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

T. C. Soesbe[1], O. Togao[1], M. Takahashi[1], and A. D. Sherry[1,2]
[1]Advanced Imaging Research Center, The University of Texas Southwestern Medical Center, Dallas, TX, United States, [2]Department of Chemistry, The University of Texas at Dallas, Dallas, TX, United States

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 signal from the regions of reduced T_2 making CEST imaging ("Off"-"On") difficult. We hypothesized that the ultra-short TE (<10 μs) 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

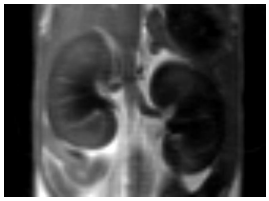
Fig. 1

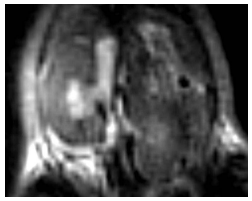
Fig. 2

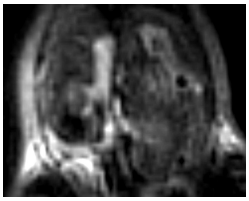
Fig. 3

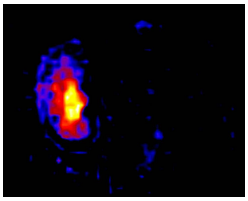
Fig. 4

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_o 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

[1] S. Zhang, *et al*., JACS, 123:1517-8, Feb 2001.
[2] K. M. Ward, *et al*., JMR, 143:79-87, Mar 2000.
[3] S. Aime, *et al*., MRM, 47:639-48, Apr 2002.
[4] R. Trokowski, *et al*., Agn Chem Int, 44:4334-6, Oct 2005.
[5] M. Lin, *et al*., Front Bio, 13:4558-75, May 2008.
[6] J. Ren, *et al*., MRM, 60:1047-55, Nov 2008.
[7] T. C. Soesbe, *et al*., ISMRM, Stockholm: #39, May 2010.
[8] T. C. Soesbe, *et al*., MRM, Submitted, Oct 2010.
[9] T. C. Soesbe, *et al*., ISMRM, Honolulu: #469, Apr 2009.
[10] D. Idiyatullin, *et al*., JMR, 181:342-9, Aug 2006.
[11] Y. K. Wu, *et al*., JACS, 130:13854-5, Oct 2008.
[12] T. C. Soesbe, *et al*., ISMRM, Stockholm: #452, May 2010.
[13] Y. K. Wu, *et al*., JACS, 132:14002-3, Oct 2010.