Quantitative MR imaging of the Amide-proton transfer, the Nuclear Overhauser effect, and MT asymmetry: a 9.4 T study

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Introduction The amide proton transfer (APT) effect is sensitive to changes in tissue pH and in concentrations of endogenous mobile proteins and peptides, and has shown great potential in stroke and cancer studies [1,2]. However, from the technical aspect, quantitative imaging of the APT effect is still challenging. The magnitude of APT is usually assessed from an MTR_{asym} image, which is the normalized difference of two images acquired at the amide proton frequency and the reference frequency, being ~3.6 ppm above and below the water resonance frequency, respectively. It is well known that MTR_{asym} has contamination from the so-called MT asymmetry caused by semi-solid macromolecules. Recently, it has been noticed that the Nuclear Overhauser effect (NOE) also contributes to the measured MTR_{asym} [3]. Depending on the irradiation pulse parameters and the magnetic field, the confounding MT asymmetry and NOE effects can dominate the MTR_{asym} images, thus greatly limit the sensitivity and hinder the quantification of the APT contrast. In this work, we report that the wide spectral separation from a high field of 9.4 T can be exploited to obtain quantitative APT and NOE images without using the asymmetry analysis.

Materials and methods All experiments were performed on a 9.4T Varian MRI system, with a volume coil excitation and surface coil reception setup. A total of nine male Sprague-Dawley rats were measured. *In vivo* Z-spectra were obtained (n = 4 rats) using a 1.5 μT and 3-s continuous wave saturation pulse, and frequency offset ranges from 10 ppm to -10 ppm. Control images were acquired at an offset of 300 ppm for signal normalization. Immediately after the irradiation, spin-echo EPI images were acquired on four slices with 1.5 mm slice thickness and 0.5 mm gap. The field of view (FOV) was 2.56 cm × 2.56 cm, and matrix size was 64 × 64. B_0 and B_1 maps were obtained to examine the homogeneity of the static magnetic field and RF field, and a T_1 map was measured with an inversion recovery pulse sequence. To examine the imaging contrast of APT, NOE, and MR asymmetry effects versus tissue acidosis, a permanent rat middle cerebral artery occlusion model (MCAO) was adopted (n = 5). The same irradiation parameters were used in MCAO studies, except at a lower resolution: FOV was 3.2 cm × 3.2 cm and four slices were acquired with 2 mm slice thickness and no gap. For quantitative data analysis, regions of interest (ROI) were selected on the cortex, corpus callosum (CC), caudate putamen (CPu), and lateral globus pallidus (LGP) areas. For both *in vivo* baseline and MCAO studies, two MTR_{asym} images, one APT and one NOE image were obtained from the Z-spectra: the MTR_{asym} images were obtained by $MTR_{asym} = [M(-\delta) - M(\delta)]/M_0$ for two offsets at δ = 3.6 ppm and 5 ppm. For APT, the reference image was chosen as the average of two images acquired at 4.2 and 3 ppm: $APT = \{0.5 \times [M(3\text{ppm}) + M(4.2\text{ppm})] - M(3.6\text{ppm})\}/M_0$, and the NOE image was obtained similarly using $NOE = \{0.5 \times [M(-2\text{ppm}) + M(-5\text{ppm})] - M(-3.5\text{ppm})\}/M_0$.

Results and discussions The averaged Z-spectrum obtained from a cortical ROI showed a small signal decrease close to the amide resonance frequency (~3.6 ppm from water), and a broader dip due to NOE at negative frequency offsets. A significant MT asymmetry is easily discerned when the negative offset side of the Z-spectrum was flipped to the positive side (red curve). The zoomed Z-spectra obtained from four ROIs show that the APT effect is relatively narrow and mostly falls within the 3.0 to 4.2 ppm range (Fig. 1B), while the broader NOE signal spans approximately within the 2 to 5 ppm range (Fig. 1C). Figs. 1B and 1C suggest that quantitative imaging of APT and NOE effects can be achieved from three offset measurements; for example, the pure APT contrast can be determined from the difference between the magnitude of 3.6 ppm and the averaged signal between 3.0 and 4.2 ppm (magenta circles). At the cortex, the magnitude of APT and NOE effects are ~3.0% and ~3.5%, respectively, whereas the MT asymmetry is about -8% at 5ppm and -4% at 10 ppm. Note that the quantitative APT and NOE values obtained from such three-offset measurements would be slightly underestimated, due to the underestimation of the reference signal. A more accurate determination of the reference signal can be obtained by fitting a wider range of Z-spectra using a model function such as a Lorentzian [4].

Fig. 2 shows images for baseline MTR_{asym} at 3.6 ppm and 5 ppm, and APT and NOE images obtained from the three-offset measurements. MTR_{asym} at 3.6 ppm, which is often used as the APT-weighted image, is negative and exhibits excellent contrast between cortex (red arrows), CC (green), and LGP (blue). However, the major contribution of these contrasts actually comes from the MR asymmetry because a quite similar imaging contrast can be seen from the MTR_{asym} image at 5 ppm.. The APT image, though much smaller in magnitude, also shows slight contrasts between these areas. Interestingly, the NOE image appears quite homogeneous. During MCAO, it is known that the APT effect will decrease due to a drop in tissue pH. Indeed, excellent lesion contrast can be found from the APT map, which shows a similar lesion size as the ADC map (Fig. 3). Note that within the lesion area, regional heterogeneity (red versus green arrows) can be easily seen from the quantitative APT map, which likely indicates different pH values. Although the lesion area can also be observed from MTR_{asym} image at 3.6 ppm, the contrast of the ipsilateral side versus the contralateral side is weaker. This is because there is almost no lesion contrast from MT asymmetry and NOE, the dominant contributors to the MTR_{asym} image.

Conclusions Quantitative APT and NOE maps can be obtained without using the asymmetry analysis because of wider spectral separation at high fields. Quantitative APT imaging may shed new insight and broaden its application to various pathological conditions.

References [1]. Zhou JY et al. Nature Med 9:1085 (2003). [2]. Sun PZ et al, JCBFM 27 :1129 (2007). [3]. Ling W et al. PNAS 105:2266 (2008). [4]. Jones CK et al. PISMRM p2735 (2011).

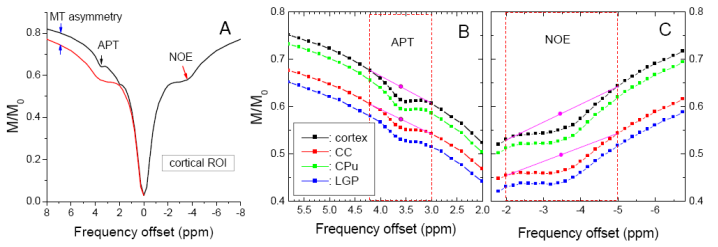

Fig. 1. (A). The averaged Z-spectrum obtained at a cortical ROI (n = 4). For better visualization, the Z-spectrum of negative frequency offsets was flipped to the positive side (red curve). The Z-spectra from four ROIs show narrow dips around the amide resonance frequency (B), and broader dips due to NOE (C).

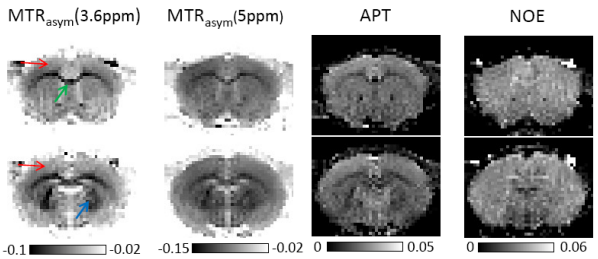

Fig. 2. *In vivo* quantitative maps of MTR_{asym} at 3.6 ppm, 5 ppm, APT, and NOE were obtained from the rat brain for two slices. Note the two MTR_{asym} maps are negative and have similar tissue contrast, where cortex, CC, and LGP areas are indicated by red, green, and blue arrows, respectively. The units here are % of M_0.

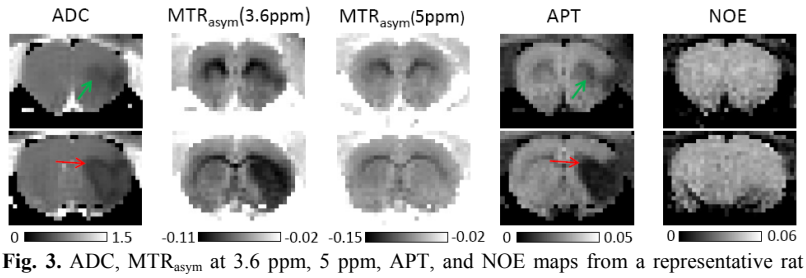

Fig. 3. ADC, MTR_{asym} at 3.6 ppm, 5 ppm, APT, and NOE maps from a representative rat under MCAO. MTR_{asym}(5ppm) and NOE have almost no contrast between ipsilateral vs. contralateral sides. MTR_{asym}(3.6ppm) map can detect large and severe lesions but is difficult to detect smaller ones. Quantitative APT map can detect lesion areas similar to the ADC map. Note the spatial correlation between the APT and ADC maps (red vs. green arrows).