Chemical Exchange Saturation Transfer (CEST) MRI of the Breast at 3T using Amide Proton Transfer (APT)

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INTRODUCTION The goal of this study is to determine if chemical exchange saturation transfer (CEST) MRI can be used to characterize human fibroglandular (FG) and tumor tissue of the breast at 3T. While X-ray mammography and ultrasound imaging play a critical role in identifying breast tumors, they do not provide quantitative information on tissue composition. Serial biopsies can reveal biochemical properties, but are invasive and subject to sampling error, potentially producing misleading results. Advanced MRI methods, such as dynamic contrast enhanced (1) and diffusion weighted imaging (2) have recently been applied to breast tumors resulting in potentially more specific measures of tumor pathology. Amide proton transfer (APT) CEST MRI has been applied to brain tumors both in animals (3) and humans (4-5), and has shown the potential to distinguish between inflammation and pathological tissue. Therefore, we hypothesized that APT CEST MRI at 3T might provide complementary yet distinct information distinguishing breast lesions from healthy tissue as well as different lesion types.

METHODS Image acquisition One breast cancer patient (53 y.o.), who had undergone neoadjuvant chemotherapy and five healthy controls (mean age 32, range 24-44) were scanned using a Philips Achieva 3T scanner (Philips Healthcare, Best, Netherlands) with a double-breast 4-channel sensitivity encoding (SENSE) receive coil (Invivo Inc., Gainesville, FL). CEST images were acquired using a 3D gradient echo (GE) sequence with single-shot turbo-field echo sequence and a SENSE factor of 2.5 (RL) resulting in nine slices with 1.5x1.5x8.0 mm³ resolution. The CEST spectra were acquired using a 0.5 µT, 500

Figure 1 - Healthy control . A) T2-weighted image of right breast, B) T2-weighted image with overlay of water reference shift map, and C) T2-weighted images with overlaid S/S0 images for the amide proton resonance (3.5ppm) and its reference (-3.5ppm), and D) *APTasym* map overlaid on T2-weighted image.

ms block pre-pulse at 33 offsets between +/- 7.0 ppm, TR/TE/flip angle = 5.2 ms/2.7 ms/9° resulting in a scan time under nine minutes. WASSR (6) spectra were also acquired with the same geometry using a 0.25 µT, 100 ms block pre-pulse at 25 offsets between +/- 1.0 ppm to correct for field inhomogeneities. Fat suppression was achieved using a Pro Set 121 pulse. In addition, T_2^*-weighted (T_2^*-w) scans were acquired at 1.0x1.0x4.0 mm³ resolution using 3D GE acquisition.

Image Analysis The data ($S(\Delta\omega)$) were non-rigidly co-registered using diffeomorphic demons with diffusion regularization criteria as implemented in Medical Image Processing, Analysis, and Visualization (MIPAV). The data were normalized to the signal intensity in the image in the absence of saturation (S_0). The WASSR spectra were used to establish the water frequency as described by Kim, et al. (6) using the maximum symmetry algorithm. The CEST spectra were shifted by the offset frequency of the WASSR spectrum minimum value and extrapolated to the acquired frequencies to account for field inhomogeneities. Amide proton transfer asymmetry

$$CEST_{asym}(\Delta\omega) = \frac{S(-\Delta\omega) - S(\Delta\omega)}{S_o}.$$

(APT_{asym}) was calculated on a voxel-by-voxel basis using: where $\Delta\omega$=3.5ppm.

Figure 2 - Region of interest analysis of CEST in healthy breast tissue. Colored lines indicate pixel spectra, black line is the mean of the region, dashed-line indicates CEST asymmetry.

RESULTS and DISCUSSION Representative results from a healthy control are shown in Fig.1: a gradient echo image (A) with overlays of the center frequency shift (B) and S/S₀ images from +/-3.5 ppm (C) used for APT_{asym} map calculation (D). The APT_{asym} map demonstrates the heterogeneity of the healthy FG tissue. Representative CEST spectra from a region of FG tissue are shown in Fig. 2. Fifteen pixels within healthy FG tissue are plotted as a function of saturation offset frequency with the group mean shown in black. The dashed line indicates the calculated $CEST_{asym}$ for this region, with an apparent peak at the resonance of amide protons (3.5 ppm). Fig. 3 shows results from the breast cancer patient where the contrast-enhanced T_1-weighted scan indicates the enhancing lesion (white arrow in panel A). Panel B shows the fat-suppressed GE image and Fig. 3C shows the APT_{asym} map overlay revealing an increase in APT_{asym} in the remaining tumor relative to its surrounding FG tissue.

Many anti-tumor agents use molecularly-targeted therapy, so it is necessary to non-invasively monitor the subsequent molecular pathophysiological changes to characterize tumor growth or treatment response. Contrary to the conventional morphological evaluation typically used to assess treatment response, CEST-derived APT_{asym}

Figure 3 - Results from treated tumor patient: A) Contrast enhanced T1-weighted image with tumor indicated by white arrow, B) T2-weighted image C) with *APTasym* overlay.

measurements are reflective of the underlying molecular composition of the tissue. Therefore, as we expand our patient set, we will test the hypothesis that APT_{asym} measurement in breast tumors are more likely to provide earlier and more specific measurements of tumor response to therapy than the conventional methods.

REFERENCES 1) Ah-See M-LW, et al., *Clin. Cancer Res.* 14(20):6580. 2) Yankeelov TE, et al., *MRI* 25(1):1. 4) Jones CK, et al., *MRM* 56:585. 5) Zhou J, et al., *MRM* 6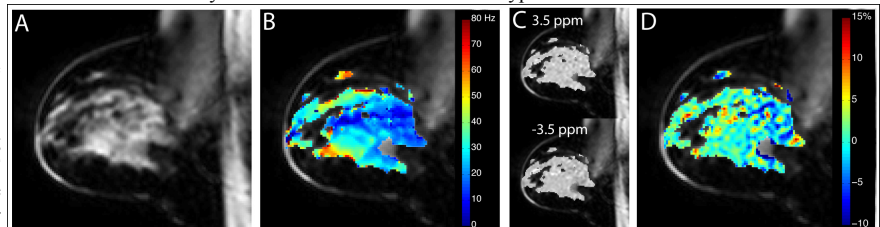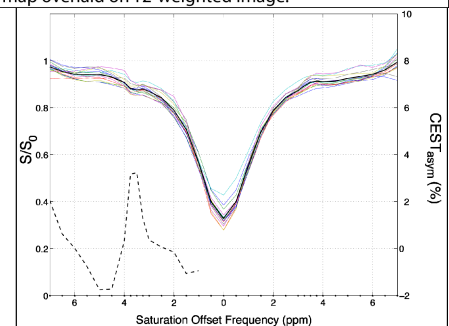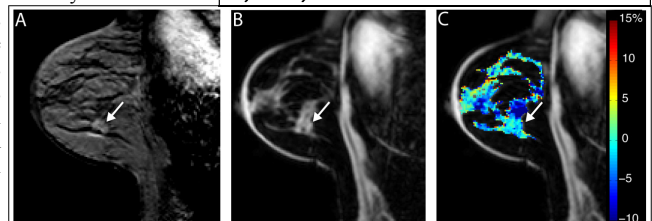0:842. 6) Kim M, et al., *MRM* 61:1441.