Fusion of Delayed Hyperenhancement MRI with Live X-ray Imaging for Guidance of Targeted Endomyocardial Injections of Therapeutic Cells

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Introduction: MRI and X-ray fluoroscopy provide complementary information for diagnosis and treatment of myocardial infarction. We have previously described a method using external fiducial markers for registering and fusing pre-procedural MR images with live X-ray [1]. Here we present the use of this technique in a swine model of myocardial infarction to guide endomyocardial injections of iron-labeled mesenchymal stromal cells to infarcts and infarct borderzones, and we present qualitative and quantitative results of targeting accuracy.

Methods: Animal procedures were approved by the NHLBI Animal Care and Use Committee. Twelve Yucatan miniswine were infarcted by balloon occlusion of the left anterior descending or left circumflex coronary artery. Occlusion times ranged from 45-90 minutes, and injection procedures were performed 3-74 days (median, 17.5 days) after the infarct was created. Iron labeled mesenchymal stromal cells (Fe-MSC) were prepared from bone marrow aspirates taken from 2 additional Yucatan miniswine. MSC were labeled with ferumoxides (Feridex, Berlex) as previously described [2] and were mixed with tissue dye for pathologic identification.

Prior to imaging 15±1 dual-modality markers were attached to the thorax using adhesive, and these served as fiducial markers. MRI was performed at 1.5T (Sonata, Siemens) using a custom designed 8-channel phased array surface coil (Nova Medical). Infarcts were visualized on breath-held delayed hyperenhancement (DHE-MRI) images acquired 15 minutes after intravenous injection of 0.2 mmol/kg Gd-DTPA using a phase sensitive inversion recovery sequence [3] having the following parameters: TR/TE, 11/4.45 ms; flip angle, 30°; inversion-time, 300 ms; FOV, 350×241 mm; matrix, 256×141 pixels; slice-thickness, 8 mm; bandwidth 140 Hz/pixel. From these images, the infarct and left ventricular (LV) endocardial and epicardial borders were manually segmented.

After additional MR imaging to identify the fiducial markers [1] the animal was transferred to the X-ray suite (Axiom Artis FC, Siemens) for the endomyocardial injections. Registration was based on the fiducial markers seen in the two types of images [1], and the manually segmented LV structures were overlayed on live X-ray images at 8 frames per second. This allowed the operator to guide the Stilletto injection catheter (Boston Scientific) to the infarct and borderzone. Additionally, the endo- and epi-cardial borders provided a measure of myocardial wall thickness. This was also displayed to the operator so that he could avoid injection into thinned regions which would present a risk of perforation. After each injection was performed, it was mapped back onto the DHE-MRI to provide a fusion-predicted injection location.

After the injections were completed, the animal was transferred back to MRI for identification of the susceptibility signature of the iron-labeled cell injections on T2*-weighted imaging (TR/TE, 15.5/3.04 ms; flip angle, 25°; FOV, 350×263 mm; matrix, 256×144 pixels; slice thickness, 6 mm; bandwidth, 260 Hz/pixels). This injection location was compared with the fusion-predicted location to quantitatively measure the *in vivo* target registration error. After 24 hr, the animal was euthanized and the heart was removed and sectioned into 3-4 mm slices for TTC-staining [4] to visualize the infarcted myocardium. The injections were also visible due to the tissue dye mixed into the injectate.

Results: A total of 130 injections were performed in 12 animals with myocardial infarctions of varying size, age and location. The wall thickness in all the hearts injected ranged from 2.6 to 17.7 mm. All animals survived to the study-specified euthanasia endpoint 24 hours after the endomyocardial injection procedure. Fig. 1 illustrates the three key features of XFM guided endomyocardial injections using our method, namely safety, targeting and accuracy. Visual inspection of the fusion-predicted injection locations mapped onto pre-injection DHE-MRI compared favorably with dye staining patterns on TTC-stained slices (Fig. 1) and the susceptibility artifacts seen on the post-injection T2*-weighted imaging (Fig. 2). Seven of 12 animals underwent post-injection MRI and analysis of target registration error. The overall *in vivo* target registration error was 3.2±2.6 mm (n=64), with an interquartile range of 1.0-4.1 mm.

Conclusions: Fusion of delayed hyperenhancement MRI with live X-ray imaging allows safe, accurate, targeted endomyocardial injections in swine.

References: [1] Gutiérrez LF *et al.*, Proc SPIE, 5744:146-156, 2005. [2] Arbab AS *et al.*, Blood 104(4):1217-1223, 2004. [3] Kellman P *et al.*, MRM 47(2):372-283, 2002. [4] Fishbein MC *et al.*, Am Heart J 101(5):593-600, 1981.

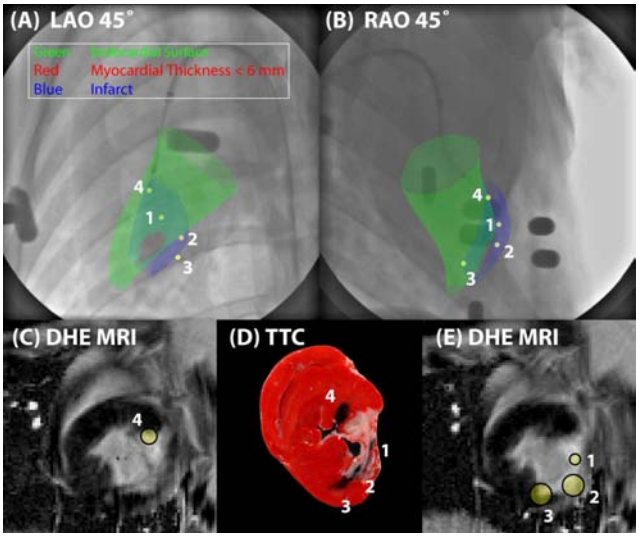

Figure 1. Fusion-guided targeting of endomyocardial injections according to infarct location (blue) and regional myocardial wall thickness (green for wall thickness>6mm, and red for wall thickness≤6). A-B demonstrate placement of the injection catheter in a "safe" peri-infarct location. Following deployment of the needle, X-ray acquisitions in orthogonal views allow reconstruction of the injection location in 3D (yellow spot, numbered 4). Previous injection locations (yellow spots, numbered 1-3) are also displayed in these views. The 3D injection locations are displayed superimposed on the pre-injection DHE MRI (C,E). A TTC-stained heart slice (D), located between the MRI slices displayed in (C, E), shows tissue-dye staining patterns that correlate well with the fusion-predicted injection locations.

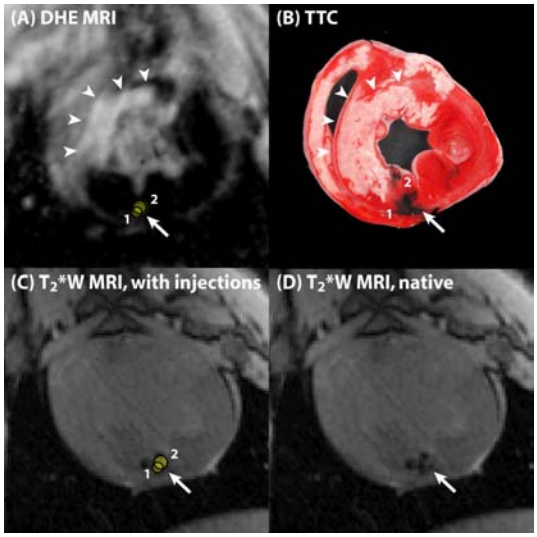

Figure 2. The locations of two fusion-guided injections of Fe-MSC mixed with tissue dye are shown relative to areas of infarction (arrowheads) demonstrated *in vivo* by DHE-MRI (A) and *ex vivo* by TTC staining (B). The fusion-guided injection locations (yellow spots, numbered 1 and 2) are displayed superimposed on the pre-injection DHE-MRI, which was used by operators to target their injections (A), as well as the post-injection T2*-weighted MRI (C) which was used to provide *in vivo* validation of the accuracy of fusion-guided injection locations. The susceptibility artifact (arrow) on this image resulting from injected Fe-MSC is better appreciated in D. The distributions of tissue dye stains on the TTC stained heart slice (B) and susceptibility artifacts (D) are very similar.