Dynamic Contrast Enhanced MRI at 7T in a Rat Model of Cerebral Glioma: Data Analysis and Model Selection

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Introduction: Dynamic Contrast Enhanced MRI (DCE-MRI) studies were conducted at 7T in 12 nude rats implanted with a U251n model of cerebral glioma. In order to account for the very strong T_2* effect occurring after the injection of contrast agent (CA), a dual-gradient, gradient-echo (2GE) sequence was run to generate a pure trace of the change in R_1 ($R_1=1/T_1$) using an analytic expression that depended on an estimate of the pre-contrast T_1. Two studies were conducted at 24-hr intervals, generating test-retest statistics. Analysis of data was performed using a previously developed model selection paradigm (1).

Theory and Methods: The Standard Model (SM) is $C(t) = K^{trans}\int_0^t C_p(\tau)e^{-k_{ep}\tau}d\tau + v_p C_p(t)$, Where t is time, C(t) is the tissue concentration of CA, $C_p(t)$ is the plasma concentration, K^{trans} characterizes the leakiness of the microvasculature in the form of the forward transfer rate constant, k_{ep} is the reverse transfer rate constant, and v_p is the vascular plasma volume fraction. C(t) and $C_p(t)$ are estimated by $\Delta R_1(t)$, the change in R_1 vs time. Four nested models were described: 0. no evidence of vascular filling, 1. no leakage (K^{trans} = k_{ep} = 0), 2. unidirectional leakage (k_{ep} ≠ 0), 3. bidirectional leakage, identified as Model 0, 1, 2, and 3, respectively, because those are the number of parameters necessary to fit the corresponding model.

MRI: All MRI image sets were acquired in a Varian/Agilent DirectDrive 7 Tesla, 20 cm bore system with a 32x32 mm^2 FOV. Prior to the 2GE sequence, and immediately after, two Look-Locker (LL) sequences (matrix 128x64, five 2.0 mm slices, NE=24 inversion-recovery echoes, TR=2000) were run so that a voxel-by-voxel estimate of T_1 in the tissue could be made pre- and post-CA administration. The 2GE sequence acquired 150 image sets at 4.0 s intervals: (matrix = 128x64, three 2.0 mm slices, NE= 2 NA=1 TE/TE/TR = 2.0/4.0/60 ms). CA (Magnevist) bolus injection was performed by hand push at image 15. Total run time was 10 minutes. A radiological arterial input function (2) (AIF), normalized so that the caudate putamen of the normal hemisphere yielded a plasma volume of 1%, was employed. For each tissue voxel, all (typically > 130) data points were fitted to model 0, 1, 2, and 3, an F-statistic was generated to select the preferred model, and the parameters available under that model were mapped. Data is summarized from Model 3 regions in all three slices.

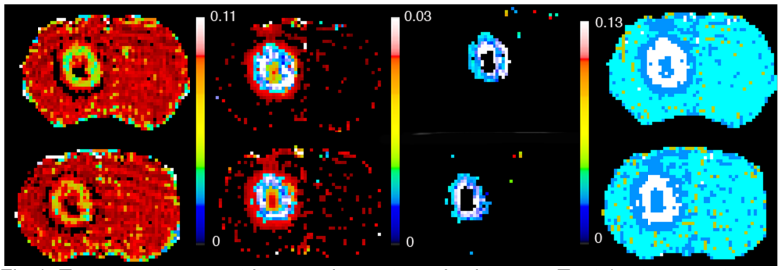

Fig 1: Test-retest parametric maps in a rat cerebral tumor. Test 1 – top row, test 2, bottom row. Left to right: v_p, K^{trans}, v_e, Model. In the Model map, white=Model 3, dark blue = 2, light blue = 1, yellow= 0 or NAN. Parameters were plotted only in the voxels where sufficient evidence existed to justify the higher-order model. Note the increase in v_e toward the tumor's necrotic core and the *decrease* in v_p in its normal surround .

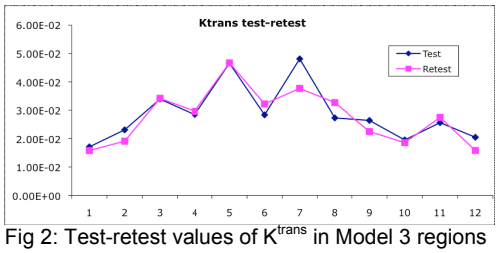

Fig 2: Test-retest values of K^{trans} in Model 3 regions of 12 animals

Results and Conclusion: Under the conditions of the experiment, the first pass of the CA produced a *signal decrease* in most tissues, particularly in the tumor and blood. However, other than in blood, a voxel-by-voxel estimate of $\Delta R_1(t)$ (*increasing* after CA) could always be stably produced by an analytical expression that utilized the predetermined (by LL) value of R_1 prior to CA. $\Delta R_1(t)$ could, in turn, be used in the SM to produced parametric maps of v_p (Models 1, 2, 3), v_p and K^{trans} (Models 2, 3), and v_p, K^{trans}, v_e (Model 3), where v_e was calculated from $v_e = K^{trans}/k_{ep}$. A typical test-retest data set is shown in Fig 1.

Parameter values in the Model 3 region varied considerably from animal to animal, typically by at least a factor of 5 (see Figure 2 for variability in K^{trans}). However, test-retest values were quite stable. Combined (2 studies) sample means and (mean test-retest difference) were as follows: v_p=1.6% (volume fraction) (13% test-retest), K^{trans}=2.8x10^{-2} min^{-1} (-3.7% test-retest) v_e=4.3% (volume fraction) (3.5% test-retest). Thus, a methodology employing 2GE MRI and model selection yields stable estimates of vascular parameters. This result supports the use of this approach in the evaluation of tumor models' response to trial therapies, and, since the technology is directly applicable to humans, also supports its use in the evaluation of therapeutic response in patients with cerebral tumors.

References: 1. Ewing JR et al. J Cereb Blood Flow Metab 2006;26(3):310-320. 2. Nagaraja TN et al. Magn Reson Med 2010;63(6):1502-1509.