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The acute and long-term effects of intracoronary Stem cell Transplantation in 191 patients with chronic heART failure: the STAR-heart study

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Aims Despite accumulated evidence that intracoronary bone marrow cell (BMC) therapy may be beneficial in acute myocardial infarction, there are only limited data available on the effectiveness of BMC's in chronic heart failure. The aim of this study was to quantitatively investigate ventricular haemodynamics, geometry, and contractility as well as the long-term clinical outcome of BMC treated patients with reduced left ventricular ejection fraction (LVEF) due to chronic ischaemic cardiomyopathy.

Methods and results Patients with chronic heart failure ($n = 391$ LVEF $\leq$35%) due to ischaemic cardiomyopathy were enrolled in the present study. Of these, 191 patients (mean NYHA class 3.22) underwent intracoronary BMC therapy. The control group (mean NYHA class 3.06) consisted of 200 patients with comparable LVEF. Assessments of haemodynamics at rest and exercise, quantitative ventriculography, spiroergometry, 24 h Holter ECG, late potentials, and heart rate variability were analysed. Over 3 months to 5 years after intracoronary BMC therapy there was a significant improvement in haemodynamics (e.g. LVEF, cardiac index), exercise capacity, oxygen uptake, and LV contractility. Importantly, there was a significant decrease in long-term mortality in the BMC treated patients compared with the control group.

Conclusion Intracoronary BMC therapy improves ventricular performance, quality of life and survival in patients with heart failure. These effects were present when BMC were administered in addition to standard therapeutic regimes. No side effects were observed.

Keywords Ischaemic cardiomyopathy • Chronic heart failure • Bone marrow cell therapy • Remodelling • Mortality

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Introduction

Prevention and/or reversal of remodelling of the left ventricle by cell therapy are an important therapeutic aim, which has been realized for the first time in patients with acute myocardial infarction.[1,2] Animal experiments[3–5] and—more recently—clinical studies[1,2,6–8] have shown that autologous bone marrow cells (BMC's) (progenitor or stem cells) may improve ventricular function, when administered directly into the coronary artery system in association with ischaemic preconditioning. Although this therapeutic procedure has been used in several thousand patients, there are many unresolved questions, especially with regard to (i) the quantitative amount of improvement in ventricular function, ventricular geometry, and contractility, (ii) the long-term effects (2–5 years) in chronic heart failure, and (iii) the late patient outcome and mortality.

Therefore, we established this clinical trial to evaluate the use of stem cell treatment in patients with chronic heart failure.

Methods

Study population

A total of 391 patients with reduced left ventricular ejection fraction (LVEF) due to ischaemic heart disease were enrolled into this prospective study. All patients had a previous myocardial infarction and had undergone initial interventional infarct treatment by percutaneous coronary intervention. The time interval between the infarct intervention

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and the admission to our clinic was 8.5 ± 3.2 years. One hundred and ninety-one patients underwent BMC therapy (BMC group). The control group consisted of 200 patients with comparable EF and diagnosis. The haemodynamic inclusion criterion in all patients was reduced LVEF (≤35%) due to old infarcts in ischaemic heart disease (ischaemic cardiomyopathy). Patients with dilated cardiomyopathy or valvular disease were excluded. General exclusion criteria were alcohol or drug dependency, acute myocarditis, HIV-, HBV-, or HCV-infections, pregnancy or evidence of malignant or haematological diseases. All patients received standard medication (*Table 1*) according to the guidelines for treatment of heart failure, including β-blockers, ACE-inhibitors (or an AT2-receptor antagonist), diuretics and, if necessary, digitalis.

Study design

Between 2003 and 2005, this novel kind of BMC therapy was proposed to all patients with a reduced LVEF due to ischaemic cardiomyopathy attending our clinic. Patients who refused to undergo bone marrow puncture and the BMC treatment, but who agreed to undergo all procedures identical to the BMC group acted as the control group for this study. The main reason for rejection of cell therapy was the uncertainty of patients about this novel treatment, since at the time many public discussions on the potential risks of (embryonic) stem cells were ongoing. Therefore, many patients refused this therapy, preferring to undergo more conventional treatment. More patients declined than accepted the BMC therapy. Not all patients that declined wanted to be included in the control group and to undergo all procedures identical to the BMC group at the 3, 12, and 60 months of follow-up. The first 200 patients that refused the BMC therapy, but agreed to undergo all procedures identical to the BMC group acted as the control group.

Coronary angiography, biplane left ventriculography, ECG at rest, spiroergometry, right heart catheterization and measurements of late potentials (LP), short-term heart rate variability (HRV), and 24-h Holter ECG were performed. Therapeutic follow-up was performed 3, 12, and 60 months (*Figure 1*) in all 391 patients. All tests were performed at each visit in every patient. The present study was approved by the ethics committee of Heinrich-Heine-University of Dusseldorf, Germany. All patients signed informed consent for participation in the cell therapy protocol and for the invasive cardiac diagnostics and interventions.

Preparation of bone marrow cells

Bone marrow (80–120 mL) was taken from the iliac crest, and mononuclear cells were isolated and identified including CD34-positive cells, AC133-positive cells, and CD45/CD14-negative cells, according to the Paul-Ehrlich-Criteria for Good Manufacturing Practice (GMP). The cells were isolated by Ficoll density separation on Lymphocyte Separation Medium (Bio Whittaker, Walkersville, MD, USA), before the residual erythrocytes were lysed with H_2O. Bone marrow cells were washed three times with heparinized saline. Viability was 93 ± 3%. Heparinization and filtration (cell strainer, FALCON) was carried out to prevent cell clotting and microembolization during intracoronary transplantation. All microbiological tests of the cell preparations used clinically were negative.

Table 1 Baseline Characteristics of the stem cell group and the control group(n = 391)

Characteristics	Stem cell group (n = 191)	Control group (n = 200)	P-value
Age	59 ± 12	60 ± 11	n.s.
BMI	30.1	30.2	n.s.
Sex (male %)	89.53	89	n.s.
EF (%)	29.4 ± 12.7	36.1 ± 13.8	n.s.
Number of injected cells ($\times 10^7$)	6.6 ± 3.3	–	–
Infarct-related coronary artery RCA/LAD/RCX (%)	33.4/49.1/17.5	31.2/50.7/18.1	n.s.
Number of stented coronary arteries until the time of BMC therapy	1.73 ± 0.72	1.7 ± 0.69	n.s.
Therapy during the acute infarct (%) (PTCA/PTCA + Stent/Primary stent)	0/84/16	0/79/21	n.s.
Number of patients with ICD	99	106	n.s.
Medications			
Aspirin (%)	100	100	n.s.
ACE-inhibitor/AT2-receptor antagonist (%)	88	89	n.s.
Diuretics (%)	80	81	n.s.
Digitalis (%)	41	42	n.s.
β-Blocker (%)	91	92	n.s.
Statins (%)	93	92	n.s.
Cardiovascular risk factors			
Diabetes mellitus (%)	27	24	n.s.
Hyperlipoproteinaemia (%)	58	54	n.s.
Smoking (%)	36	38	n.s.
Obesity (%)	62	67	n.s.
Arterial hypertension (%)	52	54	n.s.

Values are mean ± SD or number of patients (%). BMI, body mass index; EF, ejection fraction; RCA, right coronary artery; RIVA, ramus interventricularis anterior; RCX, ramus circumflexus; PTCA, percutaneous transluminal coronary angioplasty; ICD, implantable cardioverter defibrillator; ACE, angiotensin converting enzyme.

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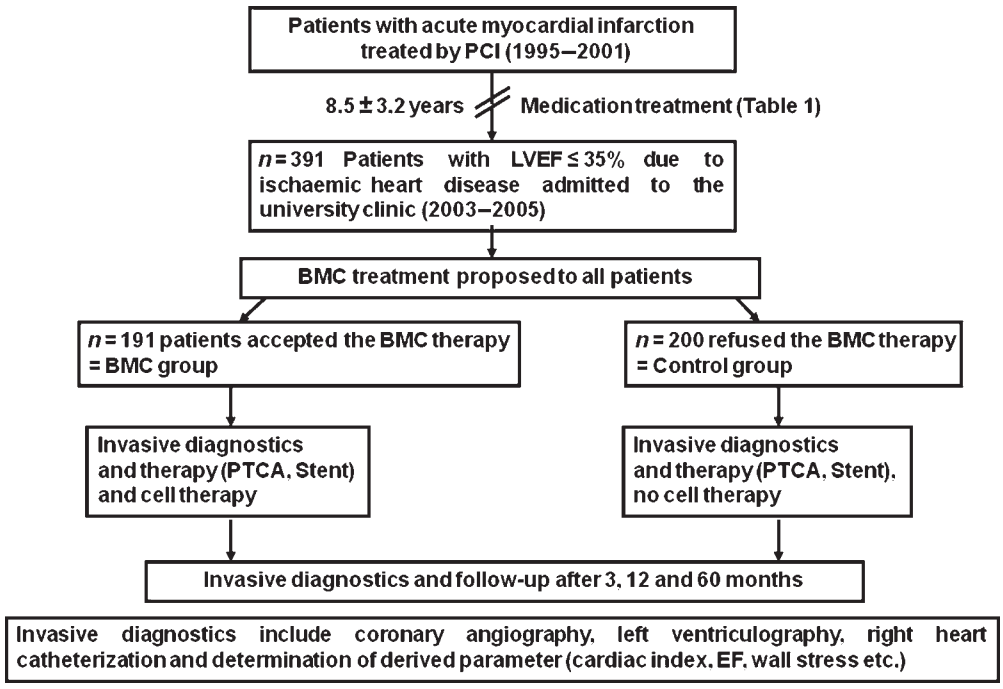

Figure 1 Study design: patient recruitment. PCI, percutaneous coronary intervention; LVEF, left ventricular ejection fraction; BMC, bone marrow cell; PTCA, percutaneous transluminal coronary angioplasty.

Transplantation of bone marrow cells

Cells were infused directly into the infarct-related artery[1,2,6] via an angioplasty balloon catheter inflated at a low pressure. The cell transplantation was performed via four fractional infusions of 5 mL of cell suspension, which was performed in parallel to balloon inflation over 4 min. Percutaneous transluminal coronary angioplasty (PTCA) prevented the backflow of cells and at the same time produced a stop-flow beyond the site of the balloon inflation to facilitate ischaemic preconditioning and infusion of cells into the infarcted zone. Thus, contact time for cellular migration was prolonged.[7] Myocardial ischaemia may promote migration of injected cells. Therefore, to achieve intensified ischaemic stimulus during PTCA and thereafter all patients received dobutamine intravenously to augment contractility with increased oxygen demand[9] for 24 h following the intervention. The mean number of injected cells was $6.6 \pm 3.3 \times 10^7$ BMC's per patient.

Functional assessment of haemodynamics

Left ventriculograms (Quantcor, version 4.0, Siemens) were obtained before coronary angiography (Judkins technique) by intraventricular injection of 20–40 mL of Ultravist®. The infarct size was calculated according to the method of Sheehan.[10] The ventriculographic determination of global and regional left ventricular (LV) geometry as well as the exact calibration methods and the methodological accuracy have been validated in our department over several years.[1,6,11] The longitudinal axis of the left ventricle was directly determined from the ventriculogram, whereas the largest transverse axis was derived from the transverse axis running vertically to the bisected longitudinal axis. For each ventriculogram a specific enlargement and aberration factor was taken into account for calibration and calculation of the volumes. The end-diastolic and end-systolic ventriculograms as well as each cine ventriculogram taken during the first half of the systole were evaluated picture by picture, until systolic wall stress, which was continuously calculated from the intraventricular pressure and the ventricular dimensions, had achieved its maximum (T_{syst}). The peak systolic wall stress (T_{syst}) was determined from the intraventricular pressure (P) (systolic pressure minus end-diastolic pressure), the ventricular radius (r), and the thickness of the ventricular wall (d) according to the Laplace equation ($T = P\ r/2d$). The interior LV radius for each cine picture was derived from the volume measurements [$r = \sqrt[3]{(3V/4\pi)}$].

Regional wall function in the infarcted and normal area, wall thickness and wall stress were determined in different ventricular wall segments.[1,6,11] Perpendicular to the longitudinal axis of the left ventricle (connecting line between the middle of the aortic valve and the ventricular apex) three to four vertical axes were established at equal distances (~0.5 cm) and the anterior hemiaxes were drawn. A tangent was drawn to the external ventricular contour in such a way that its perpendicular passed through the intersecting point of the hemiaxis and the interior ventricular contour, thus obtaining ventricular wall segments and distances of approximately centrifugal shape, when seen from a virtual ventricular centre. This technique was chosen since it helps to prevent or reduce potential overrating of the regional wall thickness, particularly in the basal and apical segments, which otherwise may occur due to distortions in the projection of the outer ventricular contours. The end-diastolic and end-systolic ventriculograms as well as each cine ventriculogram taken during the first half of systole were evaluated picture by picture, until systolic wall stress, as calculated from the intraventricular pressure and the ventricular dimensions, had achieved its maximum (T_{syst}).

End-diastolic wall stress ($T_{diast.}$) was derived from end-diastolic pressure and volume. The contractility index P_{syst}/ESV was calculated by dividing LV systolic pressure (P_{syst}) by end-systolic volume (ESV). An identical methodological procedure was performed for both stem cell and control group patients. Owing to ventricular extra-

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systoles and unfavourable image acquisition, ventriculograms from 40 patients in the BMC group and 32 patients in the control group could not be evaluated.

Spiroergometry and Holter electrocardiogram

An exercise protocol with an intensified workload up to the symptom-limited maximum (basic load of 25 W, intensification at 25 W, 2-min duration of each workload step) was chosen. The anaerobic threshold was calculated according to the V-Slope-method.[12] Exercise capacity was assessed on the basis of maximum load levels expressed in watts (W_{max}) and maximum peak oxygen uptake (VO_{2peak}).

For risk stratification LP, short-term HRV, and 24-h Holter ECG were analysed.

Statistical analysis

All data are presented as mean ± SD. Intra-individual comparison of continuous variables at baseline with those at follow-up was performed with the paired *t*-test. Comparison of non-parametric data between groups was performed with the Wilcoxon rank sum test and the Mann–Whitney test. Non-parametric correlation was calculated by the Spearman correlation. Statistical significance was assumed at a value of $P < 0.05$. For comparisons of various post-treatment evaluations vs. baseline (ventriculography, NYHA class, LP) Bonferroni alpha correction was performed and statistical significance was assumed at a value of $P < 0.0167$. Overall mortality and cardiac mortality did not differ in the STAR-study, as all deaths were cardiac deaths time-dependent cardiac mortality rates were estimated by Kaplan–Meier survival curves and *P*-values were determined by use of log rank statistics. All statistical analyses were performed with SPSS for windows (version 15).

Individual data evaluation and analyses

Over the course of this long-term trial (which was conducted between 2003 and 2008), 14 experienced and senior investigators independently analysed all clinical and haemodynamic data, as follows. Echocardiography (P. Rellecke, MD, E. Umanski, MD, C. Heinrich, MD), cardiac catheterization and stem cell transplantation (B. E. Strauer, MD, C. M. Schannwell, MD, M. Yousef, MD, M. Koestering, MD, T. Zeus, MD, M. Brehm, MD), spiroergometry (G. Sofianos, MD, T. Fleissner, MD, N. Schahab, MD) and for cell preparations and laboratory tests (P. Wernet, MD, G. Kögler, MD). The performance of invasive procedures was supervised and monitored by the quality control committee of the medical institution of the federal state. The quality control of cell preparations and the permission for cell transplantation in humans was provided by the government control administration.

Results

Baseline characteristics

Baseline characteristics of the BMC treated patients and the corresponding controls did not differ significantly (*Table 1*). Risk factor stratification revealed no differences, the NYHA classes were similar. Left ventricular systolic function, as evidenced by EF, was considerably depressed in both groups and no differences in pharmacological treatment, number of diseased coronary arteries, or cardiovascular risk factors, were present (*Table 1*).

During the acute infarct 84% of patients in the BMC group (79% of control group) underwent balloon angioplasty plus stent implantation, and in 16% of patients in the BMC group (21% of control group) primary stenting was carried out. The infarct-related artery was open in all patients. At the time of stem cell transplantation re-stenoses were not present. Ninety-nine patients in the BMC group and 106 patients in the control group had an ICD (*Table 1*).

Results 3 months after cell therapy

Physical exercise capacity

Bone marrow cell treated patients showed a considerable increase in exercise capacity (*Table 2*), likewise subjective assessment of NYHA classification (*Table 3*) revealed a significant improvement by almost one class.

Haemodynamics

Three months after BMC therapy there was an improvement in LV performance as evidenced by increases in cardiac index at rest (by 22.2%) peak oxygen uptake (by 11%), and oxygen pulse (by 6.3%) (*Table 2*). Thus, overall haemodynamics showed significantly improved cardiac performance and exercise capability.

Geometry of the left ventricle (quantitative ventriculography)

There was decrease in both end-diastolic volume (EDV) and ESV following BMC therapy. Since stroke volume increased, the EF improved from 29.4 ± 12.7 to 36 ± 13.3%. The infarct size was reduced by 11.4% (*Tables 4* and *5*).

Contractility of the left ventricle and ventricular wall dynamics

Left ventricular contractility determined by several indexes revealed increased contractile behaviour after BMC therapy: the

Table 2 Left ventricular haemodynamics before and after bone marrow cell therapy in patients with chronic ischaemic cardiomyopathy compared with the control group

Parameter	Baseline/ post-cell therapy	Chronic heart failure	
		Cell therapy	Control
CI-rest ($L/min \times m^2$)	Baseline	2.7 ± 0.63	2.8 ± 0.9
	Post	3.3 ± 0.6***	2.3 ± 1.2
	Abs.	0.56 ± 0.5	−0.45 ± 0.8
VO_{2peak} (mL/min)	Baseline	1515 ± 506	1546 ± 195
	Post	1681 ± 527**	1539 ± 180
	Abs.	158 ± 365	−29.3 ± 120
O_2-Pulse (mL/beat)	Baseline	12.8 ± 3.4	13.1 ± 4
	Post	13.6 ± 3.4**	13 ± 2
	Abs.	0.52 ± 2.1	−0.9 ± 1.2
Ergometry (Watt)	Baseline	78.7 ± 30	78 ± 9
	Post	90.7 ± 33.6***	61 ± 4
	Abs.	11.3 ± 22.9	−15.2 ± 8.7

Abs., absolute difference compared with baseline; CI, cardiac index; VO_{2peak}, peak oxygen uptake; O_2-Pulse, oxygen pulse. Three months after BMC therapy significant improvements in CI, VO_{2peak}, O_2-Pulse, and exercise capacity were documented.
***$P < 0.01$ (pre/post), **$P < 0.05$ (pre/post).

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Table 3 NYHA class and late potentials before and 3, 12, and 60 months after BMC therapy compared with the control group

Parameter	Mean/ Abs.	Chronic heart failure							
		BMC group				Control group			
		Baseline (before BMC therapy) (n = 191)	After 3 months (n = 191)	After 12 months (n = 191)	After 60 months (n = 184)	Baseline (n = 200)	After 3 months (n = 200)	After 12 months (n = 199)	After 60 months (n = 168)
NYHA (class)	Mean	3.22 ± 0.7	2.25 ± 0.7**	2.1 ± 0.7**	1.46 ± 0.5**	3.06 ± 0.6	3.5 ± 0.5	3.66 ± 0.5	3.74 ± 0.4
	Abs.	–	−0.9 ± 0.4	−0.98 ± 0.7	−1.2 ± 0.89	–	0.3 ± 0.4	0.46 ± 0.7	0.6 ± 0.87
LP (Number of simson criteria)	Mean	1.41 ± 1.13	1.01 ± 1.14**	1.11 ± 1**	0.7 ± 1**	1.43 ± 1.1	1.41 ± 1.1	1.5 ± 1.1	2.5 ± 0.6
	Abs.	–	−0.36 ± 0.87	−0.29 ± 0.9	−0.5 ± 0.91	–	−0.02 ± 0.9	0.11 ± 0.96	0.87 ± 0.56

Values are mean ± SD. Abs., absolute difference to baseline; LP, late potential; NYHA, New York Heart Association.
**$P < 0.0167$ vs. baseline (Bonferroni alpha correction).

velocity of ejection rate (volumes/second) increased, and also the slope of the ventricular function curve (P_{syst}/ESV) became steeper, indicating that not only the shortening, but also the velocity of shortening had improved following cell therapy (*Table 5*).

Arrhythmogenic indexes

After BMC therapy there was an improvement in abnormal HRV, LP, and ectopic beats in the cell therapy group (*Tables 3* and *6*).

Results 12 and 60 months after cell therapy

The beneficial effects of BMC therapy were longstanding. After 12 and 60 months there was deterioration in LV performance in the controls (*Table 4* and *Figure 2*). In contrast, BMC treated patients almost maintained the improved level of performance even after 5 years. Thus, the time course of BMC treatment is characterized by (i) an initial peak improvement (3 months) and (ii) an anti-remodelling effect (at 12 and 60 months) associated with preservation of LV function over time. The absolute difference between baseline and the 3 month follow-up for ESV and EF differed significantly between the BMC and control groups.

Mortality

Mortality was considerably reduced in the BMC group. Within a median follow-up time of 4.6 ± 1.4 years, seven patients died in the BMC group. This number is equivalent with an average mortality rate of 0.75% per year. In the control group the average mortality rate was 3.68% per year (32 patients died within a median follow-up time of 4.87 ± 1.1 years). Accordingly, the steepness of the calculated mortality curves was different in the BMC treated patients vs. the controls, demonstrating, in terms of Kaplan–Meier regression analysis, reduced mortality rates ($P < 0.01$) (*Figure 3*).

Discussion

The STAR-heart study represents the largest clinical trial of intracoronary autologous mononuclear BMC transplantation. Intracoronary BMC transplantation was first described by our group in acute myocardial infarction[1,2] and has been extended to include chronic heart failure[6] due to chronic ischaemic cardiomyopathy.

The results of our study demonstrate that in chronic heart failure there are cell-induced improvements in:

(i) haemodynamics at rest (cardiac index, stroke volume, EF etc.);
(ii) exercise capacity (NYHA classification) and oxygen uptake at rest and exercise;
(iii) left ventricular contractility indexes [velocity of ejection rate (volumes/s), P_{syst}/ESV];
(iv) left ventricular geometry (decrease in EDV, in systolic wall stress and in ESV, decrease in infarct size).

Another important result is the considerable decrease in mortality of treated patients. This result allows the conclusion that BMC therapy in chronic heart failure may prolong life.

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Table 4 Quantitative ventriculography before and 3, 12, and 60 months after BMC therapy compared with the control group

Parameter	Mean/ Abs.	Chronic heart failure							
		BMC group				Control group			
		Baseline (before BMC therapy) ($n = 191$)	After 3 Months ($n = 191$)	After 12 months ($n = 191$)	After 60 months ($n = 184$)	Baseline ($n = 200$)	After 3 months ($n = 200$)	After 12 months ($n = 199$)	After 60 months ($n = 168$)
EDV (mL)	Mean	184 ± 52	174 ± 48*	174 ± 39*	175 ± 30**	184 ± 49	185 ± 50	187 ± 37	190 ± 42
	Abs.	–	−9.9 ± 33.3	−9.2 ± 30.4	−9 ± 27.4	–	2.9 ± 32.1	3.2 ± 30.2	4.9 ± 35.1
ESV (mL)	Mean	128 ± 53	110 ± 47**	112 ± 43**	111 ± 30**	118 ± 43	120 ± 43	123 ± 40	132 ± 48
	Abs.	–	−15.9 ± 30	−14.9 ± 32	−14.4 ± 27	–	4.3 ± 29.8	4.6 ± 31.2	9.9 ± 35.7
EF (%)	Mean	29.4 ± 12.7	36 ± 13.3**	37.8 ± 13.4**	36.8 ± 9**	36.1 ± 13.8	35.5 ± 13.5	34.8 ± 12.9	32.3 ± 12.5
	Abs.	–	6.1 ± 8.3	6.4 ± 9.7	6.2 ± 8.4	–	−0.5 ± 9.1	−1.3 ± 6.7	−3.5 ± 8.9
SVI (mL/m^2)	Mean	33.1 ± 11.2	37.3 ± 12**	38.4 ± 10.6**	38.1 ± 7**	32.5 ± 11.2	32 ± 10.9	30.4 ± 10.4	28 ± 9.7
	Abs.	–	4.45 ± 10.4	5.2 ± 9.1	4.9 ± 7.1	–	−0.38 ± 8.1	−1.8 ± 8.1	−3.9 ± 7.5
P_{syst}/ESV (mmHg/mL)	Mean	1.45 ± 1	1.72 ± 1.1*	1.7 ± 0.9*	1.67 ± 0.4**	1.31 ± 0.76	1.28 ± 0.73	1.18 ± 0.43	1.1 ± 0.44
	Abs.	–	0.29 ± 0.8	0.32 ± 0.71	0.34 ± 0.4	–	−0.04 ± 0.4	−0.1 ± 0.38	−1.7 ± 0.4

Values are mean ± SD. Abs., absolute difference compared with baseline; EDV, end-diastolic volume; ESV, end-systolic volume; SVI, stroke volume index; P_{syst}/ESV, contractility index calculated by dividing LV systolic pressure (P_{syst}) by end-systolic volume.

**$P < 0.0167$ vs. baseline (Bonferroni alpha correction), *$P < 0.05$ vs. baseline.

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Table 5 Contractility of the left ventricle and infarct size before and after bone marrow cell therapy in patients with chronic ischaemic cardiomyopathy compared with the control group

Parameter	Baseline/ post-cell therapy	Chronic heart failure	
		Cell therapy	Control
MNSER (vol./s)	Baseline	1.2 ± 0.7	1.14 ± 0.5
	Post	1.31 ± 0.6***	1.05 ± 0.6
	Abs.	0.11 ± 0.3	−0.09 ± 0.3
P_{syst}/ESV (mmHg/mL)	Baseline	1.45 ± 1	1.31 ± 0.76
	Post	1.72 ± 1.1***	1.28 ± 0.73
	Abs.	0.29 ± 0.8	−0.04 ± 0.4
Global $T_{systolic}$ (10^{-3}*N*m^2)	Baseline	19.4 ± 5.9	19.1 ± 5.5
	Post	18.5 ± 5.9*	19.2 ± 5.5
	Abs.	−1.1 ± 2.7	0.3 ± 2.5
Global $T_{diastolic}$ (10^{-3}*N*m^2)	Baseline	5.1 ± 2.3	5 ± 1.9
	Post	5.2 ± 2.5	5.02 ± 1.93
	Abs.	0.2 ± 1.7	0.06 ± 0.98
Infarct size (%)	Baseline	28.1 ± 17	27.9 ± 16.9
	Post	24.9 ± 16.4**	28.4 ± 16.8
	Abs.	−4.5 ± 9.8	1.8 ± 11.1

Abs., absolute difference to baseline; MNSER, mean normalized systolic ejection rate; P_{syst}/ESV, contractility index calculated by dividing LV systolic pressure (P_{syst}) by end-systolic volume. Improvements of the MNSER and P_{syst}/ESV were documented 3 months after BMC therapy. A significant decrease in infarct size was documented.
***$P < 0.01$ (pre/post), **$P < 0.05$ (pre/post).

Table 6 Arrhythmogenic indexes before and 3 months after bone marrow cell therapy

Parameter	Baseline/ post-cell therapy	Chronic heart failure	
		Cell therapy	Control
Heart rate variability (HRV): SD of the RR-intervals (ms)	Baseline	31.7 ± 19.2	34 ± 15.2
	Post	37.2 ± 23.2***	32.6 ± 14.1
	Abs.	5.7 ± 15.8	−2.67 ± 9.8
Lown classification	Baseline	2.49 ± 1.5	2.31 ± 1.6
	Post	1.96 ± 1.6**	2.5 ± 1.7
	Abs.	−0.46 ± 1.1	0.2 ± 1.1

Abs., absolute difference compared with baseline. Significant improvements of HRV and Lown classification were documented.
***$P < 0.01$ (pre/post), **$P < 0.05$ (pre/post).

Intracoronary cell delivery

Stem cells can be administered to the heart via at least three different approaches; namely the intravenous, the intracoronary and the intramyocardial routes. Intracoronary cell administration which was used by our group for the first time in 2001[1,2] seems to enable (i) sufficient cell accumulation within the myocardium and (ii) homogenous distribution of cells to all perfused areas of the territory of the infarct-related artery. In contrast, when cells are given intravenously only a very small fraction of infused cells can reach the infarct region: assuming normal coronary blood flow of 80 mL/min per 100 g of LV weight, ~160 mL of blood per left ventricle (assuming a regular LV mass of ≈200 g) will flow per minute. This corresponds to only around 3% of cardiac output (assuming a cardiac output of 5000 mL/min).[9,13] Thus, intravenous administration of BMC would require many circulation passages to enable the infused cells to come into contact with the infarct-related artery. Throughout this long circulation and recirculation time, homing of cells to other organs could considerably reduce the number of cells dedicated to cell repair in the infarcted zone. In contrast, supplying the entire compartment of heart muscle cells by intracoronary administration obviously seems to be advantageous for tissue repair of infarcted heart muscle as all cells are able to flow through the infarcted and peri-infarcted tissue during the immediate first passage.[3,7] On the other hand, cluster deposits and disarray of myocytes have been described for intramyocardial cell injections[4,5] which could inhibit homogenous cell migration to the infarcted and peri-infarct tissue. Thus, by using the intracoronary procedure the infarct tissue and the peri-infarct zone should theoretically be enriched with the maximum number of available cells at all times.

The importance of ischaemic preconditioning (balloon dilatation)

Currently it is not known how many cells are retained in the myocardium after intracoronary infusion and also how many cells migrate into the border zone which seems to be the most active area of regeneration after an infarct. Myocardial ischaemia may be an appropriate stimulus for a stem cell to find its optimum myocardial niche.[14,15] Therefore, the ischaemia-producing stimulus by balloon dilatation during the BMC infusion (ischaemic preconditioning) seems to be important for the cell to home into the cardiac niche.[8,16] It is obvious that when cells are just injected into the coronary arteries, without preconditioning interventions, they may pass through the coronary vascular bed without significant migration into or extraction by the ventricular myocardium. Differences in the intracoronary delivery techniques used in various publications and differences results and therapeutic outcomes may be due to the non-uniform mode of BMC infusion into the coronary circulation. Precise methodological standardization seems to be important for both effectiveness of stem cell therapy in clinical heart disease and the comparability of multicentre stem cell studies.

Quantitative aspects of cell delivery

From a quantitative point of view, another consideration may be noteworthy; when a large infarct occurs (50% infarct), 50% of the LV myocardium is destroyed. The number of myocytes in a normal heart is $6–7 \times 10^9$ cells. Consequently, in such a large infarct ~$3–3.5 \times 10^9$ cells are lost. In the setting of clinical stem cell therapy, such as in the STAR-heart study and in other clinical

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trials, an average of ~66 × 10^6 cells are administered which is only 1/50th or less of the number of myocytes destroyed by a large infarct. However, this small number of cells may be important for the border zone of the infarct. Of the infused cells only a small fraction is retained in the myocardium, between 5 and 40% of injected cells is estimated[17,18] The high cell passage with only partial cell extraction by the heart muscle may help to explain why only small regenerative effects are observed after infusion of a large amount of stem cells.

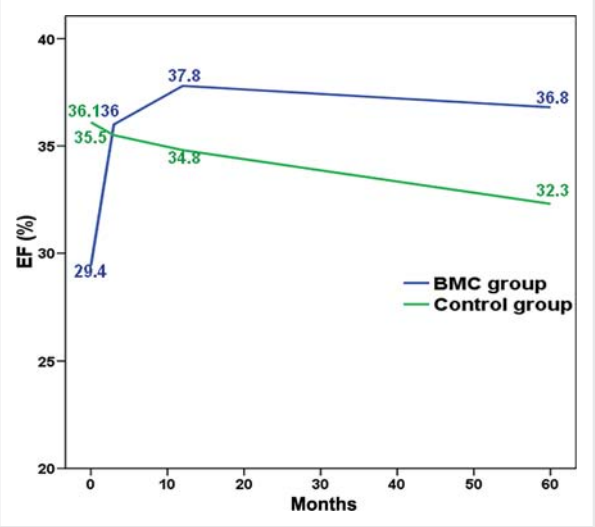

Figure 2 Ejection fraction over time in the bone marrow cell group compared with the control group.

Remodelling and mortality after intracoronary bone marrow cell transplantation

In ischaemic cardiomyopathy deterioration in LV function occurs over time (remodelling). Remodelling occurs in ~60% of cardiac patients after an acute infarction. The persistent beneficial haemodynamic effects observed over the follow-up time (3, 12, and 60 months) in this study justify the assumption that BMC treatment may overcome the possibly detrimental effects of ventricular remodelling. Further studies are now required to investigate differences in the effects of BMC therapy in chronic heart failure groups with different baseline EF. In contrast, in the control group of the STAR-heart study decreases in global and regional ventricular performance occurred, thus remodelling presumably was not prevented in these patients.

Mortality in the control group was relatively low when compared with data from the literature.[19] From the onset of AMI until the first examination in our clinic (8.5 ± 3.2 years) patients from both groups were treated and observed intensively by outpatient practitioners and hospitals. After hospitalization in our clinic, medical treatment was optimized (*Table 1*) and meticulously continued according to treatment guidelines until the end of the study. Thus, the low mortality in our control group may be due to the controlled medical treatment and to the repeated study evaluations which resulted in good compliance in all patients in both groups.

The STAR-heart study demonstrates reduced mortality after BMC therapy. The reason may be two-fold; namely a decrease in pump failure and a decrease in severe cardiac arrhythmias. The reduction in pump failure following BMC therapy may be due to the contractile and anti-remodelling action of BMCs in the failing

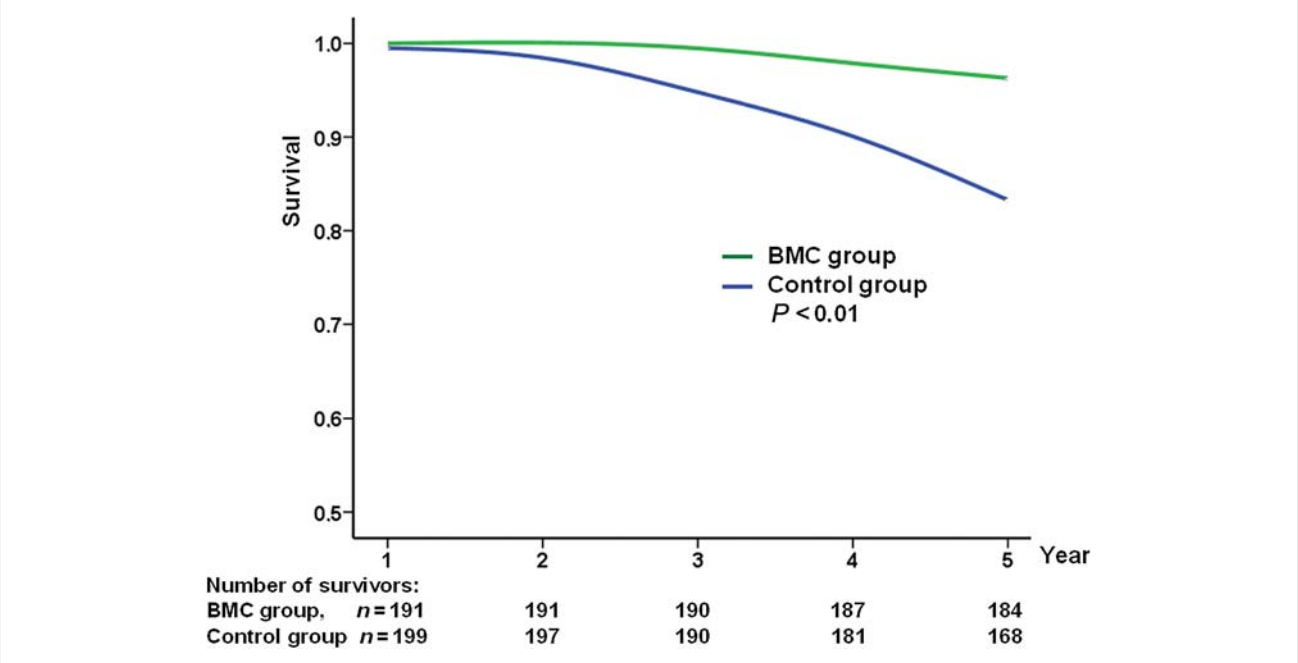

Figure 3 Effect of bone marrow cell therapy on survival in patients with chronic ischaemic cardiomyopathy.

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heart. Since these effects persisted over the years, it is reasonable to assume that they form the basis for the long-lasting anti-failure properties of BMC therapy in these cardiac patients. BMC therapy also seems to exert structural effects in the sense that remodelling may be prevented or delayed, thereby enabling better overall performance of the heart.

The second reason for the decrease in mortality in the BMC treated patients may be due to a reduction in cardiac arrhythmias. There is evidence that impaired LV function increases malignant ventricular arrhythmias and predisposes to sudden cardiac death. Large studies of the spontaneous course of ischaemic and/or dilated cardiomyopathy have demonstrated a 20–30% incidence of sudden cardiac death in relation to overall mortality induced by malignant ventricular arrhythmias. None of the patients treated in the STAR-heart study had malignant arrhythmias and there was some evidence of a decreased arrhythmogenic risk as shown by the improvement in HRV and LP.[20,21] It is possible that decreased arrhythmogenic risk in BMC treated patients obtains its haemodynamic equivalent by the BMC induced anti-remodelling properties, with improvement in LV function.

In summary, the STAR-heart study was designed to analyse ventricular performance and mortality in a large population of patients with chronic cardiac failure due to ischaemic cardiomyopathy. Results show that BMC therapy—in addition to optimized therapeutic measures—exerts beneficial longstanding effects on ventricular function, quality of life and survival. Side effects, except for the usual interventional complications, could not be detected. Thus, this therapeutic procedure may be justified and indicated when the sum of all regimens for management of advanced heart failure is not sufficient.

Clinical perspective

Advanced chronic heart failure, despite intensive pharmacological therapy and other measures, continues to represent a severe disease worldwide. Consequently, therapeutic regimens are needed, which when administered as an alternative or in addition to conventional therapy, can improve quality of life, increase ventricular performance, and increase survival. Intracoronary BMC therapy has been shown to be effective in acute myocardial infarction, and the STAR-heart study also indicates effectiveness in chronic heart failure. This study also demonstrates that this new therapy improves performance on top to all other therapeutic regimes. Moreover, (i) subjective assessment revealed amelioration of heart failure symptoms (NYHA class) compatible with better quality of life and (ii) long-term survival analysis shows that intracoronary BMC therapy prolongs life in these often hopeless cardiac conditions.

With regard to the improved treatment of heart failure, further studies are required which focus on cell based therapy, such as the dependence of myocardial regeneration on the number of transplanted cells, modified cell application measures, improved preconditioning before and during cell transplantation, and variation in cell preparation techniques. These procedures could probably lead to an additional and powerful therapeutic tool in patients with refractory heart failure.

Conflict of interest: none declared.

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