Mesenchymal Stem Cells Improve Regional Wall Function After Reperfused Myocardial Infarction

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Introduction:

Because the regenerative capacity of the heart is limited, pathologic ventricular remodeling often ensues after an ischemic event leading to decline in left ventricular function. Exogenous administration of bone marrow-derived mesenchymal stem cells (MSCs) has the potential to aid in myocardial repair (1) . However, precise targeting of exogenous MSCs to the infarcted tissue is difficult using conventional x-ray fluoroscopic delivery. Interventional MRI offers a method to accurately deliver MSCs and also monitor the response to treatment with contrast-enhanced and tagged MRI. The purpose of this study was to determine the efficacy of MSC therapy, as defined by improvements in regional contractile function following MR-fluoroscopically delivered MR-labeled MSCs (MR-MSCs) in a canine model of reperfused myocardial infarction (MI).

Methods:

MI was created by a 90-minute closed-chest coronary artery balloon occlusion followed by reperfusion under x-ray fluoroscopy in thirteen mongrel dogs (25-30 kgs). MSCs were isolated from bone marrow and magnetically labeled with 25 μg Fe/ml Feridex and 375 ng/ml poly-L-lysine (2,3) for 24h prior to injection. In six dogs, autologous MR-MSCs (3-15 x10^7 cells) were delivered under MR fluoroscopy (non-ECG-gated, real-time, SSFP sequence: 3.4 ms TR; 1.2 ms TE; 45º flip angle (FA); 128x128 image matrix; 0.5 NEX, 10 mm slice thickness (ST); 125 kHz bandwidth (BW); and 30 cm FOV) with interactive scan plan acquisition (i-drive) on a 1.5T MR Scanner (GE Healthcare) at 72h post-MI. Infarcted myocardium was identified from delayed contrast-enhanced (DCE) short-axis images (ECG-gated, inversion recovery fast gradient echo (FGRE), 0.2 mmol/kg iv bolus of Gd-DTPA imaged at 15 minutes post-injection, 7.8 ms TR; 3.4 ms TE; 25º FA; 256x192 image matrix; 8 mm ST; 32 kHz BW; 28x21 cm FOV; 2 NSA; and 175-250 ms inversion time). Using a custom -made MR-compatible, steerable guide injection catheter (4), MR-MSC injections were targeted to infarcted, normal, and peri-infarcted tissue. Follow-up short-axis DCE and tagged MRI (breath-hold, ECG-gated, FGRE with SPAMM grid tags, 7.3 ms TR, 3.3 ms TE; 256x160 image matrix; 12° flip angle; 28x21 cm FOV; 8 mm ST; 4-8 views per segment; and 32 kHz BW) were serially obtained at 1, 2, 4, and 8-weeks post-MI to evaluate MI size and regional function, respectively, in both treated and untreated dogs. At 8 weeks, animals were humanely euthanized, and the heart excised for histological staining.

MI size and location were determined using full-width half-maximum (FWHM) thresholding criteria on DCE-MRI (5). Endocardial Eulerian circumferential strain (E_{CC}) was determined in 30 regions of the tagged MR images (i.e., 6 circumferential regions in 5 base to apex slices) in each animal using HARP analysis software (Diagnosoft, Inc., Baltimore). The regions were further grouped into three categories according to infarction status based on DCE-MRI (i.e., normal (Nl), adjacent (Adj) to the infarct, or infarcted (Inf)). Systolic strain rate (SSR), as a measurement of regional function, was determined by a linear regression of E_{CC} versus time during systole in each region. SSR, where more negative strain rate represents increased contractility, was compared between animals, infarction categories, and imaging sessions. The changes in the strain rate over 8 weeks in response to therapy were determined using a feasible generalized least squares of the cross-sectional time series and compared to control MI dogs that did not receive MR-MSCs. Values are expressed as mean ± SEM; $p<0.05$ was considered statistically significant.

Results and Discussion:

Figure 1 depicts the time course of SSR over the 8-week period by tissue category. Control dogs showed initial improvement at 1 week; however at 8 weeks the infarcted ($p<0.001$) and normal ($p<0.06$) heart regions of the MR-MSC-treated group showed greater improvement in contractility than the control dogs (Figure 2). While there was no difference in infarct size at 72 h post-MI between MSC-treated and control dogs, the infarct size (as a percentage of LV mass) decreased significantly in both groups over 8 weeks (control group: 18.4% ± 4.6 vs. 9.3% ± 1.41, $p<0.05$ MR-MSC group: 21.8% ± 4.8 vs. 9.4% ± 1.68, $p<0.05$ 72 h vs. 8 weeks). At 8 weeks post-injection, MR-MSCs were visible only in the infarcted and peri-infarcted myocardium and had disappeared from the remote non-infarcted tissue; the presence and absence of MR-MSCs on MRI was confirmed by histology.

Conclusions:

Cellular therapy with MSCs early after acute MI improved regional function at 2 months when compared to non-treated animals. MRI offers an ideal method to target and determine the cardiac response to MSC treatment. These preclinical studies lend promise to the use of direct intramyocardial injections of MR-labeled MSCs to monitor the presence of MSCs and determine the success of therapy in future clinical trials.

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References:

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Figure 1: Time course of SSR