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MRI Thermometry Based on PARACEST Agents

Shanrong Zhang^{*,†,‡}, Craig R. Malloy[†], and A. Dean Sherry^{*,†,§}

[†] Advanced Imaging Resonance Center, University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd, Dallas, TX 75390-8568

[§] Department of Chemistry, University of Texas at Dallas, P.O. Box 830688, Richardson, TX 75083-0688

Noninvasive temperature monitoring has many medical applications because of the close interrelationship between tissue temperature, metabolism and physiology. Such applications include the monitoring local hyperthermia for tumor ablation,¹ the treatment of heart arrhythmias,² the local drug delivery with thermosensitive microcarriers,^{3,4} and the controlled release of gene therapy using heat-sensitive promoters.⁵ Recently, magnetic resonance imaging (MRI) has been explored as a noninvasive technique for temperature mapping.⁶ The temperature dependence of several physical parameters of water have been used for MRI thermometry, including diffusion (D),⁷ spin lattice relaxation (T₁)⁸ and shifts in the water proton resonance frequency (PRF).⁹ Among these methods, PRF thermometry is most widely applied because it is less dependent on tissue composition than the other parameters. This method is based on an early discovery of Hindman,¹⁰ who found that the water proton resonance frequency decreases linearly by *ca.* 0.01 ppm/°C over the range, 37–43°C. However, motion effects and magnetic field inhomogeneities can limit the error of this method to ±1–3°C.¹ This level of accuracy is not problematic if the temperature differences are large (*i.e.*, during tumor ablation) but is impractical if temperature differences are small. For example, the temperature heterogeneity in carotid atherosclerotic plaques is reportedly 0.2–0.3°C.¹¹ Alternatively, exogenous probes based on either paramagnetic relaxation agents that alter T₁ or T₂^{12, 13} or hyperfine shift reagents that alter the chemical shift of some observable nucleus^{14, 15} are much more sensitive to temperature but suffer other experimental limitations for *in vivo* use largely related to the concentrations required and poor spatial resolution. Thus, a method that might allow accurate measures of small temperature differentials would be highly desirable. Here we report a novel MRI thermometric method based on the use of exogenous PARACEST¹⁶ (paramagnetic chemical exchange saturation transfer) agents that sense and report temperature *via* the bulk water signal rather than a nucleus on the agent itself.

A new MRI contrast method was recently introduced where the bulk water signal intensity is altered *via* chemical exchange saturation transfer (CEST).¹⁷ This was later extended to paramagnetic systems and such small molecule agents are now referred to as PARACEST agents.¹⁶ By selective pre-saturation of highly shifted spin pool, A (*i.e.* Ln³⁺-H₂O or Ln³⁺-amide protons), the MRI signal intensity of any exchanging partner spin partner, B (*i.e.*, bulk water) will decrease in intensity if the kinetics are appropriate. For a simple 2-site exchange system,¹⁶ this may be described by $M_{SB}/M_{0B} \approx (1 + k_{BA}T_{1B})^{-1}$, where M_{SB} and M_{0B} are ¹H signal intensities of B (bulk water) with and without pre-saturation of spin A, T_{1B} is the spin lattice relaxation time of B and k_{BA} is the exchange rate constant of water from B to A. Since k_{BA} is directly related to temperature *via* the classical Arrhenius equation, changes in M_{SB}/M_{0B} may be used to measure temperature if the agent concentration is known.¹⁸ This requirement is difficult for *in vivo* applications because here the agent concentration is usually

E-mail: zhangs@u.washington.edu; sherry@utdallas.edu.

[‡]Current address: Department of Radiology, University of Washington, Box 357115, 1959 NE Pacific St, Seattle, WA 98195-7115

unknown. However, a second temperature dependent feature of such systems is the hyperfine position (δ , in ppm) of the exchanging site on the PARACEST agent; for example, hyperfine shift of lanthanide bound water protons ($\text{Ln}^{3+}\text{-H}_2\text{O}$) can vary from +500 ppm for typical Tm^{3+} complexes to -800 ppm for Dy^{3+} complexes.¹⁹ Such hyperfine shifts are highly temperature dependent²⁰ and this feature has been the basis of previous shift reagent-based thermometry experiments.^{14,15} PARACEST thermometry, however, differs in that the MRI readout signal is from bulk water present at *ca.* 55M thereby offering the potential of thermometry measurements with high spatial resolution. Variable-temperature data (Figure S1) indicates that ^1H chemical shift of the Ln^{3+} -bound water resonance vary linearly over 20–50°C according to $\delta_{\text{ppm}} = 6.9 \cdot T - 944.7$ for $\text{Dy}(\text{1})^{3+}$ and $\delta_{\text{ppm}} = -0.4 \cdot T + 64.6$ for $\text{Eu}(\text{2})^-$ (Scheme 1). These temperature responses are ~690 and ~40-fold greater than the PRF response (-0.01 ppm/°C).

The key to PARACEST thermometry then is to locate the ^1H chemical shift (δ) of the Ln^{3+} -bound water molecule in images with high spatial resolution. This may be accomplished by measuring the residual bulk water Z magnetization after a series of selective pre-saturation pulse that is varied over a small range of frequencies spanning the Larmor frequency of the Ln^{3+} -bound water molecule.²¹ For temperature imaging, this may be expanded to 3-dimensional space by acquiring one image at each saturation offset (Scheme 2). By tracing the intensity changes of a specific imaging pixel along the imaging series (Figure S2), a plot of pixel intensity *versus* frequency offset yields a typical Z-spectrum. The temperature of this pixel is obtained by identifying the minimum intensity point which corresponds to the chemical shift of the Ln^{3+} -bound water. Substitution into one of the linear relationships reported above yields the temperature in that pixel. A similar procedure is then repeated for all pixels in the image or region of interest to generate a temperature map.

To test the feasibility of this method, a 1 cm OD vial containing 10 mM $\text{Eu}(\text{2})^-$ 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^{3+} -bound water position (50 ppm). In each case, a minimum was observed in $M_{\text{SB}}/M_{\text{OB}}$ over this frequency range and the frequency of this minimum provided a direct readout of temperature using the appropriate linear equation. 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 those of the regulated air flowing over the sample. An in-plane temperature spatial resolution of $0.15 \times 0.15 \text{ mm}^2$ was obtained using this phantom. The temporal resolution (~3 min) of the experiment could be improved substantially by varying the saturation frequency over a narrower frequency range that spans the expected bound water resonance frequency and by using shorter presaturation periods.¹⁶

Although this method offers considerable potential for *in vivo* temperature mapping, factors such as RF power deposition (SAR limits), inherent tissue magnetization transfer (MT) effects, the tissue biodistribution and toxicity of such complexes and the exchange properties of a PARACEST agent in tissue must be assessed. It is important to point out that values of k_{BA} and T_{1B} need not to be known *a priori* for temperature mapping; the only requirement is that these physical parameters be appropriate for CEST. T_{1B} is of course a feature of tissue water and cannot be easily changed while k_{BA} is controlled by both the lanthanide ion and the ligand structure.¹⁹ Clearly, optimal PARACEST agents for temperature mapping can be identified by adjusting these chemical variables. Imaging studies have been performed in animals after infusion of negatively charged LnDOTA -tetraamide complexes similar to $\text{Eu}(\text{2})^-$ without adverse side-effects²² so we anticipate that $\text{Eu}(\text{2})^-$ will be well tolerated *in vivo* at the concentrations required for PARACEST thermometry. The RF power requirements depend

upon many factors including coil design, volume of power deposition, and features of the PARACEST agent itself¹⁶ but others have shown that *in vivo* CEST imaging can be performed within acceptable SAR limits.²³ Finally, the inherent tissue MT effect could potentially interfere with PARACEST temperature mapping depending on the magnitude of the MT effect in the tissue under investigation. If needed, corrections for MT could be performed by measuring asymmetry differences between presaturation frequencies on each side of the bulk water resonance.²³

In summary, the feasibility of PARACEST-based MRI thermometry has been demonstrated *in vitro*. In comparison with the classical PRF thermometry, the temperature responses of this method is substantially improved by factors of ~690 and ~40-fold for two prototype systems, Dy(1)³⁺ and Eu(2)⁻. This method is especially attractive because the imaging readout signal is bulk water (55M) which offer the potential of much higher MRI spatial resolution than current spectral imaging methods.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Temperature maps of a phantom containing 1 mL of 10 mM Eu(2)⁺ in water at pH 7.0. The temperatures of the air flowing over the sample are indicated in each figure while those reported by imaging are shown by the color bar (in units of °C).

Scheme 1.
Molecular structures of ligands **1** and **2**.

Scheme 2.

A scheme illustrating the basic procedure for generating a temperature map based on PARACEST MRI thermometry.