

Characterization of Paramagnetic Lanthanide Ion complexes as MRI Contrast Agents as a Function of Magnetic Field Strength

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Introduction Recent studies(1,2) have introduced paramagnetic lanthanide ions as a new type of imaging contrast agent. PARAMagnetic Chemical Exchange Saturation Transfer (PARACEST) works by utilizing an RF pulse at the chemical shift induced by the paramagnetic lanthanide to saturate a small pool of protons bound to the lanthanide complex. Exchange between this saturated pool and the surrounding bulk water causes a decrease in the overall water signal, resulting in a negative MRI contrast. Despite resulting in a decrease in signal intensity similar to SPIO contrast agents, CEST images have the advantage that they can be turned on and off for different lanthanide (III) paramagnetic chelates (PARACEST agents) through the use of frequency selective presaturation pulses. PARACEST agents are particularly useful due to their large chemical shifts and long life times of bound water, which can result in a more efficient transfer of magnetization to bulk water. It has been predicted that most LnDOTA-4AmCE complexes should function as PARACEST agents at 11.75T but only a few (Eu³⁺, Tb³⁺, Dy³⁺ and Ho³⁺) will be useable at low fields (1.5T) (1). On the other hand some of the potentially most effective PARACEST agents, such as those based on Yb³⁺, may not be useable below 11T. The purpose of this study is to optimize the PARACEST contrast generated from different lanthanide ion complexes at varying magnetic field strengths. To this end, three Europium (Eu) complexes were imaged at magnetic field strengths of 4.7, 11.75, 17.6 and 21.1T to generate CEST contrast and to quantify relaxation at these fields.

Methods Phantoms of the lanthanide ion complexes in water were imaged at the above magnetic field strengths using spin-echo and gradient recall echo magnetization transfer sequences. To maintain a consistent level of RF power deposition, the CEST image was generated from the difference between two images, one with a positive offset value and the other with the negative offset value. Each individual image utilized a presaturation pulse consisting of 2000 3-lobe sinc or gaussian pulses lasting 1 ms for a total irradiation time of two seconds. The offset value for each set of images was varied between 0 and ± 500 ppm, and the irradiation power was varied from 16 through 200 μ T.

Results and Discussion The results indicate an increase in contrast generation for all three Eu complexes with increased magnetic field strength (Figure 1). Eu-2 (optimal offset ~ 54 ppm) had the most overall contrast, with Eu-3 (optimal offset ~ 65 ppm) exhibiting comparable contrast. Although displaying less contrast, Eu-1 (optimal offset ~ 67 ppm) is unique in that CEST contrast is evident at the field strengths examined here but not at lower fields (e.g. clinical field strengths of 1.5 and 3 T). For the highest field strengths (red images = 17.6 T; blue images = 21.1T), the CEST images at the maximum contrast for each Eu complex are shown in Figure 2, which displays the tunable contrast enhancement related to the PARACEST agent and saturation offset. The increased contrast at higher fields is consistent with expectations the bound water shifts ($\Delta\omega$) will be larger and hence the bound lifetimes (τ_M) will be shorter while maintaining the intermediate exchange requirement, $\tau_M\Delta\omega \geq 1$. Currently most of the Eu³⁺-based agents have a bound water peak near 50 ppm at room temperature corresponding to $\Delta\omega = 10,000$ Hz and a requirement for $\tau_M \geq 100 \mu s$ (water exchange rate $\leq 10^4 s^{-1}$) for imaging at 4.7T. This is requirement is rather stringent for lanthanide complexes and consequently only a few Eu³⁺ complexes meet this condition. However, this same imaging experiment performed at 21.1T ($\Delta\omega = 45,000$ Hz) would require a Eu³⁺ complex having a $\tau_M \geq 22 \mu s$ (water exchange rate $\leq 2.2 \times 10^5 s^{-1}$), a more reasonable value to achieve experimentally.

As a first step towards *in vivo* imaging, CEST contrast also was evaluated for a range of pH values. To approximate cellular conditions, the acidity of a 10-mM Eu-2/distilled water solution was raised from a normal pH=3.0 to a pH=7.01. A separate 10-mM Eu-2 solution in 50% DMEM complete (cell culture media) was made at a pH=6.99. Phantoms of the Eu-2 solutions (pH= 3.00 and 7.01) and the Eu-2/DMEM labeling media (pH=6.99) were imaged. As shown in Figure 3, CEST images show the pH sensitivity of the PARACEST agent, and the optimal contrast offset is slightly different dependent on the pH: for the pH=3 solution, the optimal offset was found to be at 50 ppm, while the optimal offsets of the pH=6.99 and pH=7.01 were determined to be 56 and 59 ppm, respectively. Future work includes labeling cells with the Europium complexes to generate contrast, with the eventual goal of tracking cells *in vivo*.

Acknowledgements All data were collected at the Advanced Magnetic Resonance Imaging and Spectroscopy (AMRIS) facility at the University of Florida McKnight Brain Institute, Gainesville, FL, & The National High Magnetic Field Laboratory, Tallahassee, FL.

References

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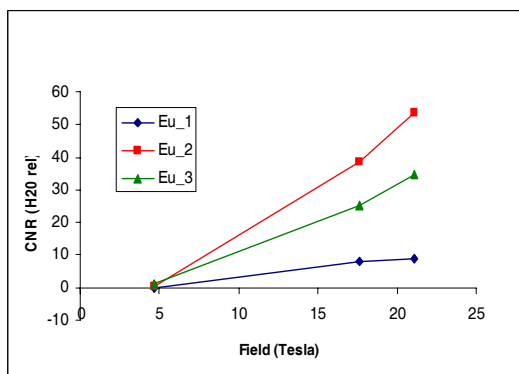


Figure 1 (above). Europium complexes at magnetic field strengths varying from 4.7 to 21.1T, demonstrating increased contrast generation at higher fields.

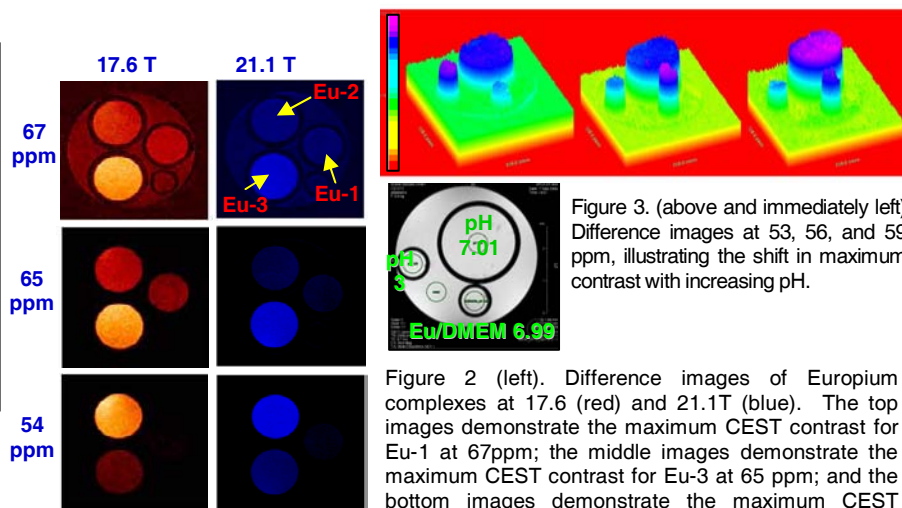


Figure 3. (above and immediately left) Difference images at 53, 56, and 59 ppm, illustrating the shift in maximum contrast with increasing pH.

Figure 2 (left). Difference images of Europium complexes at 17.6 (red) and 21.1T (blue). The top images demonstrate the maximum CEST contrast for Eu-1 at 67ppm; the middle images demonstrate the maximum CEST contrast for Eu-3 at 65 ppm; and the bottom images demonstrate the maximum CEST contrast for Eu-2 at 54ppm.