Compensatory Amide Proton Transfer Ratio (CAPTOR) Imaging to Improve the Specificity of Tissue Acidosis MRI

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**Introduction** Amide proton transfer (APT) imaging is a specific form of chemical exchange saturation transfer (CEST) MRI that utilizes labile amide protons from endogenous proteins and peptides to probe microenvironment pH. In fact, APT MRI has been used to study acute ischemic acidosis, and recently postulated as a complementary tool to perfusion and diffusion MRI in imaging stroke. However, the conventional magnetization transfer (MT) asymmetry analysis contains not only pH-dependent APT effect, but also concomitant RF irradiation contributions such as intrinsically asymmetric MT. As such, APT imaging, in its current form, may be susceptible to non-negligible MT contribution and not specific to acidosis. Here, we propose a compensatory APT ratio (CAPTOR) method that better suppresses concomitant RF irradiation effects, and demonstrated its in vivo use via a global ischemic animal model. Further evaluation of CAPTOR MRI is currently undergoing before its clinical translation.

**Theory** The amide proton transfer ratio (APTR) is given by $\text{APTR} = \Delta \text{MTR}_{\text{asym}} - \Delta \text{MTR}'_{\text{asym}}$, in which $\Delta \text{MTR}_{\text{asym}}$ and $\Delta \text{MTR}'_{\text{asym}}$ are experimentally measured and intrinsic MT asymmetry, respectively and APTR represents pH-dependent APT process. Because the center of macromolecule spectrum is 2-3 ppm away from bulk water resonance, $\Delta \text{MTR}'_{\text{asym}}$, the macromolecular MT asymmetry between ±3.5 ppm, may be comparable to the magnitude of APTR. Hence, in order to delineate pH-dependent APTR from $\Delta \text{MTR}'_{\text{asym}}$, we propose to acquire two compensatory scans around amide proton offset, and the CAPTOR is given as $\left(\frac{I_{\text{comp1}} + I_{\text{comp2}}}{2} - I_{\text{label}}\right)$. The rational is that if compensatory frequencies are beyond the bandwidth of amide protons while negligible when compared with semisolid macromolecular spectrum, CAPTOR can correct concomitant RF irradiation and asymmetric MT effects, and therefore, is more specific to pH change.

**Experimental Design and Animal Preparation** Global ischemia animal stroke model of Wistar rats (n=3) was used to evaluate CAPTOR MRI at 4.7T. Specifically, animal’s left femoral artery was ligated for blood pressure monitoring and glucose sampling. Perfusion, diffusion and relaxation MRI were acquired under anesthesia as well as immediately postmortem. Z-spectrum was obtained between ±6 ppm (1,200 Hz at 4.7T) with a frequency interval of 0.5 ppm, and the RF power was 0.75 μT. Z-spectra were interpolated per-voxel during post processing to minimize field inhomogeneity induced errors. Moreover, CAPTOR map was obtained by subtracting the label scan (3.5 ppm) from the mean of two compensatory images, each being 1 ppm away from the amide proton offset (i.e., 2.5 and 4.5 ppm).

**Results and Discussion** Z-spectrum obtained under normal condition showed a focal attenuation centered at 3.5 ppm, the labile amide proton offset, when compared with that acquired at postmortem (Fig. 1a). It is consistent with the notion that chemical exchange of endogenous amide proton is base-catalyzed, and hence, tissue acidosis leads to a decrease of chemical exchange, and therefore, an increase of Z-spectrum due to less efficient saturation transfer. Indeed, the conventional $\Delta \text{MTR}_{\text{asym}}$ showed a small yet definite focal APT peak at 3.5 ppm (Fig. 1b). In addition, the $\Delta \text{MTR}_{\text{asym}}$ change between live and postmortem states (Δ$\text{MTR}_{\text{asym}}$) confirmed a Z-spectral change centering at 3.5ppm, indicating pH-dependent amide exchange (Fig. 1c), similar as the difference obtained from direct subtraction of two Z-spectra (Ialive-Ipost) (Fig. 1d). Given that spectral distribution of composite amide protons is about 2 ppm, we chose a compensatory offset of 1 ppm from amide proton (i.e, 2.5 and 4.5 ppm) for CAPTOR imaging. Fig. 2 shows that CAPTOR map is significantly more homogeneous than $\Delta \text{MTR}_{\text{asym}}$ image. In fact, the global ischemia induced decrease in both $\Delta \text{MTR}_{\text{asym}}$ and CAPTOR, being -3.8±1.2% and -1.4±0.1%, respectively (Table 1). The fact that intra-animal difference of CAPTOR change was greatly reduced from that of $\Delta \text{MTR}_{\text{asym}}$ strongly suggests that the proposed CAPTOR imaging is more specific to pH-dependent amide exchange. Further evaluation of CAPTOR imaging is needed before its clinical translation.

**References**