

Manganese-enhanced MRI (MEMRI) enables measurement of regional myocardial viability and to evaluate the regenerative effects by human induced pluripotent stem cell derived cardiomyocytes (iCMs)

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Target Audience

Cardiovascular stem cell therapy and multimodality molecular imaging.

Purpose

Human induced pluripotent stem cell (iPSC) derived cardiomyocytes (iCMs) hold the potential to regenerate the myocardium to enable permanent restoration. Manganese agent specifically enters live cells and cells via L-type Ca²⁺ channels to enable direct evaluation of myocardial viability. Persistent engraftment of the reporter gene transduced iCMs associated with significant increase in regional viability and in left ventricular ejection fraction (LVEF) suggests myocardial regeneration. This study evaluates whether the iCMs regenerates the injured murine myocardium.

Methods

0.5 million iPSCs and iCMs were delivered into the injured SCID murine myocardium: iPSCs (n=6), reporter-gene (RG) transduced iCMs (n=12), and PBS control (n=10). Cardiac MRI was performed to assess LVEF and manganese-enhanced MRI (MEMRI, 3T Signa HDx, GEHC, WI), using SeeMore intravenously (Eagle Vision, PA) on days 14 and 28 days post-MI. (LVEF: FSPGR: TR 24 ms, TE 10 ms, FOV 5, FA 45, NEX 4, Slice thickness 1.0 mm, 256x256 and MEMRI: IR-FGRE:TR 13 ms, TE 6 ms, FOV 5, FA 30, NEX 3, Slice thickness 1.0 mm, 256x192). Bioluminescence imaging (BLI, Xenogen IVIS 200, MA) was also performed to assess iCM engraftment.

Results

The mean LVEF on day 28 post-MI demonstrated significant improvement by the iCMs vs. iPSCs and PBS control: iCMs: 36.1±7.5%*, iPSCs: 19.5±5.9%, and PBS: 22.0±10.2% (*p<0.05). Similarly, the mean MEMRI enhancement volume normalized to the LV volume on day 28 post-MI demonstrated significant improvement by the iCMs vs. iPSCs and PBS control: iCMs: 65.1±13.5%* vs. iPSCs: 48.3±16.6%, vs. PBS: 45.5±16.5% (*p<0.05). Finally, BLI signal, indicating iCM engraftment, demonstrated the following signal on day 14: 1.3±0.52 x10³p/s/cm²/sr and on day 28: 4.2±2.2 x10³p/s/cm²/sr. These data demonstrated significant correlation between LVEF and BLI in the iCM group (r=0.66, p=0.04), suggesting the importance of stem cell engraftment and functional improvement.

Discussion and Conclusions

Multimodality MRI-BLI platform allows reliable in vivo detection of myocardial regeneration through evaluation of stem cell engraftment, myocardial viability, and cardiac function. The findings suggest that the iCMs regenerate the injured myocardium.

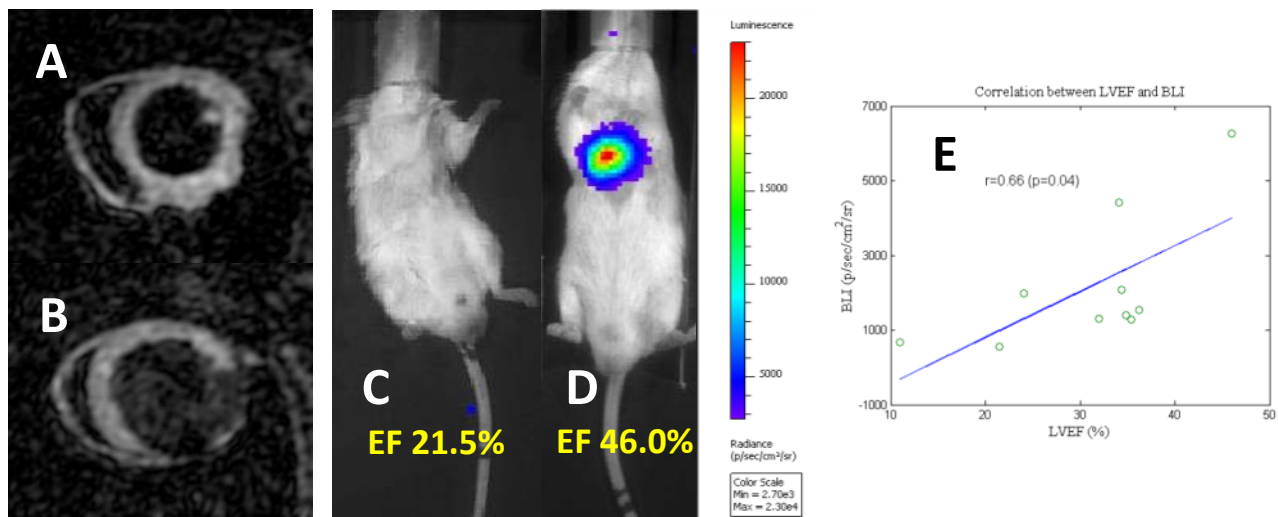


Figure. (A)-(B): MEMRI images of healthy myocardium and myocardial infarction area. (C)-(D): BLI signal of PBS and iCMs. (E): Significant correlation was seen between BLI and LVEF (r=0.66, p=0.04).