In vivo contrast enhanced MRI for quantification of cardiac function and infarct size after stem cell therapies in mice

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Introduction Local ischemia in the heart during myocardial infarction will result in massive cell death of rhythmically contracting cardiomyocytes. Unfortunately, regeneration of cardiomyocytes is rare and during left ventricular (LV) remodeling affected tissue is replaced by non-contractile fibrotic tissue. Stem cell-based therapies can either provide the heart with new functional cardiomyocytes or exert paracrine effects, thereby positively affecting LV remodeling [1].

In this study, the global effects of skeletal myoblast (SM) and mesenchymal stem cell (MSC) transplantation on infarcted mouse hearts were determined noninvasively with *in vivo* contrast enhanced cardiac MRI. Both cell types were isolated from Swiss mice to enable a direct comparison.

Methods Myocardial infarction was induced in male Swiss mice by either cryoinjury or permanent occlusion (ligation) of the left coronary artery, immediately followed by injection of PBS (sham) or $2{\cdot}10^5$ GFP-positive SM or MSC in the centre of the infarction [2]. Cells were isolated from 17.5d embryos and adult mice respectively. Non-operated Swiss mice served as controls. Each group consisted of 1-4 mice.

After 14 days, long- and short-axis ECG and respiratory triggered CINE FLASH images (TE/TR/α/NEX/FOV/matrix = 1.8ms/7ms/15°/6/3x3cm^2/192x192) were acquired at 9.4T to determine LV global functional parameters. Infarct size was assessed on T_1w short-axis multislice FLASH images (TR/α/slice thickness = 63ms/60°/1mm) acquired before and up to 30min after the injection of 0.3mmol Gd-DTPA/kg. Data analysis was performed with CAAS-MRV FARM software (Pie Medical Imaging).

Results Two weeks after the induction of myocardial infarction, infarct size was reduced by transplantation of either SM and MSC in both cryoinjured and permanently occluded hearts (figures 1&2). Ejection fractions (EF), end-diastolic and -systolic volumes (EDV and ESV, respectively) were improved in all treatment groups, except for mice with cryoinjury transplanted with SM. However, all functional parameters were still impaired compared to control mice. End-diastolic mass was decreased by ~17% in mice with permanent occlusion transplanted with SM or MSC, whereas only a minor decrease was found in mice with cryoinjury (not shown).

Therapy was most effective in mice with permanent occlusion, where relative infarct size was decreased by 13.8% and 34.5% after transplantation of SM and MSC respectively. This was accompanied by an increase in EF of 24.8% and 63.6%, achieved by a reduction in EDV and ESV of 30-40%.

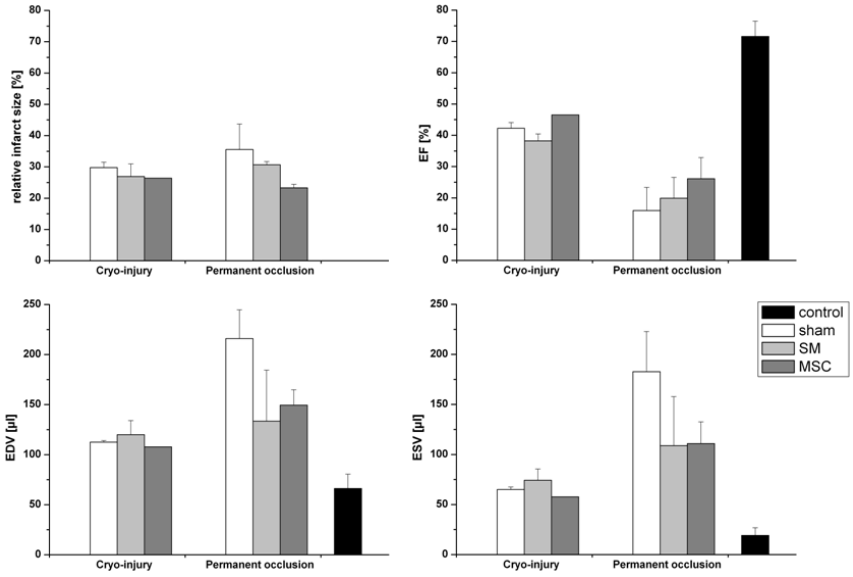

Figure 1: Infarct size, EF, EDV and ESV as determined from *in vivo MRI* data.

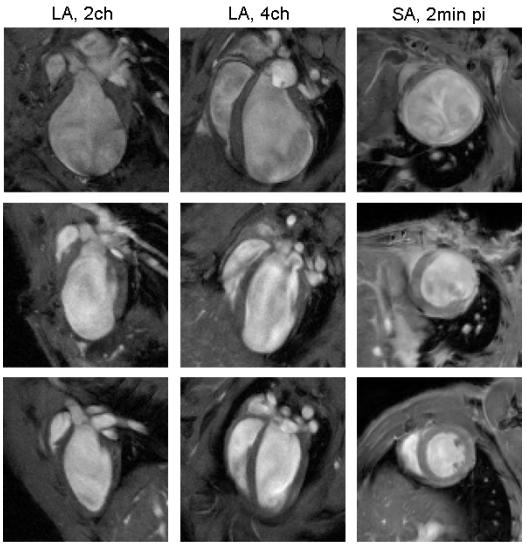

Figure 2: Top: mouse heart 14d after permanent occlusion; middle: heart 14d after permanent occlusion and MSC transplantation; bottom: control heart

Discussion Skeletal myoblasts and mesenchymal stem cells exerted positive effects on myocardial viability and global cardiac function in mice with a permanent occlusion of the coronary artery. Furthermore, SM and MSC partially prevented hypertrophy, since myocardial mass was reduced. Transplantation of MSC had the largest influence on infarct size and ejection fraction.

In mice with cryoinjury, MSC also performed better than SM. However, global myocardial damage induced by cryoinjury was smaller than by permanent occlusion, thereby limiting the detection range. Furthermore, the local environment of stem cells in cryoinjured myocardium might be less optimal for cells to affect LV remodeling compared to the permanent occlusion model.

Although recent MRI studies have already shown improvements in LV functional parameters by cell transplantation, this study is, to our knowledge, the first to report both improved cardiac performance and smaller infarct size after stem cell therapies in mice [3, 4].

References 1. Röll W. et al. *Nature*; 450:819-826, 2007. 2. Röll W. et al. *Circulation*; 105:2435-2441, 2002. 3. Arai T. et al. *MRM*; 55:203-209, 2006. 4. Winter EM. et al. *Circulation*; 116-917-927; 2007.