Blood-Tumor Permeability (K) Measured with Dynamic Contrast Enhanced MRI and C14-AIB Autoradiography in a Rat Brain Tumor Model, a Validation Study

M. C. Ferrier[1], H. Sarin[2], S. H. Fung[1], B. Schatlo[2], S. Gupta[3], R. Pluta[2], D. Thomasson[1], J. A. Butman[1]

[1]Department of Radiology, NIH, Bethesda, MD, United States, [2]Department of Neurosurgery, NIH, Bethesda, MD, United States, [3]Applied Science Lab, General Electric, Baltimore, MD, United States

Introduction: Dynamic contrast-enhanced MRI (DCE-MRI) is being increasingly used to characterize and quantify contrast medium behavior in tumors and tissues. Of particular interest is the measure K^{trans} which defines vascular permeability. In brain tumors, this measure has been shown to correlate with tumor grade, and may provide a biomarker of treatment efficacy.[1] The General Kinetic Model (GKM) is a 2-compartment 3 parameter pharmacokinetic model of contrast exchange between the plasma and the extracellular extravascular space (Eq.1). DCE-MRI allows for estimation of the 3 free parameters (K^{trans}, v_e, and fPV) of the GKM. In our model, the solution is obtained by iteratively adjusting these three parameters so that the convolution of a measured VIF with the transfer function fits the measured concentration at each voxel location.[2] In this work, we sought to validate tumor permeability measurements obtained by DCE-MRI by comparing the K^{trans} obtained from our solution of the GKM and DCE-MRI with the "gold standard" of quantitative autoradiography (QAR) using C14-AIB (□-aminoisobutyric acid) in a rat brain tumor model.

Methods:

Animal model: RG2 brain tumor cells were implanted into the brains of 6 adult Fisher-344 rats. MRI and autoradiography were performed 9-13 d post implantation.

MRI technique: Images were obtained on a Philips Intera 3.0 T MRI and dedicated 7 cm rat solenoid rf-coil (Philips Research Laboratories, Hamburg, Germany). A low flip angle (FA =3) 3D FFE sequence with parameters otherwise matching the DCE-MRI was obtained. DCE-MRI was performed using 3D T1-FFE sequence, 30 volumes were obtained over 10 min (20 sec/ volume). Geometric parameters were slice thickness 1mm, 16 slices oversampled to 32, FOV 768 mm, matrix 256x224. Contrast parameters were TR 8.1 TE 2.3 FA 12. After a one minute delay, 0.5cc/kg bolus of Gd-DTPA (Magnevist, Berlex) was injected via femoral vein over 1 minute, followed by 2 minute saline flush.

Autoradiography: QAR was performed within one hour of DCE-MRI scanning. Briefly, 33 - 100 µCi C14-AIB was injected via femoral vein cannula, while blood was continuously withdrawn from the contralateral femoral artery at a rate of 0.033 ml/min for 15-20 minutes using a Harvard pump. At the experimental endpoint, the animal was immediately guillotined, and the brain was rapidly removed and frozen. Serial 40 µm sections were placed on Fuji computed radiography film for 3 days with standards. The arterial samples were spun and plasma supernatant was collected.

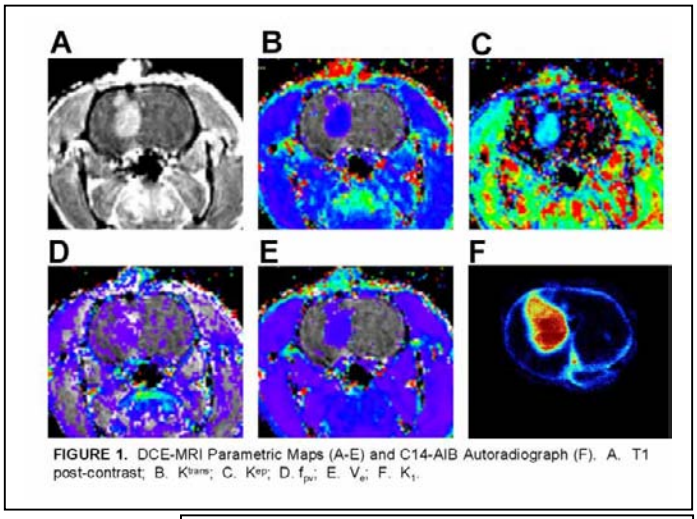
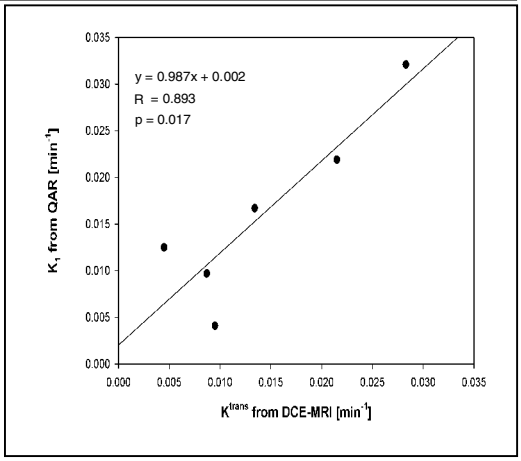


FIGURE 1. DCE-MRI Parametric Maps (A-E) and C14-AIB Autoradiograph (F). A. T1 post-contrast; B. K^{trans}; C. K_{ep}; D. f_{pv}; E. V_e; F. K_1.

DCE-MRI analysis: DICOM data was processed using a custom-made IDL pharmacokinetic analysis package (Cinetool, GE Healthcare, Milwaukee, WI). T1 maps were computed using the two flip angle technique, and signal intensities were converted to concentrations. A VIF was identified automatically. Tissue concentration C_t was estimated by convolving the VIF with the transfer function and including a term fro fractional plasma volume according to:

(1) $$C_t = K^{trans} (VIF \otimes e^{-Ktrans\ t\ /\ Ve}) + f_{pv} (VIF)$$

Best fit solutions were obtained by iteratively adjusting the three parameters (K^{trans}, v_e, and fPV) to minimize error between the measured and estimated tissue concentrations, both using a voxel-wise analysis and for ROIs drawn in the largest tumor section.



***QAR analysis*:** Because C14-AIB is trapped intracellularly once it crosses the BBB [3], unidirectional model can be assumed and the transfer constant can be directly calculated according to:

(2) $$K_1 = (C_t - f_{pv}\, C_p(T)) / (\langle C_p(t) \rangle\, T)$$

Here f_{pv} is assumed to be 2.2% based on prior studies [4], T is sample withdrawal time, $C_p(T)$ is the plasma concentration at the end of experiment, and $\langle C_p(t) \rangle$ is the average plasma concentration during the experiment. C_t is tissue concentration.

Results: Representative parametric maps obtained from the DCE-MRI are compared with the C14-AIB QAR are shown in Figure 1. The K values obtained using DCE-MRI and C14-AIB QAR are graphed in Figure 2. The slope of the regression line is close to unity. The average f_{pv} measured by DCE-MRI was 2.2 ± 0.7, essentially identical to published values.[4]

Discussion: The two independent measures of blood-tumor permeability were nearly identical, particularly at higher values of K^{trans}. This validates DCE-MRI as an accurate measure of blood-tumor permeability in comparison to the "gold standard" of C14-AIB in the rat tumor model. Planned slice-to-slice co-registration of QAR to MRI will allow for comparison of these measures at a finer scale. Our method of solving the GKM makes several assumptions. By performing a slow infusion, a relatively long sampling interval (20 sec) can be used, while still accurately sampling the dynamics of the VIF. Since this sampling time is long compared to the capillary transit time, the arterial and venous concentrations can be assumed equivalent, allowing for the use of large venous sinuses to be sampled for estimation of the VIF. The concordance of our K^{trans} values with the K_1 from QAR indicates that these assumptions are valid, and suggests that our DCE-MRI method may accurately measure permeability values in human brain tumors as well.

References: [1] Turetschek et al., J Mag Res Imag, 2004; 20: p.138-144. [2] Butman et al., ASNR, 2003. [3] Blasberg et al. J Cereb Blood Flow, 1983; 3: p.8-32. [4] Nakagawa et al. J Neurooncol, 1988; 6(2): p.157-68.