Quantitative modeling of in-vivo amide proton transfer measurements in the human brain indicates a dominant signal contribution from proteins with short T2 relaxation times

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Introduction:

Amide proton transfer (APT) imaging[1] has shown promise as an indicator of tissue pH[1,2] and as a marker for brain tumors[3]. In stroke, APT hypointensities are correlated with decreased pH. Measuring pH could help distinguish benign oligemia from the ischemic penumbra and predict patient outcome. In brain tumors, it is generally assumed that the APT hypertintensities are caused by increased protein concentration, however, viable alternatives include an increased intracellular pH, decreased magnetization transfer (MT) from semisolid protons or combination thereof. Quantifying the amide proton concentration and exchange rates would provide valuable insights into the lesions' pathology and may help predict chemotherapeutic outcomes based on tumor pH. McMahon et al[4] proposed a technique, quantification of exchange as a function of saturation power (QUESP), for measurement of amide proton parameters. In the brain, however, these measurements are complicated by the intrinsic MT asymmetry which tends to cancel out the APT signal. Recently, we proposed a technique dubbed saturation with frequency alternating RF irradiation[5,6] (SAFARI) designed to correct for direct water saturation and intrinsic MT asymmetry in APT measurements. In this abstract we use QUESP in combination with SAFARI to measure the amide proton transverse relaxivity (T_{2s}), exchange rate (k_{sw}) and concentration (M_{0s}) in the healthy human brain.

Methods:

All images were acquired on 3T GE SIGNA EXCITE scanner. The SAFARI method requires the acquisition of four images: one S_{sat}(+3.5ppm) with RF irradiation at the label frequency, one S_{sat} (-3.5ppm) with RF irradiation at the control frequency and two S_{sat} (SAFARI) with RF irradiation applied simultaneously at both frequencies. The single-slice APT imaging sequence consisted of a 250ms CW-RF irradiation followed by a single shot spin-echo EPI acquisition [TR=2s, TE=20.2ms, FOV=24cm, matrix=96x96, slice thickness=8mm]. Dual frequency preparation was achieved by CW saturation with amplitude modulation given by $\mathbf{B_1}(t)=\sqrt{2}B_1\sin(\omega_s t)$. This generates a frequency response with components at $+\omega_s$ and $-\omega_s$. Three healthy volunteers were scanned after giving written informed consent. For QUESP, APT images were acquired at eight saturation powers B1=0, 0.25, 0.5, 1.0, 1.5, 2, 3 and 4 μT. Images were acquired with 12 averages at each power, for a total acquisition time of 18min. The experiment was also performed in a control phantom (no CEST, no MT, T_{1w}=600ms T_{2w}=65ms) at a wider range of RF powers up to 6μT. A z-spectrum was acquired at frequency pairs from ±200 to ±1500Hz at 1μT (and at 2 μT in only one volunteer). The APT effect was quantified by asymmetry analysis: MTR_{asym}= [S_{sat}(-3.5ppm)-S_{sat}(+3.5ppm)]/ S_0 and by the SAFARI parameter: MTR_{SAFARI} = [S_{sat}(+3.5ppm)+S_{sat}(-3.5ppm)-2 S_{sat}(SAFARI)]/S_0. To quantify amide proton parameters, the APT-SAFARI contrast was modeled using the Bloch equations for a two-pool exchange model. Numerical simulations were performed in MATLAB for the following grid of parameters: amide proton content M_{0s}=1/[10 25 50 75 100 125 150 175 200 300 500 1000 1500 2000] M_{0w}, longitudinal relaxation times T_{1w}=1.5s, T_{1s}=0.77s[8], transverse relaxation times T_{2w}=60ms, T_{2s}=[0.5 1 2 3 4 5 10 20 30 35 60]ms and chemical exchange rate from the amide group to free water k_{sw}=[10 15 20 25 30 35 40 45 50 60 75 90 100 150 200 300 400 500 1000]Hz. In-vivo amide proton parameters were estimated by finding the best fit between the experiment and simulation grid.

Results and Discussion:

Figure 1 compares MTR_{asym} (no B0 correction) and MTR_{SAFARI} maps in a healthy volunteer. At low power, MTR_{asym} is negative indicating that MT asymmetry dominates over the APT effect. As the power increases, the APT signal increases and MTR_{asym} maps become positive. Therefore, without proper modeling of the MT effect, MTR_{asym} cannot be used for quantification of amide proton parameters. In contrast, MTR_{SAFARI} is positive indicating that the MT asymmetry has been removed. At low power, MTR_{SAFARI} is small due to incomplete amide proton saturation. As the power increases MTR_{SAFARI} increases and levels off once amide protons are fully saturated.

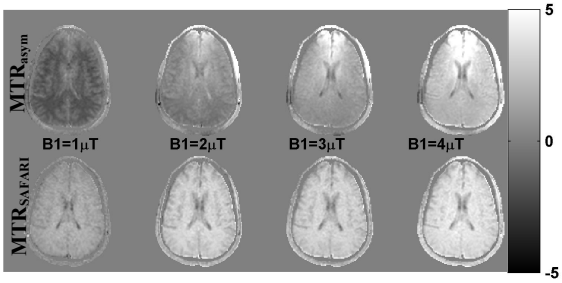

Figure 1: MTR maps in the healthy brain as a function of RF power.

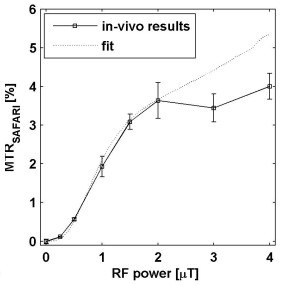

Figure 2: MTRsafari in normal human white matter.

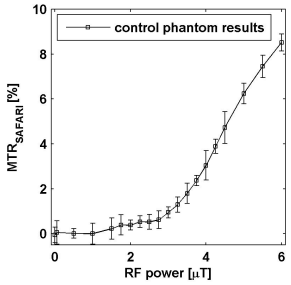

Figure 3: MTRsafari in the absence of CEST agent.

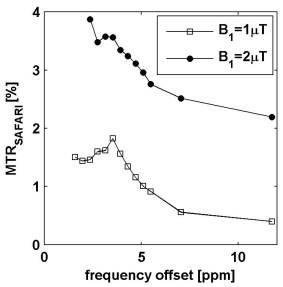

Figure 4: MTRsafari spectrum in normal human white matter.

Figure 2 plots MTR_{SAFARI} in a white matter ROI as a function of RF power and Figure 3 shows a similar experiment in a control phantom. The control phantom has no amide protons, therefore MTR_{SAFARI} should be zero. t-tests reveal that MTR_{SAFARI} in the phantom was not significantly different from zero for RF powers up to 1μT. In addition, MTR_{SAFARI} remains under 0.5% up to 2μT. At higher powers, direct water saturation (and MT in-vivo) becomes too large to be corrected by the SAFARI strategy. Because our simulation model does not account for MT, only data points at 2μT and below were used in the fit. The best fit shown in Figure 2 was T_{2s}=2ms, k_{sw}=45Hz and M_{0s}=1/175M_{0w}. The measured exchange rate is fairly consistent with previous reports[1,7]. The measured T_{2s} is shorter than the T_{2s} in the tens of milliseconds typically measured in protein solutions, suggesting the in-vivo amide proton signal has a contribution from bound proteins. A short T_{2s} might explain why larger powers (approx. 2μT) are required to saturate amide protons than predicted by simulations[8] assuming a T_{2s} of 33ms. It is also consistent with the fact that no sharp amide proton peak has been measured on the z-spectrum in-vivo. Figure 4 shows the MTR_{SAFARI} spectrum in the white matter ROI. A significant amide proton peak was detected at both power levels. Note that although the APT effect is larger at 2μT there is an increase in direct water saturation compared to 1μT. The peak width is on the order of 300Hz, consistent with a short T_{2s}. Finally, it should be noted that our model has assumed amide protons have a single resonance frequency at 3.5ppm from the water line. However, it is known that the amide proton chemical shift is a function of protein structure[9], and this model is therefore an oversimplification. The MTR_{SAFARI} spectrum is also consistent with the peak being a composite of individual amide protons with a range of chemical shifts of 2ppm[9]. Further studies are needed to evaluate how such a model would impact the T_{2s} measurement.

References: [1]Zhou et al. NatMed 9:203. [2]Sun et al. J Cereb Blood Flow Metab 27:2007. [3]Wen et al. Neuroimage 51:2010. [4]McMahon et al. MRM 55:2006. [5]Scheidegger et al, ISMRM 2987:2010. [6]Scheidegger et al, ISMRM 5142:2010. [7]Van Zijl et al. MRM 49:2003. [8]Sun JMR 175:2005. [9]Wagner JACS 105:1983