Amide Proton Transfer Imaging with Improved Robustness to Magnetic Field Inhomogeneity

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Introduction Amide proton transfer (APT) imaging[1] is an application of chemical exchange saturation transfer (CEST) imaging[2] that generates contrast from exchangeable protons on the backbone of endogeneous mobile proteins and peptides. In a conventional APT experiment, a label image is acquired with RF irradiation of amide protons at 3.5ppm, and subtracted from a reference image with RF irradiation at -3.5ppm. This asymmetry analysis allows quantification the CEST effect while correcting for direct water saturation due to RF spillover. However, because the asymmetry analysis is dependent on the reference and label scan being applied at symmetric frequencies around the water line, it is very sensitive to B_0 inhomogeneities. Initial *in-vivo* human brain APT images[3,4] have produced poor results near the ears and sinuses where air-tissue interfaces lead to susceptibility artifacts, unless specialized B_0 inhomogeneity correction methods[4,5] are used. In addition, asymmetry analysis fails to separate the APT contrast from the intrinsic magnetization transfer (MT) asymmetry, and therefore, APT weighted images still reflect the MT properties of white and gray matter. In this abstract we propose a novel alternating frequency pulsed-RF saturation scheme for APT imaging combined with a 3-way subtraction that is less sensitive to B_0 inhomogeneity than traditional asymmetry analysis and suppresses MT asymmetry effects.

Methods Our subtraction strategy requires acquiring three images. One image [Ssat(+3.5ppm)] was acquired with all presaturation pulses applied at the amide proton frequency, a second with all pulses applied at minus the frequency [Ssat(-3.5ppm)], and a third with presaturation pulses of the same power alternating between both frequencies [Ssat(±3.5ppm)]. If power is sufficient, then both the single positive frequency and the dual frequency images should saturate the amide proton line. Subtracting 2x the dual frequency image from the sum of positive and negative frequency images should give a CEST signal equivalent to the positive frequency irradiation. Assuming off-resonance and MT effects are linear in power, they will subtract out, even if B_0 shifts the line or MT is asymmetric. Below we refer to this subtraction approach as Saturation with Frequency Alternating Radiofrequency Irradiation (SAFARI).

Healthy volunteers were imaged in a 3T GE SIGNA EXCITE scanner. The APT imaging sequence consisted of a 3 second pulsed-RF irradiation followed by a single shot EPI acquisition [TR=5s, TE=63.3ms , FOV=24cm, matrix=96x96, slice thickness=8mm]. Several RF pulse trains were tested including 7.5ms inversion Hanning pulses repeated every TR_{RF}=12.5ms, and inversion Blackman pulses with pw=[9ms, 15ms] and TR_{RF}=[15ms, 25ms, 35ms, 50ms, 70ms, 100ms]. Forty-eight images were acquired for each SAFARI scan: 12 at positive frequency, 12 at negative frequency and 24 with alternating frequency preparations interleaved in time. In addition, one unsaturated S_0 image was acquired for control. Total scan time was 3 minutes. The CEST effect was evaluated by conventional MT ratio asymmetry analysis: $MTR_{asym}=[S_{sat}(-3.5ppm)-S_{sat}(+3.5ppm)]/S_0$ and by SAFARI: $MTR_{SAFARI}=[S_{sat}(+3.5ppm)+S_{sat}(-3.5ppm)-2\,S_{sat}(\pm3.5ppm)]/S_0$. To evaluate the robustness of the pulse sequence against B_0 inhomogeneities, APT imaging was performed at 3.5ppm with and without a shift of irradiation frequencies by 100Hz (RF irradiation at +550Hz /-350Hz vs. +450Hz/-450Hz, respectively).

Results and Discussion Conventional MTR_{asym} (Fig. 1A) shows a significant white-gray matter contrast that is reminiscent of MT imaging contrast. The MTR_{asym} map has values ranging mostly between ±2%. Although this is similar to MTR_{asym} values found in the literature, it does not match the positive signal predicted for APT imaging alone. Negative MTR_{asym} values are likely due to the intrinsic MT asymmetry competing against the APT effect. In comparison, the proposed MTR_{SAFARI} (Fig. 1C) method yields a significantly more homogeneous APT map that exhibits no white-gray matter contrast. The map has APT values in the +2% range. Taken together these results strongly suggest that the proposed alternating frequency method can separate the amide proton transfer ratio from the intrinsic MT asymmetry. MTR_{SAFARI} also performs much better in the presence of B_0 inhomogeneity than MTR_{asym}. Fig. 2A shows a large susceptibility artifact above the sinuses that is corrected on the MTR_{SAFARI} map (Fig. 1C). In the presence of a 100Hz B_0 inhomogeneity across the entire field of view, MTR_{asym} (Fig. 1B) completely fails at detecting the APT effect. Instead it is dominated by asymmetric RF spillover. In contrast, MTR_{SAFARI} performs much better (Fig. 1D) and remains similar to the on-resonance MTR_{SAFARI} map (Fig. 1C).

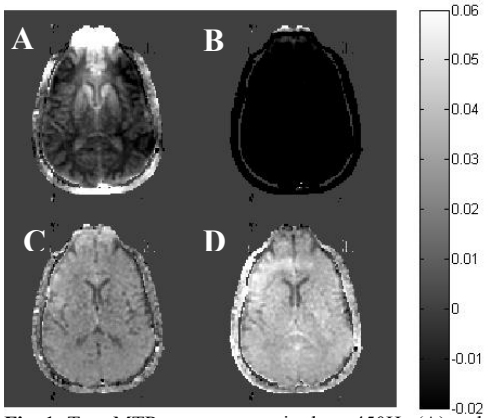

Fig. 1: Top: MTR_{asym} maps acquired at ±450Hz (A) and +550Hz/-350Hz (B). Bottom: MTR_{SAFARI} maps acquired at ±450Hz (C) and +550Hz/-350Hz (D)

The SAFARI pulse sequence was evaluated with several RF pulse trains. Fig. 2 shows that MTR_{asym} maps are unchanged with varied RF pulse width and TR_{RF}. As TR_{RF} increases beyond the exchange time, the CEST contrast should decrease due to inefficient amide proton saturation. This was observed experimentally by increasing TR_{RF} up to 100ms for a given RF pulse. Fig. 3 shows that the MTR_{SAFARI} intensity for an ROI in the occipital cortex decreases by ~50% at long TR_{RF} . If T_1 were known the curve could be fitted to estimate the exchange rate.

In conclusion, SAFARI APT imaging shows a clearer APT contrast free of the confounding MT asymmetry seen in traditional MTR_{asym} analysis. It also is much more robust in the presence of B_0 inhomogeneity and eliminates the need for specialized B_0 correction. Finally, it might provide a novel strategy for measuring exchange rates in vivo. Further evaluation is needed to assess whether alternating frequency APT imaging will permit improved characterization of brain pathology in clinical applications.

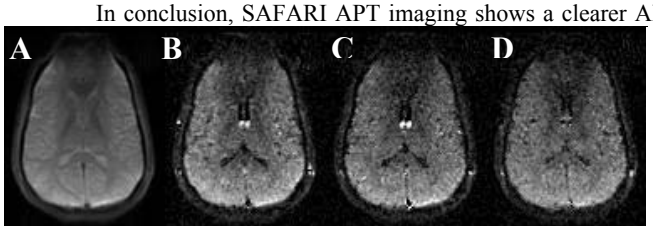

Fig. 2. MTR_{SAFARI} with varying pw and TR_{RF}. A) S_0, B) pw/ TR_{RF} =9ms/15ms, C) pw/ TR_{RF} =9ms/25ms, D) pw/ TR_{RF} =15ms/25ms.

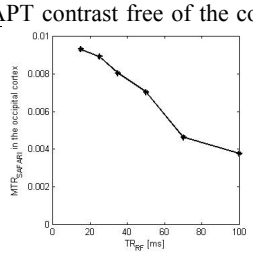

Fig. 3: MTR_{SAFARI} vs TR_{RF}

References: (1) Zhou et al. Nat Med 2003; 9:1085-1090. (2) Ward et al JMR 2000;143:79-87. (3) Jones et al MRM 2006;56:585-592. (4) Zhou et al, MRM 2008:60:842-849. (5) Sun et al, MRM 2007;58:1207-1215.