In-Vivo Cardiac IRON Imaging of MR Fluoroscopically Delivered Mesenchymal Stem Cells

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Introduction: The use of superparamagnetic particles has shown promise for contrast generation in cardiovascular stem cell research [1]. However, the resultant negative contrast created by susceptibility artifacts can be difficult to discriminate from other potential sources of signal voids, and interrogation of the stem cell injection cites necessitates imaging with a high spatial resolution. High resolution *in vivo* imaging is limited by constant cardiac and respiratory motion. For these reasons, we have combined ***IRON*** imaging, an imaging methodology that enables the hyperintense visualization of superparamagnetic particles, with vector ECG triggering and real-time navigator technology. The use of this method for the signal enhanced visualization of magnetic nanoparticle-labeled mesenchymal stem cells (MSCs) injected in a dog heart was investigated.

Methods: *Concept IRON:* Using a spectrally selective saturation pre-pulse with the frequency $\omega_{IRON}=\omega_0$, the excitation angle α_{IRON} and the bandwidth BW_{IRON}, the signal from on-resonant protons can be suppressed. However, this saturation pulse does not affect off-resonant protons (ω_{off}; $-0.5*BW_{IRON} \geq \omega_{off} \leq 0.5*BW_{IRON}$) in close proximity to the iron labeled stem cells. Therefore, signal enhancement adjacent to these particles is expected while the on-resonant background should appear hypointense. *Implementation:* IRON was implemented on both a 1.5T Philips Intera and a 3T Achieva system. The implementation allows for a flexible combination of the IRON pre-pulse with vector ECG triggering and all the imaging sequences available on the scanner. BW_{IRON} and α_{IRON} can be adjusted on the user interface of the console. As shown in Figure 1, the IRON pre-pulse immediately precedes the imaging part of the sequence, and follows the 2D selective navigator for respiratory motion suppression. *In vivo study:* Two mongrel dogs were subjected to a 90-min closed-chest acute myocardial infarction (AMI). At 48hrs post-reperfusion, four (first dog) to ten injections (2nd dog) of ~$7x10^6$ allogeneic MSCs labeled with Feridex (Berlex Laboratories) were placed under MR fluoroscopy into the infarcted region of the myocardium as seen on delayed contrast enhanced images (0.2mmol Gd, DCE, Figure 2A). At 5hrs (3T) and 24hrs (1.5T) post-injection, the dogs were imaged using navigator-gated and corrected 3D IRON FSE imaging (Figure 1A, 1mm gating window, tracking factor=1.0, FOV/matrix=280mm/512, thickness=2mm, TE/TR=8.4/1200ms, Echo train length (ETL)=18, $\alpha_{IRON}=95°$, $BW_{Water}=100Hz$). Additional navigator-gated and corrected 3D segmented k-space gradient echo (TE/TR=2.85/10ms, thickness=3mm, FOV/matrix=270mm/489, FA=25) and DCE images were acquired. The dog that was imaged at 1.5T was then sacrificed, the heart excised, and IRON/gradient-echo imaging was repeated. At 3T, 2D breath-hold IRON imaging including spectrally selective fat saturation was performed (FOV/matrix=360mm/512, thickness=5mm, TE/TR=7.0/960ms, echo train length (ETL)=8, $\alpha_{IRON}=95°$, $BW_{Water}=100Hz$).

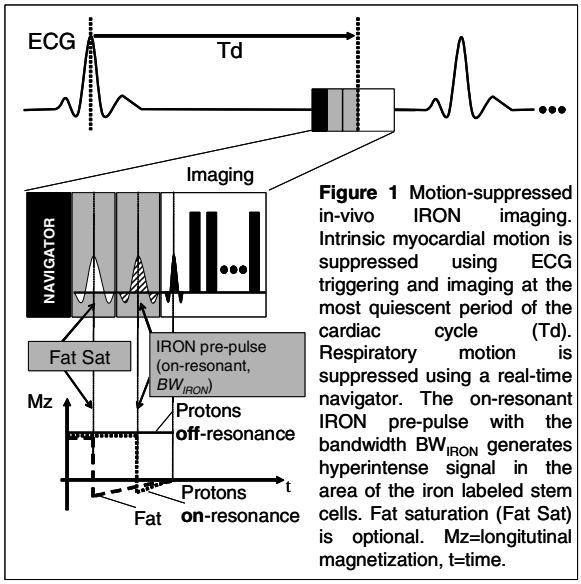

Figure 1 Motion-suppressed in-vivo IRON imaging. Intrinsic myocardial motion is suppressed using ECG triggering and imaging at the most quiescent period of the cardiac cycle (Td). Respiratory motion is suppressed using a real-time navigator. The on-resonant IRON pre-pulse with the bandwidth BW_{IRON} generates hyperintense signal in the area of the iron labeled stem cells. Fat saturation (Fat Sat) is optional. Mz=longitutinal magnetization, t=time.

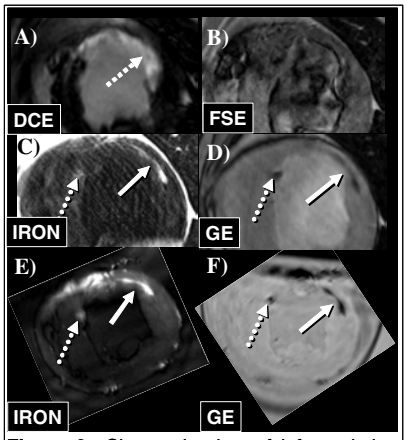

Figure 2 Short axis view of infarcted dog model before (A) and after (C-F) MSC injection. *In-vivo* imaging is shown in A-D and *ex-vivo* imaging in E & F. A) Delayed hyper enhancement (DCE) imaging. B) Fast spin-echo imaging (FSE) C) IRON imaging D) Gradient-echo (GE) imaging. E) *IRON* imaging F) Gradient-echo imaging.

Results: *In vivo* mid-ventricular DCE, FSE, IRON, and gradient echo images obtained at 1.5T are shown in Figure 2A-D. On the IRON image (Figure 2C), an excellent suppression of the myocardium with selective enhancement of the MSC injection in the regions of both solid and dotted arrows are visible. The injection sites correspond well with areas of signal void in the gradient-echo image (arrows, Figure 2D) and mapped directly to the infarcted myocardium (Figure 2A, hatched arrow). Signal enhancement and engraftment of the MSCs was further confirmed on the ex-vivo IRON and gradient-echo images shown in Figure 2E&F (arrows). For the dog that was imaged at 3T, similar results were obtained (Figure 3).

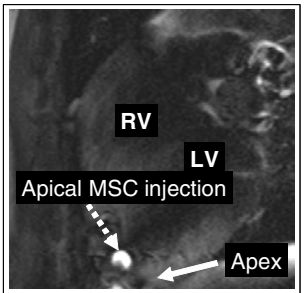

Figure 3 3T *in-vivo* IRON image including fat signal suppression of an apical MSC injection (dashed arrow) in an infarct dog model. LV=left ventricle, RV=right ventricle.

Conclusions: *IRON* is an MR imaging methodology that enables the hyperintense visualization of superparamagnetic nanoparticles at different magnetic field strengths. Extended with vector ECG triggering, real-time navigator technology, and 3D imaging, *in vivo* high resolution IRON imaging was successful in selectively enhancing magnetic nanoparticle-labeled MSCs that were injected into the infarcted myocardium. The method remains to be compared with alternative approaches. [2-4].

References:**1.)** Kraitchman Circulation 2003. **2.)** Seppenwoolde MRM 2003. **3.)** Coristine ISMRM 2004. **4.)** Cunningham MRM 2005.