

The role of quantitative Tc-99m-MIBI gated SPECT/F-18-FDG PET imaging in the monitoring of intracoronary bone marrow cell transplantation

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Abstract

BACKGROUND: A lot of unresolved questions still exist concerning the exact mechanism of the beneficial effects of bone marrow cell (BMC) transplantation for myocardial regeneration. The aim of this communication is to report the cases of patients with and without post-transplantation left ventricular function improvement.

MATERIAL AND METHODS: To this study we included consecutive patients with irreversible damage after a first acute

ST-elevation myocardial infarction treated by coronary angioplasty with stent implantation. The irreversible damage was identified by dobutamine echocardiography and confirmed by rest gated Tc-99m-MIBI gated SPECT and in the majority of patients by F-18-FDG PET imaging as well. Using 4D-MSPECT software, we quantified MIBI/FDG uptake and gated SPECT left ventricular ejection fraction, end-diastolic/end-systolic volumes (LVEF, EDV/ESV) before BMC therapy and 3 months later.

RESULTS: The results obtained in the initial group of patients in this study (27 patients in the BMC treated group, 16 patients in the control group) have been published previously [Eur J Nucl Med 2005; 32 (Suppl 1): S46]. Among the BMC group, we identified 13 responders to therapy with average LVEF improvement from $43.3\% \pm 11\%$ to $51.4\% \pm 10.4\%$ and EDV/ESV improvement from 145 ml/84 ml to 133 ml/67 ml. The remaining 14 patients were non-responders to therapy with no significant change in LVEF ($39.1\% \pm 8.1\%$ versus $39.8\% \pm 7.4\%$), the EDV/ESV increased from 166 ml/105 ml to 188 ml/116 ml. Responders to the cell therapy had prevailing MIBI uptake in the range of 31–50% of maximum in the infarction territory. On the other hand, non-responders to BMC therapy had prevailing MIBI uptake in the range of 0–30% of maximum. Two cases are presented in this report.

CONCLUSIONS: Further studies with a larger cohort of patients would be helpful to evaluate our findings. We observed strong interindividual differences in the effectiveness of the cell therapy. Prevailing residual MIBI uptake in the range of 31–50% of maximum was in the subgroup of responders to the cell therapy.

Key words: acute myocardial infarction, myocardial viability, bone marrow cell trans, MIBI SPECT, FDG PET

Introduction

Clinical outcome after myocardial infarction (MI) depends on the extent of irreversible damaged myocardium. Recent studies report on a new approach of bone marrow cell (BMC) transplan-

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tation for myocardial regeneration in animal models and in humans [1–7]. However, a lot of unresolved questions still exist concerning the exact mechanism of beneficial effects of cell transplantation. Nuclear medicine methods enable the evaluation of myocardial perfusion, function and metabolism providing well-validated diagnostic information on myocardial viability assessment [8–11]. The aim of this communication is to report the role of imaging methods used to confirm repair of infarcted myocardium due to BMC transplantation; we analysed the cases of patients with and without the benefit of this therapy.

Material and methods

We demonstrate cases from our prospective multicentre study. In November 2003, we started monitoring the effects of intracoronary BMC therapy to determine the impact of the dose of transplanted cells on myocardial function and perfusion, and to identify the potential interindividual differences in the effectiveness of the cell therapy. The results obtained in the initial patients in this study have been published previously [12]. To the study we included consecutive patients with irreversible damage after a first acute ST-elevation MI treated by coronary angioplasty with stent implantation. The irreversible damage was identified by dobutamine echocardiography and confirmed by rest gated Tc-99m-MIBI gated single-photon emission computed tomography (SPECT) and in the majority of patients by F-18-fluorodeoxyglucose (FDG) positron emission tomography (PET) imaging as well. The patients were randomized to two BMC treated groups (lower and higher cell dose) or to the control group without cell transplantation therapy. The echocardiography, gated rest MIBI SPECT, and FDG PET were repeated 3 months later. The institutional ethics committee approved the study and written consent was obtained from each patient.

Echocardiography

Echocardiography examinations were performed using Vivid 7 (GE/Vingmed, Milwaukee, Wisconsin, USA) with an M3S transducer. After resting echocardiography including colour Doppler tissue imaging, low-dose dobutamine was performed to assess myocardial viability. Dobutamine was administered with an infusion pump at doses of 5, 10, and 20 $\mu\text{g}/\text{kg}/\text{min}$ each for 5 minutes. Parasternal long axis and three apical views were digitally stored at rest and at the last minute of all doses of dobutamine for subsequent wall motion analysis. Regional wall motion analysis was performed using a 16-segment model recommended by the American Society of Echocardiography [13] and a conventional scoring system was used (1 — normokinesis, 2 — hypokinesis, 3 — akinesis, 4 — dyskinesis) for each segment. The akinetic and dyskinetic segments with no improvement in thickening after any dose of dobutamine were regarded as irreversibly damaged.

Gated Tc-99m-MIBI SPECT acquisition

All examinations were performed in one centre using standard methodology. 740 MBq Tc-99m-MIBI was injected at rest. Gated single photon emission computed tomography (gated SPECT) imaging acquisition began 1 hour after MIBI injection using a 2-detector Siemens e.cam gamma camera (Siemens Medical Solutions, Erlangen, Germany) equipped with low-energy, high-reso-

lution parallel-hole collimators. Sixty-four projections were acquired in a 64×64 matrix over 180° from the 45° right anterior oblique projection to the 45° left posterior oblique projection. Images were gated at 8 frames per cardiac cycle. Processing was performed using a Butterworth filter with a frequency cut-off of 0.45 cycles/pixel and an order of 5.0. No attenuation correction was used.

F-18-FDG PET Acquisition

F-18-FDG-PET was performed with a whole-body PET scanner ECAT ACCEL (Siemens Medical Solutions, USA) producing 21 continuous tomograms spaced 5.1 mm apart with a slice thickness of 13 mm. To achieve the optimal glucose metabolic situation, hyperinsulinaemic-euglycaemic clamping was used. Patient preparation started with the determination of the glucose level. According to the value measured, a sugar dose of 25–50 g was applied orally. One hour later, the repeat glucose level was determined and, depending on its level, a dose of insulin in the range of 1–4 IU was administered simultaneously with FDG (200–250 MBq intravenously). Acquisition was started 50 minutes after the administration of FDG and images of glucose utilization were acquired for 15–20 minutes (depending on the patient's weight) in a 3D mode. Transaxial reconstructions were rotated and displayed in the short axis plane and in the vertical and horizontal long-axis planes.

Gated SPECT and PET data analysis

Images were interpreted visually by a consensus of two experienced nuclear cardiologists. Each study was interpreted separately in a blinded fashion. The extent and severity of perfusion and metabolism abnormality, gated SPECT rest LV ejection fractions and LV end-diastolic/end-systolic volumes were obtained through the use of automated, commercially available software 4D-MSPECT (the University of Michigan, Ann Arbor, MI, USA). The tracer uptake was analysed on computer-generated polar maps. In perfusion analysis, the polar maps of each patient were compared on a pixel-by-pixel basis with a MIBI normal database derived from 70 normal volunteers. Pixels with a MIBI activity > 2.5 SD below the corresponding normal mean values were considered abnormal. Perfusion defect was automatically expressed by the computer as the number of abnormal pixels divided by the total number of LV pixels $\times 100$ [8]. Nonviable myocardial area (infarct size) was expressed as a percentage of the left ventricle with FDG uptake below 50% having concomitant perfusion SPECT defect (perfusion-metabolism match area). The superimposition of FDG and MIBI uptake defects and the quantification of resultant common defects defining the infarct size were performed automatically by the 4D-MSPECT software.

Implantation of mononuclear bone marrow cells into the myocardium

Autologous mononuclear bone marrow cells were transplanted via a percutaneous transluminal catheter located in the infarct-related artery using the method described by Strauer et al. [2]. After insertion of a catheter, the balloon was inflated at the site of previous angioplasty and stent implantation. Following that, a total of seven balloon inflations lasting for three minutes were carried out. Individual inflations were separated by three-minute

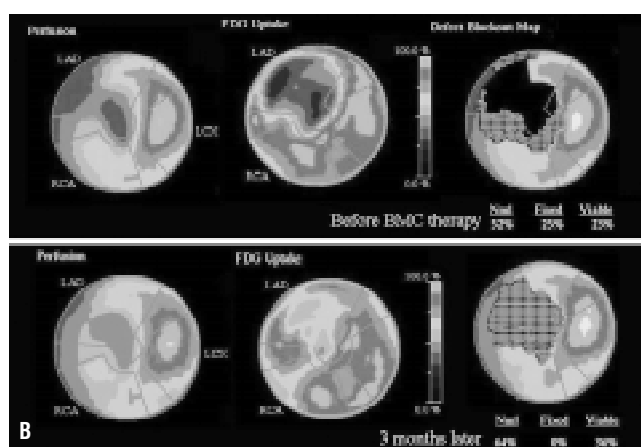
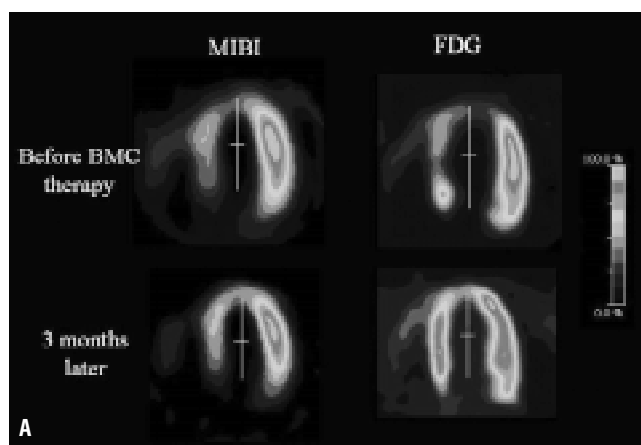


Figure 1AB. Responder to BMC therapy. Before BMC therapy, the images in the horizontal long axis (Figure 1A, top) and the polar maps (Figure 1B, top) showed Tc-99m-MIBI SPECT and F-18-FDG PET distribution with the presence of an extensive nonviable myocardium (25% of total left ventricle). At 3 months after BMC transplantation, horizontal long axis slices (Figure 1A, bottom) and polar plots (Figure 1B, bottom) demonstrated an improvement in perfusion and metabolism.

intervals of balloon deflation. At the onset of each balloon inflation 3 ml of mononuclear bone marrow cell suspension was injected into the infarct-related artery distal to the site of occlusion. This procedure was performed 5 to 9 days after the onset of MI and assured direct transport of bone marrow cells into the infarcted area. Two cell doses were randomly applied: the lower dose of 1×10^7 cells (LD group) and the higher dose of 1×10^8 cells (HD group). In both patient groups, the number and duration of balloon inflations and the cell suspension volume were identical.

Case report 1

42-year-old male, successfully treated by BMC transplantation (Figure 1). There was evidence of irreversible injury after acute MI treated by primary angioplasty with stent implantation confirmed both by dobutamine echocardiography and nuclear imaging. Before BMC therapy, Tc-99m-MIBI SPECT and F-18-FDG PET images showed the presence of the perfusion — metabolism match

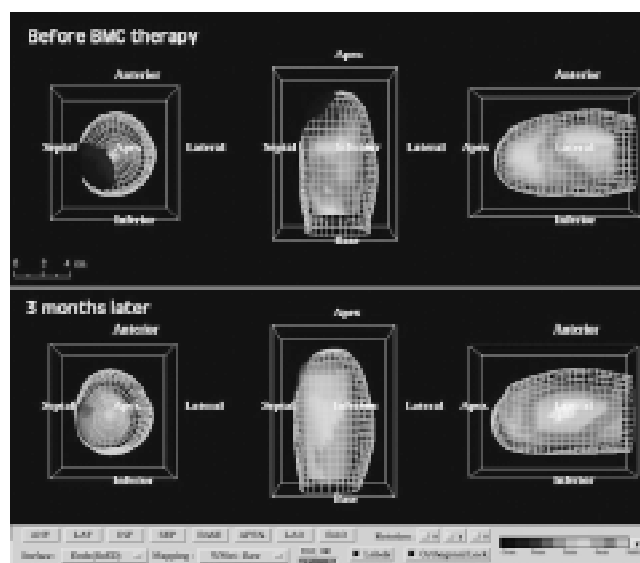


Figure 1C. Gated SPECT 3D images of endocardial surface silhouettes at end-diastole and end-systole demonstrated post-transplantation improvement in LV function (see also the text in the case report 1).

with both tracers uptake < 50% of maximum. Quantitative analysis using 4D-MSPECT software indicated an extensive nonviable myocardium (25% of total left ventricle). BMC intracoronary transplantation was performed on post-infarction day 7 (1×10^8 cells). At 3 months after BMC transplantation, MIBI SPECT and FDG PET imaging demonstrated improvement in perfusion and metabolism. Gated SPECT 3D images confirmed post-transplantation improvement in regional wall motion, LVEF (from 45% to 49%), end-diastolic volumes (from 210 ml to 187 ml), and end-systolic volumes (from 115 ml to 96 ml).

Case report 2

48-year-old male, unsuccessfully treated by BMC therapy (Figure 2). After acute MI treated by primary angioplasty with stent implantation, dobutamine echocardiography identified an irreversible injury, which was confirmed by nuclear imaging. Before BMC therapy, the images showed very low MIBI and FDG uptake corresponding with the perfusion - metabolism match pattern. Quantitatively, the extent of nonviable myocardium was 40% of total left ventricle. On post-infarction day 7, the patient underwent cell intracoronary transplantation (1×10^7 cells). After BMC therapy, the extent of nonviable myocardium was unchanged (38% of total left ventricle). Gated SPECT showed no post-transplantation improvement in regional wall motion, LVEF remained unchanged at baseline 39%, and no significant decrease in end-diastolic volumes (260–256 ml) and end-systolic volumes (158–156 ml).

Discussion

The therapeutic potential of bone marrow cells has recently been described in patients with acute MI [1–6]. However, no previous study analyzed the cause of interindividual differences

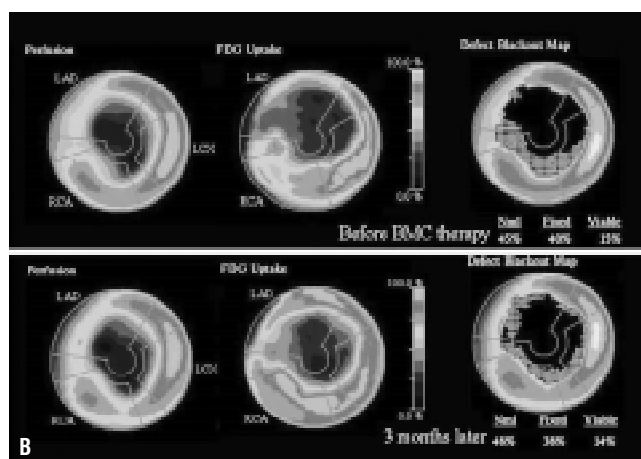
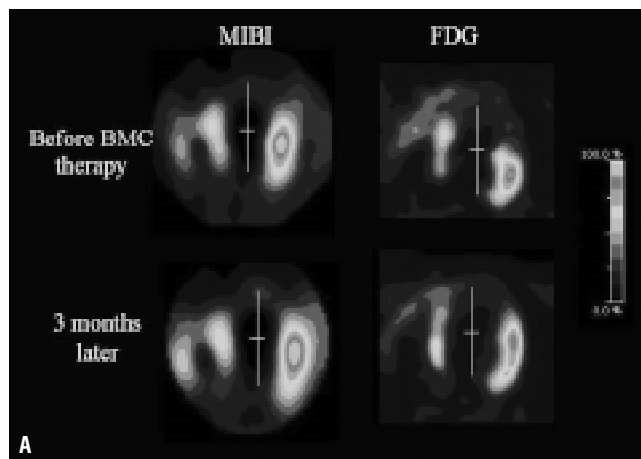


Figure 2AB. Non-responder to BMC therapy. Before BMC therapy, the images in the horizontal long axis (Figure 2A, top) and the polar maps (Figure 2B, top) showed very low MIBI and FDG uptake corresponding to large nonviable myocardium (40% of total left ventricle). Horizontal long axis slices (Figure 2A, bottom) and polar plots (Figure 2B, bottom) at 3 months after BMC transplantation demonstrated that the extent of nonviable myocardium remained unchanged (38% of total left ventricle).

in the effectiveness of the cell therapy. First of all, it was absolutely necessary to confirm correctly the presence of irreversible injury in the left ventricular dysfunctional segments prior the cell therapy. The irreversible damage in this study has been identified by dobutamine echocardiography and confirmed by radionuclide imaging. It is generally accepted that in patients with ischemic heart disease, contractile reserve has a lower sensitivity to detect viable dysfunctional myocardium than myocardial perfusion SPECT [9]. Metabolic imaging with F-18-FDG PET currently represents the gold standard for myocardial tissue viability assessment with higher sensitivity than perfusion imaging [10, 11].

The results obtained in the initial patients in this study (27 patients in the BMC treated group, 16 patients in the control group) have been published previously [12]. Among the BMC group, we identified 13 responders to therapy with average LVEF improve-

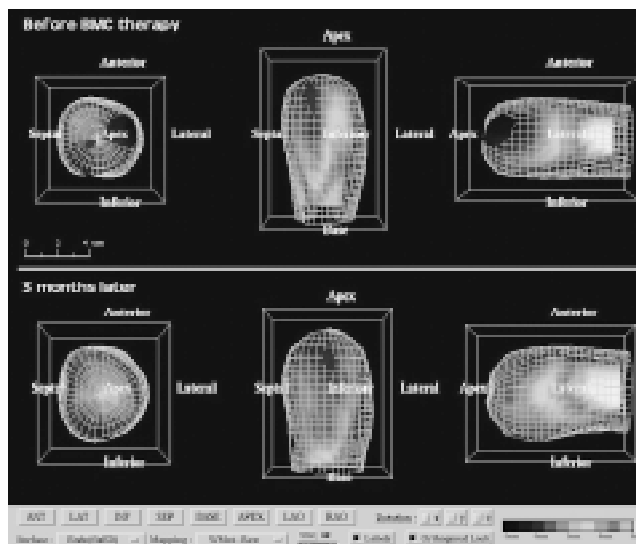


Figure 2C. Gated SPECT 3D images of endocardial surface silhouettes at end-diastole and end-systole demonstrated no post-transplantation improvement in LV function (see also the text in case report 2).

ment from $43.3\% \pm 11\%$ to $51.4\% \pm 10.4\%$ and EDV/ESV improvement from 145 ml/84 ml to 133 ml/67 ml. The remaining 14 patients were non-responders to therapy with no significant change in LVEF ($39.1\% \pm 8.1\%$ versus $39.8\% \pm 7.4\%$) - the EDV/ESV increased from 166 ml/105 ml to 188 ml/116 ml. For the identification of responders and non-responders to cell transplantation, we studied perfusion and metabolism characteristics of patients with and without the benefit of BMC therapy. We used a polar map with 10% decrements in MIBI uptake displayed in colour layers. The level of minimum MIBI uptake in each infarcted nonviable region was determined. In case report 1 we demonstrated a patient who was successfully treated by BMC transplantation. Similarly to this patient, we observed prevailing MIBI uptake in the range of 31–50% of maximum in the dysfunctional segments among other responders to therapy. In contrast, the patients with very low MIBI uptake < 30% of maximum prevailed in the subgroup of non-responders. In case report 2 we present a patient without any benefit from BMC therapy with a typical example of very low MIBI uptake.

In conclusion, we observed strong interindividual differences in the effectiveness of cell therapy. Further studies with a larger cohort of patients would be helpful to evaluate our findings. However, our preliminary results suggest that prevailing MIBI uptake in the range of 31–50% of maximum identified responders to the cell therapy (supposedly those patients with the presence of at least the minimum amount of myocytes with cell membrane integrity in the infarcted lesion). On the other hand, prevailing infarction MIBI uptake in the range of 0–30% identified non-responders (those patients without any significant residual viability).

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References

1. Orlic D, Kajstura J, Chimenti S et al. Bone marrow cells regenerate infarcted myocardium. *Nature* 2001; 410: 701–705.
2. Strauer BE, Brehm M, Zeus T et al. Repair of infarcted myocardium by autologous intracoronary mononuclear bone marrow cell transplantation in humans. *Circulation* 2002; 106: 1913–1918.
3. Stamm C, Westphal B, Kleine HD et al. Autologous bone-marrow stem-cell transplantation for myocardial regeneration. *Lancet* 2003; 361: 45–46.
4. Tse HF, Kwong YL, Chan JFK, Lo G, Ho CL, Lau CP. Angiogenesis in ischaemic myocardium by intramyocardial autologous bone marrow mononuclear cell implantation. *Lancet* 2003; 361: 47–49.
5. Assmus B, Schachinger V, Teupe C et al. Transplantation of progenitor cells and regeneration enhancement in acute myocardial infarction (TOPCARE-AMI). *Circulation* 2002; 106: 3009–3017.
6. Döbert N, Britten M, Assmus B et al. Transplantation of progenitor cells after reperfused acute myocardial infarction: evaluation of perfusion and myocardial viability with FDG-PET and thallium SPECT. *Eur J Nucl Med* 2004; 31: 1146–1151.
7. 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.
8. Dakik HA, Howell JF, Lawrie GM et al. Assessment of myocardial viability with ^{99m}Tc-sestamibi tomography before coronary bypass graft surgery. *Circulation* 1997; 96: 2892–2898.
9. Canty JM, Fallavollita JA. Hibernating myocardium. *J Nucl Cardiol* 2005; 12: 104–119.
10. Matsunari I, Taki J, Nakajima K et al. Myocardial viability assessment using nuclear imaging. *Ann Nucl Med* 2003; 17: 169–179.
11. Baer FM, Voth E, Schneider ChA, Theissen P, Schicha H, Sechtem U. Comparison of low-dose dobutamine-gradient-echo, magnetic resonance imaging and positron emission tomography with ¹⁸F flourodeoxyglucose in patients with chronic coronary artery disease. *Circulation* 1995; 91: 1006–1015.
12. Kaminek M, Meluzin J, Myslivecek M et al. Cardiac MIBI SPECT/FDG PET: can we predict repair of infarcted myocardium by bone marrow cell therapy? *Eur J Nucl Med* 2005; 32 (Suppl 1): S46.
13. Schiller NB, Shah PM, Crawford M et al. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. *J Am Soc Echocardiogr* 1989; 2: 358–367.