Temperature Mapping of Mouse Brain Tissue Using MRI-PARACEST Contrast Agents

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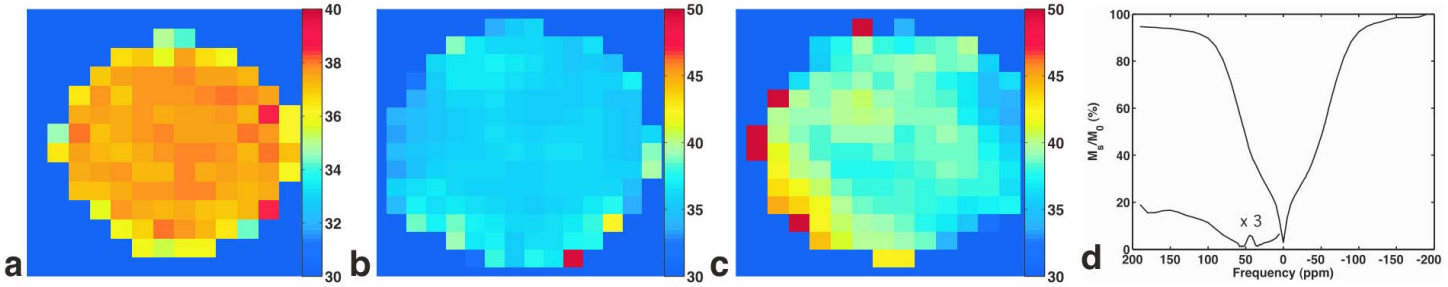
Introduction: *In-vivo* monitoring of tissue temperature can provide insight into metabolic and physiological changes induced by disease processes. Zhang *et al* [1] recently reported a MRI thermometric method based on the use of paramagnetic chemical exchange saturation transfer (PARACEST) agents [2,3,4], and we described a novel MRI-PARACEST compound (Eu^{3+}-DOTAM-Gly-Phe) with optimal CEST sensitivity at body temperature [5]. However the sensitivity of current PARACEST agents may be reduced *in-vivo* due to the magnetization transfer (MT) from protons associated with endogenous macromolecules. Here we demonstrate the feasibility of temperature mapping of mouse brain tissue using Eu^{3+}-DOTAM-Gly-Phe.

Methods: The relationship between temperature and the bound water chemical shift of a PARACEST agent (10 mM solution of Eu^{3+}-DOTAM-Gly-Phe, pH 7.0) was measured at 9.4 Tesla [5]. Temperature maps were created for three different phantoms. The first phantom (phantom A) consisted of an aqueous solution containing 10 mM Eu^{3+}-DOTAM-Gly-Phe (pH 7.0). The second phantom (phantom B) contained 5% bovine serum albumin (BSA) and 15 mM Eu^{3+}-DOTAM-Gly-Phe (pH 7.0). Heating the BSA phantom to 80 ^{o}C for 10 minutes resulted in cross-linking which produced an inherent broad magnetization transfer (MT) effect similar to that observed in *in-vivo* CEST spectra. The third phantom (phantom C) contained mouse brain tissue with 4 mM Eu^{3+}-DOTAM-Gly-Phe (pH 7.4) and also produced a broad MT effect similar to that observed in *in-vivo* CEST spectra. CEST images were acquired on a Varian 9.4T small animal MRI scanner at 37.5 ^{o}C using a two-dimensional fast low angle shot (FLASH) pulse sequence (field of view (FOV) = 25 × 25 mm^2, data matrix: 64 × 64, TR = 4.3 ms, echo time (TE) = 1.9 ms, and flip angle = 6^{o}), preceded by a continuous presaturation pulse (saturation power = 15 μT, saturation time = 5 s). A series of images were acquired by varying the frequency of the presaturation pulse from -150 to 150 ppm with 10 ppm steps from ±60 to ±150, 1 ppm steps from ±30 to ±60, and 5 ppm steps from –30 to + 30 ppm. Temperature was maintained at 37.5 ^{o}C by blowing warm air over the phantoms using a Model 1025 Small Animal Monitoring and Gating System (SA Instruments Inc., Stony Brook, NY). CEST spectra were generated on a pixel-by-pixel basis. For phantom A, the bound water chemical shift associated with each pixel was determined by fitting each CEST-spectrum to the modified Bloch equations [6]. For phantoms B and C, the bound water chemical shift associated with each pixel was determined by calculating the asymmetry between the halves of the CEST-spectrum and then fitting the asymmetry curve to a Gaussian function.

Results and Discussion: The bound water chemical shift was independent of sample pH (data not shown). The relationship between temperature (T) and chemical shift ($\Delta\omega$) is $\Delta\omega = -0.2559T + 52.517$ [5]. Temperature maps obtained from phantoms A, B, and C are presented in Fig. 1. The average temperature excluding pixels at the boundary measured in phantom A (Fig. 1a) was 37.54 ± 0.23, while in phantom B (Fig. 1b) it was 36.12 ± 0.47, and in phantom C (Fig. 1c) it was 38.55 ± 0.95 ^{o}C. The average CEST-spectrum with asymmetry curve from phantom C is given in Fig. 1d. The measurement of temperature in phantom A (aqueous solution) was straight forward due to the clear presence of the bound water peak, which was not obscured by the inherent MT effect typically observed in biological samples. As a result, the measured temperature displayed a relatively uniform temperature distribution, with a standard deviation of less than 0.3 ^{o}C. Temperature measurement in phantoms B (containing BSA) and C (containing brain tissue) had greater variability with a standard deviation of less than 0.5 ^{o}C for phantom B, and less than 1.0 ^{o}C for phantom C at body temperature (37.5 ^{o}C). These values are however very promising, particularly when considering that a relatively low concentration of PARACEST agent was used (4 mM for phantom C) compared to previous studies [1]. The slight underestimation of the actual temperature in phantom B, and the slight overestimation of the temperature in phantom C may be due to a true temperature difference between the phantom and the temperature probe, or it may suggest the applied calibration requires modification for non-aqueous materials. Regardless, these preliminary results are the first demonstration of temperature mapping in the presence of the inherent MT effect observed in tissue.



Conclusion: Temperature mapping is feasible with current PARACEST agents in the presence of the broad MT effect from protons associated with macromolecules present in tissue.

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