Measuring in vivo tumor pHe with a PARACEST MRI contrast agent

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Abstract: We have developed a PARACEST MRI contrast agent that can measure pH in a concentration-independent manner. This agent measures pH over a range of 6-7.9 pH units, with a precision of 0.206 pH units and an accuracy of 0.089 pH units. We have developed CEST MRI methods that can detect this PARACEST agent in vivo. We have used our PARACEST agent and CEST MRI methods to measure the extracellular pH (pHe) within a subcutaneous tumor and muscle of a MDA-MB-231 breast cancer model.

Introduction: Extracellular pH is a biomarker for tumor growth, invasion, and metastatic potential, and also contributes to chemoresistance.[1,2] Chemical Exchange Saturation Transfer (CEST) MRI can measure pH with high spatial resolution and without requiring specialized clinical hardware.[3] A PARAmagnetic CEST (PARACEST) agent, Yb-DO3A-oAA, has two pH-depndent CEST effects (Fig. 1A, 1B).[4] This report quantifies the pH range, precision, and accuracy of this measurement and demonsrates in vivo pHe measurements of a tumor and leg muscle using the PARACEST agent and our in vivo CEST MRI method.

Methods: CEST spectra of phantoms of Yb-DO3A-oAA were acquired using a 600 MHz NMR spectrometer by applying selective saturation at 14.2 μT for 5 sec. A sum of three Lorentzian lineshapes was fit to each CEST spectrum. Phantoms of Yb-DO3A-oAA were tested that ranged in pH (6.0-7.9 pH units), concentration (4.5-18 mM), and T_{1sat} relaxation (0.73-1.42 sec). MR spectroscopy of IEPA was also used to measure pH.[5]

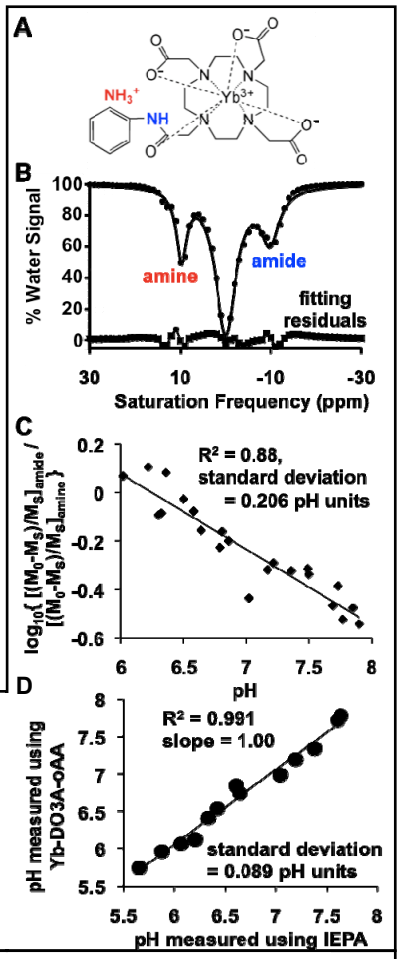

Figure 1. A) The amine and amide of Yb-DO3A-oAA B) show CEST effects at +10 and -10 ppm. C) A $\log_{10}$ ratio of the CEST effects is correlated with pH with a precision of 0.206 pH units. D) The pH measured with CEST MRI matched pH

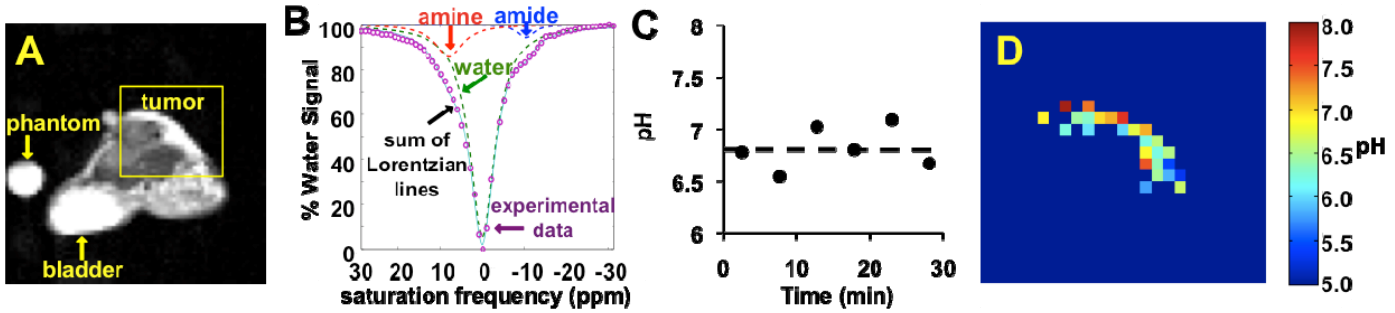

Figure 2. Measurement of in vivo tumor pH with a PARACEST agent. A) A CEST-FISP MR image with selective saturation at 30 ppm shows the location of the tumor and phantom. B) The CEST spectrum of the tumor ROI at 23.4 minutes after injection shows CEST effects from the amine and amide. C) The average pH of the tumor was determined from the CEST effects and the CEST-pH calibration. The average of these six measurements was pH 6.82 with a standard deviation of 0.21 pH units. D) The pH map of the tumor ROI at 23.4 minutes shows an average pH of 6.8 and a pixel-wise standard deviation of 0.4 pH units.

After establishing a CEST-pH calibration with a CEST-FISP pulse sequence[6] using a 300 MHz MRI scanner, 50 μL of 100 mM Yb-DO3A-oAA was directly injected into a MDA-MB-231 flank tumor, and CEST MR images were acquired for 28 min. A similar in vivo study was conducted by directly injecting the same amount of Yb-DO3A-oAA into muscle.

Results: The CEST effects of Yb-DO3A-oAA were correlated with pH as measured with a microelectrode over a range of 6-8 pH units and a precision of 0.206 pH units (Fig 1C). The pH measurements with the PARACEST showed an accuracy of 0.089 pH units compared to MRS of IEPA (Fig. 1D). The ratio of these CEST effects and the pH measurement was independent of concentration and T_{1sat}. The measurement of in vivo pHe in tumor and muscle tissue is shown in Figure 2.

Discussion: These results demonstrate that this PARACEST agent can measure pH with excellent precision and accuracy, and can be used to measure in vivo pHe in tumor and muscle. Detection sensitivity limits this method to direct injections into tissues of interest.

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