Modeling of Look-Locker Estimates of the Magnetic Resonance Imaging Estimate of Longitudinal Relaxation Rate in Tissue after Contrast Administration

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Introduction: Dynamic Contrast-Enhanced (DCE) MRI studies assume a linear relationship between tissue water protons' relaxation rate R_1 (R_1=1/T_1) and contrast agent (CA) concentration **[1]**. If water protons exchange rapidly between different tissue compartments on the time scale of the relaxation, ΔR_1 can serve as a measure of the tissue concentration-time curve **[1, 2]**, allowing the use of pharmacokinetic theory **[3]** to estimate vascular parameters in cerebrovascular diseases **[2, 4]**. Using a Look-Locker (LL) **[5]** estimate of R_1 with appropriate boundary conditions, we demonstrate that R_1 estimates show a nearly linear response with tissue CA concentration **[6]**. On the other hand, using an incomplete representation of equilibrium intercompartmental water proton exchange, Li et al. **[7]** proposed that parametric estimates of the vascular parameters under this criterion would be substantially biased. Herein, using a three-site two exchange [3S2X] model, we evaluate the influence of water proton equilibrium intercompartmental exchange kinetics across the vascular wall and cell membrane on a monoexponential estimate of the relaxation rate R_1 for a LL measurement.

Materials and Methods: Tissue was modeled as three compartments: blood, extra-, and intra-cellular space that are linked by exchange of water protons across the vascular wall and cellular membrane. In brain areas with vascular damage, a typical small CA such as a gadolinium analog injected into the blood leaks from the plasma into the interstitial space, but not into the cell, and changes the extracellular water protons relaxation rate. The relaxation rates of blood (R_{10b}), extracellular (R_{10e}), and intracellular (R_{1i}) protons of water in the absence of CA were set to 0.5, 0.5 and 0.56 s^{-1}, respectively. A change in the R_1 of the compartment as a function of CA concentration, [CA], was determined using a linear relationship: $R_1 = R_{10} + \Re\,[CA]$, where R_1 and R_{10} denote the R_1 in the presence and absence of CA, the longitudinal relaxivity ($\Re$) of the contrast agent was taken to be 4.2 $mM^{-1}s^{-1}$. The rates of exchange across the transvascular wall and cell membrane were set to 2.0 s^{-1} and 1.81 s^{-1} and their water content fractions were 0.02, and 0.8, respectively **[8]**. MR signals evolving from a 3S2X model were constructed using a LL sequence (tip angle, $\theta = 18^0$, inter excitation time, τ = 50 ms, and total sampling points, N = 24) **[6]**. The constructed signals were then fitted using in-house software based on the Simplex algorithm written in C **[2]**. The arterial input function (AIF), *i.e.*, the plasma CA concentration [CA_p] *vs.* time **[4]**, shown in Fig. 1 was used to evaluate the effect of water exchange in DCE-MRI experiments as applied to estimating the total tissue CA concentration *vs.* time. The CA_{tiss} (t), time course was plotted using the following an efflux-corrected Patlak graphical equation **[3]**:

$$CA_{tis}(t) = K^{trans}\int_0^t e^{-k_b(t-\tau)} CA_p(\tau)d\tau + c_p v_p \qquad \text{[Eq.1]},$$

where K^{trans} and k_b ($k_b = K^{trans}/v_e$) are the transvascular transfer rates from blood to tissue and from tissue to blood, respectively, and v_p is the plasma volume fraction. Using an observable tissue ΔR_1 into Eq. 1, the modeled data is plotted **[2]**, where the slope and intercept of a linear fit represent the transvascular transfer rate constant K^{trans} and vascular volume v_p for adjusted hematocrit. These measured values were compared with the truth model values to assess the effects of equilibrium intercompartmental water exchange in a 3S2X model.

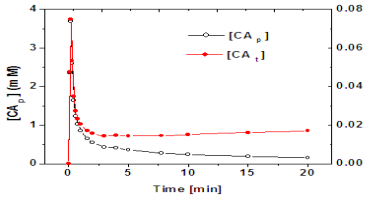

Fig.1.The time course of blood plasma CA concentration [CA_p] (left ordinate) and total tissue CA concentration [CA_t] (right ordinate). The later was calculated using Eq. 1, when K^{trans} = 2.0 x 10^{-3} min^{-1} and u_b = 0.02.

Results: In Fig. 2, the Patlak graphical plot for a range of K^{trans} (0.01, 0.005, and 0.00125 min^{-1}: top to bottom) is plotted to determine the systematic errors in estimating K^{trans} in a 3S2X model. In this setting, k_{be} = 2.0 s^{-1} and u_b = 0.02 and k_{ie} = 1.81 s^{-1} and u_b = 0.8, where k_{be} and k_{ie} denote the rates of water exchange from the intravascular to the extracellular space and intracellular to the extracellular space, respectively, and u_b is the intravascular water content fraction. The slopes of these lines vary by 87%, while the estimates of K^{trans} vary about 4% from model truth. Fig. 2 shows the behavior of the Patlak plot under the variation of u_b (0.06, 0.04, 0.01: top to bottom), when K^{trans} = 4.0 x 10^{-3} min^{-1}, k_{be} = 2.0 s^{-1}, k_{ie} = 1.81 s^{-1}, and u_i = 0.8 in a 3S2X model. Herein, the slopes are virtually identical and vary by < 3%, whereas the u_b is underestimated as much as 60%.

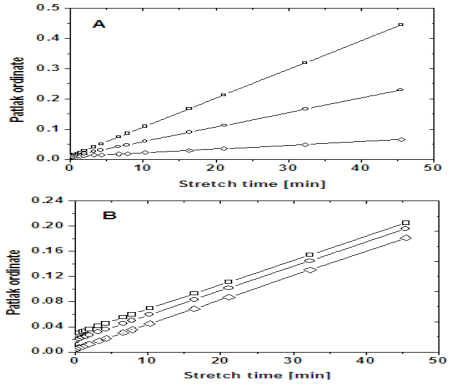

Fig. 2. Patlak's graphical plots in a 3S2X model with Patlak ordinate and efflux-corrected term 'stretch time' as abscissa. A: K^{trans} (0.01, 0.005, and 0.00125 min^{-1}: top to bottom), when u_b = 0.02. B: Intravascular water content fractions u_b (0.06, 0.04, and 0.01: top to bottom), when K^{trans} = 4 x 10^{-3} min^{-1}.

Discussion and conclusions: In this study, an analytical equation associated with a LL sequence in a 3S2X model was used to study the effects of water exchange using an experimentally measured AIF. The extended Patlak plot is a revealing technique that shows the influence of exchange kinetics on estimates of K^{trans} and vascular volume. The practical consequence of this study is that an extended Patlak plot linearizes in the leaky microvessels, which accurately measures the K^{trans}, but underestimates the volume of the intravascular blood water. This analytical model can be extended further to assess the water exchange effect on a pharmacokinetic analysis using more widely used short TR gradient echo sequences commonly used in clinical DCE experiments.

References:

[1] Buckley, D, *et al.*; MRM 60:1011 (2008). **[2]** Ewing, JR, *et al.;* JCBFM 26(3):310 (2006). **[3]** Patlak, CS, *et al.*; JCBF&M 3(1):7 (1983). **[4]** Nagaraja, TN, *et.al.;* MRM 63(6):1502 (2010). **[5]** Gelman, N, *et al.*; MRM 45:71 (2000). **[6]** Paudyal, R, *et al.;* Proc. of 17th Intl. MRM meeting, p. 721 (2009). **[7]** Li, X. *et al.*; PNAS 105(46):17937(2008). **[8]** Quirk, JD, et al.; MRM 50(3): 493 (2003).