Evaluation of pH and vascular perfusion in a lung fibrosis mouse model using respiration gated acidoCEST MRI

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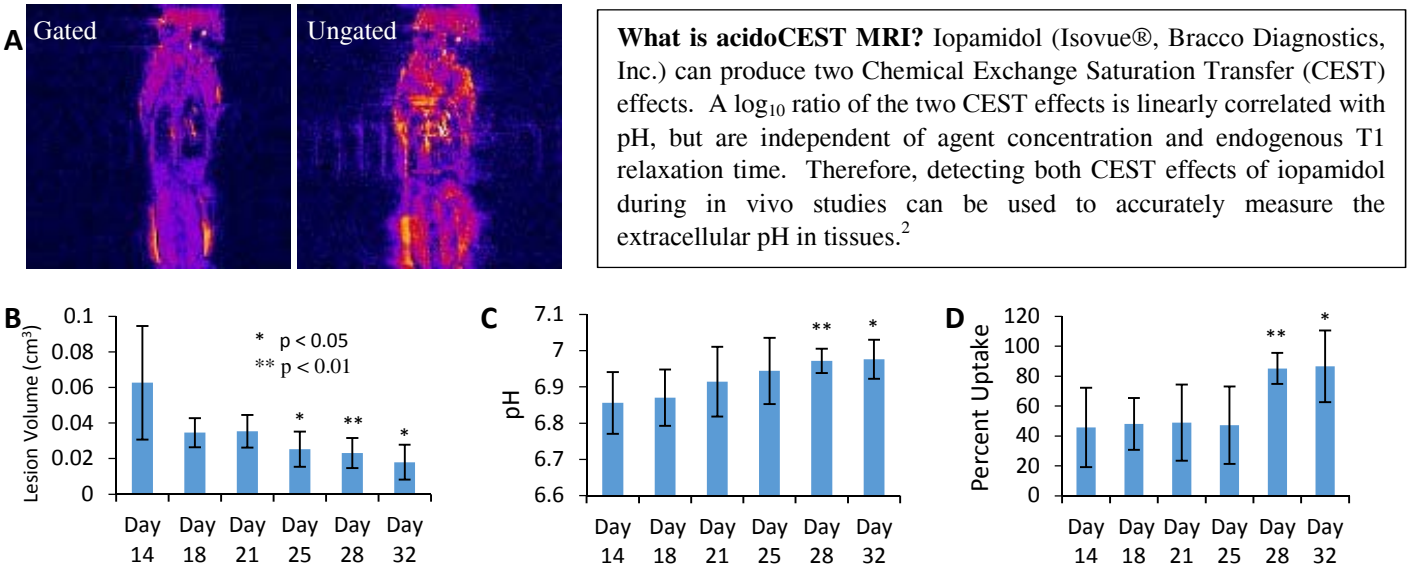
Introduction: During the development of idiopathic pulmonary fibrosis, it is hypothesized that there is an acidosis-dependent activation of transforming growth factor beta (TGF-β) resulting in activation of fibroblasts, thus producing scar tissue and causing impaired lung function that often results in death.[1] Directly measuring pH of fibrotic lesions in a mouse model may significantly strengthen the hypothesis that fibrosis is associated with acidosis. This study uses a novel respiration gated acidoCEST-MRI method to noninvasively measure the pH of lung fibrotic lesions to correlate pH with fibrotic lesion volume.[2]

Methods: 15 C57BL/6 mice were exposed to 2 units/kg of bleomycin by inhalation to create the fibrotic model. 7 mice were imaged on day 14, day 21 and day 28 post exposure and the remaining 8 mice were imaged on day 18, day 25 and day 32 post exposure. Prior to the imaging scan, a bolus of 200 µL iopamidol at 300 mgI/mL was injected i.v. via the catheter. Another bolus of 500 µL iopamidol was injected into the i.p. cavity at 150 µL/hr. A novel respiration gated CEST-FISP pulse sequence with a 5 second saturation period consisting of 2.8 µT power, 90 Hz bandwidth and 54 saturation frequencies between +10 and -10 ppm was used to obtain an acidoCEST MRI result in 5.8 minutes on a 7T Bruker MRI scanner. This acidoCEST MRI scan was repeated six times. To generate pixel-wise pH maps of the lesions, the six CEST spectra for a pixel were averaged, Gaussian filtering was used to smooth the CEST spectrum, each CEST spectrum was fitted to a single function with a sum of three Lorentzian line shapes using Matlab and only CEST effects greater than $2\sqrt{2}$*noise were retained (which represents a 95% probability that the CEST effect is real), and the pH was determined form a CEST-pH calibration performed using an identical acidoCEST MRI protocol. In addition, the percent of lesion volume that showed at least one CEST effect was used to calculate percent uptake of the agent, which was used as a biomarker to estimate vascular perfusion. A T2-weighted image was used to measure lesion volume, using a basic RARE8 sequence.



What is acidoCEST MRI? Iopamidol (Isovue®, Bracco Diagnostics, Inc.) can produce two Chemical Exchange Saturation Transfer (CEST) effects. A $\log_{10}$ ratio of the two CEST effects is linearly correlated with pH, but are independent of agent concentration and endogenous T1 relaxation time. Therefore, detecting both CEST effects of iopamidol during in vivo studies can be used to accurately measure the extracellular pH in tissues.[2]

Figure 1. A. Images of a C57BL/6 control mouse without infection using a gated CEST-FISP sequence vs. a non-gated CEST-FSIP sequence. B-D. Average lesion volume, pH and percent uptake values in the pulmonary fibrosis mouse model. Plotted bar graphs were taken from average values of the 15 mice from each of the six time points that acidoCEST MRI was performed.

Results: Using a respiration gated sequence significantly reduces motion artifacts in CEST-FISP MR images (Fig. 1A). The pH and percent uptake values show a significant increase at Day 28 and 32 relative to Day 14, while the lesion volumes showed a significant decrease during this time period (Fig. 1B-D).

Discussion: These results support the hypothesis that acidosis is associated with the development of idiopathic pulmonary fibrosis. More generally, this study shows that respiration gated acidoCEST MRI can measure pH of lung tissue. Providing opportunities to investigate other pathologies and biological processes that require noninvasive measurements of lung pH.

References: 1) Rosas, I. O., et al. (2013). Am J Respir Crit Care Med 188(7): 765-766. 2) Chen, et al. (2013). Magn Reson Med, *Accepted for publication.*