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Technical Note

Comparison Between Intensity Normalization Techniques for Dynamic Susceptibility Contrast (DSC)-MRI Estimates of Cerebral Blood Volume (CBV) in Human Gliomas

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Purpose: To compare “standardization,” “Gaussian normalization,” and “Z-score normalization” intensity transformation techniques in dynamic susceptibility contrast magnetic resonance imaging (DSC-MRI) estimates of cerebral blood volume (CBV) in human gliomas. DSC-MRI is a well-established biomarker for CBV in brain tumors; however, DSC-MRI estimates of CBV are semiquantitative. The use of image intensity transformation algorithms provides a mechanism for obtaining quantitatively similar CBV maps with the same intensity scaling.

Materials and Methods: The coefficient of variance (CV) in normal-appearing white matter and relative contrast between tumor regions and normal tissue was compared between the three CBV transformations across five different MR scanners in 96 patients with gliomas.

Results: The results suggest all normalization techniques improved variability and relative tumor contrast of CBV measurements compared with nonnormalized CBV maps. The results suggest Gaussian normalization of CBV maps provided slightly lower CV in normal white matter and provided slightly higher tumor contrast for glioblastomas (WHO grade IV) compared with other techniques.

Conclusion: The results suggest Gaussian normalization of leakage-corrected CBV maps may be the best choice for image intensity correction for use in large-scale, multicen-

ter clinical trials where MR scanners and protocols vary widely due to ease of implementation, lowest variability, and highest tumor to normal tissue contrast.

Key Words: cerebral blood volume; CBV; dynamic susceptibility contrast MRI; DSC; MRI; glioma; brain tumor

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SUSCEPTIBILITY-BASED MAGNETIC RESONANCE IMAGING (MRI) methods of estimating relative cerebral blood volume (CBV), otherwise known as dynamic susceptibility contrast (DSC)-MRI, utilize a bolus of a gadolinium-chelated contrast agent to induce a magnetic susceptibility gradient between contrast-containing vessels and surrounding tissue. During dynamic image acquisition, the signal in a particular image voxel near the bolus transiently decreases, which is related to a change in relaxation rate thought to be proportional to the fraction of blood volume within each image voxel (1). DSC-MRI methods have been successfully utilized to provide measures of CBV in patients with brain tumors (2–5), providing information needed to predict tumor grade (2,6,7) and survival (3).

Although DSC-MRI methods are well-established perfusion techniques for evaluation of brain tumor vascularity and angiogenesis, CBV measurements are nonquantitative (relative) and can vary within the same tissue type, or the same patient, across different scan dates and different MR scanners. As a result, CBV measurements are typically normalized to contralateral white matter tissue. As the size of the region of interest (ROI) and location must be carefully chosen, often by an experienced radiologist, this method often introduces unnecessary bias into the results and can be time-consuming.

To overcome these challenges, Bedekar et al (8) implemented a method of grayscale “standardization” first described by Nyul and Udupa (9,10) for standardizing grayscale anatomical MRI data that also

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suffers from the same inherent nonquantitative disposition. By using a training set of CBV data, Bedekar et al (8) were able to demonstrate a reduction in inter-patient and interstudy variability for the same tissue type, enabling easy and accurate comparison across studies. Despite these promising initial findings, the image standardization algorithm requires sophisticated implementation of piecewise, nonlinear histogram matching via a training set for a specific MR protocol and MR scanner. In the context of large multicenter clinical trials, these extra steps may require additional time and resources that are not readily available. Therefore, there remains a need for image intensity correction algorithms that provide ease of implementation as well as low variability across different scanner platforms, field strengths, and scan protocols.

Image intensity “normalization,” or correction via scaling or translation (not filtering), is utilized in many areas of research, including source localization in magnetoencephalography studies (11). As such, many easy-to-implement image-processing tools have been developed to accomplish intensity normalization. One such technique is known as “Gaussian normalization,” where intensity values are divided by the standard deviation of the image data within the brain. In the current study, we examined normal-appearing white matter (NAWM) variability in CBV measurements across MR platforms and field strengths in glioma patients using either untransformed, “raw” CBV maps, “standardized” CBV maps (12), “Gaussian normalized” CBV maps, and “Z-score normalized” CBV maps. Additionally, we examined relative contrast of CBV hot spots with respect to NAWM. We hypothesized that Gaussian normalized CBV maps would provide at least equal performance to the standardization transformation, but without the need for training sets for each MR scanning protocol.

MATERIALS AND METHODS

Patient Population

All patients participating in this study signed Institutional Review Board-approved informed consent to have their data in our institution’s neuro-oncology database. Data acquisition was performed in compliance with all applicable Health Insurance Portability and Accountability Act (HIPAA) regulations. This retrospective study spanned November 1 2010 to March 1 2011, after a total of $n = 100$ sequential patients received two or more DSC-MRI scans as part of their clinical follow-up (average time between follow-up scans = 1.92 ± 0.07 SEM months). Of these 100 patients, a total of $n = 96$ patients had high-quality, artifact-free DSC-MRI data for two or more scan days. Patients were not selected based on a particular histological type or treatment regimen. No patients had a change in treatment during the follow-up period. Additionally, all patients had stable disease between the follow-up timepoints. Table 1 illustrates patient information.

MRI

Imaging studies were performed on five different MRI scanners capable of echoplanar imaging: 1) a 1.5T GE

Table 1
Patient Characteristics

Total Patients	96
Histology	
WHO IV	51
GBM	51
WHO III	24
Anaplastic Astrocytoma	19
Anaplastic Oligodendroglioma	3
Mixed Anaplastic Glioma	2
WHO II	21
Astrocytoma	13
Oligodendroglioma	4
Mixed Low Grade Glioma	4
Gender	
Male	51
Female	45
Age	49.7 $\pm$ 15.8 SD

Signa HDxt, 2) a 1.5T GE Genesis Signa, 3) a 1.5T Siemens Sonata, 4) a 3.0T Siemens Trio, and/or 5) a 1.5T Siemens Avanto. Standard clinical images were obtained for all patients at all follow-up times including precontrast T1-weighted images, T2-weighted images, fluid attenuated inversion recovery (FLAIR) images, diffusion-weighted images, and (after DSC-MRI) postcontrast T1-weighted images.

A 0.025 mmol/kg preload dose of a gadolinium contrast agent was administered prior to DSC-MRI to diminish contrast agent extravasation (5,13,14). A 3–5 cc/sec bolus of either gadopentetate dimeglumine (Gd-DTPA; Magnevist, Bayer Schering Pharma, Leverkusen, Germany), administered at a dose of 10–20 cc (0.075 mmol/kg), or gadobenate dimeglumine (Gd-BOPTA; Multihance, Bracco Diagnostics, Princeton, NJ), administered at a dose of 9–20 cc (0.075 mmol/kg), was used for DSC acquisition and subsequent postcontrast T1-weighted images (total of 0.01 mmol/kg) using a power injector. DSC-MRI scan parameters varied slightly for each MR scanner in the study (Table 2), with echo times (TE) ranging from 23–50 msec, repetition times (TR) ranging from 1250–1400 msec, flip angles (FA) ranging from 30–35°, 40–90 repetitions (temporal timepoints), slice thickness ranging from 4–7 mm with interslice gap ranging from 0–1.5 mm, number of slices ranging from 6 to 20, and matrix size ranging from 80 $\times$ 96 to 128 $\times$ 128.

DSC-MRI Data Analysis

Data analysis was performed offline using commercially available postprocessing software (IB Neuro v. 2.0; Imaging Biometrics, Elm Grove, WI). DSC-MRI analysis consisted of the following steps: 1) truncation of the first five timepoints in the DSC-MRI time series, since the MR signal does not reach steady state before this time; 2) calculation of the prebolus signal intensity on a voxel-wise basis; 3) conversion of truncated DSC-MRI time series to a concentration-time curve based on the T2* relaxivity of the contrast agent; and 4) estimation of CBV on a voxel-wise basis by using a 120 point trapezoidal integration with correction for leakage, as described in previous publications (5,13–15).

Table 2
DSC-MRI Scanning Parameters

Scanner	TE	TR	FA [deg]	Reps	Thickness (skip)	# Slices	Matrix
1.5T GE Signa HDxt	35	1250	30	50	5 (1.5)	20	80 × 96
1.5T GE Genesis Signa	50	1250	35	80	5 (1.5)	6	128 × 64
1.5T Siemens Sonata	25	1270	35	90	5(0)	15	128 × 128
3.0T Siemens Trio	23	1240	35	90	4(0)	20	128 × 128
1.5T Siemens Avanto	41	1400	35	40	7(0)	16	128 × 128

CBV maps were “standardized” using the approach outlined by Bedekar et al (8). Briefly, a two-step piecewise linear transformation was used as described elsewhere (9,10). The data were first trained from a group of representative patients ($n = 10$ from data collected previously, not included in the current study) on each of the different MR scanners and protocols (as seen in Table 2). This training step was incorporated into the IB Neuro v. 1.1 software package, and the resulting $n = 96$ patients were processed accordingly. “Gaussian normalization” was performed using custom *c*-code and bash scripts courtesy of the National Institutes of Mental Health Magnetoencephalography Core Facility (3dNormalize; NIMH MEG Core, Bethesda, MD; kurage.nimh.nih.gov/meglab/Med/3dNormalize). Briefly, leakage corrected CBV estimates on a per-pixel basis, $CBV_{\text{leakage-corrected}}$, was divided by the standard deviation of leakage-corrected CBV measurements from the whole brain, $\sigma_{CBV \text{ Whole Brain}}$.

$$CBV_{\text{Gaussian}} = \frac{CBV_{\text{leakage-corrected}}}{\sigma_{CBV \text{ Whole Brain}}} \quad [1]$$

Although higher-grade tumors may have more heterogeneity in CBV measurements, the standard deviation of CBV taken from the whole brain (thousands of voxels) is likely to be minimally affected by individual high-grade components within the tumor. “Z-score normalization” is defined as the image signal intensity on a per-pixel basis, $CBV_{\text{leakage-corrected}}$, was subtracted from the mean leakage-corrected CBV measurement from the whole brain, $\mu_{CBV \text{ Whole Brain}}$, divided by the standard deviation of leakage-corrected CBV measurements from the whole brain, $\sigma_{CBV \text{ Whole Brain}}$. The resultant maps reflect a statistical Z-score value with respect to whole brain CBV measurements.

$$Z_{CBV} = \frac{CBV_{\text{leakage-corrected}} - \mu_{CBV \text{ Whole Brain}}}{\sigma_{CBV \text{ Whole Brain}}} \quad [2]$$

Statistical Analysis

For comparison of reproducibility and variability in normal tissue over time, circular ROIs 1 cm in diameter were placed in anatomically similar NAWM regions, contralateral to the primary tumor site, on T2/FLAIR images for each patient on two different days. Correct ROI placement was confirmed independently by two investigators. The coefficient of variance (CV), a measure of dispersion calculated by dividing the mean by the standard deviation in CBV

across follow-up times, was calculated for NAWM using each of the CBV techniques (raw, standardized, Gaussian normalized, Z-score normalized).

$$CV = \frac{\sigma_{CBV \text{ Day2-Day1}}}{\mu_{CBV \text{ Day2-Day1}}} \times 100\% \quad [3]$$

A one-way analysis of variance (ANOVA) and Tukey’s test for multiple comparisons was used to test whether there were differences in CV between the different CBV normalization techniques. Additionally, a two-way ANOVA and Bonferroni post-hoc test for multiple comparisons was used to test whether there were significant differences in CV due to both CBV normalization technique and MR scanning protocol/system, such as whether or not differences in CV were dependent on the same scanner being used or different scanners were used during longitudinal follow-up.

Next, a measure of relative contrast between the tumor regions and normal tissue was calculated for each patient on the baseline (first perfusion scan session) based on the highest CBV measurement within the T2/FLAIR and contrast-enhancing lesion, divided by the mean CBV measurement from the circular 1-cm diameter ROI within the contralateral NAWM. A two-way ANOVA and Bonferroni post-hoc test for multiple comparisons was used to compare relative contrast between the different CBV normalization techniques, while controlling for tumor World Health Organization (WHO) histology/grade.

RESULTS

Leakage-corrected “raw” (nontransformed) CBV maps provided relatively reasonable localization of intratumoral regions with elevated vascularity (Fig. 1b); however, the physical values of CBV were dramatically different upon follow-up (Fig. 1b,g). Standardized and Gaussian normalized CBV maps, qualitatively, provided equal localization of high vascularity regions (Fig. 1c,d) and appeared stable over follow-up times (Fig. 1c,d,h,i). Elevated regions of vascularity were easily isolated as positive Z-score values on Z-score normalized CBV maps (Fig. 1e).

The CV was found to differ significantly between the different CBV normalization techniques (Fig. 2a; paired one-way ANOVA; $P < 0.0001$). Specifically, there was a significantly lower CV in all transformed CBV measurements compared with the raw CBV maps (Tukey’s test; $P < 0.01$ for Raw CBV vs. Standardized CBV, Gaussian Normalized CBV, and Z-Score

Figure 1. Anatomical and perfusion MR images of a patient with recurrent glioblastoma (WHO grade IV). **a:** Postcontrast T1-weighted images. **b:** Raw (untransformed) CBV maps. **c:** Standardized CBV maps. **d:** Gaussian Normalized CBV maps. **e:** Z-score normalized CBV maps.

Normalized CBV). Although not statistically significant, a slightly lower CV was observed in the Gaussian normalized CBV maps compared with both the standardized and Z-score normalized CBV maps (Fig. 2a). When splitting the cases based on whether DSC data was collected on the same scanner or different scanners (Fig. 2b), the results suggested a significant difference between CBV techniques (two-way ANOVA; CBV Technique, $P < 0.0001$); however, MR protocol (same scanner vs. different scanners) and the interaction were not significant factors (two-way ANOVA; MR Protocol, $P = 0.0534$; Interaction, $P = 0.8752$). Multiple comparisons testing suggested similar trends to the pooled CV results, mentioned above, suggesting all transformed CBV measurements had significantly lower CV compared with raw (untransformed) CBV maps when follow-up scans were performed on differ-

ent MR scanners (Bonferroni posttest; $P < 0.01$ for Raw CBV vs. Standardized CBV, Gaussian Normalized CBV, and Z-Score Normalized CBV). Again, Gaussian normalized CBV maps had a slightly lower CV compared to standardized CBV maps, although this difference was not statistically significant (Bonferroni posttest, $P > 0.05$).

Relative contrast between tumor regions and normal white matter tissue, defined as the maximum CBV within the contrast-enhancing tumor divided by the mean CBV within NAWM, was found to be significantly different between CBV techniques (Fig. 3; two-way ANOVA; CBV technique, $P < 0.0001$), tumor histological grade (two-way ANOVA; WHO Grade, $P < 0.0001$), and the interaction between the CBV technique and tumor grade (two-way ANOVA; Interaction, $P = 0.0052$). As expected, relative contrast between

Figure 2. Coefficient of variance (CV) for different CBV techniques and MR protocols. **a:** CV for different CBV techniques. **b:** CV for different CBV techniques, stratified by whether the patients received follow-up scans on the same MR scanner or different MR scanners.

Figure 3. Contrast-to-noise ratio (CNR), measured as tumor hot spot CBV (maximum) divided by mean CBV in NAWM, evaluated for the different CBV intensity normalization techniques and different WHO grades.

tumor and normal tissue increased with increasing WHO grade. Also, a significantly higher relative contrast was observed in Gaussian normalized CBV compared to standardized CBV within WHO grade IV tumors (Bonferroni posttest; $P < 0.05$ for WHO grade IV), suggesting Gaussian normalized CBV provides slightly higher relative tissue contrast compared to standardized CBV in the context of high-grade gliomas.

DISCUSSION

Malignant transformation of gliomas is characterized by an increase in tumor vascularity, or angiogenesis. DSC-MRI estimates of CBV are well-established biomarkers for evaluating glioma vascularity in vivo. Despite promise as an important biomarker, DSC estimates of CBV are only semiquantitative, or relative, measures of tumor blood volume. As such, measurements of tumor and normal tissue CBV can vary quite dramatically across different patients, different scan sessions in the same patient, and different MR scanners and protocols. This limitation effectively inhibits the use of DSC-MRI estimates of CBV in multicenter clinical trials and reduces accurate quantitative assessment of CBV maps clinically. Although all normalization techniques provided improved CBV variability and tumor contrast compared with raw (untransformed) CBV maps, Gaussian normalization of CBV maps had slightly lower coefficient of variance when examined independently of MR scanning protocol, and had slightly lower CV when taking into consideration the MR scanning protocol. Additionally, the results suggest Gaussian normalization of CBV maps provided slightly better relative contrast compared to the other normalization techniques, especially in glioblastoma. It is important to note, however, that a standardized image acquisition protocol is encouraged for use in multicenter clinical trials to further reduce this variability.

Standardization of CBV maps was first proposed by Bedekar et al (8) as a method to translate CBV values into a standard image intensity scale.

Results from these studies demonstrated a lower CV compared with raw (untransformed) CBV values, while accurately maintaining the original image contrast characteristics. Results from the current study had much higher estimates of the CV for standardized CBV values than originally reported by Bedekar et al (8), which is likely due to both the method of obtaining ROIs of NAWM as well as the additional variability caused by follow-up scans on different MR scanners, using slightly different scanning protocols, and potentially differing field strengths in the current study. Further, our results support the observation that standardization of CBV values maintains similar image contrast to the raw CBV maps.

As mentioned by Bedekar et al (8), a potential disadvantage of the standardization technique is the necessity of training the standardization algorithm for each MR protocol and each body part examined. Alternatively, Gaussian normalization (and Z-score normalization) does not require this additional training step and, as our results demonstrate, performs at least as well as standardized CBV maps when evaluating variability across different MR platforms. Additionally, Gaussian normalized CBV values, unlike standardized CBV values, demonstrated an increase in contrast between tumor regions and background normal tissue. It is important to note that our measure of tissue contrast used the maximum CBV within the tumor regions divided by the mean CBV within NAWM, which is in contrast to other studies that examined the mean CBV within tumor regions (14). Taking this into consideration, our measures of relative CBV contrast were comparable to these studies, where mean CBV was as high as 3.5 for some grade II gliomas (14) (max CBV in our study was ≈ 6.5 for grade II gliomas) and mean CBV was as high as 11 in grade IV glioblastomas (14) (max CBV in our study was ≈ 17 for grade IV glioblastomas).

Although not explicitly tested in the current study, we observed very little difference in normalized CBV measurements between 1.5T and 3.0T MR scanners beyond differences in physical image resolution. DSC-MRI at 3.0T typically allows for higher image resolution due to increased signal-to-noise in the raw time series data, as well as higher T2* sensitivity resulting in more signal dropout during first pass of the bolus. Similarly, we observed no real difference in CBV measurements between different contrast agents, regardless of their different T1 and T2 relativities. It is important to note that most patients were given the same contrast agent during follow-up if they were scanned on the same system; however, some patients did receive different contrast agents on different scanners during follow-up. It is important to note that these were qualitative observations and we did not explicitly test for these differences.

Other interesting approaches to overcome the problems associated leakage is to use combined T1 and T2* measurements. For example, Law et al (16) described a novel method of separating the T1 and T2* components of the DSC time series collected

without a preload. This technique was shown to provide a stable measurement of CBV. Alternatively, a dual-echo acquisition of the DSC time series can be used to provide differential sensitivity to T1 and T2* effects (17–19), which has also been shown to provide stability in CBV measurement. Regardless, there is a general consensus that some form of leakage-correction or compensation should be employed for accurate estimation of CBV in patients with brain tumors (13,14).

We purposefully designed our study to explore the effects of using different MR scanners, and scanning protocols, on different CBV transformed values since this is similar to data being acquired from multiple institutions as part of American College of Radiology Imaging Network (ACRIN) efforts to evaluate antiangiogenic agents. Stability of a perfusion biomarker in normal tissue across MR scanning protocols and scanner platforms is important to draw conclusions on drug efficacy. Our results suggest the use of Gaussian normalization of CBV values may be the best choice for intensity normalization in multicenter clinical trials.

Limitations

The primary limitation in the current study was accurate placement of circular ROIs in the same position on different scan dates. Although two investigators verified that placement of these ROIs was similar between the different scan dates, this is likely a significant factor in the calculated CV measurement for all scans. Alternatively, we could have implemented image registration as performed previously (8); however, image registration can be difficult and inaccurate with lower resolution CBV data. Further, collection of an image slab (compared with whole brain coverage) makes image registration difficult.

Another possible confound to the current study was lack of control for the particular treatment paradigms each patient underwent. Although patients did not experience a change in their clinical management, nor a change in their disease status, it is possible that treatment effects could have led to some difference in CBV measurements between follow-up timepoints. Future studies aimed at assessing the effectiveness of normalization procedures on detecting treatment effects are warranted to properly address these limitations.

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