

## Monitoring the effects of bicarbonate treatment on tumor extracellular pH using acidoCEST MRI

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**Introduction:** Extracellular pH (pHe) is a hallmark for tumor microenvironment.<sup>1</sup> We have developed a non-invasive MRI method that can accurately measure pHe to assess tumor acidosis, termed “acidoCEST MRI”. This method measures a ratio of the Chemical Exchange Saturation Transfer (CEST) effects of Iopromide (Ultravist<sup>®</sup>), a FDA approved contrast agent for X-ray/CT. Iopromide has two amides that generate different CEST effects, and a ratio of these CEST effects is correlated with pH over a range of 6.0-7.2 pH units, with a precision of 0.06 pH units, and in a manner that is independent of the agent's concentration and the sample's T1 relaxation time. We have applied acidoCEST MRI to monitor the effects of bicarbonate treatment on tumors of mammary carcinoma.

**Methods:** A CEST-FISP pulse sequence (2.8  $\mu$ T, 5 sec, 90 Hz),<sup>2</sup> with 54 saturation frequencies (+10 to -10 ppm) was used to acquire an acidoCEST image in 4.7 min on 7T MRI scanner. Each CEST spectrum was fitted to a single function that consisted a sum of three Lorentzian line shapes (Matlab R2012B).<sup>3</sup> A mouse model of MDA-MB-231 mammary carcinoma subcutaneous flank tumor was treated with 200 mM of bicarbonate ad libitum. acidoCEST MRI was performed 1 day before and 1 day after introducing bicarbonate treatment.<sup>4</sup> A bolus of 200  $\mu$ L of 976 mM iopromide was injected i.v., followed by an infusion of 150  $\mu$ L/hour of iopromide. Six series of acidoCEST spectroscopic images were acquired for 28 min.

**Results:** We were able to measure an increased in pH in tumor before and after bicarbonate therapy. The precision for each acidoCEST measurement was  $\pm 0.095$ . The precisions before and after bicarbonate treatment were comparable,  $\pm 0.092$  and  $\pm 0.098$  respectively. As shown in figure 1, only half of the mice studied showed a significant increase in pH after bicarbonate treatment. This is because the limit of quantification of acidoCEST using Iopromide as contrast agent was pH 7.20. Mouse #7 and #8 had necrotic tumor.

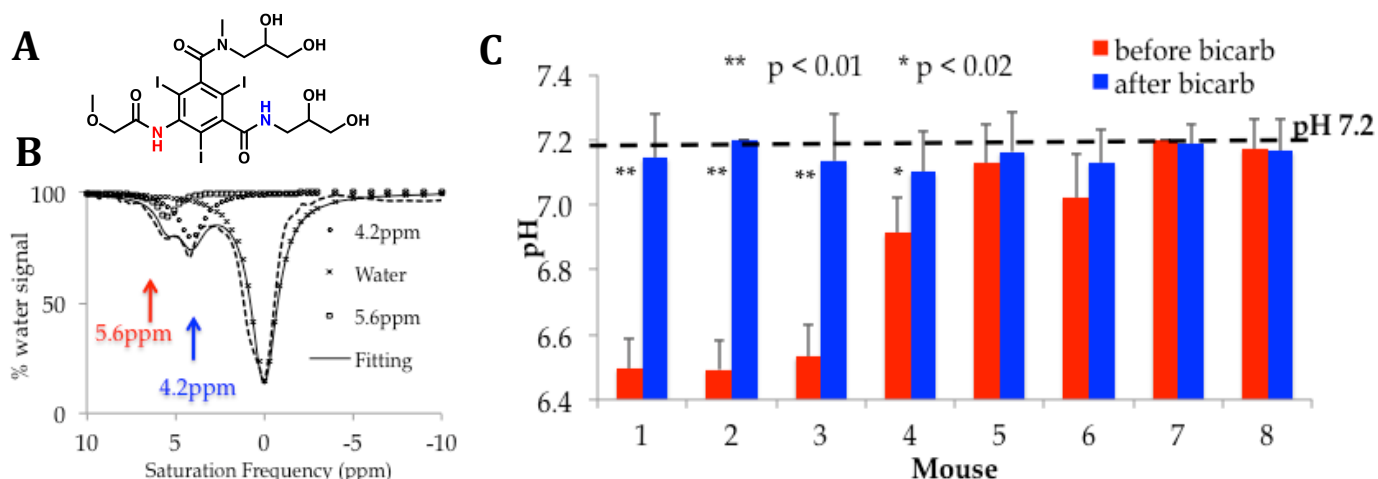


Figure 1: A) The structure of Iopromide. B) Iopromide CEST spectrum fitted with sum of three Lorentzian line shapes. C) Histogram showing acidoCEST measurement before an after bicarbonate treatment. Error bars represent standard deviation of 6 acidoCEST measurements in 28 minutes.

**Discussion:** acidoCEST MRI using Iopromide as contrast agent can measure pH of the tumor with good precision and can be applied to monitor pH-modulating therapy such as bicarbonate treatment. Our method has strong clinical translation potential because it uses low saturation powers, incomplete saturation, and a clinically approved contrast agent.

**References:** 1) Gillies RJ, et al., *Cancer Met Rev* 2007, 26:311-317. 2) Shah TS, et al., *Magn Reson Med*, 2009, 65:432-437. 3) Sheth VR, et al., *Contrast Media Mol Imaging* 2012, 7 26-34. 4) Robey IF, et al., *Cancer Res*, 2009, 69:2260-2268.