Initial Application of pH-weighted Imaging with Pulsed CEST to Image an Acute Ischemic Stroke Patient

Alan J Huang[1,2], Craig Jones[1,3], Richard Leigh[4], Samson Jarso[1,3], and Peter van Zijl[1,3]

[1]FM Kirby Research Center for Functional Brain Imaging, Johns Hopkins University, Baltimore, MD, United States, [2]Department of Biomedical Engineering, Johns Hopkins University, Baltimore, MD, United States, [3]Russell Morgan Department of Radiology and Radiological Sciences, Johns Hopkins University, Baltimore, MD, United States, [4]Department of Neurology, Johns Hopkins University, Baltimore, MD, United States

Introduction: Stroke, the third leading cause of death and leading cause of disability, affects fifteen million people worldwide(1). Acute ischemic stroke (AIS), caused by the occlusion of cerebral blood vessels by an arterial embolus or thrombus, accounts for approximately 85% of stroke cases(2). Thrombolytic treatment with intravenous tissue plasminogen activator (IV tPA) to restore blood flow can reduce tissue infarction if given within the FDA-approved time window of three hours after onset of ischemia(3). This restriction results in most AIS patients not being treated with IV tPA. Patients who present outside of the IV tPA treatment window are considered for more invasive treatments. Currently, a common way of selecting patients for treatment is by using MRI to look for a mismatch between tissue receiving poor blood flow (imaged with perfusion weighted imaging (PWI)) and tissue that likely (but not always) infarcted (imaged with diffusion weighted imaging (DWI))(4). However, recent literature has shown that this method can overestimate the amount of poorly perfused tissue, which results in patients being inappropriately taken for aggressive therapy(5). A physiological parameter that could be more indicative of tissue at risk of infarction is pH because tissue acidosis occurs when blood flow has reduced to a point when aerobic metabolism is impaired yet cellular ion gradients are still maintained. It has recently been shown that chemical exchange saturation transfer (CEST) of endogenous proteins and peptides, so-called amide proton transfer (APT) MRI, is sensitive to changes in pH(6). Preclinical ischemia models have confirmed that APT may predict areas that go to infarction better than PWI or DWI(7). Our hypothesis is that the region of reduced pH in ischemic stroke patients may better represent the region of brain at risk of infarction if untreated. Here we explore the feasibility of using APT MRI to visualize tissue at risk of infarction.

Experimental Methods: An 87 year old female patient and a 64 year old female healthy volunteer were consented and scanned on a Philips 3T Achieva Scanner with body-coil excitation and a 32-channel SENSE receive coil. The patient was imaged 62 hours after onset of ischemia. Pulsed CEST was used to acquire images weighted by pH(7). Diffusion tensor images (DTI) and dynamic susceptibility contrast-based (DSC) perfusion weighted images (PWI) were also acquired. Individual scan parameters were: DTI: 2.2 mm isotropic voxels, b-value = 700 mT/m, 32 directions, TE/TR = 71/7043 ms, 70 slices acquired; PWI: 2.2x2.2x4.4 mm^3 voxels, TE/TR = 40/1500 ms, 80 dynamics acquired, 22 slices acquired; pulsed CEST: 2.2 mm isotropic voxels, saturation pulse duration = 25 ms, saturation pulse amplitude = 1 μT, TR/TE = 65/7 ms, 60 slices acquired. Pulsed CEST images were acquired at 61 frequencies: ±9 , ±7 , ±5 , ±4.5 , ±4.3 , ±4.1, ±3.9 , ±3.7, ±3.5, ±3.3, ±3.1, ±2.9, ±2.7, ±2.5, ±2.0, ±1.5, ±1.4, ±1.3, ±1.2, ±1.1, ±1.0, ±0.9, ±0.8, ±0.7, ±0.6, ±0.5, ±0.4, ±0.3, ±0.2, ±0.1, and 0 ppm (relative to the water frequency). Four unsaturated volumes were acquired with the same sequence with the RF saturation pulse turned off and averaged together to get S_0. Total scan time for pulsed CEST was 10 min 34 s. The healthy volunteer did not receive a perfusion scan. Images from DTI, DSC PWI, and pulsed CEST were motion-corrected and co-registered to DTI scans using CATNAP(8). Next, the images were skull-stripped using the brain extraction algorithm from FSL(9). A mean diffusion weighted image was generated from the DTI scan, and voxels exhibiting signal intensity greater than one and a half standard deviations above the mean of the mean diffusion image were designated as diffusion lesions. The pulsed CEST data were processed on a voxel-wise basis as follows: 1) The center frequency shift map was determined by fitting a Lorentzian lineshape to a sub-spectrum of the following frequencies: ±9 , ±7 , ±5, ±1.0, ±0.9, ±0.8, ±0.7, ±0.6, ±0.5, ±0.4, ±0.3, ±0.2, ±0.1, and 0 ppm. 2) Using the center frequency shift map, the z-spectra were shifted so that the center frequency of each voxel was at 0 ppm. 3) Next, magnetization transfer ratios, (MTR) at +3.5 ppm and -3.5ppm were calculated by averaging signal intensities at ±3.7, ±3.5, and ±3.3 ppm. 4) Finally, the MTR asymmetry (MTR_{asym}(+3.5 ppm)) maps were calculated by subtracting MTR(-3.5 ppm) from MTR(+3.5 ppm)(6). PWI data were computed on a voxel-wise basis to generate a TTP map. Next, the TTP map was further processed by generating a TTP delay map using the contralateral normally perfused tissue as reference (10). Furthermore, cutoffs of the TTP delay map were applied at ≥2, ≥3, ≥4, ≥5, and ≥6 seconds. These cutoffs were chosen because recent publications comparing PET and MR methods for identifying penumbral blood flow have confirmed that a TTP delay of four seconds corresponds closely to the PWI penumbra(11-12). Also, to study how the pH penumbra estimates tissue at risk of infarction differently than the PWI penumbra, we applied two thresholds (MTR_{asym}(+3.5 ppm)≤ -2 and MTR_{asym}(+3.5 ppm)≤ -3) to determine the pH penumbra and overlapped the pH penumbra mask with maps at the different TTP delay cutoffs.

Figure 1

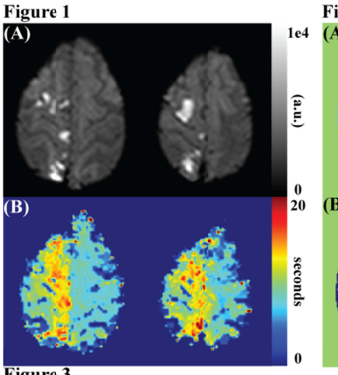

Figure 2

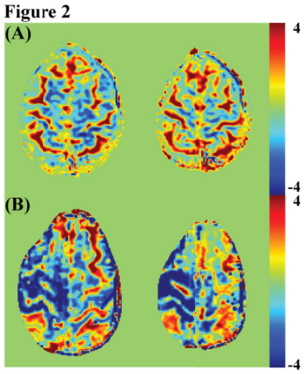

Figure 3

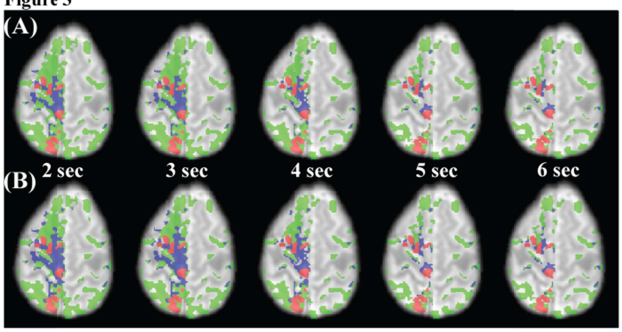

Figure 1. (A) Diffusion weighted scan (mean diffusion weighted image) and (B) Perfusion weighted scan of ischemic stroke patient (time to peak image).
Figure 2. MTR_{asym} (+3.5 ppm) image of (A) healthy volunteer and (B) ischemic stroke patient.
Figure 3. Images of diffusion lesion (red), possible pH penumbra (blue), and perfusion penumbra (green) overlaid on CEST M_0 image.
(A) pH penumbra was determined with MTR_{asym}(+3.5 ppm) ≤ -3.
(B) pH penumbra was determined with MTR_{asym}(+3.5 ppm) ≤ -2.

Results and Discussion: Fig. 1 shows that this patient, who presented with left lower extremity weakness, had several diffusion positive regions (Fig. 1A) and a perfusion deficit covering the entire vascular territory of the right anterior cerebral artery (Fig. 1B). This can be seen by an increase in the time to peak of the patient's right hemisphere (left in image; radiological convention). In Fig. 2, the healthy control's MTR_{asym} image (Fig. 2A) is compared to the patient's MTR_{asym}(+3.5 ppm) image (Fig. 2B) over a similar region of interest. Notice that the healthy control's MTR_{asym}(+3.5 ppm) image is symmetric between the two hemispheres whereas the ischemic patient's MTR_{asym}(+3.5 ppm) image is asymmetric because of possible tissue acidosis in the right hemisphere. In Fig. 3, two different thresholds for the pH weighted images are used (Fig. 3A: MTR_{asym}(+3.5 ppm) ≤ -3 and Fig 3B: MTR_{asym}(+3.5 ppm) ≤ -2) to determine the pH penumbra. Notice that the pH penumbra is contained around the diffusion lesions. Additionally, the PWI penumbra appears to overestimate the tissue at risk of infarction.

Conclusion: We present an initial application of using pulsed CEST to image possible pH changes in an acute ischemic stroke patient. Comparison of MTR_{asym}(+3.5 ppm) images between a healthy volunteer and an ischemic stroke patient show a reduction in the MTR_{asym}(+3.5 ppm) in the region of delayed perfusion that was attributed to tissue acidosis. Comparison of the pH penumbra to the PWI penumbra (by using different TTP delay thresholds) shows that the pH penumbra localizes a region smaller than the PWI penumbra. Therefore, APT MRI shows sensitivity to pH changes that are not visible using diffusion or perfusion imaging.

References: 1. World Health Report, 2002. 2. Rymer MM et al. Neurol Res. 2005. 3. Donnan GA et al. Lancet Neurol. 2009. 4. Barber PA et al. Neurology 5. Kucinski T et al. AJNR Am J Neuroradiol. 2005. 6. Zhou J et al. Nat med. 2003. 7. Sun et al. JCBFM 2007. 8. Jones et al., ISMRM Proceedings 2776, 2011. 9. Landman BA et al. Neuroimage. 2007. 10. Smith SM. Hum Brain Mapp. 2002. 11. Neumann-Haefelin T et al. Stroke. 1999. 12. Sobesky J et al. Stroke. 2004. 13. Zaro-Weber O et al. Stroke. 2010. **Funding:** P41 RR 01524