rCBV Estimates in Tumor and Normal Brain Depend on Choice of Data Acquisition and Analysis Methods

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Introduction. Determination of relative cerebral blood volume (rCBV) from the first-pass dynamic susceptibility contrast (DSC) signal can be confounded by a leaky blood brain barrier, as is often the case with brain tumors. Under these conditions, contrast agent leaks out of the vessels into the brain or tumor tissue thereby diminishing the susceptibility effect of the agent as it passes through the vasculature. Since its introduction in the early 1990's a plethora of DSC-MRI data acquisition and analysis strategies have been developed; each demonstrating feasibility and relevance with regard to evaluating the blood volume of brain tumors with different approaches to minimize or correct for leakage effects. As DSC-MRI is translated from the research realm to mainstream clinical use it is imperative to determine the extent of the effects these different strategies have on perfusion quantification. The goal of this study was to investigate how differences in DSC-MRI data acquisition and analysis methods influence rCBV estimates in tumor and normal brain. Preliminary work on this topic has been published previously [1].

Methods. A prospective study was performed on 19 patients with high-grade intracranial tumors who underwent rCBV analysis. Acquisition was performed on a 1.5T GE CV Scanner (GE Healthcare, Milwaukee, Wisconsin) equipped with 4 G/cm gradients. Three sets of experiments were designed to evaluate four published DSC-MRI data acquisition methods. The following general acquisition parameters were used in each of the experiments: FOV=24 cm^2, matrix=64x64, TR=1100 msec, slice thickness=5mm, interslice gap=0-1.5mm, number of slices=12, number of samples (reps)=180. Table 1 provides a breakdown of the specific differences in acquisition methods.

Table 1: Breakdown of Specific Differences in Acquisition Methods

	Acquisition Method A [2,3]	Acqusition Method B [4,5,7,8]	Acquisition Method C [12-16]	Acquisition Method D [10,11]
Subjects	n=9	n=6	n=15	n=4
Pulse Sequence	Vendor GRE-EPI	Vendor GRE-EPI	Vendor GRE-EPI	Custom GRE-SPIRAL
Flip Angle (α)	90	35	90	90
Number of Echoes	1	1	1	2
Echo Time (TE)	30 msec	54 msec	30 msec	3.3 msec, 30 msec
Gd-DTPA Dose	0.1 mmol/kg	0.1 mmol/kg	0.2 mmol/kg	0.1 mmol/kg
Gd-DTPA Injection Time	60th time point	15th time point	60th time point	60th time point
Pre-Load Administered	No	No	Yes	No

The first set of experiments was designed to evaluate the efficacy of a loading dose in diminishing competing T1 effects resulting from contrast agent extravasation. Specifically, two acquisitions were performed *in series* on the same patients using a standard GRE-EPI sequence (α=90°, TE=30 msec). For the first acquisition, method A was used to acquire images during injection of a standard dose of Gadodiamide (0.1 mmol/kg, Omniscan) and for the second acquisition, method C was used to acquire images during injection of a double dose of Gadodiamide (0.2 mmol/kg, Omniscan). The second set of experiments was designed to evaluate the efficacy of a low flip angle acquisition in diminishing competing T1 effects from contrast agent extravasation. As before, two acquisitions were performed *in series* on the same patients. For the first acquisition, method B was used to acquire low flip angle images during injection of a standard dose of Gadodiamide and for the second acquisition, method C was used to acquire images during injection of a double dose of Gadodiamide. Note that administration of the standard dose of contrast agent during the first scans (in both experiments) also served as the loading dose to diminish competing T1 leakage effects during the second scans. The third set of experiments was designed to evaluate the efficacy of a dual-echo acquisition in diminishing competing T1 leakage effects (acquisition method D) during injection of a standard dose of Gadodiamide.

Data analysis was performed offline using AFNI and additional programs developed at our institution. Six published DSC-MRI data analysis methods were evaluated for each of the four data acquisition methods described above. After converting the MR signal intensity time courses, S(t), to ΔR2*(t) concentration-time curves [4,5,10,11], rCBV was estimated on a voxel-wise basis using: I) trapezoidal integration over the first 120 time points of ΔR2*(t) [12,15], II) trapezoidal integration over the first 120 time points of ΔR2*(t) with correction for contrast agent extravasation [13-16], III) integration of a gamma-variate function fit to ΔR2*(t) [2,4], IV) trapezoidal integration of ΔR2*(t) after correction for post-bolus baseline shift [5,6], V) trapezoidal integration of negative enhancement of S(t) [3,9], and VI) calculating the maximum signal drop of S(t) [4,5]. The rCBV estimates obtained from each analysis method were normalized to the mean normal appearing white matter rCBV value corresponding to each method. Contralateral normal brain and non-necrotic enhancing tumor regions of interests (ROIs) were drawn and used to extract mean rCBV values for comparisons.

Results and Discussion. Figures 1-4 display mean rCBV estimates as a function of analysis method for each of the data acquisition methods described in Table 1. A disparity in mean rCBV was found to exist among and between acquisition and analysis methods, especially in regions of tumor. Since high-grade tumors are known to exhibit increased vascularity it would be expected that tumor rCBV should exceed normal brain rCBV. This was found to be the general case for data acquisition methods C and D (Figures 3 and 4). However, as demonstrated by the negative tumor rCBV values for two analysis methods in Figure 1, extravasation of contrast agent can result in an underestimation of rCBV if analysis methods are not used to prevent or correct for the competing T1 leakage effects (e.g., the 120pt trapezoidal integration with leakage correction analysis method resulted in increased tumor rCBV relative to normal brain rCBV in Figure 1). Figures 2-4 demonstrate that data acquisition methods can also successfully minimize the effects of contrast agent extravasation. Some of the remaining variability across analysis methods may be explained at least in part by the different sensitivities to any residual dipolar T2 or susceptibility-based leakage effects. In terms of best tumor-to-normal brain contrast and consistency across data analysis methods the most robust data acquisition methods appear to be methods C and D (Figures 3 and 4). Future work will include performing survival analysis and correlations with tumor grade, along with histological validation with the goal of defining the most accurate method to determine rCBV in brain tumors.

Figure 1: rCBV estimates obtained from Acquisition Method A (high grades, n=9).

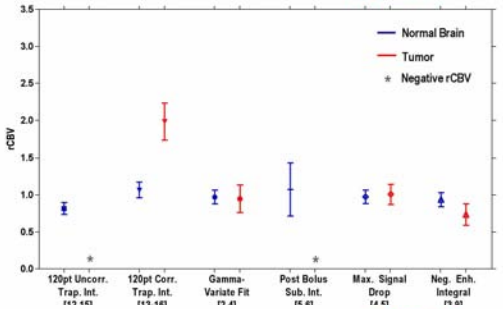


Figure 2: Mean rCBV estimates obtained from Acquisition Method B (high grades, n=6).

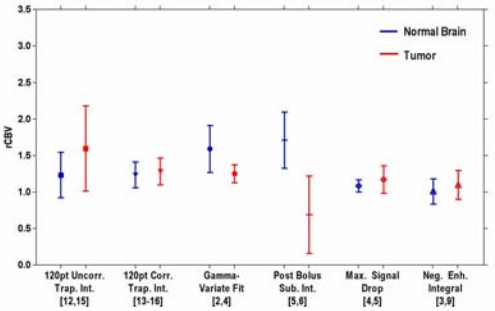


Figure 3: Mean rCBV estimates obtained from Acquisition Method C (high grades, n=15).

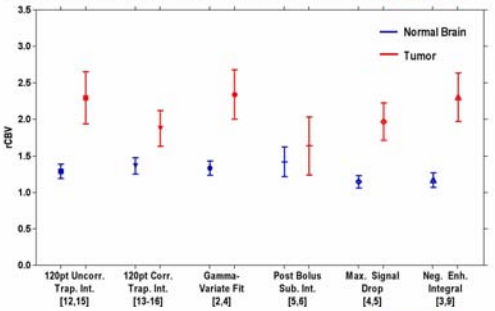
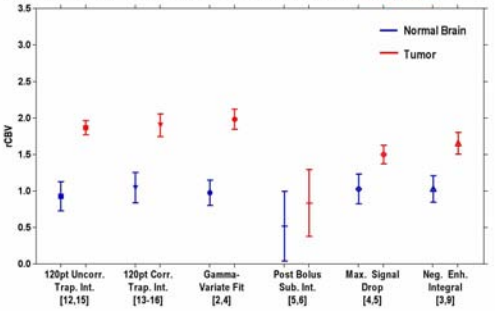


Figure 4: Mean rCBV estimates obtained from Acquisition Method D (high grades, n=4).



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