MRI Look Locker Estimates of the Longitudinal Relaxation Rate Are Approximately Linear in Contrast Agent Tissue Concentration

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Introduction: The finite rate of equilibrium exchange of water protons between intra- and extracellular spaces affects an estimate of the tissue longitudinal relaxation rate constant R_1 when contrast agent (CA) is administered intravenously and subsequently extravasates, but remains confined to extracellular space (1). Under conditions of short repetition time and/or high CA concentrations, large systematic errors in R_1 estimates can be encountered. These conditions are often encountered in MRI permeability estimates in cerebral tumor models (2). Since R_1 is frequently used as a measure of CA concentration, errors in estimating R_1 can lead to large errors in estimates of vascular permeability. We have evaluated the effect of transcytolemmal water exchange on the relationship between a monoexponential estimate of the longitudinal relaxation rate of tissue water protons, R_1, *vs.* the relaxation rate of the extracellular space R_{1ec}, which is directly proportional to CA concentration. We modeled the estimate of R_1 using a TOMROP (T one by Multiple Read Out Pulses) sequence (3). TOMROP is an imaging version of the Look-Locker sequence (LL) The modeling was then confirmed by experiment, comparing in the same animal the change in the TOMROP-estimated R_1 in a rat 9L cerebral tumor after the administration of the MR CA Gd-BSA to the autoradiographically estimated concentration of this CA's radiotracer analog Radioionated Serum Albumin (RISA).

Material and Methods: The TOMROP signal in the transcytolemmal water exchange system utilizing the modified Bloch equations is:

$$s(t) = \left[m_{ss} + \left(c_1 m(0) - m_{ss1}\right) e^{-D_1^* t} + \left(c_2 m(0) - m_{ss2}\right) e^{-D_2^* t} \right] \sin(\theta)\, e^{-R_2^* TE} \qquad [1]$$

where, m (0) is the longitudinal magnetization just prior to the first RF pulse. The steady state magnetizations m_{ss1} and m_{ss2} are related to the shorter (D_1) and longer (D_2) relaxation rate constant, in which $m_{ss}=m_{ss1}+m_{ss2}$, and $D_{i=1,2}^*$ is the effective relaxation rate. The total acquisition time is t = j τ, where j = number of MR sampling points, τ is the equal interval sampling time, and $c_1+c_2=1$. We simulated the recovery of the post inversion longitudinal magnetization vector (Equation[1]), with inversion efficiency 1, flip angle 18^0, inter-echo interval 50 ms, with 24 sample images for a total acquisition time of 1200 ms, typical experimental parameters in animal studies of vascular permeability (5), but ignoring the attenuation component $e^{-R^*_2 TE}$. The model parameters were varied across a reasonable MRI and physiological ranges (1, 4), *i.e.* intracellular relaxation rate R_{1ic}~ 0.56 sec^{-1}, 0.5 < R_{1ec} < 20.0 sec^{-1}, and1.0 < f < 4.0 sec^{-1}. These values of the water exchange rate span the measured value (4) of the intra- to extra-cellular rate constant of exchange in a rat brain of f = 1.81 s^{-1}, assuming a fractional intracellular water content $u_{ic} \sim 0.8$. Simulations were performed using a program written in ANSI C and implemented in a UNIX system. Complex Gaussian-distributed noise was added to the simulated signal so that it contained noise typical of that known to represent statistical variation of the detection system, and then fitted to a single exponential model of magnetization recovery from inversion using our standard methods. 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 (5). 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.

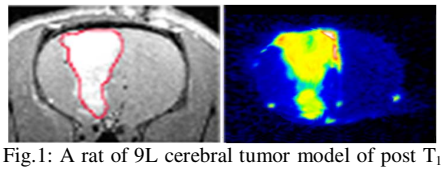

Fig.1: A rat of 9L cerebral tumor model of post T_1 weighted image with ROI (left), autoradiographic RISA concentration map (right).

Results and Discussions: A typical T_1 weighted image and its counterpart QAR map are shown in Fig.1. In Fig.2a the modeling of R_1 vs. R_{1ec} shows an approximately linear response for f = 1.81 sec^{-1}, a typical rate of intra- to extracellular water exchange. For clarity, this relationship is modeled with a SNR of 200, although it is very unlikely that this SNR can be achieved in practice. The deviation of points in a curve relative to the regression line at the lower (R_{1ec} = 0.5 sec^{-1}) and upper (R_{1ec} = 20 sec^{-1}) extreme ends as well as at the middle (R_{1ec} =10 sec^{-1}) region are about 25.0%, 7.0%, and 5.0%, respectively. Fig.2b displays typical ROI data from Fig.1 (left). There is a change in tissue relaxation rate in the cerebral tumor region relative to the normal, but always less than 0.3 sec^{-1}. Thus, referring to the model curves of Fig.2a, we see that the experimental tumor curve supports the assumption of the linearity of the TOMROP estimate of ΔR_1 as a function of CA tissue concentration. Fig.2c plots of a pixel-by-pixel scatter plot of ΔR_1 in the last MRI Look-Locker image set (25 minutes after injection), against the QAR map of RISA concentration in the tumor ROI. This plot demonstrates that the ΔR_1 map of MR image is well correlated with an autoradiographic estimate of indicator concentration (r = 0.75, p < 0.0001). The intracellular water proton pre exchange lifetime is about 550 ms, which is larger than the sampling time scale but small relative to the total TOMROP acquisition time of 1200 ms. This allows the ensemble of tissue water protons to become approximately equivalent, and as a result the estimation of R_1 scales approximately a linear with R_{1ec} for a Look-Locker Sequence. An extended simulation (not shown) demonstrates that the curves behave more linearly as a rate of mixing between the compartment increases. This result indicates that consideration of the full two-site exchange model, which includes transcytolemmal water exchange, allows the description of experimental conditions in which the measured R_1 will be linear in tissue CA concentration.

References: 1. Landis, C.S., et al., MRM, 1999; 42: p. 467. 2. Yankeelov, T.E. et al., MRM, 2003; 50: p.1151. 3. Brix, G., et.al, Magnetic Resonance Imaging, 1990; 8: p.351. 4. Quirk, J. D., et al., MRM; 2003; 50: p. 493. 5. Ewing, J.R., et al., Journal of Cereb. Blood Flow & Metab. 2006; 26: p. 310.

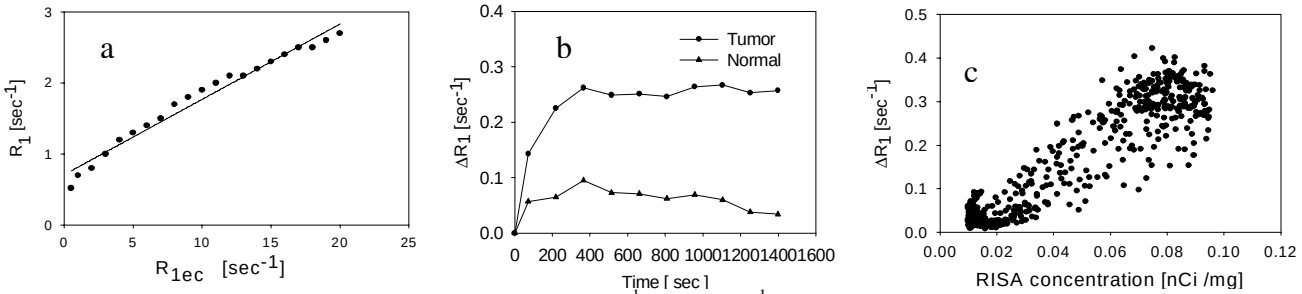

Fig.2. a: Modeling result of R_1 versus R_{1ec}, when R_{1ic} = 0.56, sec^{-1}, f = 1.81 sec^{-1} and u_{ic} = 0.8, b: ΔR_1 versus time from LL T_1 maps, c: Scatter plot of MRI ΔR_1 versus autoradiographic RISA concentration.