a substantial increase (>5%) in LV ejection fraction (A) and in patients without a substantial increase in LV ejection fraction (B).
Pearson correlation coefficient (C) between change in LV dyssynchrony and change in LV ejection fraction (r=-0.77, P<0.01).

In Figure 2, an example is shown of a patient in whom a decrease of LV dyssynchrony was observed after bone marrow cell injection. Two of seven patients without a substantial increase in LVEF showed an improved LV dyssynchrony.

Baseline LV dyssynchrony was similar in bone marrow cell treated patients as compared to control patients (164±72 ms vs. 161±48 ms, P=NS). In control patients no improvement in LV dyssynchrony was observed during the 3 months follow-up period (161±48 ms vs. 181±41ms at 3 months, P=NS).

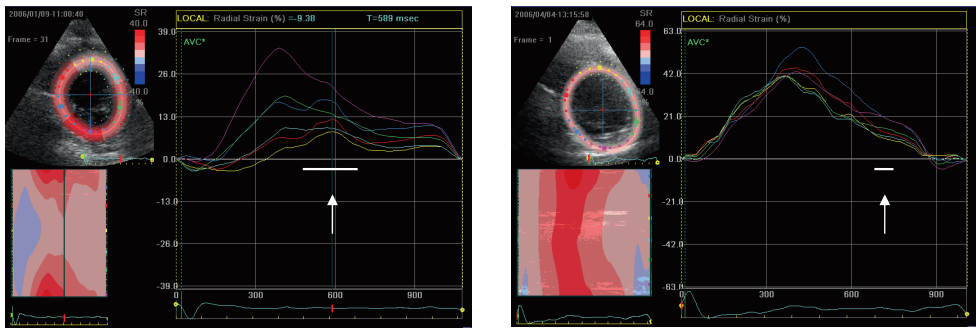


Figure 2. Example of speckle tracking radial strain analysis of a representative patient. The graphs show time-strain curves through one cardiac cycle, with each colored line representing one segment. The white arrows point the differences in time to peak strain between the earliest activated segments and the latest activated segments. Three months after intramyocardial injection of autologous bone marrow–derived mononuclear cells, LV dyssynchrony is significantly reduced.

Left Ventricular Strain

In the bone marrow cell injection group, AFI demonstrated a modest improvement in global strain from -7.7±4.7% at baseline to -8.5±4.9% at 3 months (P=0.04). Global strain particularly improved in patients with a substantial increase in LVEF (-8.7±4.6% at baseline vs. -10.6±4.5% at 3 months, P<0.01) (Figure 3A), whereas global strain remained unchanged in patients without a substantial improvement in LVEF (-6.6±4.9% vs. -6.4±4.5%, P=NS) (Figure 3B). As shown in Figure 3C, there was a significant relation between the increase in LVEF and the improvement in global strain (r=0.84, P< 0.01). An example of an increase in global strain after bone marrow cell injection is showed in Figure 4.

AFI-determined global strain at baseline did not significantly differ between the bone marrow cell group and the control group. (-7.7±4.7% vs. -6.1±2.5%, P=NS). During the 3 months follow-up period, global strain remained unchanged in control patients (-6.1±2.5% at baseline vs. -5.4±2.3% after 3 months, P=NS).

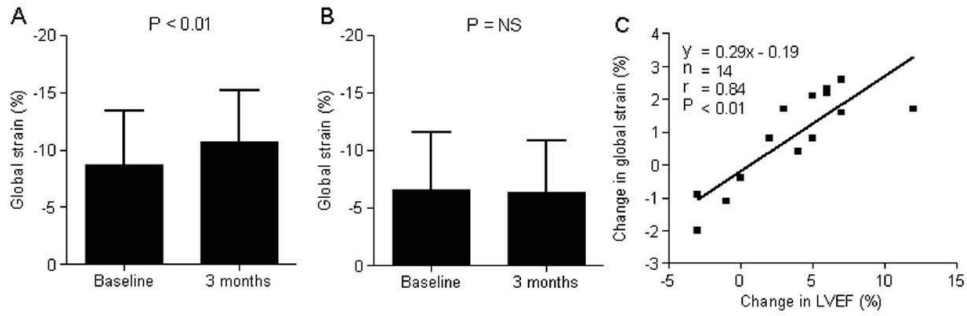
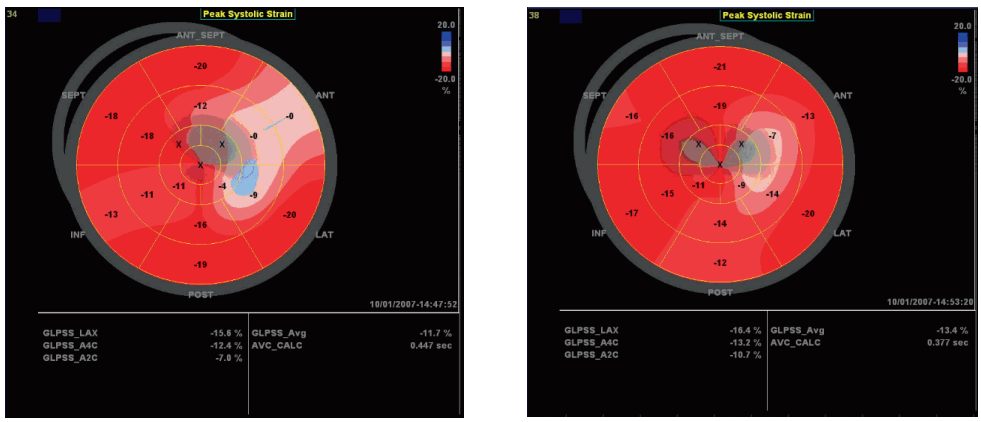


Figure 3. Global strain at baseline and at 3 months follow-up as assessed by AFI in patients with a substantial increase (≥5%) in LV ejection fraction (A) and in patients without a substantial increase in LV ejection fraction (B). Pearson correlation coefficient (C) between change in global strain and change in LV ejection fraction (r=0.84, P<0.01).



Baseline 3 months

Figure 4. Bull's-eye view of a patient with reduced global strain as generated by automated function imaging. For each segment the strain value is shown, as well as a global strain value for the entire LV. Three months after bone marrow cell injection, global strain has improved, as can be derived form the bull's eye view and the global strain value which is shown in the right-below.

DISCUSSION

The main finding from the current study is that intramyocardial bone marrow cell injection in patients with severe post-infarction heart failure was associated with a significant increase in LVEF. In addition, patients with a substantial improvement in LVEF displayed a significant reduction in LV dyssynchrony and an increased global strain.

Various studies have reported that cardiac bone marrow cell transplantation may improve LV systolic function in patients with acute or chronic myocardial infarction[4-6]. For example, LV angiography at 3 months follow-up in the REPAIR-AMI study revealed that bone marrow cell transplantation in patients with acute myocardial infarction was associated with a 5.5±7.3% increase in LVEF, whereas no significant improvement was observed in control patients. Similarly, the TOPCARE-CHD investigators reported that bone marrow cell transplantation in patients with chronic myocardial infarction was associated with a 2.9±3.6% increase in LVEF. In line with these previous findings, a significant improvement in LV systolic function was observed in the current study. In particular, nuclear imaging revealed a 4±4% increase in LVEF.

In the present study, the improvement in LV systolic function was also evaluated by changes in global strain. Strain is a measure for tissue deformation and was originally derived from tissue doppler imaging (TDI) measurements. In 2002, Greenberg et al. demonstrated with the use of pressure-volume loops in dogs that strain provided a reflection of global LV contractility[15]. Moreover, strain imaging has been proven to be valuable for the evaluation of LV function in the clinical setting. For example, TDI-derived strain imaging allowed for detection of subclinical LV dysfunction in asymptomatic patients with severe mitral regurgitation[16].

More recently, AFI has been introduced for the assessment of myocardial strain. The software algorithm allows angle-independent assessment of a global strain value for the entire LV, with the use of standard two-dimensional echocardiographic images. Myocardial motion is analyzed by tracking stable acoustic markers in three longitudinal two-dimensional-image planes. Subsequently, the results for each plane are combined and displayed in a single bull's eye summary, together with a global strain value for the left ventricle. Validation studies point out that strain as assessed by AFI is closely correlated to TDI-derived strain[17]. Moreover, global strain measurements by AFI showed a strong correlation with echocardiographic wall-motion score index ($r=0.68$, $P<0.0001$) in post-infarction patients and healthy subjects[14].

In the current study, AFI demonstrated a modest improvement in global strain from -7.7±4.7% to -8.5±4.9% ($P=0.04$) at 3 months follow-up. Moreover, the change in strain was related to the change in LVEF (Figure 3C) and the improvement in strain was most outspoken in patients with an increase in LVEF.

To date, the mechanism by which the transplanted cells may enhance myocardial contractility is only partially understood[7]. To some extent, the improvement in LV

function may be related to (partial) cardiac resynchronization, as suggested recently by Chang and coworkers[8].

The findings in the current study support these preliminary data and indicated a substantial reduction in LV dyssynchrony (from 173±64 ms to 116±64 ms, P=0.01) in the patients with an improvement in LVEF after cell therapy. Assessment of LV dyssynchrony was performed using speckle tracking strain analysis. This novel technique allows non angle-dependent calculation of myocardial radial strain, using stable acoustic markers. Subsequently, LV dyssynchrony is derived from differences in time to peak strain among the different LV regions, as previously reported[18]. The significant reduction in LV dyssynchrony observed in the patients with an improvement in LVEF, and the absence of resynchronization in patients without an increase in LVEF, supports the relation between these 2 parameters, although it can not be concluded from the current study that an improvement in LVEF is secondary to LV resynchronization.

Obviously, the current study was not primarily designed to assess the underlying cellular mechanism of bone marrow cell transplantation improving LV dyssynchrony. Based on the findings from pre-clinical studies it can be hypothesized that bone marrow cells may improve intraventricular conduction since these cells have been shown to couple functionally and electrically with adjacent host cardiomyocytes[19]. In addition, it could be hypothesized that bone marrow cell-induced neovascularization could have enhanced re-coordination of the LV contraction pattern, but currently data to support this hypothesis are not available.

The present study has some limitations. First, a placebo effect from bone marrow cell transplantation cannot be ruled out since the current study did not comprise a randomized, double-blind, placebo-controlled control group. Although the placebo effect plays an important role in the subjective evaluation of heart failure symptoms, LVEF, global strain, and LV dyssynchrony, are objective parameters. Still, the current findings need confirmation in randomized, placebo-controlled studies. Second, it should be emphasized that the study population only comprised post-infarction heart failure patients who were ineligible for implantation of a CRT device. As a consequence, additional studies are required to assess the effect of bone marrow cell therapy on LV dyssynchrony in patients with conventional indications for CRT.

In conclusion, the results of the current study document that intramyocardial bone marrow cell injection in patients with heart failure and previous myocardial infarction improved LVEF; this improvement in LVEF was accompanied by a reduction in LV dyssynchrony and an increase in global strain.

REFERENCES

1. Tomita S, Mickle DA, Weisel RD, et al. Improved heart function with myogenesis and angiogenesis after autologous porcine bone marrow stromal cell transplantation. *J Thorac Cardiovasc Surg* 2002;123:1132-1140
2. Fuchs S, Baffour R, Zhou YF, et al. Transendocardial delivery of autologous bone marrow enhances collateral perfusion and regional function in pigs with chronic experimental myocardial ischemia. *J Am Coll Cardiol* 2001;37:1726-1732
3. Kawamoto A, Gwon HC, Iwaguro H, et al. Therapeutic potential of ex vivo expanded endothelial progenitor cells for myocardial ischemia. *Circulation* 2001;103:634-637
4. Strauer BE, Brehm M, Zeus T, et al. Regeneration of human infarcted heart muscle by intracoronary autologous bone marrow cell transplantation in chronic coronary artery disease: the IACT Study. *J Am Coll Cardiol* 2005;46:1651-1658
5. Assmus B, Honold J, Schachinger V, et al. Transcoronary transplantation of progenitor cells after myocardial infarction. *N Engl J Med* 2006;355:1222-1232
6. Schachinger V, Erbs S, Elsasser A, et al. Intracoronary bone marrow-derived progenitor cells in acute myocardial infarction. *N Engl J Med* 2006;355:1210-1221
7. Wollert KC, Drexler H Clinical applications of stem cells for the heart. *Circ Res* 2005;96:151-163
8. Chang SA, Kim HK KH, Kim YJ Restoration of synchronicity of the left ventricular myocardial contraction with stem cell therapy: new insights into the therapeutic implication of stem cell therapy in myocardial infarction. *Circulation* 2006;114:II567
9. Rector TS, Kubo SH, Cohn JN Validity of the Minnesota Living with Heart Failure questionnaire as a measure of therapeutic response to enalapril or placebo. *Am J Cardiol* 1993;71:1106-1107
10. Perin EC, Silva GV, Sarmento-Leite R, et al. Assessing myocardial viability and infarct transmurality with left ventricular electromechanical mapping in patients with stable coronary artery disease: validation by delayed-enhancement magnetic resonance imaging. *Circulation* 2002;106:957-961
11. Cerqueira MD, Weissman NJ, Dilsizian V, et al. Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart: a statement for healthcare professionals from the Cardiac Imaging Committee of the Council on Clinical Cardiology of the American Heart Association. *Circulation* 2002;105:539-542
12. Bax JJ, Schinkel AF, Boersma E, et al. Extensive left ventricular remodeling does not allow viable myocardium to improve in left ventricular ejection fraction after revascularization and is associated with worse long-term prognosis. *Circulation* 2004;110:II18-II22
13. Leitman M, Lysyansky P, Sidenko S, et al. Two-dimensional strain-a novel software for real-time quantitative echocardiographic assessment of myocardial function. *J Am Soc Echocardiogr* 2004;17:1021-1029
14. Reisner SA, Lysyansky P, Agmon Y, et al. Global longitudinal strain: a novel index of left ventricular systolic function. *J Am Soc Echocardiogr* 2004;17:630-633
15. Greenberg NL, Firstenberg MS, Castro PL, et al. Doppler-derived myocardial systolic strain rate is a strong index of left ventricular contractility. *Circulation* 2002;105:99-105
16. Lee R, Hanekom L, Marwick TH, Leano R, Wahi S Prediction of subclinical left ventricular dysfunction with strain rate imaging in patients with asymptomatic severe mitral regurgitation. *Am J Cardiol* 2004;94:1333-1337
17. Perk G, Tunick PA, Kronzon I Non-Doppler two-dimensional strain imaging by echocardiography--from technical considerations to clinical applications. *J Am Soc Echocardiogr* 2007;20:234-243

18. Suffoletto MS, Dohi K, Cannesson M, Saba S, Gorcsan J, III Novel speckle-tracking radial strain from routine black-and-white echocardiographic images to quantify dyssynchrony and predict response to cardiac resynchronization therapy. *Circulation* 2006;113:960-968

19. Pijnappels DA, Schalij MJ, van Tuyn J, et al. Progressive increase in conduction velocity across human mesenchymal stem cells is mediated by enhanced electrical coupling. *Cardiovasc Res* 2006;72:282-291

GLOSSARY

REPAIR-AMI	Reinfusion of Enriched Progenitor Cells and Infarct Remodeling in Acute Myocardial Infarction
TOPCARE-CHD	Transplantation of Progenitor Cells and Recovery of Left Ventricular function in Patients with Chronic Ischemic Heart Disease