The Effects of Equilibrium Intercompartmental Water Exchange Kinetics on MRI Estimation of Tissue Concentration of Contrast Agents

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Introduction: In cerebral tissue, water protons in a voxel are distributed in the red blood cells, plasma space, and extra-and intracellular space, respectively (1, 2). The equilibrium transport of water protons across the transendothelial walls and the transcellular membranes of a three-site two exchange (3S2X) model significantly affects the estimate of the tissue water longitudinal relaxation rate, R_1, when contrast agent (CA) is introduced to the tissue and compartmentalized (2,3). MR signal evolving from compartmentalized tissue generally demonstrates a multiexponential behavior. Typically, in contrast enhanced–MRI, the tissue concentration of the CA is measured via R_1 by assigning a monoexponential relaxation rate, i.e., the ensemble of tissue water relaxes with a single R_1 (3). Thus, it is necessary to account for the effects of exchange kinetic on R_1, because the large systematic errors in estimation of tissue concentration of CA can lead to subsequent errors in estimates of tracer kinetic parameters in cerebral tumor models (2). We addressed the effect of equilibrium intercompartmental water exchange kinetics on tissue water R_1 utilizing the TOMROP (T one by Multiple Read Out Pulses) sequence (4), an imaging variant of the Look-Locker (LL) pulse sequence, on the Bloch-McConnell formalism of a 3S2X model (5). Herein, the relationship between a monoexponential estimate of R_1 and the relaxation rate of the extracellular space R_{1e} (i.e., a function of Gd-concentration) is presented. The modeling is confirmed by experiment, comparing in the same animal ΔR_1 in a rat 9L cerebral tumor after the administration of Gd-BSA to the autoradiographically estimated concentration of this CA's radiotracer analog Radioionated Serum Albumin (RISA).

Material and Methods: A signal from a 3S2X model, i.e., blood, extra- and intracellular space, particularized to the Look-Locker pulse sequence is given by

$$S(t) = \left\{M_{ss} + \left(p_1 M(0) - M_{ss1}\right)E_1^* + \left(p_2 M(0) - M_{ss2}\right)E_2^* + \left(p_3 M(0) - M_{ss3}\right)E_3^*\right\}\sin\theta\, e^{-R_2^* TE} \qquad [1]$$

where M(0) is the magnetization just before the first RF pulse, $E^*_{1,2,3} = e^{-D^*_{1,2,3}t}$, $D^*_{1,2,3}$ is the effective longitudinal relaxation rate, $M_{ss1,2,3}$ is the steady state magnetization , M_{ss} is the total steady state magnetization, $p_{1,2,3}$ is the fractional population, and $X_{1,2,3}$ is the weight factors associated with the short, intermediate and long relaxation rates, respectively, of a 3S2X model. Model TOMROP signals were generated utilizing typical experimental parameters in animal studies of vascular permeability (5), with inversion efficiency 1, flip angle 18^0, inter-echo interval 50 ms, and 24 sampling points for a total acquisition time of 1200 ms with reasonable values of MR and physiological parameters of cerebral tissue (7), in which $e^{-R^*_2 TE} \sim 1$. The relaxation rates of the blood R_{1b} and extracellular space R_{1e} were varied over the range [0.5, 20.0] s^{-1}, and the intracellular water R_{1i} was set to 0.56 s^{-1} (6). The exchange rate from blood to the extracellular space for a typical cerebral tumor was assigned to k_{be} = 10.0 s^{-1} for the fractional blood water content u_b = 0.. The range of transcellular rate of exchange was [0.5- 10.0] s^{-1}.This range is chosen in congruence with measured rate of exchange of k_{ie} = 1.81 s^{-1} for a fractional intracellular water content, $u_i \sim 0.8$; respectively, in a rat brain (6). Simulations were performed using a program written in ANSI C and implemented in a UNIX system. Gaussian-distributed noise was added to the TOMROP signal using the Box and Muller algorithm. The simulated data was then sampled as in our experiment, fitted using established in-house techniques, and estimates of tissue R_1 were then plotted against the relaxation rate of the extracellular space R_{1e}. In MRI procedures, two initial TOMROP images sets were followed by the injection of Gd-BSA, and then ten more TOMROP data sets were collected on a 7T MRI system, with 145 sec interval per TOMROP set (7). The last set of TOMROP images (25 minutes after injection) was chosen as a comparison set, since it corresponded most closely in time post-injection to the QAR data set subsequently taken using RISA as the indicator. For each TOMROP study, the slice with the largest cross section of tumor was identified. The corresponding QAR slice was selected by visually matching the MRI and QAR maps. The QAR and T_1 maps were co-registered. R_1 was measured in normal and leaky (tumor) areas as an MRI measure of tissue concentration.

Results and Discussions: A typical T_1 weighted image, ΔR_1 map and its counterpart QAR map are shown in Fig.1. Figure 2a shows the relationship between the modeled TOMROP estimation of R_1 versus R_{1e} predicted by a 3S2X model. The relaxation curve shows a nearly linear curvilinear response for k_{be}=10.0 s^{-1} and u_b= 0.05 at a SNR level of 200.The quadratic term is about 2.3% of the linear term, thus, it doesn't break the linearity even for a wider range of R_{1e}. Fig.2b is a family of curves for the different k_{ie} [10.0, 5.0, 2.0, 1.0 and 0.5 s^{-1}] demonstrate that the slope of the curves does change about 35% as the rate of exchange varies over the range of 10.0-0.5 s^{-1}, respectively. Figure 2c is the scatter plot ($r = 0.845$, $p < 0.0001$ between the mean values of autoradiographic estimates of RISA concentration and ΔR_1 MRI in the tumor ROI. A generalizing estimating equation analysis of 15 clusters of data shows good correlation ($r = 0.727$, $p < 0.0001$) between these two measurements. The pre-exchange lifetime of the blood and intracellular compartments are on the order of 500 ms and 550 ms. The recovery of longitudinal magnetization in the TOMROP experiment, which covers 1.2 seconds, may allow the ensemble of tissue water to express all the components of its relaxation, and thus allow a single estimate of R_1 to reflect tissue concentration of CA. As a result, the estimation of R_1 scales approximately a linear in tissue CA concentration with the description of experimental conditions.

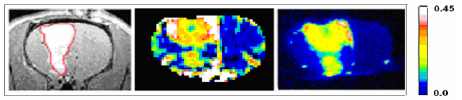

Fig.1. A rat of 9L cerebral tumor model of post T_1 weighted image with ROI (a). ΔR_1 map (b). Autoradiographic RISA concentration map (c).

References: 1. Li, X. et.al., Magn. Reson .Med 54 (6): 1351- 1359, 2005. 2. Yankeelov, T. E. et al., Magn Reson Med 50(6): 1151-1169, 2003. 3. Buckley, D. et al., Magn Reson Med 60(5): 1010-1119, 2008. 4. Brix, G. et al., MRI, 8(4): 351-356, 1990. 5. McConnell, HM at el., Chem. Phys. **28**(3):430-431, 1958. 6. Quirk J.D. et al., (2003), Magn Reson Med 50(3): 493-499, 2003. 7. Ewing J. R., et al., J Cerb Blood Flow & Meta 26(3): 310-20, 2006.

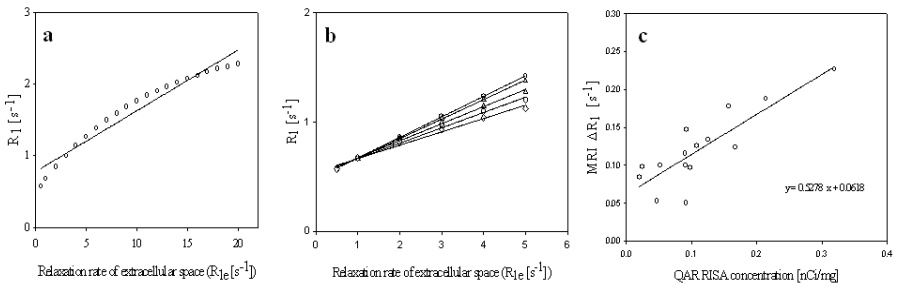

Fig.2. Graphs of modeling results of a 3S2X model (a, b). Scatter plot of ΔR_1 MRI vs. RISA concentration of QAR (c).