Repeatability of Standardized and Normalized rCBV in Patients with Newly Diagnosed GBM

Melissa A Prah[1], Eric S Paulson[2], Dominique L Jennings[3], Elizabeth R Gerstner[4], Tracy T Batchelor[4], Steven M Stufflebeam[3], and Kathleen M Schmainda[1,5]

[1]Radiology, Medical College of Wisconsin, Milwaukee, WI, United States, [2]Radiation Oncology, Medical College of Wisconsin, Milwaukee, WI, United States, [3]Radiology, Massachusetts General Hospital, Charlestown, MA, United States, [4]Neurology, Massachusetts General Hospital, Boston, MA, United States, [5]Biophysics, Medical College of Wisconsin, Milwaukee, WI, United States

Target Audience: Neuro-oncologists, neuro-radiologists, neuro-surgeons, brain tumor imaging scientists.

Purpose: Relative cerebral blood volume (rCBV) estimates, derived from dynamic susceptibility contrast (DSC) MRI, have been increasingly used to evaluate the vascular properties of brain tumors. The information provided by rCBV estimates has been used to assist clinicians in the identification of tumor grade, type, progression, aggressiveness, and treatment response. Although the accuracy of several methods for rCBV estimation has been investigated (1), the repeatability of these methods has not, including a comparison between standardized (sRCBV) and normalized (nRCBV) rCBV approaches. The goal of this study was to compare the repeatability across five commonly used post-processing methods in the estimation of standardized and normalized rCBV in patients with newly diagnosed GBM, prior to initiation of treatment.

Table 1: *rCBV estimation methods (1).*

rCBV Estimation Methods	
Method 1	120-point Numeric Integration of ΔR2*(t) with the Trapezoid Rule
Method 2	120-point Numeric Integration of ΔR2*(t) with the Trapezoid Rule and Correction for T1 Extravasation Effects
Method 3	Area under Gamma-Variate Fit to ΔR2*(t)
Method 4	Maximum Signal Drop of S(t)
Method 5	Negative Enhancement Integral of S(t)

Methods: ***Acquisition:*** MRI was performed twice, within 8 days, for 38 subjects with newly diagnosed GBM. Extreme motion artifact [1], poor contrast injection [2], and initiation of treatment [2] excluded 5 subjects from analysis. Data obtained included DSC-MRI and pre- and post-contrast enhancing T1-weighted images. All data was acquired on a 3T system, using the same imaging protocol (DSC GRE-EPI: TE=31ms, TR=1.48sec, 0.1 mmol/kg preload, 0.1-0.2mmol/kg dose during DSC data collection). ***Processing:*** The standardized and normalized rCBV (sRCBV and nRCBV) estimates for all five methods were calculated from unmodified DSC data using software developed at the Medical College of Wisconsin (MCW). A summary of these methods is shown in Table 1, and described in detail in (1). Data was standardized or normalized for each visit separately, with standardization files created at MCW (3) or manually drawn NAWM ROIs, respectively. ***Analysis:*** DSC, T1+C, and T1 weighted images were co-registered using 6 degrees of freedom and normalized mutual information cost function. Enhancing tumor volume ROIs were determined, for each respective visit, using a semi-automated, threshold-detection algorithm incorporating standardized T1+C and T1 images (2). Normal-appearing brain ROIs were also drawn for comparison. Repeatability metrics were calculated for mean rCBV estimates within the tumor and normal brain ROIs separately. These calculations are described in detail in (4).

Results: Repeatability metrics obtained for all rCBV analysis methods are shown in Table 2 for tumor ROIs, and sorted in order of greatest repeatability as determined by the repeatability coefficient (RC) for sRCBV and nRCBV separately. Also contained in the table are the 95% CI ranges for RC, standard deviations including between-subject (bSD), within-subject (wSD), and total standard deviations (tSD), and the within-subject coefficient of variation (wCV). The RC shows greatest consistency for methods 2 and 3 for both sRCBV and nRCBV. In general, signal-based rCBV analysis methods were among the least repeatable, particularly for method 4. The sRCBV shows greater consistency than nRCBV between visits (Fig 1), where wCV is also much less overall. This was consistent in both normal brain and tumor. In Fig 1, sRCBV and nRCBV are scaled differently, and thus the overall RC 95% CI cannot be accurately compared for the extent of range. Figure 2 also provides a visual comparison of methods 1-5 for sRCBV and nRCBV estimates in approximately the same slice from the same subject, for each visit, where all images show the same respective scale for sRCBV or nRCBV across methods and visits. In general, wCV was higher for nRCBV in normal brain and tumor, compared to sRCBV. However, no significant differences were obtained in RC values in normal brain compared to tumor (sRCBV: p=0.35; nRCBV: p=0.11). Interestingly, wCV was significantly higher in normal brain compared to tumor (p=0.008) for sRCBV, likely due to lower mean values in normal brain. However, wCV was comparable in normal brain and tumor for nRCBV (p=0.75).

Table 2: *Repeatability metrics in tumor.*

Standardized rCBV Estimates							
Method	RC	RC_L	RC_U	bSD	wSD	tSD	wCV
2	3869	5093	3121	2814	1397	3142	0.18
3	4214	5547	3399	2773	1521	3163	0.17
1	4261	5609	3437	2526	1538	2958	0.19
4	4591	6043	3703	6220	1658	6437	0.13
5	5250	6911	4235	5410	1895	5732	0.16
Normalized rCBV Estimates							
Method	RC	RC_L	RC_U	bSD	wSD	tSD	wCV
2	1.78	2.34	1.44	0.71	0.64	0.96	0.31
3	1.95	2.57	1.57	0.77	0.70	1.04	0.25
5	2.07	2.73	1.67	1.38	0.75	1.57	0.24
1	3.16	4.16	2.55	1.05	1.14	1.55	0.39
4	3.54	4.66	2.86	0.25	1.28	1.30	0.56

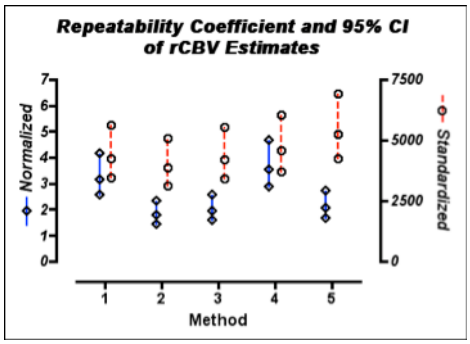

Figure 1: *RC with 95% CI for sRCBV and nRCBV in tumor.*

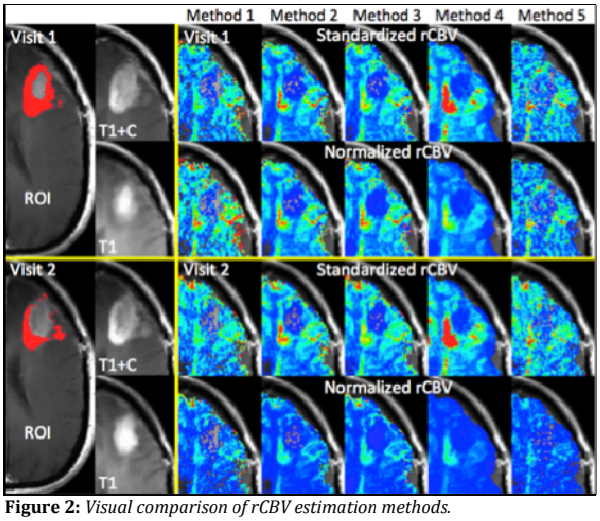

Figure 2: *Visual comparison of rCBV estimation methods.*

Discussion: Characterization of the repeatability of rCBV measures is important for determining when a change in these values is an accurate representation of tumor growth or response to treatment. These results show that there is a clear difference among the repeatability of various methods for estimating rCBV. Consistent with previous reports (1), method 2, the leakage-corrected estimate of rCBV, demonstrates the best repeatability for both standardized and normalized values. In general, standardization of rCBV maps decreases variability both within and across methods.

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