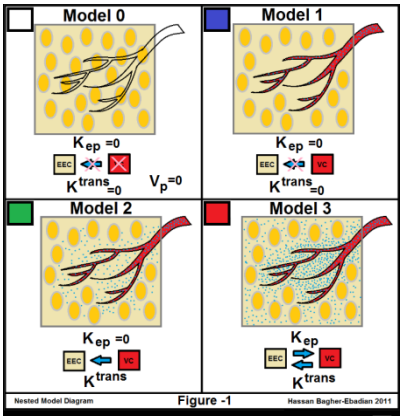
Comparison of Signal Intensity and Standard Techniques for Estimation of Pharmacokinetic Parameters in DCE-T1 Studies of Glioblastoma: Using Model Selection

Hassan Bagher-Ebadian[1,2], Siamak P Nejad-Davarani[1,3], Rajan Jain[4], Douglas Noll[3], Quan Jiang[1], Ali Syed Arbab[4], Tom Mikkelsen[5], and James R Ewing[1,2]

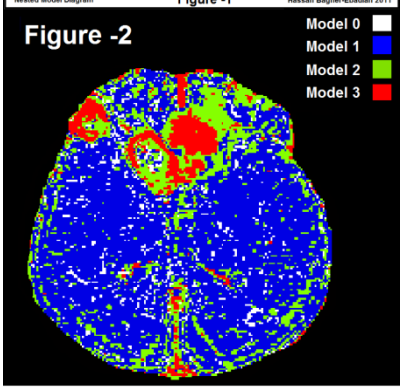
[1]Neurology, Henry Ford Hospital, Detroit, Michigan, United States, [2]Physics, Oakland University, Rochester, Michigan, United States, [3]Biomedical Engineering, University of Michigan, Ann Arbor, Michigan, United States, [4]Radiology, Henry Ford Hospital, Detroit, Michigan, United States, [5]Neurosurgery, Henry Ford Hospital, Detroit, Michigan, United States

Introduction: In Dynamic Contrast-Enhanced magnetic resonance imaging (DCE-MRI), the time trace of Contrast Agent (CA) concentration can be analyzed with an appropriate pharmacokinetic model to characterize tissue pathology [1]. By fitting the DCE-MRI data to pharmacokinetic model, physiological parameters can be estimated that relate to permeability or hemodynamic properties such as microvascular permeability, plasma volume, extracellular volume, or tissue perfusion [2,3,4]. DCE pharmacokinetic models rely on the construction of an observation equation which demands conversion of the measured signal intensity time course data (S_t) into an indicator concentration time course. The standard approach utilizes the longitudinal relaxation rate change (ΔR_1) to construct the concentration-time curve of the CA [1,4,5]. This process depends on the accurate estimation of pre injection longitudinal relaxation times (T_1) and signal intensity (S_0) prior to administration of CA. Recent studies have proposed that the normalized signal intensity SI $[(S_t-S_0)/S_0]$ be used instead of ΔR_1 in DCE-MRI permeability analyses [1,2,5]. However, we know of no assessment of the agreement in the estimated permeability parameters using different measures of CA concentration (SI, (ΔR_1)). The goal of this study is to evaluate the use of SI, as opposed to ΔR_1, in the estimation of permeability parameters in DCE-T1 3D-Spoiled-Gradient-Echo (SPGRE) studies in the brains of ten treatment-naïve patients with glioblastoma (GBM).



Theory: In this study a model selection technique [6, 7] is used to compare the two measures of CA concentration-time curves in estimating permeability parameters. As shown in figure1, four different nested models with as many as three parameters (plasma volume: v_p, forward vascular transfer constant: K^{trans}, and the reverse vascular transfer constant: k_{ep}) are used to compare the techniques. Model 0, 1, 2 and 3 describe regions presenting with no evidence of vasculature filling with CA, no leakage of CA, with reduced rates of CA leakage (generally enclosed Model 3 regions), and presenting high rates of CA leakage respectively.

MR Imaging and Data Processing: All studies were performed in a 3T GE Excite HD MR system using a standard eight-channel phased-array RF coil and receiver. DCE-T1studies were conducted in 10 treatment-naïve patients with GBM. Before CA administration, T_1 mapping was performed using a 3D SPGRE sequence with Variable Flip Angle (VFA). Sequence parameters were as follows: TE/TR ~ 0.84/5.8 ms, flip angles, θ_i, of 2, 5, 10, 15, 20, and 25º, matrix of 256 X128, FOV of 240 mm, 16 slices, 5 mm slices, no gap. The maps of T_1 were used to establish baseline precontrast values for the dynamic SPGRE procedure that followed. The 3D SPGRE DCE-T1 sequence was then begun (70 image sets ~5.9s per image set, θ=20º and other parameters as above). About 20s after starting, a dose of Magnevist (0.1 mmol/kg) was injected (IV) at a rate of 4 mL/s. ΔR_1 was calculated analytically for each voxel using the assumed value of the tip-angle, θ , the estimated pre-contrast value of T_1, and the ratio of the post-contrast to baseline pre-contrast MRI signal. An analytical expression was used to estimate the time trace of (ΔR_1), and that in turn was used as a measure of the CA concentration-time curve. A nonlinear least squares optimization using the Levenberg-Marquardt (LM) Algorithm [8] was used to fit model 3 to the experimental data, while the linear least-squares method was used for the linear models (models 0–2). Using a manually chosen Arterial Input Function (normalized to white matter), the SI and ΔR_1 data in all voxels were fitted with the linear models 0, 1, 2 and non-linear model 3. Sum Squared Error (SSE) maps for the fitted parameters in all three models were calculated and used for statistical model comparison. Three F-test maps were constructed using the SEE maps that served for model comparison. Model 0 vs. 1, Model 1 vs. 2 and Model 2 vs. 3 were tested with the F-test criteria and a final regional map, and three maps of permeability parameters were constructed accordingly. Figure 2 illustrates an exemplary regional map for a typical patient.



Results and Conclusion: In the patient population, compared to the ΔR_1 technique, the SI technique underestimated the plasma volumes (v_p) for different regions (32% in normal but enhancing core, 26% in white matter, 17% in gray matter, and 32% in Model 2 and 24% Model 3 regions). In contrast with the ΔR_1 technique, the SI technique also underestimated K^{trans} around 22% and 28% in regions associated with Model 2 and 3 respectively. The SI technique also overestimated k_{ep} around 23% in the model 3 region compared to ΔR_1. The mean calculated interstitial space $v_e = K^{trans} / k_{ep}$ (only in Model 3) was underestimated about 38% in the SI technique compared to the ΔR_1 technique. In Model 3 regions, excellent curve fits were obtained in both of the techniques to explain the variation of the ΔR_1 and SI data (mean R^2 = 0.99 and 0.97 for ΔR_1 and SI techniques respectively). Results imply that the SI technique is biased with respect to the ΔR_1 technique in estimation of the pharmacokinetic parameters. This study confirms that using the SI profile instead of ΔR_1 in analysis of DCE-MR data can result in significant biasing in estimation of permeability parameters.

Table-1: Summary of Estimates of Vascular Parameters in 10 Patients

The parameters v_p and v_e are dimensionless fractional volumes for plasma volume and interstitial volume, respectively. The parameter K^{trans} has units of min^{-1}.

Model	Model 1 (core)	Model 2		Model 3			
Permeability Parameters	v_p ± S.D	v_p ± S.D	K^{trans} ± S.D (min^{-1})	v_p ± S.D	K^{trans} ± S.D (min^{-1})	v_e ± S.D	R^2
Mean ± S.D(ΔR_1 -Technique)	0.0213 ± 0.0195	0.028 ± 0.025	0.0019 ± 0.0019	0.037 ± 0.019	0.019 ± 0.010	0.076 ± 0.048	0.9912
Mean ± S.D (SI-Technique)	0.0144 ± 0.0163	0.019 ± 0.021	0.0014 ± 0.0027	0.028 ± 0.024	0.013 ± 0.016	0.045 ± 0.034	0.9724

References:

[1] Heilmann, et al., Invest Radiol 41(6): 536-543, (2006).
[2] Choyke, et al., J Magn Reson Imaging 17(5): 509-520, (2003).
[3] Ludemann, L., et al., Invest Radiol 37(10): 562-570, (2002).
[4] Tofts, P. S., J Magn Reson Imaging 7(1): 91-101, (1997).
[5] Ashton, E., et al., Proc. Intl. Soc. Mag. Reson. Med. 15 2813, (2007).
[6] Ewing JR., et al., J Cereb Blood Flow Metab 2006;26:310–320.
[7] Bagher-Ebadian H., et al., J Mag. Reson Med in press (2011).
[8] Marquardt D., J Soc Ind Appl Math;11:431–441, (1963).