The Effects of Equilibrium Intercellular 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 multieponential 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 $R_{\text{ex}}$ (i.e., a function of Gd-concentration) is presented. The modeling is confirmed by experiment, comparing in the same animal $\Delta R_1$ in a rat 9L cerebral tumor after the administration of Gd-BSA to the autoradiographically estimated concentration of this CA’s radiotracer analog Radioiodinated 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

$$S(t) = \left\{ M_{ss} + (p_1 M(0) - M_{ss}) e_1 + (p_2 M(0) - M_{ss2}) e_2 + (p_3 M(0) - M_{ss3}) e_3 \right\} \sin \theta e^{-E_1 t}$$

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, $M_{ss,2,3}$ is the steady state magnetization, $M_0$ 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 times, 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°, 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 $E_1$ $= 1$. The relaxation rates of the blood $R_{\text{in}}$ and extracellular space $R_{\text{ex}}$ were varied over the range $[0.5, 20.0]$ s\(^{-1}\), and the intracellular water $R_{\text{ic}}$ set to 0.56 s\(^{-1}\) (6). The exchange rate from blood to the extracellular space for a typical cerebral tumor was assigned to $k_{\text{ex}}$ = 10.0 s\(^{-1}\) for the fractional blood water content $u_{\text{b}} = 0$. 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 $k_{\text{ex}}$ = 1.81 s\(^{-1}\) for a fractional intracellular water content $u_{\text{c}} = 0.8$; 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 $R_{\text{ex}}$. 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 as 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, $\Delta R_1$ 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 $R_{\text{ex}}$ predicted by a 3S2X model. The relaxation curve shows a nearly linear curvilinear response for $k_{\text{ex}}=10.0$ s\(^{-1}\) and $u_{\text{c}}=0.05$ 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 $R_1$ values of MR and physiological parameters of cerebral tissue (7), in which $E_1$ $= 10.0$ s\(^{-1}\). $R_{\text{ex}}$ 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 $k_{\text{ex}}$ = 10.0 s\(^{-1}\) for the fractional blood water content $u_{\text{b}} = 0$. 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 $k_{\text{ex}}$ = 1.81 s\(^{-1}\) for a fractional intracellular water content $u_{\text{c}} = 0.8$; 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 $R_{\text{ex}}$. 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 as 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.