In vivo MRI Using Positive Contrast Techniques for Tracking of SPIO Labeled Cells

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INTRODUCTION

To improve the detection specificity to SPIO labeled cells, approaches that result in positive contrast (white marker) have been proposed. Stuber et al. [1] used spectrally selective inversion RF pulses to pre-saturate on-resonant water (IRON) and Seppenwoolde et al. [2] achieved positive contrast by dephasing the background signal with a slice gradient (White Marker, also referred as GRASP in [3]). Recently, we proposed a susceptibility gradient mapping (SGM) technique that calculates positive contrast images in a post-processing step from a regular gradient echo data set [4]. In this study, the efficacy of these techniques was investigated in vivo using SPIO labeled glioma tumor model in rats.

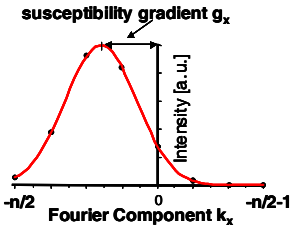

Figure 1. Echo shift caused by local susceptibility gradient.

METHODS

SGM: An object with a magnetic susceptibility that deviates from the surrounding creates a local magnetic gradient, which leads to an echo shift in k-space (Figure 1) with gradient echo imaging [5]. The SGM method determines this echo shift for every voxel in two (2D SGM) or three (3D SGM) spatial dimensions by local 1D FFT, which is used to further determine the strength of the susceptibility gradient. ***White Marker:*** The amplitude of the rephasing gradient is decreased (Figure 2A) such that it creates a gradient imbalance reducing the signal intensity in areas with homogeneous B_0. The gradient balance is restored in locations where a negative local gradient caused by SPIO nanoparticles is present. ***IRON:*** The sequence employs a spectrally selective saturation pre-pulse (Figure 2B). The signals originating from on-resonant protons are therefore suppressed while the saturation pulse does not affect off-resonant protons in close proximity to the SPIO nanoparticles. ***Phantom:*** The phantom is composed of five vials embedded in distillated water with ferumoxides-protamine sulfate (FEPro) labeled cells [6], free iron (diluted from Ferumoxides) or PBS suspended in 1ml gel. ***In vivo:*** 1×10^6 FEPro labeled C6 glioma cells were implanted subcutaneously into the flanks of 5 nude rats. C6 glioma cells are rapidly growing cells and therefore the sensitivity of the MRI techniques could be addressed during the formation of tumor mass and dilution of the SPIO nanoparticles in the cells. ***MRI:*** MRI was performed on a 3T Intera whole-body scanner (Philips Medical System, the Netherlands) using a dedicated 7 cm rat solenoid rf-coil. For each rat, White Marker, IRON and gradient echo images were acquired.

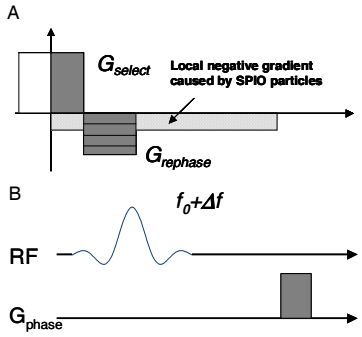

Figure 2. Sequence diagram of White Marker (A) and IRON (B).

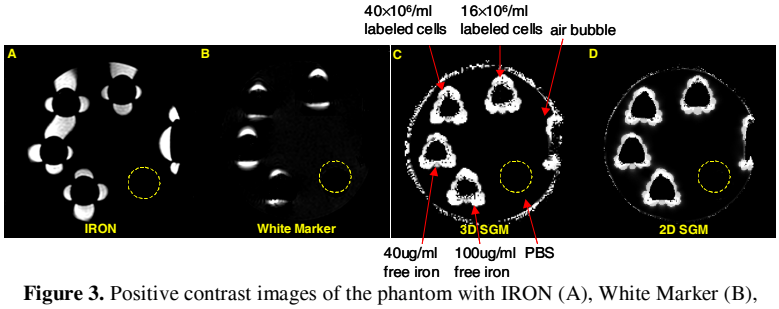

Figure 3. Positive contrast images of the phantom with IRON (A), White Marker (B), 3D SGM (C) and 2D SGM(D) techniques.

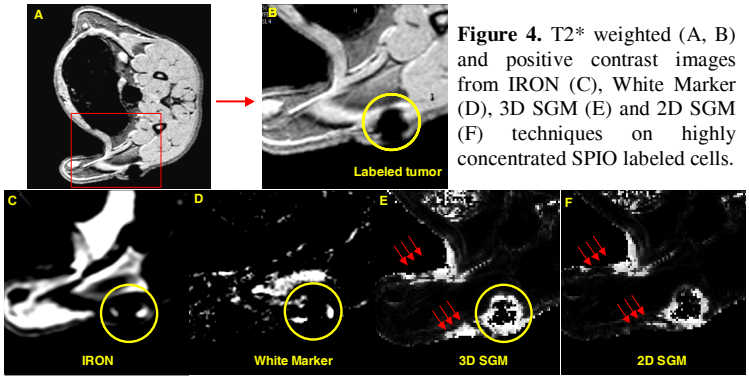

Figure 4. T2* weighted (A, B) and positive contrast images from IRON (C), White Marker (D), 3D SGM (E) and 2D SGM (F) techniques on highly concentrated SPIO labeled cells.

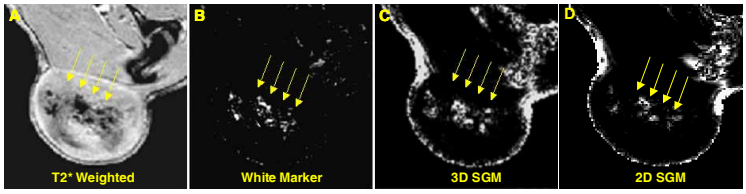

Figure 5. T2* weighted (A) and positive contrast images from White Marker (B), 3D SGM (C) and 2D SGM (D) on relative diluted SPIO labeled cells.

RESULTS

Phantom: All three techniques generated bright signals surrounding the vials with either SPIO labeled cells or free irons (Figure 3). No positive signal was observed surrounding the vial with PBS (yellow circle). The 3D SGM and 2D SGM best outlined the region of interest. The White Marker only highlighted a small portion of the water surrounding the vials, which heavily depended on the geometry of the dipole field induced by the SPIO nanoparticles. Both SGM and IRON highlighted the air bubble as well. ***In vivo:*** Images in Figure 4 were acquired with the labeled tumor size at approximately 0.5 mm representing highly concentrated SPIO labeled cells. The 3D SGM technique clearly illustrated the tumor border with bright signals while both IRON and White Marker techniques failed to fully outline the region of interest. However, the 3D SGM also posed more susceptibility artifacts because of its 3D nature. These artifacts were reduced on the 2D SGM (red arrows), which only included the susceptibility gradients in two dimensions. In Figure 5, SPIO nanoparticles became diluted resulting in a lower concentration as tumor cells proliferated. The positive contrast signals from White Marker, 3D SGM and 2D SGM corresponded well to the dark regions on the T2* image induced by SPIO nanoparticles (yellow arrows). IRON was unable to generate any positive contrast image (image not shown) at this low SPIO concentration.

CONCULSION

Three different positive contrast techniques, IRON, White Marker (or GRASP) and SGM have been investigated for the detection of SPIO labeled cells using experimental tumor model in vivo. All three techniques can generate positive contrasts in the vicinities of SPIO labeled cells. However, they all have certain limitations that need to be addressed especially for in vivo applications. The SGM technique demonstrates the ability to generate bright signals for SPIO labeled cells at both high and relative low concentrations. The positive contrast images of SGM are calculated from standard 2D or 3D gradient echo sets; therefore there is no need for special sequence and extra scans. And it also provides the flexibility to adjust contrast level to achieve the optimum results for a specific object.

Reference: 1. Stuber et al. ISMRM 2005;2608. **2.** Seppenwoolde et al. Magn Reson Med 2003;50:784-790 **3.** Mani et al. Magn Reson Med 2005;55:126-135. **4.** Dahnke H et al ISMRM 2006;361. **5.** Reichenbach et al, JMRI 1997;7:266-279. **6.** Arbab et al. Blood 2005;104:1217-1225.