

# PARACEST Agents: Novel Probes for MR Thermometry

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## Introduction

Noninvasive temperature monitoring has many medical applications because of the close interrelationship between tissue temperature, metabolism and physiology. Currently, the water proton resonance frequency (PRF) method is the most widely used thermometric technique.<sup>[1]</sup> The method is however sensitive to motion and magnetic field inhomogeneities due to its small temperature dependency (0.01 ppm per °C). Recently, exogenous temperature probes based on either paramagnetic contrast agents<sup>[2, 3]</sup> or shift reagents<sup>[4, 5]</sup> have been shown to increase the temperature sensitivity. Although these methods are relatively sensitive, some experimental issues need to be resolved before applications of such agents *in vivo* will be practical. For example, the temperature response of the contrast agent method may be irreversible<sup>[2]</sup> procedure dependent ( $T_c \uparrow \neq T_c \downarrow$ );<sup>[3]</sup> or limited in spatial resolution because the agent must be detected directly at mM concentrations. Here, a novel MRI thermometric method based upon chemical exchange saturation transfer (CEST) imaging is presented. Although the method requires addition of an exogenous paramagnetic CEST (PARACEST) agent<sup>[6]</sup>, thermal measurements with high image resolution are possible because the effect is detected *via* imaging of bulk water (55.5M).

## Results and Discussion

CEST is based upon selective pre-saturation of spin **A** (*i.e.* any exchangeable R-NH<sub>2</sub>, R-NH, R-OH or Ln<sup>3+</sup>-shifted H<sub>2</sub>O protons) to alter the signal intensity of an exchanging spin **B** (typically bulk water) by an amount that depends upon the rate of chemical exchange between the two pools and the relaxation times. Most simply it is described by  $M_{SB}/M_{OB} \approx (1 + k_{BA}T_B)^{-1}$ , where  $M_{SB}$  and  $M_{OB}$  are <sup>1</sup>H signal intensities of **B** (bulk water) with and without pre-saturation, respectively;  $T_B$  is the spin lattice relaxation time of **B**; and  $k_{BA}$  is the exchange rate of water from **B** to **A**. Thus, the magnitude of the CEST decrease, ( $M_{SB}/M_{OB}$ ), provides a direct measure of temperature if the concentration of the CEST agent is known. This, unfortunately, is not usually the case for experiments *in vivo*. Alternatively for PARACEST agents, one can take advantage of the known temperature dependence of the paramagnetic lanthanide induced shift (LIS) effect. As reported previously,<sup>[7]</sup> the <sup>1</sup>H chemical shifts of lanthanide bound water (Ln-H<sub>2</sub>O) range from +500 ppm for Tm<sup>3+</sup> complex to -800 ppm for Dy<sup>3+</sup> complex. Further variable temperature experiments revealed that <sup>1</sup>H chemical shifts of Ln-H<sub>2</sub>O change linearly with temperature in a range of 20 – 50 °C, for example,  $\delta = -0.4 \cdot T + 64.6$  and  $\delta = 6.9 \cdot T - 944.7$  for europium (Eu) and dysprosium (Dy) DOTA-tetraamide complexes, respectively. If the <sup>1</sup>H chemical shifts ( $\delta$ ) of Ln<sup>3+</sup>-bound water molecules are known, the temperature can be readily obtained by using these linear calibrations.

To test the feasibility of the method, a 1 cm OD vial containing 1 mL of 10 mM EuDOTA-4AmC in water (pH 7) was imaged at different controlled temperatures using a 2 cm RF surface coil and a 4.7T animal imaging magnet. Typically, a series of CEST images were obtained by applying a 2 s presaturation pulse ( $B_1=735$  Hz) over a small range of frequencies surrounding the Eu<sup>3+</sup>-bound water position (50 ppm). In each case, a minimum was observed in  $M_{SB}/M_{OB}$  over this frequency range and the frequency of this minimum provided a direct readout of temperature using the appropriate linear equation (above). The temperature images illustrated in Figure 1 show that even small temperature gradients across this 1 cm vial are easily detected by MRI. The temperature images as indicated by the color bars matched closely to that of the air flowing over the sample. This indicates that PARACEST agents may potentially be useful as novel, high resolution thermometric imaging probes.



**Figure 1.** Temperature maps of a phantom containing 1 ml, 10 mM EuDOTA-4AmC in water at pH 7.0. The temperature of the air flowing over the sample are indicated in each figure while those reported by imaging are shown by the color bars.

## Conclusions

PARACEST agents were tested *in vitro* as new MRI thermometric probes. In comparison with the traditional PRF method (temperature dependency: 0.01 ppm per °C), the temperature response of such agents are ~40 (Eu: 0.4 ppm per °C) and 690 (Dy: 6.9 ppm per °C) –fold greater, respectively. What makes it especially unique is that the imaging object is the bulk water (55.5M), therefore, the spatial resolution (voxel volume) would be much higher than that available using shift reagents.

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