Strategies to Improve Temporal Resolution of PARACEST MRI

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Introduction:

Numerous advantages have been shown for Endogenous Chemical Exchange Saturation Transfer (CEST) MRI,[1] and MRI detection of exogenous CEST contrast agents with a PARAmagnetic ion (PARACEST).[2,3] However, MRI detection of (PARA)CEST suffers from poor temporal resolution.[4] A typical (PARA)CEST protocol consists of 2 MRI scans with "on resonance" selective saturation at the MR frequency of a proton pool that exchanges with water, and an "off-resonance" selective saturation as a control to account for direct water saturation. Each saturation period can last as long as 10 seconds for optimized detection sensitivity. Therefore, the acquisition time can range from 10 to 30 minutes, using a standard T1-weighted spin echo sequence. Therefore, new MRI pulse sequences are required to improve temporal resolution for (PARA)CEST MRI.

Methods:

3 different PARACEST contrast agents, Tm(III)DOTAM-Gly,[2] Eu(III)DOTAM-Gly[2] and Yb(III)DO3A-oAA, were used as model PARACEST MRI contrast agents for all investigations. Phantoms with a range of contrast agent concentrations were prepared in phosphate-buffered saline to maintain a pH of 7.4. CEST spectra and T_1 relaxation times of each contrast agent were determined by a 600 MHz Varian NMR spectrometer. MR parameters were optimized for PARACEST detection, including the saturation delay, saturation power and interpulse delay. MRI studies were performed on a 9.4T Bruker Biospec animal MRI scanner equipped with a 35 mm birdcage RF coil. A MSME sequence was used for the standard PARACEST MRI protocol, a RARE sequence was used in the protocol to investigate rapid acquisitions without compensation, and a FLASH sequence was used to investigate rapid acquisitions with short compensation. A 6 weeks old female athymic NCR nu/nu mouse was used for *in vivo* dynamic contrast enhanced MRI studies with intravenous injection of contrast agent.

Results and Discussion:

The progressive behavior during PARACEST can be depicted by a 2-site exchange model, and mathematically described by Bloch-McConnell equations. The removal of saturation leads to a reduced CEST effect due to longitudinal magnetization recovery. Two strategies were tested for contrast agents with different T_1 relaxation times (Figure 1). For contrast agents with moderate to long T_1 times, a strategy that employs multiple echos after a single saturation and excitation can be easily implemented by modifying a RARE sequence. For contrast agents with relatively short T_1 times, CEST signal loss due to longitudinal relaxation can be compensated by inserting a short saturation period before each k-space line scan to maintain steady state saturation conditions. A quantitative study with phantoms that ranged from 1.5 to 3 sec in T_1 time has shown the temporal resolution has been improved up to 64 fold with a single shot RARE, while the contrast loss is about 10%. The overall contrast per second has been boosted 57-fold, from 0.0365% s^{-1} to 2.1% s^{-1}. To prevent CEST signal loss from T1 relaxation and long-T2 weighting, moderate speed was used for *in vivo* application on a tumor mouse model. With the aid of this method, contrast enhanced MRI was achieved with a temporal resolution of 3 minutes per CEST image, which is sufficient for monitoring dynamic contrast changes following an injection bolus. An alternative strategy with compensation has been investigated based on a modified FLASH for contrast agents with short T1. Simulation basing on mathematic model has been used to predict the dramatically boosted temporal resolution with fully preserved CEST signals. Further optimization of this strategy is still under investigation.

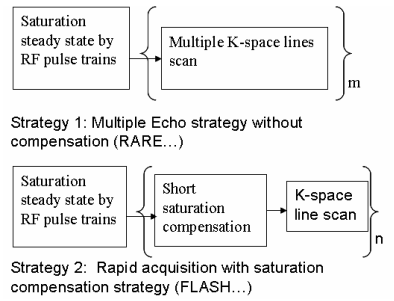

Figure 1: Schematic of two strategies to improve temporal resolution for PARACEST MRI studies.

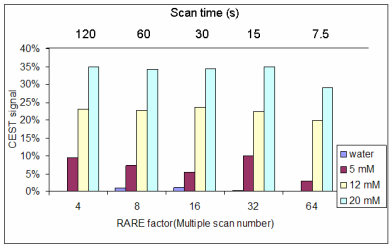

Figure2. The PARACEST effect of different concentrations of Eu(III)-DOTAM-Gly at different temporal resolutions. Selective saturation as applied at +50ppm and 35 μT for 2.2 sec prior to the RARE sequence.

Conclusion:

We have developed two different strategies to improve temporal resolution for PARACEST MRI, depending on the T_1 relaxation times of the agents. With the aid of proposed rapid acquisition strategies, PARACEST MR images can be acquired within 7.5 s with moderate spatial resolution and minor signal loss. With such temporal resolution, PARACEST MRI can monitor dynamic contrast changes, which provides new opportunities to apply PARACEST MRI for dynamic imaging studies.

References:

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