Can Nuclear Overhauser Enhancement Mediated Chemical Exchange Saturation Transfer (NOE-CEST) Offer a New Insight in Acute Stroke Diagnosis?

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Target Audience: Physicists and clinicians interested in chemical exchange saturation transfer (CEST) magnetic resonance imaging (MRI) for stroke.

Purpose: After an ischemic stroke the brain undergoes complex cascade of physiological adaptations in an attempt to maintain tissue viability. Anaerobic glycolysis is one of the defence mechanisms, leading to tissue acidification and a drop in the saturation effect observed in CEST MRI at the resonance offset of amide protons [1-2]. The dynamic evolution of the cellular environment following stroke implies that other saturation transfer mechanisms might provide insight regarding cerebral injury which may potentially be useful for acute stroke management. In this work, CEST data in acute stroke patients were acquired to explore whether nuclear Overhauser enhancement mediated CEST (NOE-CEST) [3] provides information about ischemic injury complementary to apparent diffusion coefficient (ADC) mapping and pH-weighted imaging using amide proton transfer (APT).

Methods: *Subject recruitment & MRI.* Four patients presenting with acute ischemic stroke symptoms within 6 hours of onset were recruited and scanned using a 3T Siemens Verio scanner according to a National Research Ethics Committee approved protocol. For each patient, T_1 structural imaging, DWI and single-slice CEST imaging following [1, 2] were acquired: 50 Gaussian pulses, where each pulse had a flip angle of 184°, duration of 20 ms and 50% duty cycle; the CEST plane was selected by an attending clinician based on the presenting DWI lesion. The patient's 1-week/month follow-up fluid attenuated inversion recovery (FLAIR) scan was used to define the extent of infarction.

Data processing & analysis. A 3-pool exchange model (water, amide and NOE-CEST) following [2] was fitted to the collected CEST data. B_0 inhomogeneity in the data was corrected using the fitted water centre frequency obtained from the model-based analysis. APTR* = $[S_{water}(+\Delta) - S_{water+amide}(+\Delta)]/S_o$, and NOE* = $[S_{water}(-\Delta) - S_{water+NOE\text{-}CEST}(-\Delta)]/S_o$, were used to quantify the APT and NOE-CEST effects respectively, where S is the simulated signal at the resonance frequency of the labile pool of interest (Δ = 3.5 ppm) using the fitted parameters from the pool denoted by the subscripts (water, amide and NOE-CEST) and S_o refers to the fitted unsaturated signal. All the different imaging modalities were registered to the patient's own T_1 image using FLIRT in the FSL package [4] for analysis.

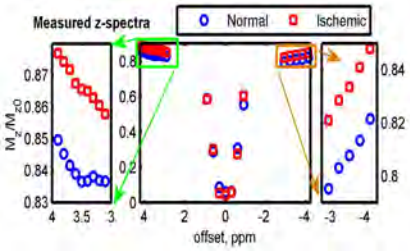

Fig. 1: Measured z-spectra in ischemic and normal tissue of a representative patient.

Results: Fig. 1 shows the measured z-spectra after B_0 correction from a representative patient; the saturation effects around ± 3.5 ppm were smaller in the ischemic tissue when compared to the contralateral normal appearing tissue. In this cohort of 4 patients, there were two discrete patterns of tissue response to acute ischemia: Fig. 2 shows patient results where both APTR* and NOE* matched the area of acute ADC reduction and FLAIR defined infarct at follow-up; Fig. 3 shows patient results where there is a reduction in both ADC and APTR* but not NOE*. In the areas where NOE* was maintained in patient 4, there was no clear infarction in the follow-up FLAIR.

Discussion: This work is the first demonstration of NOE-CEST in acute human stroke. It shows that NOE-CEST provides complementary information to both ADC and pH-weighted imaging in defining final tissue outcome. It was observed that when both APTR* and NOE* were reduced, this tissue progressed to infarction. When only APTR* was reduced and NOE* was maintained, this tissue or certain region of this tissue was not part of the final FLAIR defined infarct. The NOE-CEST effect has been reported to be pH insensitive [5], these results support the independence of the APT and NOE-CEST effects in stroke. Proposed mechanisms of attenuated NOE-CEST effect include lowered intracellular protein content, greater intracellular protein mobility and alterations in protein structural integrity [6], and are not thought to be pH-weighted as is the case for APT [5], all of which may be pertinent when predicting tissue fate in acute stroke. Further work is required to optimise the sequence, to investigate the optimal method to quantify this broad saturation effect, and to study how lipid signal [7] and treatment interact with the NOE-CEST effect. This proof of principle study demonstrates that NOE-CEST signal may reveal different tissue injury pathways. Thus, analysing APT and NOE-CEST effects independently may improve stratification of patients for treatment.

References: 1. Harston *et al.*, Brain, in press. 2. Tee *et al.*, NMR in Biomedicine, 27:1019-29, 2014. 3. van Zijl *et al.*, MRM, 65: 927–948, 2011. 4. Jenkinson *et al.*, NeuroImage, 17:825-41, 2002. 5. Jin *et al.*, MRM, 69:760-70, 2013. 6. Paech *et al.*, PLoS ONE, 9:e104181. 7. Lu *et al.*, MRM, in press.

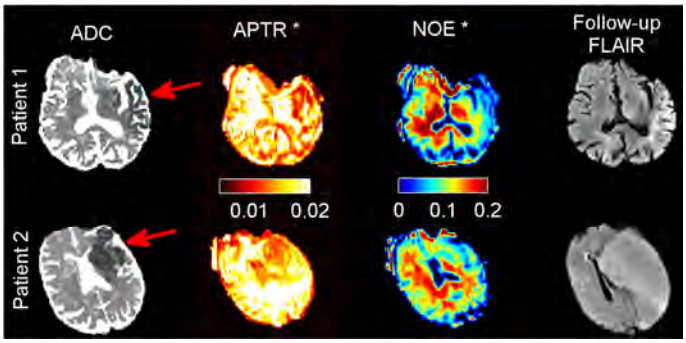

Fig. 2: 2 patients with APTR* and NOE* reduction matched to the area of acute ADC signal change progressing to infarction at follow up.

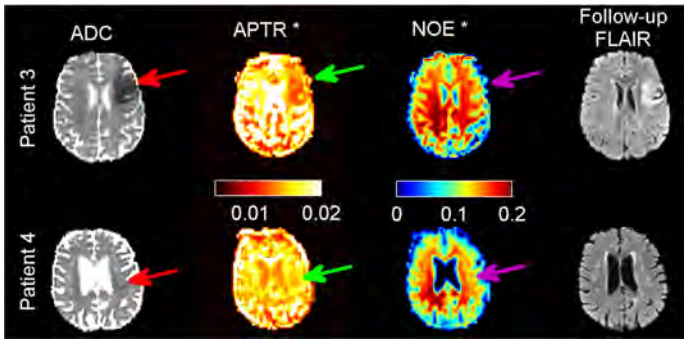

Fig. 3: 2 patients with acute ADC and APTR* signal changes, but mismatched with the NOE* signal (red, green and purple arrows respectively); where no NOE* signal change was seen, the tissue or part of the tissue did not progress to infarction.