In vivo magnetic resonance imaging of Eu$^{3+}$-based PARACEST contrast agents using SWIFT

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Introduction

Paramagnetic chemical exchange saturation transfer (PARACEST) agents use water molecule exchange with lanthanide ions (Ln$^{3+}$) and radiofrequency (RF) spin saturation to create negative contrast in MRI [1]. If the rate of exchange between the bound and bulk water locations is much slower than their frequency difference (i.e. $k_{ex} << \Delta \omega$) then RF spin saturation at the shifted bound water frequency ($\Delta \omega$) will cause indirect partial saturation of the bulk water signal through chemical exchange [2]. One advantage that PARACEST agents have over Gd-based $T_1$ agents is that image contrast can be turned off and on via the RF saturation pulse frequency. Some published applications of PARACEST include measures of tissue pH [3], $Zn^{2+}$ ion concentration [4], beta-cell function [5], and the tissue distribution of glucose [6]. We have recently shown that chemical exchange of water molecules between Eu$^{3+}$-based PARACEST agents and bulk water can also facilitate $T_2$ exchange ($T_{2exch}$) [7, 8]. $T_{2exch}$ causes a significant reduction in the bulk water $T_2$ (i.e. negative contrast) for agents with high local concentrations, intermediate exchange rates, and large chemical shifts. The negative contrast is present even when the RF saturation pulse is omitted, causing the PARACEST agents to behave like susceptibility or $T_2$ agents. A current challenge for in vivo imaging of PARACEST agents is that a significant $T_{2exch}$ contribution can make the regions of agent uptake appear dark in both the “Off” (saturation at -$\Delta \omega$) and “On” (saturation at $\Delta \omega$) images when using conventional sequences like gradient-echo and fast spin-echo [7-9]. The minimum TE for these sequences (1 to 10 ms) is not short enough to capture dark signal from the regions of reduced $T_2$ making CEST imaging (“Off”-“On”) difficult. We hypothesized that the ultra-short TE ($<10 \mu s$) used in the sweep imaging with Fourier transform (SWIFT) sequence [10] could reclaim the loss in signal due to $T_{2exch}$ and enable fast and sensitive in vivo PARACEST imaging. We investigated this hypothesis at 9.4 T using a EuDOTA-(gly)$_4$, PARACEST agent and the SWIFT Launch Kit from Steady State Imaging.

Materials and Methods

In vivo mouse data were acquired on a Varian 9.4 T small animal MRI system using the SWIFT-compatible 27 mm diameter surface coil and software (beta version 580) from Steady State Imaging. Images were acquired at 37 °C using the SWIFT pulse sequence (TR/TE = 1.23 ms/<10 μs, averages = 1, dummy scans = 512, np = 128, views/spirals = 8192/4, sw = 125 kHz, FOV = 50 mm, resolution = 0.39 mm). The SWIFT “fatsat” function was used to create a 0.5 second long, 20 μT saturation pulse for each nturbo (64 views). The total scan time for each image was 5 minutes. A 1.0 mmol/kg dose of EuDOTA-(gly)$_4$ was administered in 200 μL to the healthy mouse via tail vein injection immediately before imaging.

Results

Fig. 1: An example of negative contrast in the kidneys from $T_{2exch}$ using fast spin echo (TE = 10 ms) Fig. 2: A 0.39 mm thick coronal slice of the mouse kidney using SWIFT (TE < 10 μs) with saturation at $\Delta \omega = -52$ ppm (“Off” image). Fig. 3: The same slice as in Fig. 2 but now with saturation at $\Delta \omega = 52$ ppm (“On” image) showing negative contrast in the kidney due to saturation transfer with the EuDOTA-(gly)$_4$ PARACEST agent. Fig. 4: CEST image (i.e. “Off”-“On”) where the signal intensity is a function of agent concentration. Signal from the other kidney is out-of-plane in this image.

Conclusions

These data show that the negative effects caused by $T_{2exch}$ on PARACEST imaging can be overcome using the ultra-short TE achieved with SWIFT. Along with TE times that are two-orders of magnitude smaller than conventional gradient-echo 3D imaging, other advantages of SWIFT imaging include insensitivity to motion and flow noise, insensitivity to $B_0$ inhomogeneities from susceptibility changes, and fast and silent acquisition of true 3D data. Some potential applications for in vivo SWIFT-CEST imaging include measuring a Eu$^{3+}$-based polymeric agent for improved PARACEST sensitivity [11], a Tb$^{3+}$-based agent to measure the PARACEST effect outside of the magnetization-transfer (MT) window [12], and a Eu$^{3+}$-based agent for measuring extracellular pH in mouse models of human carcinoma [13].

References