

On Resonance Low B1 Pulses for Contrast Enhancement Using PARACEST Agents

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Introduction

The Chemical Exchange Saturation Transfer (CEST) contrast enhancement method uses exchange mediated saturation transfer between protons bound to the contrast agent and bulk protons¹. Usually the saturation is achieved by the application of CW RF irradiation at the frequency of the bound protons. The advantages of this method include the sensitivity of the CEST molecule to its environment²⁻⁵ and the ability to control the contrast effect externally via RF irradiation. A new class of MRI CEST contrast agents based on paramagnetic lanthanide complexes was recently introduced⁶. The large chemical shift of bound water protons and their slow exchange lifetimes are potential advantages for these paramagnetic CEST (PARACEST) agents⁶. The PARACEST method can potentially detect microMolar concentrations of the agent; however, the achievement of a maximal effect for a given concentration of PARACEST agent may require the application of CW irradiation that is above FDA guidelines⁷.

We undertook a different approach that applies an RF pulse train to the bulk water resonance frequency. These RF pulses need to be sensitive to exchange and relaxation parameters of the system and could require a lower total power deposition than the CW irradiation applied to the bound water. Another potential advantage is that there is no need to know the exact position of the bound water peak. The intuitive pulse form could be the application of a long, low-power 360° pulse on bulk water resonance. After the pulse non-exchanging water spins will return to the Z axis. The exchanging protons will "leak away" during RF application and, hence, will not experience a full 360° rotation. The resultant Z magnetization of the bulk protons will thus decrease. We have implemented this approach, using low power WALTZ-16 pulses applied on the water resonance to achieve PARACEST contrast enhancement.

Methods

The sequence designated WALTZ-16* is based on a WALTZ-16 pulse train⁸ in which the 90° pulses were replaced by 2.5 msec pulses; total RF pulse train time amounts to 220 msec. Magnetization dynamics under the influence of the WALTZ-16* at different experimental conditions were simulated using MATLAB. Experiments were performed on a Varian Unity INOVA 400MHz vertical wide bore and 200MHz horizontal wide bore spectrometers. Based on the results of the simulations, the WALTZ-16* pulses used a B₁ in the range of 200 ± 100Hz. In spectroscopy experiments the WALTZ-16* pulse was applied before the 90° pulse. In imaging experiments the WALTZ-16* pulse was applied before a standard spin-echo sequence. At 400MHz the imaging parameters were: the in-plane resolution of 780x780μm² or 200x200μm², TR/TE=30s/30ms, 2mm slice thickness, with total scan time of 15-70min. At 200MHz the imaging parameters were: the in-plane resolution of 78x78μm², TR/TE=1s/15ms, 2mm slice thickness with total scan time of 5 min.

Results

Simulations were performed of the relative magnetization size after the application of the WALTZ-16* pulse as a function of free water exchange lifetimes, τ_a , and chemical shift difference, Δ . The relative magnetization size is defined as M_z/M_0 , where M_z is the Z-magnetization after the application of the WALTZ-16* and M_0 is initial magnetization. A decrease in M_z/M_0 corresponds to a lower intensity of the bulk water resonance and, in imaging, to the darkening of the image. In the long T₁ and T₂ limit, the maximal contrast effect achievable with 100μM PARACEST is obtained with bound water exchange lifetimes of about 3 μsec (corresponding to about 2 sec free water lifetime), together with the largest chemical shift difference possible. The contrast effect is also determined by the T₁ and T₂ of the bulk water. T₂ values in the range 0.1-1s have a big influence on the magnitude of M_z/M_0 . T₁ values of 1s and higher do not strongly influence the contrast. The influence of the relaxation times of the bound water was found to be negligible.

To validate the simulation of the contrast effect in real systems, spectroscopic and imaging experiments were performed. At 400 MHz, water samples with the PARACEST, TmDOTAM, at different concentrations were investigated: 1mM, 600μM, 250μM, 125μM, 12.5μM and 0 μM. Figure 1 shows measured M_z/M_0 as a function of TmDOTAM concentration ([TmDOTAM]) after the application of WALTZ-16* train in spectroscopic and imaging experiments. There is good agreement between spectroscopic and imaging experiments. In the spectroscopy experiments [TmDOTAM] as low as 12 μM can be detected by a magnetization decrease of 4%. Images were acquired in a phantom containing different [DyDOTAM] at 200 MHz. These results are presented in Figure 2: (a) images with WALTZ-16* placed very far off-resonance (effectively switched off), (b) on-resonance and (c) difference image.

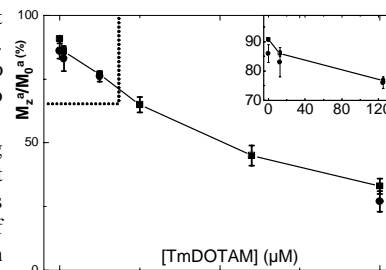


Figure 1. Relative magnetization after an application of WALTZ-16* on the bulk water at the different concentrations of TmDOTAM. Squares and circles correspond to the spectroscopy and imaging results, respectively.

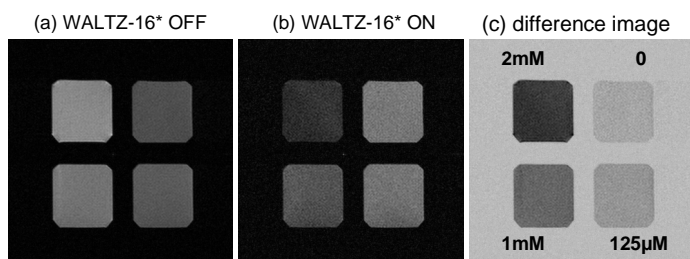


Figure 2. Images of phantoms containing 0, 125μM, 1mM and 2mM DyDOTAM

Conclusion

The WALTZ-16* sequence can be used to detect PARACEST agents with an RF intensity as low as 200 Hz, for concentrations as low as a few tens of micromoles for the appropriate agent (Tm,Dy). On-resonance WALTZ-16* is sensitive to exchange lifetimes and transverse relaxation times of bulk water. WALTZ-16* is an example of possible contrast enhancement by phase and amplitude modulated RF pulses. We suggest that these phase and amplitude modulated RF pulses can potentially lead to more sensitive and less power demanding RF trains. Work is in progress to extend this approach to *in vivo* studies.

References

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Discussion

The simulations predict that for a maximal effect size, τ_a of the order of 2s and the largest Δ possible are desirable. Hence, PARACEST complexes containing Eu, which have smaller Δ , are not optimal. Taking into account the simulations of the T₂ influence and experimental observations, it can be concluded that the total effect size will be determined by both, T₂ and τ_a of the bulk water. In the spectroscopy experiments, concentration of TmDOTAM as low as 12 μM could be detected. In the imaging experiments, while 12 μM agent can also be distinguished on average, the practical concentrations required are expected to be higher due to higher errors in signal intensity.