IVIM and DSC metrics are heightened in rat C6 brain tumors.

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INTRODUCTION The Intravoxel Incoherent Motion (IVIM) theory[2] assumes diffusion within live tissue is more complex than simple random Brownian motion. The theory includes a faster water diffusion component representing the microcirculation of blood through capillaries, and there remains some debate as to what this perfusion fraction actually represents. Ex vivo brain studies in animals suggest that it represents cerebral spinal fluid (CSF) rather than microcapillary perfusion[1]. However, phantom studies utilizing blood flow suppressing gradients indicate that the perfusion fraction is in fact related to blood perfusion[2]. Brain tumors are known to have heightened microvasculature as tumors create vessels for self-subsistence. We therefore hypothesized that IVIM-derived perfusion measures would be heightened in C6 brain tumor model in rats if indeed IVIM were related to blood perfusion.

METHODS *Rats* Rats were injected with the C6 glioma cell line and imaged on days 14, 17, and 20 post-injection. Tumors were localized to the right hemisphere. In total, 23 rats were imaged resulting in 69 separate imaging sessions. 26 scans were excluded due to poor quality scans and/or lack of DSC imaging data leaving 43 scans to be further analyzed.

Imaging All images were acquired on a 9.4T Bruker scanner. DWI, DSC, and contrast enhanced T1-weighted images (T1+C) were acquired. DWI images were acquired with spin echo EPI with TR/TE = 1500/50ms, FA = 90°, Matrix = 128x128, Thickness = 1mm, FOV = 35mm, and b-values of 0, 50, 100, 500, 1000, and 2500 s/mm^2. DSC images were acquired with GRE EPI with TR/TE = 500/18.76ms, FA = 38.9°, Matrix = 128x128, Thickness = 1mm, FOV = 35mm for a total of 120 volumes. T1+C images were acquired with TR/TE = 1500/7.5ms, FA = 121.4°, Matrix = 256x256, Thickness = 1mm, FOV = 35mm.

Data Analysis IVIM modeling was accomplished using Equation 1 where f_p is the fractional perfusion, D_t represents the pure molecular diffusion, and D_p is the pseudodiffusion, or perfusion related diffusion. For this analysis, a segmented approach was chosen. Since D_p is much greater than D_t, its effect can be neglected when b > 200 s/mm^2. Therefore, D_t can be estimated by linearly fitting the natural log of Equation 2 and f_p by evaluating Equation 3. D_p can then be calculated by fitting Equation 1. All curve-fitting analyses were performed in Matlab. rCBV was calculated as described previously using an integration under the gamma-variate fit technique corrected for leakage effects[3]. Tumor masks were manually drawn on the T1+C images to include areas of heightened intensity. Contralateral normal tissue ROIs were then drawn in a similar location and size of the tumor. DWI and DSC images were coregistered to the T1+C images. IVIM and DSC derived parameters including f_p, D_t, D_p, and rCBV, were averaged in both the tumor and normal ROIs and compared between ROIs and across rats using a two sample t-test. Correlations between IVIM derived parameters and DSC derived parameters were assessed using a Pearson's correlation coefficient. Since multiple scan dates from the same rat were used in the analysis, the effect of rat number was regressed out of the data and the data was then correlated.

$$\frac{S_b}{S_0} = (1 - f_p)\cdot e^{-b\cdot D_t} + f_p \cdot e^{-b\cdot(D_t + D_p)} \quad (1)$$

$$S_b = S_{\text{int}} \cdot e^{-b\cdot D_t} \quad (2)$$

$$f_p = \frac{(S_0 - S_{\text{int}})}{S_0} \quad (3)$$

Table 1		f_p	D_t (s/mm^2)	D_p (s/mm^2)	rCBV
Mean	Tumor	0.247	$7.84\cdot10^{-4}$	0.0226	6323
	Normal	0.159	$6.41\cdot10^{-4}$	0.0251	5176
Standard Deviation	Tumor	0.429	$9.70\cdot10^{-5}$	0.0065	970
	Normal	0.356	$7.20\cdot10^{-5}$	0.0064	1171
P-value		< 0.0001	< 0.0001	0.078	< 0.0001

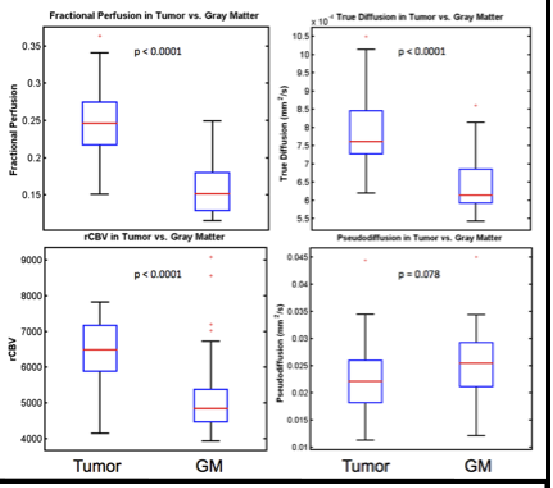

Figure 1 Boxplots comparing IVIM parameters in Tumor vs. contralateral gray matter. Fractional perfusion, D_t, and rCBV were all significantly higher ($p < 0.0001$) in tumor vs. contralateral gray matter. D_p was lower in tumor vs. contralateral gray matter, but the results were not significant.

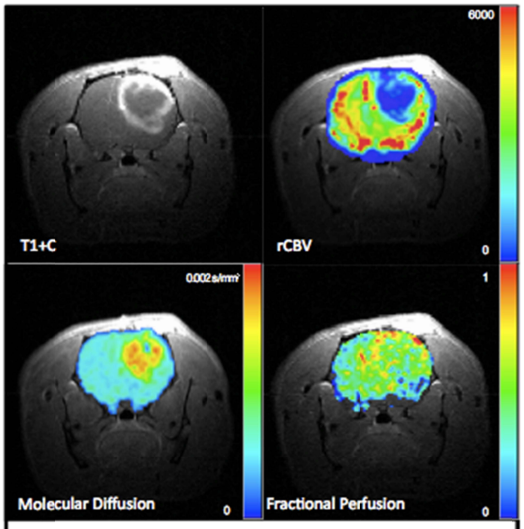

Figure 2 Example parametric maps of DSC and DWI derived parameters from a representative rat with a C6 glioma.

RESULTS Results from the comparison of IVIM and DSC derived parameters between tumor and normal contralateral brain are shown in Table 1 and Figure 1. f_p, D_t ,and rCBV were significantly greater in tumors compared to contralateral normal brain. None of the IVIM parameters correlated with rCBV. Figure 2 shows examples of parametric maps from a representative rat.

DISCUSSION This study demonstrates that IVIM metrics are heightened in brain tumors. Although rCBV was also higher in tumors, no correlation was found between IVIM parameters and rCBV. This indicates fractional perfusion may not be related to blood perfusion in brain tumors. Nonetheless, both rCBV and fractional perfusion were heightened in tumors. Thus, while not related to DSC-derived blood volume measures, fractional perfusion may still be of biological relevance.

RERERENCES

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