

Measuring in vivo tumor pHe with a DIACEST MRI contrast agent

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Abstract: We have developed a CEST MRI method that can measure pH using Ultravist[®], a contrast agent that is clinically approved for X-ray/CT imaging. Using Ultravist[®] as a DIACEST agent, we have measured pH over a range of 6.2-7.4 pH units, with a precision of 0.070 pH units, in a concentration-independent manner. We have developed CEST MRI methods that can detect this DIACEST agent in vivo. We have used this DIACEST agent and CEST MRI methods to measure the extracellular pH (pHe) within a subcutaneous tumor and leg muscle of a mouse model of PANC-1 pancreatic cancer.

Introduction: Extracellular pH (pHe) is a biomarker for tumor growth, invasion, and metastatic potential, and also contributes to chemoresistance.^{1,2} Chemical Exchange Saturation Transfer (CEST) agents that have two CEST effects that arise from at least one amide can measure pH in a concentration-independent manner.^{3,4} Ultravist[®] is a clinically-approved X-ray/CT contrast agent that has two amides (Figure 1A). This report quantifies the range and precision of this measuring pH with CEST MRI of Ultravist[™], optimizes an in vivo CEST MRI method for this application, and then demonstrates an in vivo pHe measurement of tumor and muscle tissues using in vivo CEST MRI.

Methods: CEST spectra were acquired with a CEST-FISP pulse sequence and a 300 MHz MRI scanner.⁵ Selective saturation was applied at 2 μ T for 5 sec and a 90 Hz bandwidth, with saturation frequencies ranging from +10 to -10 ppm. A single function that consisted of a sum of three Lorentzian line shapes was fit to each CEST spectrum using custom routines written

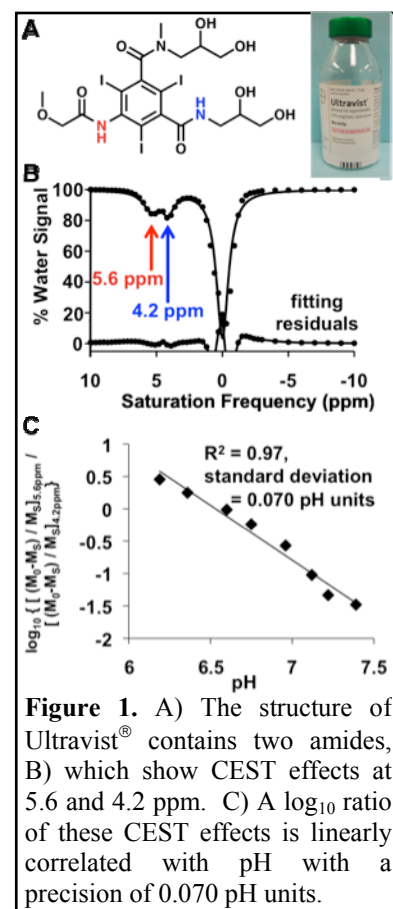


Figure 1. A) The structure of Ultravist[®] contains two amides, B) which show CEST effects at 5.6 and 4.2 ppm. C) A log₁₀ ratio of these CEST effects is linearly correlated with pH with a precision of 0.070 pH units.

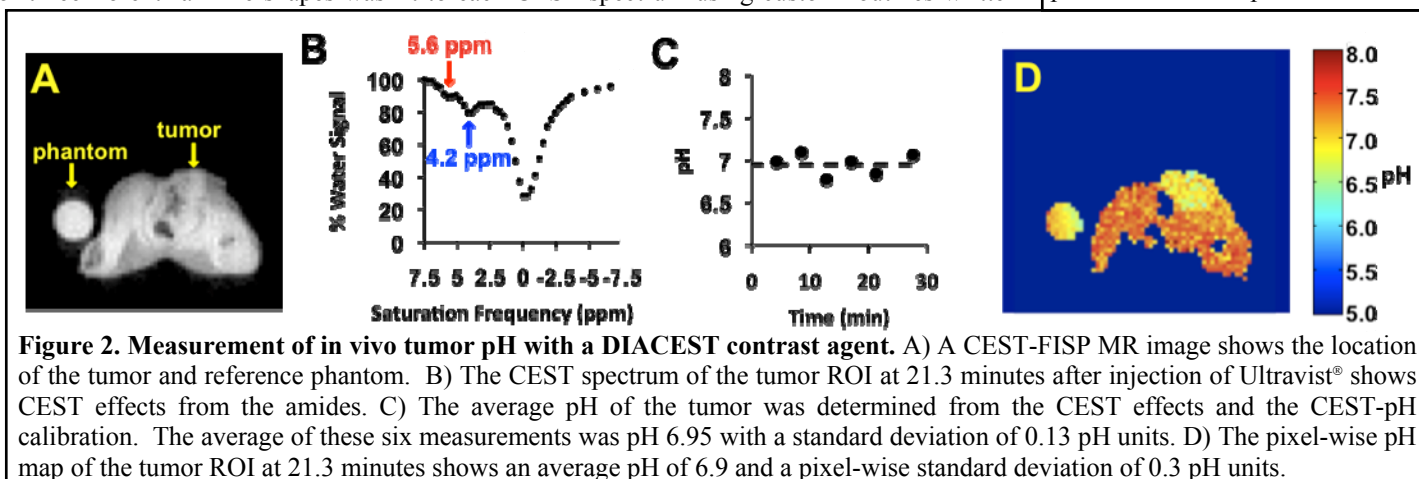


Figure 2. Measurement of in vivo tumor pH with a DIACEST contrast agent. A) A CEST-FISP MR image shows the location of the tumor and reference phantom. B) The CEST spectrum of the tumor ROI at 21.3 minutes after injection of Ultravist[®] shows CEST effects from the amides. C) The average pH of the tumor was determined from the CEST effects and the CEST-pH calibration. The average of these six measurements was pH 6.95 with a standard deviation of 0.13 pH units. D) The pixel-wise pH map of the tumor ROI at 21.3 minutes shows an average pH of 6.9 and a pixel-wise standard deviation of 0.3 pH units.

for Matlab R2009B. Phantoms of Ultravist[®] were tested that ranged in pH (6.2-7.4), concentration (12.5 - 600 mM), and T_{1sat} (0.82 - 2.5 sec). A subcutaneous flank tumor model of PANC-1 pancreatic cancer was injected i.v. with 200 μ L of 972 mM Ultravist[®], and six series of MR CEST spectroscopic images were acquired for 28 min.

Results: Ultravist[®] showed two CEST effects (Figure 1B). A ratio of these CEST effects was correlated with pH (Figure 1C), which was independent of concentration and T_{1sat} relaxation. The ratio of the CEST effects was independent of saturation time, indicating that pH may be measured with incomplete saturation that may accelerate imaging times. The measurement of in vivo pHe in tumor and muscle tissue is shown in Figure 2.

Discussion: These results show that Ultravist[®] can measure tumor pHe over the physiological pH range with high precision. The use of low saturation powers, incomplete saturation, and a clinically approved contrast agent facilitates clinical translation.

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