# X-ray Fusion with MRI for Delivery of Encapsulated Stem Cell Therapeutics

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**Introduction:** Over 650,000 cardiovascular percutaneous interventional procedures were performed in 2004 using X-ray fluoroscopic imaging. Although MRI offers excellent soft tissue detail that cannot be obtained with X-ray angiography of the heart, the lack of MR-compatible devices and difficulties with monitoring cardiovascular patients prevents the substitution of interventional MRI techniques in many cardiovascular patients. However, the ability to fuse MRI data with conventional X-ray fluoroscopic data may provide a valuable interim platform for guiding cardiovascular procedures. In particular, we sought to combine X-ray interventional delivery of "X-ray-visible cellular" therapeutics[1] with MRI.

**Methods:**

***Phantom studies:***

Static phantoms were imaged on a clinical 1.5T MRI scanner (Espree, Siemens) with a special table transfer to an X-ray angiographic system (Miyabi table with Axiom Artis dFA, Siemens). Fiducial markers (8-10) containing both MR (Magnevist, Berlex Laboratories, Inc) and X-ray contrast agents (Omnipaque, GE Healthcare) were affixed to the surface of the phantom. Three dimensional MRIs that included the markers were acquired for registration to the X-ray images. T1- and T2-weighted images were acquired for anatomical detail. The phantom was then transferred to the X-ray angiographic system. Static images were acquired at 20 degree intervals from 60° RAO to 60° LAO. Markers were identified on both the 3D MRI and static X-ray images and co-registered using a custom analysis package written in Matlab.[2] Injection targets were segmented by hand on the high resolution MRIs and subsequently displayed on the active X-ray fluoroscopic images. An MRI-compatible needle (Chiba-type MREye, Cook) was guided to the target under direct X-ray fluoroscopic visualization where an injection of visible and MR-detectable dye was performed. The phantom was subsequently transferred to the MR scanner for validation of the injections followed by gross dissection of the phantom for visual confirmation.

***Synthesis of x-ray visible encapsulated stem cells:***

The synthesis of X-ray visible stem cells is based on a one-step modification of the original alginate microencapsulation methods of Lim and Sun[3] by the addition of a radiopaque agent, i.e., barium sulfate or perfluorooctyl bromide. An electrostatic generator is used to create microcapsules containing alginate and bone-marrow-derived stem cells, which are then crosslinked in a $CaCl_2$ solution. After incubation of the microcapsules in poly-L-lysine, a second layer of alginate is established to enhance capsule strength and create uniform porosity. Using this method, X-ray visible capsules (XCaps) can be created with uniform diameters in the 300 μm range.

***In Vivo Study:***

The flowchart for X-ray fusion with MRI in acute myocardial infarction is shown in Figure 1. As in the phantom study, large field-of-view 3D volumes were obtained for localization of 8 markers placed on the anterior and posterior chest wall. Conventional ECG-gated, cine TrueFISP and inversion recovery delayed contrast-enhanced MRIs (after a 0.2 mmol/kg bolus of gadolinium-based contrast agent) were acquired to determine areas of wall thinning and non-viable myocardium, respectively (Fig 2), in a canine model of reperfused myocardial infarction. Transfer to X-ray fluoroscopy using the Miyabi table system assisted with minimal patient movement between imaging modalities. Single frame fluoroscopic images were acquired for X-ray localization of the markers. Translation and rotation of the MRI data to the X-ray frame of reference was achieved using standard techniques previously described.[2, 4] However, pin cushion effects of the X-ray angiography system were minimal due to the use of a flat-panel detector in the current X-ray angio configuration. A custom modified injection catheter that accommodates the larger diameter of the XCaps was employed. XCaps were then injected in <0.5 cc injections into the peri-infarcted and infarcted tissue.

**Results:**

Targeting to specific locations in the phantom was achieved with minimal error primarily in the anterior posterior direction (Fig 3). XCaps could be readily visualized during the injection phase. Due to the linking of the X-ray contrast agent to the alginate capsule, individual injection sites persisted throughout the entire injection period without a need for creating markers on the images. Fifteen injections were performed during conventional physiological monitoring of the invasive blood pressure and electrocardiogram. Injections were associated with minor arrhythmias that did not persist.

**Conclusion**

We present here the first application of an X-ray visible stem cell therapeutic to the heart. By employing the X-ray's strengths of interactivity and cardiovascular patient monitoring with the soft-tissue detail of MRI, injections can be targeted to the myocardium without the production of specialized MR-compatible devices. These studies show promise as a unique platform for the rapid translation of stem cell labeling to cardiovascular applications.

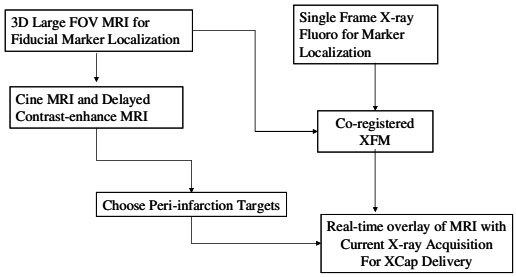


Figure 1: Flowchart of MRI and X-ray acquisition for co-registration of images and cardiovascular fluoroscopic delivery of XCaps guided by delayed enhance viability MR images.

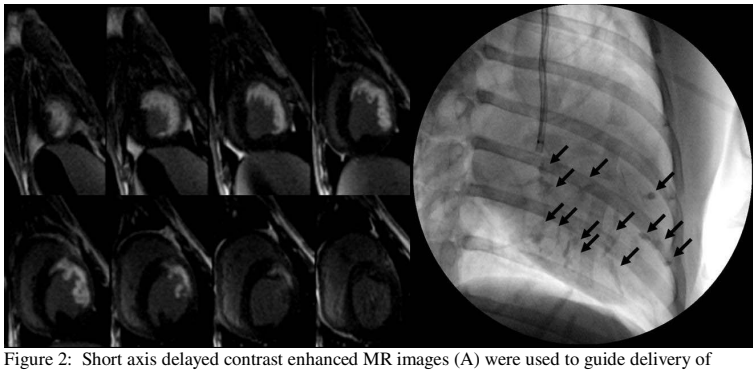

Figure 2: Short axis delayed contrast enhanced MR images (A) were used to guide delivery of Xcaps loaded with stem cells to infarcted and peri-infarcted regions of an infarcted canine heart under x-ray fluoroscopy (B).

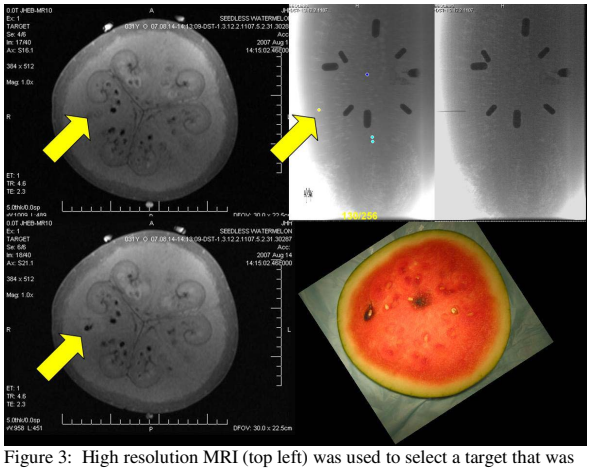

Figure 3: High resolution MRI (top left) was used to select a target that was invisible under X-ray (top middle). The target appears as a yellow dot on the X-ray image. The radioopaque needle (top right) was guided under X-ray fluoroscopy to the target and visible/MR-detectable dye was injected. Correct targeting appeared as hypointensity on MRI and as a dark region in the gross photograph.

References

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