

Temperature Imaging with a MRI-PARACEST Contrast Agent: Eu-DOTAM-Gly-Phe

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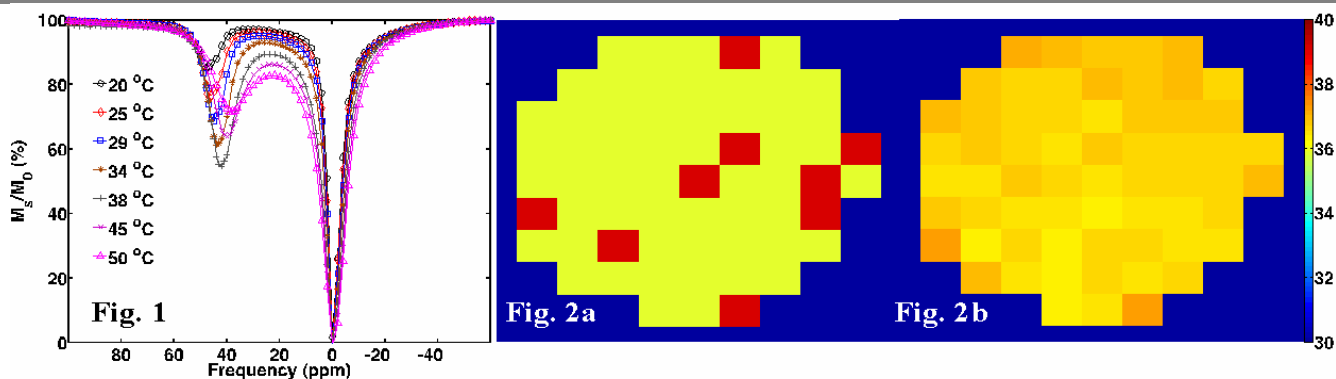
Introduction: There is a close-relationship between tissue temperature and metabolism/physiology. Therefore, measuring tissue temperature may reveal alterations in tissue metabolism or indicate pathophysiological conditions (i.e. within tumors). Zhang *et al* recently reported a MRI thermometric method based on the use of paramagnetic chemical exchange saturation transfer (PARACEST) agents [1,2,3,4]. Specifically, the linear relationship between temperature and the chemical shift of the Lanthanide(III)-bound water resonance associated with the PARACEST agent can be used to measure temperature distribution. This method requires that the proton chemical shift (CS) of the bound water molecules be accurately measured on a pixel-by-pixel basis by generating CEST spectra from image signal intensity. Zhang *et al* proposed the acquisition of a series of images preceded by a saturation pulse, each image acquired using a different saturation frequency to determine the Larmor frequency of bound water. By tracing the intensity changes of a pixel along the image series, the temperature can be obtained by identifying the chemical shift of the minimum intensity point of bound water [1]. There are two major limitations with this method. First, many images must be acquired to obtain the correct chemical shift, and second, the minimum intensity point may not be easy to identify. Here we reported a method that incorporates the fitting of such experimental CEST-spectra to the modified Bloch equations [5] in combination with a new PARACEST agent to measure temperature.

Methods: A new PARACEST agent containing europium (Eu) metal, cyclen ring, CH₂CO linker, and glycine (Gly) - phenylalanine (Phe) dipeptide sequence as functionalized side chains was synthesized (Eu-DOTAM-Gly-Phe). The relationship between temperature (20-50 °C) and pH (6-8), and the bound water chemical shift was determined in a 10 mM solution of Eu-DOTAM-Gly-Phe on a 9.4T Varian MR Spectrometer by adding a frequency selective saturation pulse (B₁=22 μT and duration time = 10 s) prior to the standard FID pulse sequence (TR= 14 s). The effect of the saturation frequency step size (0.2, 0.5, 1, and 2 ppm) on the determination of the chemical shift of the bound water spins was compared with and without data fitting. CEST images were acquired of a phantom containing 10 mM Eu-DOTAM-Gly-Phe at 37.5 °C (the temperature was monitored and controlled by blowing hot air using a Model 1025 Small Animal Monitoring and Gating System (SA Instruments, Inc., Stony Brook, NY)) on a Varian 9.4T MRI using a fast spin echo pulse sequence (FOV: 20 × 20 mm², TR=7 s, 16 echoes, and TE=11 ms), preceded by a frequency selective saturation pulse (B₁=20 μT, saturation range=35-75 ppm in steps of 1 ppm, saturation time = 5 s). CEST-spectra were generated on a pixel-by-pixel basis and fit to the modified Bloch equations [5] to determine the CS of the bound water and generate temperature maps.

Results and Discussion: The chemical shift of the bound water resonance was independent of pH for this agent. The CEST-spectra are shown for various temperatures in Figure 1 at physiological pH (pH=7.0). M_s is the signal intensity of bulk water following saturation; M₀ is the maximum value of all M_s. Varying the saturation frequency step size (0.2, 0.5, 1, and 2 ppm) had a large effect on the measured bound water CS (42, 43, 43, and 42.6 ppm respectively) when data fitting was not used, but almost no effect when fitting was incorporated (42.92, 42.95, 42.97, and 42.86 ppm respectively). The relationship between temperature and chemical shift without and with data fitting to the Bloch equations (using 2 ppm step size) was $\Delta\omega = -0.30169T + 53.815$, and $\Delta\omega = -0.2559T + 52.517$, respectively. Using these relationships, the temperature maps generated for the phantom are given in Figure 2a and 2b, respectively. Table 1 summarizes the measurement accuracy and variability associated with each map and demonstrates that with data fitting the temperature map has a smaller standard deviation (Fig 2b), and is closer to the expected 37.5 °C.

Table 1. Statistic Results of Temperature Maps.

	Min (°C)	Max (°C)	Mean (°C)	Median (°C)	Std (°C)	Range (°C)
Without Fit (Fig. 2a)	35.85	39.16	36.32	35.85	1.169	3.315
With Fit (Fig. 2b)	36.27	37.26	36.67	36.64	0.202	0.991



Conclusion: The fitting of experimental CEST spectra to the Bloch equations increased the precision of the method as expected, and allowed the creation of accurate and precise temperature maps in a phantom using a new PARACEST compound (Eu-DOTAM-Gly-Phe).

Acknowledgements and References: Funding provided by Robarts Research Institute and CIHR/UWO Strategic Training Initiative in Cancer Research and Technology Transfer. (1) Zhang SR *et al*, J Am Chem Soc 2005;127:17572-17573. (2) Zhang SR *et al*, J Solid State Chem 2003;171:38-43. (3) Ward KM *et al*, J Magn Res 2000;143:79-87. (4) Aime S *et al*, Magn Reson Med 2002;47:639-648. (5) Woessner DE *et al*, Magn Reson Med 2005;53:790-799.