DCE-MRI Rat Cerebral Glioma Blood Volume Determination with Extravasating CR

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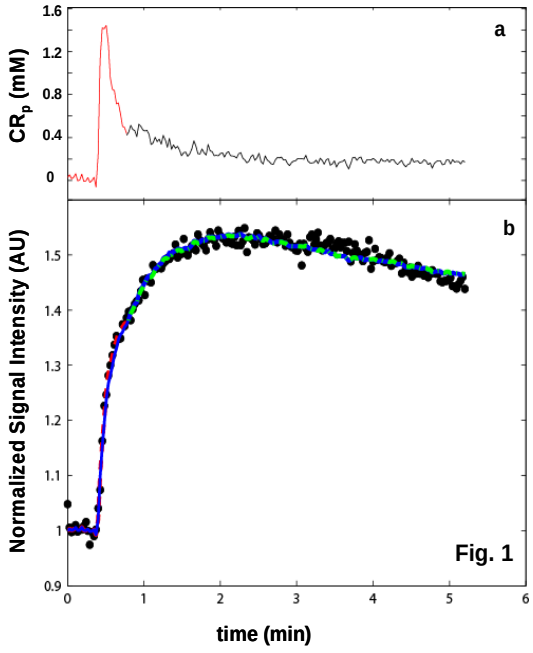
INTRODUCTION The accurate determination of tumor blood volume fraction (v_b) is a highly desired imaging biometric goal. It is commonly thought that this is difficult, if not impossible, for Dynamic-Contrast-Enhanced (DCE) MRI because angiogenic malignant tumor vessels allow fast contrast reagent (CR) extravasation. Most DCE-MRI pharmacokinetic models modify derivations for directly-detected tracers, and do not take advantage of equilibrium intercompartmental water exchange (shutter-speed) effects. These can cause significant signal-weighting changes during the indirectly-detected CR bolus passage. Starting with the rate law for simultaneous relaxation of the blood, interstitial, and intracellular ^1H_2O signals, a three-site-exchange shutter-speed pharmacokinetic model, BALDERO (Blood Agent Level Dependent and Extravasation Relaxation Overview) [1] includes these aspects. Here we demonstrate the use of BALDERO to measure v_b values in rat brain gliomas that exhibit significant CR extravasation.

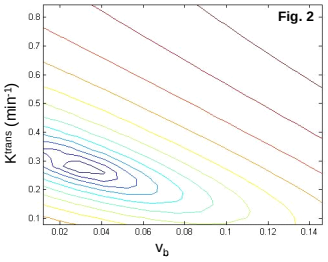
METHODS MRI studies were performed with an 11.75 T instrument (Bruker, Billerica, MA). Coronal-equivalent head images from four male athymic nude rats were acquired six to seven weeks after U87 glioma cells were inoculated into the right brain hemispheres. For each, 50 µmol/kg of GdDTPA-BMA (Omniscan, after 1:2 dilution) was injected *via* a jugular vein catheter, followed by ~ 0.24 mL saline flash. A quadrature volume RF transmit coil was used along with a surface receive RF coil placed on the animal's head. The three-slice fast-gradient-echo DCE-MRI sequence parameters were: TR 25 ms, flip angle 20°, slice thickness 1.0 mm, rectangular FOV (5.12 x 2.56) cm^2, 128 read-out points with 50% phase encoding steps. These resulted in an image matrix of 128 x 64, and a 1.6 s time-resolution.

RESULTS Arterial input function (AIF) data were taken from the sagittal sinus of a fifth rat experiencing a similar injection. The AIF is plotted, as plasma CR concentration, [CR_p], in **Figure 1a**, and was temporally registered with each tissue data time-course before fitting. The Fig. 1b circles report the time-course of the mean tumor ROI signal intensity (divided by that before CR arrival, S/S_0) for one animal. The three solid curves represent successive BALDERO fittings of different DCE time-course segments. The red curve, covering only the first-pass, shows the fitting using only two variable parameters: K^{trans}, the volume-weighted CR extravasation rate constant, and p_b, the mole fraction ("population") of tissue water in blood. The τ_b^{-1} (unidirectional rate constant for water extravasation) value was fixed at 3.3 s^{-1}. With the thus-fitted K^{trans} (0.28 min^{-1}) and p_b (0.038) as initial starting value and fixed, respectively, the blue curve shows the BALDERO fitting of the entire time-course using only K^{trans} and p_o, the mole fraction of tissue water in extravascular extracellular space, as fitting parameters. The green curve, which largely overlaps the blue one, is a fitting of the data points occurring only after the first-pass. The negligible difference between these, and the relative continuity of the fitted segments, clearly indicates the dominance of different model parameters at different CR passage periods. (The "texture" of the fitted curves arises from that of the AIF, which is numerically incorporated into the analytical BALDERO.)

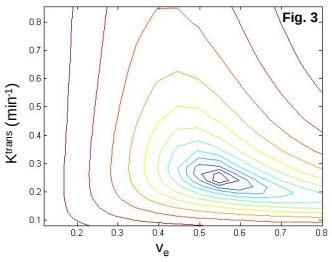


To gain confidence in these fittings, parameter sensitivities to the DCE data were tested with comparisons that effected parametric grid searches. **Figure 2** shows a contour plot of the natural logarithm of the chi square statistic, $\chi^2 = \Sigma\,[S_{data}(t) - S_{model}(t)]^2$, for only the first-pass data (~ first 48 s, red in Fig.1). Only K^{trans} and v_b (= $p_b \cdot f_W$, where f_W is the volume fraction accessible to mobile aqueous solutes) were varied, while others were fixed at reasonable values [1]. Other parameters tested in the same pair-wise manner were: K^{trans}, v_b, τ_b^{-1}, v_e (extravascular, extracellular space [EES] volume fraction = $p_o \cdot f_w$), and τ_i (mean intracellular water molecule lifetime). These could be called "chi-by-eye" contours, since they measure the χ^2 value ("goodness") of comparisons of the data with model curves calculated for the parameter values given by the coordinates. The χ^2 value decreases as the contour color shifts in the blue direction. Only the K^{trans},v_b pair showed consistently (for all animals) the well-defined funnel-type contours [2,3] required.

Figure 3. shows the only well-behaved contour pair (K^{trans}, v_e) when the entire time-course data are used for the chi square statistic. The p_b value was fixed at that from the first-pass fitting. Figs. 2 and 3 confirm the feasibility of our successive fitting approach.



The average parameter values returned by entire time-course fittings for the four animal tumors studied are [mean (±SD)]: v_b = 0.038 (± 0.01), v_e = 0.52 (±0.065), and K^{trans} = 0.262 (±0.026) min^{-1} .



DISCUSSION Our results demonstrate that with proper modeling, v_b can be estimated from T_1-weighted DCE-MRI data, even in the presence of rapid CR extravasation. As extravascular CR accumulates with time, the contribution of the blood ^1H_2O signal diminishes, but during the CR first-pass (even with some CR extravasation), its importance cannot be neglected [1]. Water exchange effects are important in DCE-MRI modeling. If τ_b is held vanishingly small [1 ms] (as in most other models), the values returned for v_b are typically underestimated by ~25%. Analogously, holding τ_i vanishingly small leads to significant v_e and K^{trans} underestimations [1]. For the low dose used here (about half standard human dose), however, the actual intercompartmental exchange rate constants seem to be inaccessible. The accuracy of AIF estimation plays an important role in all BALDERO parameter determinations. Since the rat brain AIF is hard to measure well, the v_b and v_e values returned could include systematic errors. However, large lesion-averaged v_e values [4] might not be unexpected for the aggressive U87 glioma, which can harbor extensive necrotic regions: v_e is related to the "cellularity" complement. It is important to note that tumor blood perfusion flow (f) can also be directly determined from the Fig. 1 data (BALDEROF) [2,3]. When fast MR imaging with pure T_1-weighted [5] DCE-MRI acquisitions become reality, better AIF estimations and thus even more accurate K^{trans}, v_b, v_e, and f determinations will result, especially at high field.

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REFERENCES **1.** Li, Rooney, Springer, *MRM* **54**: 1351-59(2005) [erratum, *MRM* **55**:1217(2006)]. **2.** Li, Jerosch-Herold, Springer, *PISMRM* **14**:1165 (2006). **3**. Jerosch-Herold, Li, Springer, *PISMRM* **14**:787 (2006). **4.** Gullino, *Extracellular Compartments of Solid Tumors*, Plenum Press, New York, 1975; Vol. **3**, p. 327. **5.** Idiyatullin, Corum, Park, Garwood, *JMR* **181**: 342-349 (2006).