Applications of Off-Resonance Positive Contrast Imaging Using FLAPS

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Introduction: Magnetic susceptibility variations can lead to regions of signal voids in T_2*-weighted images [1-2]. However, recent developments have shown that spins affected by slowly varying magnetic fields due to susceptibility variations can be visualized as signal enhancements (positive contrast) instead of signal losses [3-6]. Among these methods, Fast Low Angle Positive contrast Steady-state free precession (FLAPS) imaging has been proposed for time-efficient acquisition of positive contrast images. The FLAPS technique takes advantage of the unique spectral response of the steady-state free precession (SSFP) signal to generate signal enhancement from off-resonant spins while suppressing the signal from on-resonant spins at relatively low flip angles. While this method has been studied theoretically and with systematic phantom experiments, to date, there has been no report showing the usefulness of FLAPS imaging for practical applications. This work aims to evaluate the feasibility of the FLAPS imaging method for potential applications in cellular imaging and interventional MRI studies.

Methods: *Ex-vivo Cellular Imaging:* MCF-7/WS8 cells (ATCC) were grown in RPMI medium supplemented with 10% Fetal bovine serum, 2 mM L-glutamine, 0.1 mM non-essential amino acids, 0.1 x Antibiotic-antimicotic (Invitrogen, USA), and 0.1 mg/mL insulin from bovine pancreas (Sigma-Aldrich, USA) in a humidified 5% CO_2 atmosphere. A medium containing iron was prepared by mixing 250 μL of Feridex (2.83 mg of Fe) with 300 μL of SuperFect reagent (Quiagen, USA). The mixtures were incubated for 30 minutes prior to combining with 10 mL of serum free RPMI medium. This medium was applied on 10 million cells attached to the bottom of the 75 cm^2 cell culture flask. Following an overnight incubation (approximately 16 hours), serum-free media with Feridex was removed and cells were rinsed with 10 mL of serum-free media and then grown in 10 mL of complete media for 24 hours. At that time cells were detached from the flask by trypsinazation (trypsin, Invitrogen, USA). Cells were re-suspended in 2 mL of 0.1% trypsin and were mixed with 10 mL complete media and centrifuged at 750 g and re-suspended in 1 x phosphate buffered saline PBS (Invitrogen, USA); following another precipitation, cells were washed in 0.2 M glycine, then in 1 x PBS and re-suspended in fresh PBS. 1.3 million cells were injected into the freshly excised liver, submerged in saline water bath and imaged with 3D FLAPS. Scan parameters were: flip angle (α) = 10^o; averages = 2; field-of-view (FOV)/slab thickness (ST) = 15 x 20 cm^2 / 6.5 cm; T_R/T_E = 5.35/2.68 ms; resolution = 0.6 x 0.6 x 0.6 mm^3; scan time (TA) < 4.5 minutes. *Ex-vivo Interventional Device Visualization:* Two interventional devices (catheter and guidewire) were studied. A 0.018 inch coronary guidewire (Glidewire Gold, Terumo Medical, Japan), routinely used for x-ray coronary angiography procedures and a 2F catheter (Cordis, USA; filled with 25 μM Fe (Feridex IV, berlex, USA); ends sealed) were placed in fresh lamb blood, positioned perpendicular to the static field and were imaged separately with 3D FLAPS. Scan parameters were: $\alpha = 15^o$; FOV/ST = 12.5 x 20 cm^2/15 cm; T_R/T_E = 6.0/3.0 ms; averages = 1; spatial resolution = 0.8 x 0.x 8 x 2 mm^2; TA approximately 70 s. All imaging studies (cells and devices) were performed in a 3T Tim Trio (Siemens, Germany) with a product head coil for signal reception.

Results: Results from 3D FLAPS imaging of labeled cells and the interventional devices are shown in Fig. 1 and Fig. 2, respectively. Signal enhancements surrounding the cells and the interventional devices are clearly visualized. Also note that the full lengths of the interventional devices are also visible. Respective contrast-to-noise ratios (CNR), computed as signal differences between signal enhancement regions and the background, normalized by the standard deviation of noise, are: 19± 1.1(cells), 41± 0.9 (catheter), and 91± 18 (guidewire). CNR values are reported as mean ± standard error over measurements from three different regions showing signal enhancements.

Discussion and Conclusion: In this work we showed that FLAPS imaging, a time-efficient off-resonance positive contrast imaging method, has the potential for practical applications such as cellular and/or interventional MRI. The advantage of using FLAPS-based imaging to localize labeled cells is appealing because it permits a "dual" signal characteristic (both positive and negative contrast) of regions surrounding the labeled cells. This feature permits the visualization of spatial location of the cells as dark signal regions surrounded by a rim of hyper-intensity. This may potentially be used as spatial template for identifying / detecting implanted cells or other labeled media *in vivo*. For interventional MRI desiring the use of passive interventional devices, acquisition speed and low heating offered by FLAPS imaging may be ideally suited.

References: [1] Luedeke KM, MRI 1985;3:329; [2] Schenck JF, Med Phys 1996;23(6):815; [3] Cunningham CH, MRM 2005;53:999; [4] Stuber M, 13th ISMRM p. 2608; [5] Mani V, MRM 2006;55:126; [6] Dharmakumar R, Phys Med Biol. 2006;51:4201.

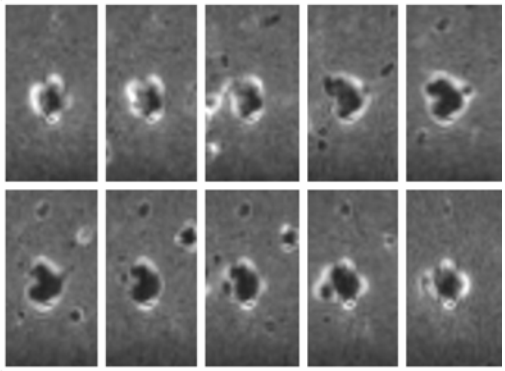

Fig. 1 Multiplanar reformations (MPF) from the 3D cellular imaging studies in *ex-vivo* liver. Each sub-image is a select MPF of ferumoxide-labelled cells injected into the *ex vivo* liver tissue. Note the appearance of positive contrast surrounding focal regions of the labeled cells.

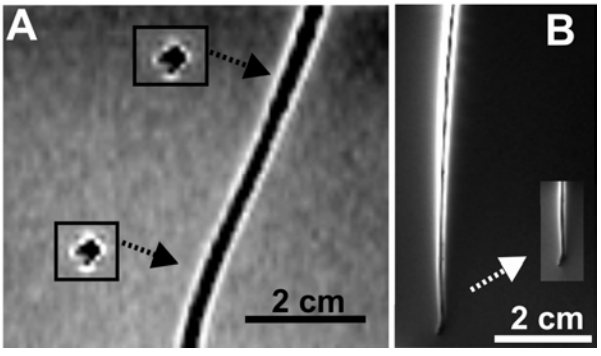

Fig. 2 Visualization of FLAPS-based images of catheter (A) and guide wire (B) at 3T. 2F catheter and the guidewire are shown length-wise based on curved maximum intensity projection. The 2 insets in (A) are the cross-sectional images of the catheter. The inset in (B) shows a close-up of the guidewire acquired at a higher resolution with 2 averages.