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 risk1. 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 mm3), DWI (TR/TE=230/68 ms; spatial resolution=2x2x4 mm3) and FLAIR (TR/TE=9000/120 ms; spatial resolution=1.1x1.1x5 mm3) imaging was performed upon admission. CEST scans (3D gradient echo; slices=16, B1-block (1 μT), spatial resolution=0.8x0.8x5 mm3, 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 B0 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 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 (hypointense 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 (hypointense 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 APT2 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 asymmetry map showing less reduced APT effect from baseline and consistent with (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.

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.