IMPROVING DETECTION SPECIFICITY OF IRON OXIDE NANOPARTICLES (IONPS) USING THE SWIFT SEQUENCE WITH LONG T2 SUPPRESSION

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Target Audience: Scientists and clinicians interested in short T_2 imaging, long T_2 tissues and/or fat suppressions, contrast agents, tumor cell labeling and targeting.

Purpose: Iron oxide nanoparticles (IONPs) have been widely used as a T_2/T_2* contrast agent in MRI. To avoid signal loss caused by IONPs, pulse sequences, such as Ultrashort TE (UTE) and Sweep Imaging with Fourier Transform (SWIFT), can be implemented to acquire MR signals of IONPs, since the echo times of these sequences are in a few microseconds [1-3]. But in the UTE and SWIFT images, long T_2 tissues and fat may also appear bright, posing a challenge to discriminate IONPs from surrounding tissues [4]. In this work, IONPs were used to target tumor cells grafted in mice. In order to improve the detection specificity of the IONPs delivered to tumors, we hypothesized to embed saturation pulses into the SWIFT sequence to suppress long T_2 tissues and fat.

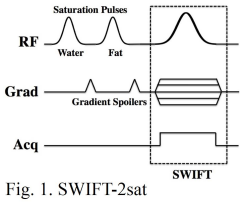

Fig. 1. SWIFT-2sat

Methods: The water-soluble IONPs with carboxyl groups on the surface (10 nm, from Ocean Nanotech, Inc.) were coated by an RGD derivative, c(Arg-Gly-Asp-DTyr-Lys), for tumor cell targeting. About 10^6 mouse breast cancer cells (4T1) were subcutaneously injected to the right hind leg of nude mice, and the tumors were allowed to grow to about 200 mm^3. The RGD-IONPs (10 mg Fe/Kg) were intravenously injected to the tail veins of the mice, and given 24 hours to target and accumulate in the tumors. In vivo scans were conducted first using FSE (2D, TR/TE = 2 s/30 ms, ETL = 8, FOV = 3.5^2 cm^2, thk = 1 mm, 256^2), SPGR (3D, $\theta = 6°$, TR/TE = 6.5/3.15 ms, FOV = 50^3 mm^3, 256^3), and SWIFT (3D, $\theta = 6°$, TR = 6 ms, spokes = 64,000, FOV = 50^3 mm^3, 256^3). To highlight the delivered RGD-IONPs in the tumors, the SWIFT-2sat sequence, as shown in Fig. 1, was designed by inserting two Gaussian pulses centered at water and fat frequencies into SWIFT, followed by gradient spoilers. The pulse durations and flip angles were set to 8 ms and 90° for in vivo scans.

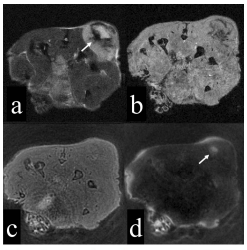

Fig. 2. In vivo images (a) FSE, (b) SPGR, (c) SWIFT, and (d) SWIFT-2sat. The arrows point to the RGD-IONPs inside the tumor.

After the in vivo scans, the tumor was harvested and fixed by Formalin for 72 hrs. Then, an agar gel phantom, consisting of the tumor specimen and two vials of vegetable oil and 1 mM IONP suspension, was made for ex vivo scans. The phantom images were obtained using FSE (TR/TE = 2.5s/30 ms, FOV = 35^2 mm^2, thk = 1 ms, 256^2), SPGR (TE = 3.15/10.84 ms, TR = 2.5 s, FOV = 35^2 mm^2, thk = 1 ms, 256^2), SWIFT (parameters same as those of in vivo study), and SWIFT-2sat. To further investigate SWIFT-2sat, the water saturation pulse varied from 8 ms to 32 ms, and the fat saturation pulse was still set to 8 ms.

All MR experiments were performed on a 7 T Varian Magnex small animal scanner (Agilent Technologies, Santa Clara, CA). The animal protocols were approved by the Institutional Animal Care and Use Committee of University of Georgia.

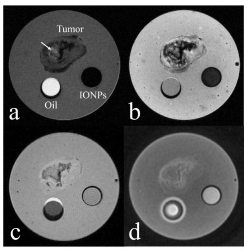

Fig. 3. Ex vivo images acquired by (a) FSE, (b) SPGR (TE = 10.84 ms), (c) SPGR (TE = 3.15 ms), and (d) SWIFT.

Results: Fig. 2 presents the in vivo images with systematic delivery of RGD-IONPs after 24 hours. Signal void caused by RGD-IONPs in the T_2 weighted FSE image (Fig. 2a) was observed inside the tumor (pointed by the arrow). Similar signal loss could be found in the T_1 weighted SPGR image (Fig. 2b). Benefiting from the extremely short TE of SWIFT, no significant signal void appeared in Fig. 2c, but image contrast was poor in the tumor. Because of the saturations of tissues and fat in and surrounding the tumor, the RGD-IONPs were successfully highlighted in the SWIFT-2sat image (Fig. 2d), indicated by the arrow. However, magnetic field inhomogeneity has degraded the performance of the saturation pulses, as tissues were not completely suppressed at the air-tissue boundary.

Fig. 3 presents the phantom images, consisting of 1 mM IONPs suspension, vegetable oil, and the tumor specimen. IONP-induced signal loss inside the vial was observed in both T_2 and T_2^* weighted images (Figs. 3a-b), while the IONP suspension showed similar intensity with the agar gel in the T_1 weighted SPGR image (Fig. 3c). Due to the ultra-short TE, the IONP suspension showed positive contrast to the agar gel in the SWIFT image (Fig. 3d). Based on the negative contrast in Figs. 3a-b, the distribution of the delivered RGD-IONPs could be fairly specified in the tumor. However, with long echo times, the signal void led to a poor signal-to-noise ratio (SNR). In Fig. 3a, a presumable necrotic core was indicated by the arrow. In Figs. 3c-d, the tumor region is associated with a better SNR but a poor image contrast, making it hard to specify the RGD-IONPs.

Figs. 4a-d compared the performance of different pulse lengths (8, 16, 24, and 32 ms) for long T_2 suppression, with a fixed 8 ms pulse for fat suppression. As shown, the tumor tissue, agar gel, and oil were well suppressed, and the RGD-IONPs were clearly delineated from surrounding tissues, indicating a good performance of SWIFT-2sat in general. Comparisons among the different images demonstrated that a short pulse may decrease the signal from IONPs. For example, details of the RGD-IONPs distribution were lost more in Fig. 4a than in Fig. 4d. But on the other hand, a long pulse was more sensitive to the magnetic field off-resonance, resulting in that the agar gel beneath the tumor was not fully suppressed in Fig. 4d.

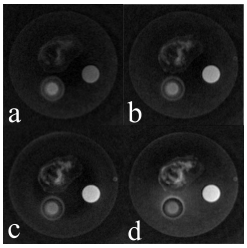

Fig. 4. Ex vivo images acquired by SWIFT-2sat with (a) 8 ms, (b) 16 ms, (c) 24 ms, (d) 32 ms Gaussian pulse for long T_2 suppression.

Discussion: Both *in vivo* and *ex vivo* experiments were conducted using various pulse sequences to acquire MR images for detection of IONPs deposited in the implanted tumors. Generally, T_2/T_2^* weighted images are usually associated with a poor SNR, which is attributed to the signal incoherence caused by the IONPs. Such an effect is manifested by negative contrast in MR images, which compromises the detection of IONPs as a contrast agent. The SWIFT sequence can improve the SNR of the IONP deposited regions, however, the contrast between IONPs and surrounding tissues and fat is improved only marginally. In order to further improve the detection specificity of IONPs, we introduced herein the SWIFT-2sat sequence, which combines SWIFT with two long Gaussian pulses, targeting water and fat frequencies, respectively. It is demonstrated that long T_2 tissues and fat can be efficiently saturated in the acquired SWIFT-2sat images. On the other hand, short T_2 species, mainly IONPs in this study, are minimally influenced due to their insensitivity to the long RF pulses.

Conclusion: Compared with pulse sequences such as FSE and SPGR, the SWIFT-2sat sequence effectively suppressed long T_2 tissues and fat while generated minimum influence on short T_2 species, such as the RGD-IONPs distributed inside the tumor, and consequently improved detection specificity of IONPs.

References: [1] Tylor DJ et al, JMRI 2007;25(2):279-289. [2] Idiyatullin D et al JMR 2006;181(2):342-349. [3] Garwood M JMR 2013;229:49-54. [4] Larson PE et al MRM 2006;56(1):94-103.