Application of Chemical Exchange Saturation Transfer (CEST) MRI in Acute Human Stroke Patients Demonstrates New Potential for Visualization of Tissue Acidosis and Infarction Risk

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Target Audience: Stroke clinicians and imaging scientists interested in clinical application of chemical exchange saturation transfer (CEST) contrast

Purpose: *The purpose of this study is to apply a pH-sensitive CEST protocol in acute (≤4.5 hrs post-onset) and subacute (4.5-24 hrs post-onset) stroke patients to understand the extent to which amide proton transfer (APT) contrast may be used to identify metabolically-impaired tissue at highest risk for infarction.* Reducing stroke-related mortality requires improving our ability to accurately identify tissue at risk for infarction in the acute setting, and to use this information to titrate aggressive therapy. Diagnostic imaging in patients suspected of acute stroke focuses on identifying salvageable tissue from the spatial mismatch in hyperintensity on transit time maps derived from perfusion weighted imaging (PWI) and on diffusion weighed imaging (DWI). However, PWI generally requires intravascular contrast agents, which can cause severe side-effects in patients with impaired renal function, and more importantly identification of irreversible tissue damage thresholds appear to vary according to data acquisition parameters and post-processing method. However, pH may be a more sensitive indicator of infarction risk, as tissue acidosis is known to occur in extreme stages of cortical hypoperfusion (<25 ml/100g/min). CEST imaging has been shown to provide contrast sensitive to base-catalyzed chemical exchange of labile amide and water protons, and indeed CEST imaging in animal models of stroke has shown potential for identification of infarction risk[1]. However, no human studies have been performed in acute stroke, largely owing to obvious difficulties of performing experimental methods in this setting. Here, we apply for the first time CEST imaging in human acute stroke patients in conjunction with one-month follow-up scans to assess final infarct size.

Methods: *Experiment.* Patients (n=10; age=66+/-12 yrs) presenting with acute (n=7) and subacute (n=3) stroke and healthy volunteers (n=5) provided consent and were scanned at 3T (Philips) using body coil transmission and SENSE head coil reception. In order not to delay treatment, only patients having contraindications to thrombolysis or patients awaiting mechanical thrombectomy were included. In patients, PWI (TR/TE=1481/30 ms; spatial resolution=1.7x1.7x5 mm^3), DWI (TR/TE=2303/68 ms; spatial resolution=2x2x4 mm^3) and FLAIR (TR/TE=9000/120 ms; spatial resolution=1.1x1.1x5 mm^3) imaging was performed upon admission. CEST scans (3D gradient echo; slices=16, B_1=block (1 μT), spatial resolution=0.8x0.8x5 mm^3, Δω=-640 Hz (-5 ppm) to 640 Hz (+5 ppm) at 40 Hz (0.3 ppm) spacing) were performed in patients and healthy volunteers. Follow-up FLAIR imaging was performed in patients one month post-stroke to characterize tissue progressing to infarction. *Analysis.* CEST data were normalized, corrected for motion, and baseline drift. Voxel-wise CEST spectra were corrected for B_0 inhomogeneity by fitting data to a Lorentzian and the minima shifted to Δω=0 ppm. CEST spectra were further analyzed by calculating the APT asymmetry (S(Δω=-3.5ppm) – S(Δω=3.5ppm), and the integral of CEST-spectra around the APT[2] resonance (3.5+/-0.5 ppm). Acute data were co-registered to the follow-up FLAIR and masks were generated using standard segmentation routines to characterize tissue (i) progressing to infarction (hyperintense on follow-up FLAIR), (ii) in the PWI/DWI mismatch tissue defined by prolonged time-to-peak (TTP) but normal DWI, (iii) with high risk of infarction (hyperintense on acute DWI), and (iv) normal appearing white matter. Z-spectra were calculated along with multiple measures of CEST contrast including asymmetry and the integral of the z-spectrum in vicinity (3.5+/-0.5 ppm) of the APT[2] effect.

Results and Discussion: In acute patients, average time from symptom onset was 126+/-66 min. Two patients underwent IV-thrombolysis and two underwent mechanical thrombectomy; no treatment decisions were made based on CEST findings. Fig. 1A shows a representative APT integration map for a control and patient volunteer with right MCA territory infarct and DWI/PWI mismatch. Note the lack of contrast in the control APT map relative to the clear hyperintensity in right MCA territory and left ACA and ACA/MCA watershed area on the patient map, reflective of reduced APT effect from baseline and consistent with acidosis. Control volunteers exhibited an expected white matter APT effect = 1.9+/-0.27%. Patients exhibited a broader range of CEST asymmetry (0-6%), in a manner that varied with stroke location. Fig. 1B shows a 58 yr/M presenting approximately four hours after acute onset with left arm and leg paralysis. CEST imaging showed reduced APT effect, consistent with increased acidosis, in tissue progressing to infarction (red) relative to tissue that did not progress (green) and healthy appearing white matter (black). Fig. 1C shows a 57 yr/M presenting 1hr 10 min following symptom onset, with complete occlusion of right M1, right sided DWI lesion with large PWI deficit, and left hemiparesis and neglect. A similar trend in the z-spectrum is apparent in this patient. The remaining eight patients showed unique contrast that varied regionally. While we observed several promising trends that motivate clinical potential for this approach, several limitations of conventional analyses were observed as well. Asymmetry calculations provided non-specific results in many patients, which was attributed to asymmetric magnetization transfer effects and motion that may occur preferentially at different frequency offsets. In stroke patients, motion presents a confound that may preclude comparisons between temporally distinct time points (e.g., +/-3.5 ppm) or for z-spectrum fitting. Voxel composition may also vary regionally, as infarcted tissue may partial volume more with CSF/water, also minimizing the ability to characterize this effect.

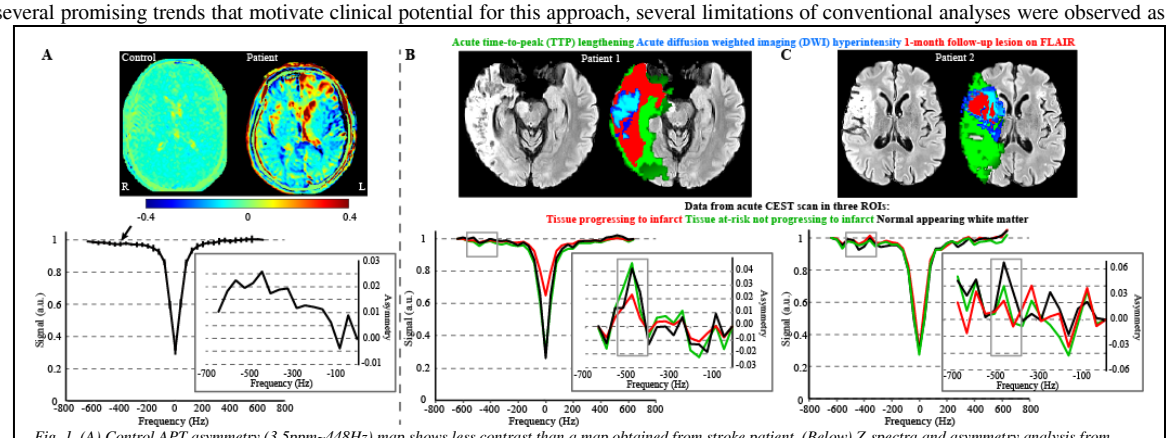

Fig. 1. (A) Control APT asymmetry (3.5ppm~448Hz) map shows less contrast than a map obtained from stroke patient. (Below) Z-spectra and asymmetry analysis from white matter in all controls. (B, C) Patient CEST data shows reduced APT asymmetry in tissue progressing to infarct at one month follow-up, consistent with tissue acidosis, relative to tissue with delayed TTP and healthy white matter (see text for patient details).

Conclusions: This work is the first demonstration of pH-weighted APT CEST imaging in human acute stroke and shows that CEST provides unique contrast compared to DWI and PWI in tissue that progresses to infarction by one-month follow up. We also discuss ongoing limitations of CEST in the acute stroke setting and provide an outline of technical hurdles that must be overcome before CEST may be applied routinely in this important patient population.

References: [1]Sun PZ, et al. JCBFM. 2007 Jun;27(6):1129-36. [2]Zhou J, et al. Nat Med. 2003 Aug;9(8):1085-90.