

In-Vivo Temperature Measurement using ParaCEST MRI Contrast Agents at 9.4T

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Target audience: Physicists and chemists developing paramagnetic magnetic resonance imaging (MRI) contrast agents that produce contrast using chemical exchange saturation transfer (CEST), particularly those scientists developing agents with *in-vivo* applications.

Purpose: Paramagnetic CEST (paraCEST) MRI contrast agents can be designed to produce temperature dependent image contrast.^{1,2} However, *in-vivo* temperature measurement using paraCEST agents is difficult because paraCEST agents have low *in-vivo* sensitivity due to magnetization transfer (MT) effects from endogenous macromolecules.^{3,4,5} Agents may also modify local T_1 and T_2 relaxation time constants, apparent diffusion coefficients (ADCs) and the measured MT effect. The purpose of this study is to determine whether changes in these MRI tissue parameters affect temperature measurement following direct intramuscular injection of contrast agent.

Methods: The synthesis of Eu^{3+} -DOTAM-Gly-Phe has been previously described.⁶ The bound water chemical shift of this agent is linearly dependent on temperature (Eqn. [1]: $\text{Temperature} = (\delta 3.8 - \text{chemical shift})/0.302$).¹ All MRI experiments were performed using a 9.4T horizontal bore Agilent (Palo Alto, CA) MRI scanner equipped with a 3 cm millipede RF volume coil. **Agent Injection:** 25 μL of 100 mM paraCEST agent dissolved pH 7.0 phosphate buffered saline (PBS) was injected directly into the left leg muscle over 2 minutes in C57BL/6 mice (N=3). **Imaging:** T_1 (~9 min), T_2 (~13 min), ADC (~11 min) and CEST (~28 mins) maps were sequentially acquired before and beginning approximately 10 minutes after paraCEST agent injection. A fiber optic temperature probe was inserted intramuscularly in the right leg muscle as a gold-standard tissue temperature measurement. **MRI Acquisition Parameters:** All MRI images were acquired with a field of view = $32 \times 32 \text{ mm}^2$, matrix size = 64×64 , and slice thickness = 2 mm. Five slices were acquired for T_1 , T_2 and ADC maps while CEST maps were acquired for a single slice due to time constraints. **T_1 mapping:** An inversion-prepared fast low angle shot (FLASH) pulse sequence was used (inversion times = 0.234, 0.503, 0.831, 1.233, 1.751, 2.480, 9.226 seconds, recovery delay = 15 seconds, total acquisition time = 8 min and 51s). **T_2 mapping:** A multi-echo spin-echo pulse sequence was used (echo time (TE) = 20 ms, # of echoes = 8, echo spacing (ESP) = 20 ms, total acquisition time = 13 min and 20s). **ADC mapping:** A set of Stejskal-Tanner images were acquired using a spin-echo diffusion-weighted pulse sequence (b-values = 0, 200 and 400 s/mm^2 , total acquisition time = 10 min and 58s). **CEST mapping:** A standard fast spin-echo (FSE) pulse sequence was preceded by a 5s, 14 μT saturation pulse (repetition time (TR) = 5000 ms, effective TE = 10 ms). A total of 83 saturation pulse frequencies were used to acquire CEST spectra including $\pm 1 \times (100, 80, 59 \text{ to } 29 \text{ (ppm steps)}, 25, 20, 15, 10, 5, 3, 2, 1 \text{ ppm})$ and 0 ppm (total spectra acquisition time was 27 min and 42s). Animal procedures were performed according to a protocol approved by the Western University Animal Use Subcommittee. Macromolecular MT effects were quantified using the area under the negative half of the paraCEST spectrum. Only pixels that generated observable CEST contrast (ie. contrast to noise ratio (CNR) $\geq 2\sqrt{2}$)⁷ were used to generate temperature maps using Eqn. [1]. Correlation coefficients were measured between T_1 , T_2 , ADC, and MT effect magnitude and temperature values.

Results: Tissue temperature (Figure 1) measured using paraCEST contrast (mean \pm STD = 30.1 ± 0.1) agreed well with the temperature measured by the probe

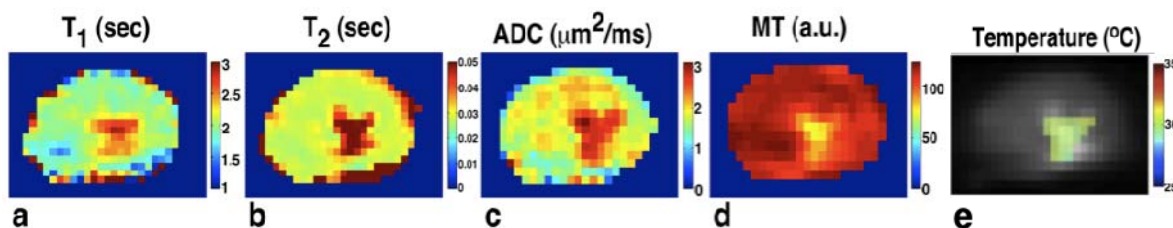


Figure 1: T_1 , T_2 , ADC, MT and temperature maps acquired from a mouse hind leg immediately after direct injection of paraCEST agent.

in the contralateral leg (mean \pm STD = 29.6 ± 0.1). Injection of the paraCEST agent caused significant changes in local T_1 , T_2 , ADC and MT values (Figure 1). However, post-injection T_1 , T_2 , and MT values did not significantly correlate with paraCEST measured temperature (data not shown). In contrast, ADC was correlated with paraCEST measured temperature values.

Discussion: Observed changes in tissue relaxation and MT effects suggest that direct injection of paraCEST agent into leg muscle forms a pocket or 'bubble' of paraCEST solution in the tissue. Despite these changes in tissue MR characteristics the local measure temperature was consistent with an independent measurement in the opposite leg. These results confirm that direct intramuscular injection is a reasonable means to deliver paraCEST contrast agents.

Conclusion: Tissue temperature was measured *in-vivo* using paraCEST MRI contrast. Temperature measurement using paraCEST contrast chemical shift was accurate despite changes in local T_1 , T_2 , ADC, and MT following drug delivery.

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