Improved Perfusion MR Imaging Assessment of Intracerebral Tumor Blood Volume and Antiangiogenic Therapy Efficacy in a Rat Model with Ferumoxytol¹

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Purpose:

To evaluate the consistency of tumor blood volume measurements and antiangiogenic therapy efficacy assessments with a low-molecular-weight gadolinium-based contrast agent (GBCA, gadodiamide) versus an iron oxide nanoparticle (ferumoxytol) in the presence or absence of a loading dose of contrast agent before perfusion magnetic resonance (MR) imaging (preload method).

Materials and Methods:

The protocol was approved by the institutional animal care and use committee. U87MG tumor cells were implanted intracerebrally in 13 rats. All 13 rats underwent 11.75-T MR imaging with gadodiamide (60 μ L) 13 days after tumor implantation. The next day, nine rats underwent MR imaging with ferumoxytol (60 μ L). Immediately after ferumoxytol imaging, six rats received bevacizumab (45 mg/kg). MR imaging was repeated 48 hours after bevacizumab treatment with gadodiamide and 72 hours after treatment with ferumoxytol. Each study included three consecutive dynamic susceptibility-weighted contrast material-enhanced (DSC) MR acquisitions, which were performed without preload, with single-dose preload, and with double-dose preload. Tumor relative cerebral blood volume (rCBV) was estimated from each DSC MR acquisition. Two-way repeated measures analysis of variance was performed to test for differences between groups with both contrast agents.

Results:

DSC MR imaging with gadodiamide and without preload showed low rCBV (≤ 1.75) in nine of the 13 tumors; estimated rCBV increased progressively with both single- and double-dose preloads ($P < .001$). Conversely, rCBVs obtained with ferumoxytol were high (> 1.75) and remained constant with all three acquisitions. The magnitude of rCBV decrease after bevacizumab administration was dependent on the dose of gadodiamide preload, whereas the magnitude of rCBV decrease with ferumoxytol was constant regardless of whether contrast agent preload was used.

Conclusion:

With GBCA, tumor rCBV can be underestimated without preload and becomes dose dependent with preload correction. Conversely, ferumoxytol provides consistent assessment of tumor rCBV and antiangiogenic therapy efficacy.

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Angiogenesis as an essential feature of brain tumors has become a target for multiple novel therapies (1,2). Bevacizumab (Avastin; Genetech, South San Francisco, Calif), an antiangiogenic monoclonal antibody that targets vascular endothelial growth factor, has been shown to improve overall survival time in both animal models (3) and clinical studies of recurrent glioblastoma (4,5). Current criteria used in neurooncology to evaluate treatment response are based on conventional T2-weighted and contrast material-enhanced T1-weighted magnetic resonance (MR) imaging sequences and cannot be reliably used after chemo- and radiation therapy or antiangiogenic treatment. An alternative technique is measurement of relative cerebral blood volume (rCBV) with dynamic susceptibility-weighted contrast-enhanced (DSC) perfusion MR imaging. Perfusion MR imaging has shown utility for characterizing histopathologic features and differentiating brain abnormalities (6,7); grading gliomas (8–11); assessing the prognosis of patients with glioma (11–14); predicting early recurrence, progression, or malignant

transformation (15); and differentiating recurrent tumor from chemotherapy- or radiation-induced injury (16–19). DSC MR imaging is gaining use as a noninvasive approach with which to assess tumor angiogenesis and monitor antiangiogenic therapy (20–22).

Any condition that causes disruption of the blood-brain barrier (BBB) and increases vasculature permeability may lead to leakage of low-molecular-weight gadolinium-based contrast agents (GBCAs) with a molecular diameter on the order of 1 nm from the vascular compartment to the interstitial space. Extravasation of GBCA results in interstitial signal intensity changes (T1, T2, and T2* weighted) that confound the intravascular susceptibility-induced signal intensity changes seen during passage of the contrast agent through the vasculature (23) and may lead to underestimation of rCBV, especially in lesions with highly permeable vasculature (17–19).

To improve the diagnostic accuracy of DSC MR imaging, several methods have been proposed for contrast material extravasation correction, including the use of small-flip-angle gradient-echo (6,9,24) or dual-echo (25,26) perfusion acquisitions, postprocessing with multiple mathematic correction algorithms (23,27,28), and the use of blood pool iron oxide contrast agents (19,21,22,29–31). One of the most common contrast material extravasation correction methods is administration of a loading dose of GBCA before perfusion image acquisition. This is referred to as the “pre-load method” (23,27). We hypothesized that blood volume estimation would be more reliable in lesions with a disrupted BBB when a blood pool contrast agent is used to minimize extravasation arti-

facts (19,22,29–31). The inability of the ultrasmall superparamagnetic iron oxide ferumoxytol to cross the disrupted BBB in the short term (minutes to hours) owing to the large size of the iron nanoparticles (~30 nm) and long half-life (~14 hours) provides an attractive alternative to GBCA for blood volume measurements (31).

Ferumoxytol is approved by the U.S. Food and Drug Administration for iron replacement therapy in adults with chronic kidney disease, and its off-label use has shown utility in brain imaging (19,29,31). Because ferumoxytol is not eliminated by the kidneys, it may also serve as a safe alternative to GBCA in patients who are at risk for nephrogenic systemic fibrosis (32).

The goal of this study was to evaluate the consistency of tumor blood volume measurements and antiangiogenic therapy efficacy assessments with a low-molecular-weight GBCA (gadodiamide) versus an iron oxide nanoparticle (ferumoxytol) in the presence or absence of a loading dose of contrast agent before perfusion MR imaging.

Advances in Knowledge

- The results of this rodent study confirm that measurements of brain tumor relative cerebral blood volume (rCBV) obtained with low-molecular-weight gadolinium-based contrast agents (GBCAs) are underestimated owing to extravasation artifacts.
- The administration of a loading dose of GBCA before perfusion MR imaging (known as the “pre-load method”) improves the accuracy of rCBV estimations; however, rCBVs are dependent on the dose of contrast agent used for preload.
- More consistent estimations of rCBV are provided with ferumoxytol iron oxide nanoparticles than with GBCAs regardless of the permeability of the tumor vasculature and whether preload is used.

Implication for Patient Care

- Perfusion MR imaging with ferumoxytol offers the promise of consistent and reliable measurement of tumor blood volume, which may improve the assessment of actively growing tumor as well as the response to antiangiogenic therapy in patients with brain tumors.

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Abbreviations:

BBB = blood-brain barrier
DSC = dynamic susceptibility-weighted contrast material-enhanced
GBCA = gadolinium-based contrast agent
 K^{trans} = volume transfer constant
rCBV = relative cerebral blood volume
ROI = region of interest
 v_e = extravascular-extracellular space volume fraction

Author contributions:

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Figure 1: Study schema. Time course, treatments, MR examinations performed, and number of rats studied at each point are shown. *Ax* = axial, *Cor* = coronal, *d.d.* = double dose, *IV* = intravenous, *s.d.* = single dose, *T1W* = T1-weighted, *T2W* = T2-weighted.

Figure 2

Figure 2: Effect of antiangiogenic therapy on tumor rCBV assessed with gadodiamide (*Gd*) or ferumoxytol (*Fe*). Anatomic contrast-enhanced T1-weighted images (*T1W+CM*) show tumor enhancement with gadodiamide but not with ferumoxytol. Decrease of T2 signal and gadodiamide enhancement after treatment is apparent. Tumor rCBV is variable without preload, with single-dose (*s.d.*) preload, and with double-dose (*d.d.*) preload when gadodiamide is used, whereas rCBVs obtained with ferumoxytol are the same regardless of preload dose. Note that rCBV decreased after bevacizumab treatment for both contrast agents.

15 volumes, rapid administration of a 60- μ L bolus of contrast agent was performed via the tail vein catheter by using a power injector at a rate of 3 mL/min, followed immediately by a 240- μ L saline flush at the same injection rate. DSC data collection continued for another 100 volumes (3 minutes 20 seconds). We performed three consecutive DSC MR acquisitions with $\sim$ 5 minutes between sequential contrast agent administrations. Either 60 μ L of undiluted gadodiamide (Omniscan, GE Healthcare, Waukesha, Wis; 0.12–0.15 mmol/kg) or 60 μ L of 15 mg/mL ferumoxytol (Feraheme, AMAG Pharmaceuticals, Cambridge, Mass; 3.75–4.5 mg/kg) was used as a contrast agent bolus. Each previous contrast agent injection served as a preload for the subsequent perfu-

sion study. Thus, the first DSC MR acquisition had no contrast agent preload, the second DSC MR acquisition had a single-dose preload, and the third DSC MR acquisition had a double-dose preload. After the DSC MR acquisitions, contrast-enhanced T1-weighted images were obtained in both the coronal and axial planes to visualize tumor enhancement.

Two of the 13 rats underwent dynamic contrast-enhanced (DCE) MR imaging with gadodiamide to measure tumor vasculature permeability 12 days after tumor implantation. The parameters for three-section fast gradient-echo DCE MR imaging were as follows: 25/1.4, 20° flip angle, 1.0-mm-thick sections, 4.48 $\times$ 2.24-cm² rectangular field of view, 128 $\times$ 64 matrix, and 1.6-second

temporal resolution. On the next day, the same rats underwent three sequential DSC MR acquisitions with use of gadodiamide to assess tumor rCBV.

Image Processing

All data were acquired and processed by two authors (S.G. and X.L.), who at the time of analysis had 4 and 15 years of experience in this field, respectively. All data obtained at first-pass DSC MR imaging were processed by using Lupe (Lund University Perfusion Evaluation) perfusion image analysis software with a singular value decomposition-based calculation method as described by Ostergaard et al (35), uncorrected for contrast agent leakage. Color-coded rCBV maps were created on a voxel-wise basis. Within the enhancing lesion, a 1-mm²

(4 × 4-pixel) region of interest (ROI) with the highest rCBV on the ferumoxytol perfusion map and the same ROI on the gadodiamide perfusion map were analyzed by using National Institutes of Health ImageJ software. The same ROIs for a given rat applied across all three consecutive DSC MR acquisitions. The rCBV was calculated as the ratio of the blood volume in a tumor ROI to that in a normal-appearing, contralateral brain tissue ROI. Areas depicting major vessels were excluded. An rCBV of more than 1.75 was considered high, and an rCBV of 1.75 or less was considered low. These values have been widely used as threshold values in previous publications and in clinical practice (12,13,19).

In the six rats that received bevacizumab, rCBV values were calculated by using the same ROI before and after treatment. The percentage rCBV change after treatment was captured from each DSC MR acquisition (no preload and single- and double-dose preload) and for both contrast agents.

DCE pharmacokinetic modeling employs the Tofts model (36) with two model parameters, K^{trans} (volume transfer constant) and v_e (extravascular-extracellular space volume fraction). For this, the arterial input function for each animal was derived from selected pixels in the sagittal sinus as previously described (37). The tumor precontrast T1 value was determined from measurements by using the same fast gradient-echo sequence at nine different flip angles ranging from 5° to 75°.

Statistical Analysis

Two-way repeated measures analysis of variance was performed to test for differences between three sequential DSC MR acquisitions performed with each contrast agent before and after treatment as well as to assess differences in treatment response between sequential DSC MR acquisitions for each contrast agent. A Bonferroni posttest correction was applied. The dependency between contrast preload dose and rCBV value was assessed with repeated one-way analysis of variance with posttest for linear trend. The paired *t* test was used

Figure 3

Figure 3: Signal intensity–time curves compare DSC perfusion with (a, c) gadodiamide (*Gd*) and (b, d) ferumoxytol (*Fe*) in (a, b) tumor and (c, d) normal brain. When gadodiamide is used without preload, contrast agent extravasation in the tumor results in an increase in signal intensity above that at baseline (a). With single-dose (*s.d.*) or double-dose (*d.d.*) contrast agent preload, residual T2* effect can be seen as a signal intensity decrease after the first pass of contrast agent bolus. All of the above confound accurate measurement of tumor blood volume. No difference is seen in signal intensity–time curves in the region of brain with intact BBB (c). With ferumoxytol, signal intensity–time curves are the same with and without preload in tumor (b) and normal brain (d), suggesting that there is no extravasation of contrast agent bolus in regions with either disrupted or intact BBB.

to compare rCBV values between contrast agents for paired perfusion studies. Statistical analysis was performed by using software (Prism; GraphPad Software, La Jolla, Calif). $P < .05$ was considered indicative of a statistically significant difference.

Results

Influence of Contrast Agent Preload on rCBV Estimation

Figure 2 shows anatomic MR images and color-coded rCBV maps from a single rat with use of gadodiamide and ferumoxytol before and after bevacizumab treatment. DSC MR acquisitions with use of gadodiamide in highly vascular U87 tumor showed low blood volume (rCBV ≤ 1.75) without contrast agent preload and an apparent increase in rCBV after single- and double-dose gadodiamide

preload. Conversely, the rCBVs obtained with ferumoxytol were high (>1.75) and constant on three consecutive DSC MR acquisitions. The signal intensity–time curves from ROIs in tumor (Fig 3a, 3b) and normal brain (Fig 3c, 3d) demonstrate the differences in contrast agent extravasation between gadodiamide and ferumoxytol. The T1 effect is apparent on the signal intensity–time curve derived from the DSC MR acquisitions with use of gadodiamide obtained without contrast agent preload (Fig 3a) as a post-bolus increase in signal intensity above that at baseline. Following single- and double-dose gadodiamide preloads, a post-bolus signal intensity decrease known as a residual T2* effect became apparent (Fig 3a); this can result in overestimation of the rCBV (23). Conversely, the signal intensity–time curves for each of the three consecutive DSC MR acquisitions with use of ferumoxytol were similar

Figure 4

Figure 4: Bar charts compare tumor rCBV measured with gadodiamide and ferumoxytol before and after antiangiogenic therapy. Data are means and standard errors. Before treatment, 13 rats were evaluated with gadodiamide and nine with ferumoxytol. After treatment, six rats were evaluated with each contrast agent. The difference in rCBV without preload and with single-dose (s.d.) or double-dose (d.d.) preload is significant when gadodiamide was used before and after therapy (***) indicates $P < .001$). When ferumoxytol was used, rCBVs are the same regardless of preload dose. Note that rCBVs decreased after treatment independent of contrast agent.

Figure 5

Figure 5: Treatment response estimated with DSC perfusion imaging with gadodiamide (left) and ferumoxytol (right). With gadodiamide, the percentage decrease in tumor rCBV after antiangiogenic treatment varies among no preload, single-dose (s.d.) preload, and double-dose (d.d.) preload groups in each individual rat ($n = 6$). Conversely, with use of ferumoxytol, treatment response is the same regardless of preload dose.

to each other, not only within the tumor but also in contralateral, normal-appearing parenchyma (Fig 3b, 3d). The mean rCBV ($\pm$ standard deviation) in all 13 rats derived with use of gadodiamide without contrast agent preload was 1.39 ± 0.28 ; nine of the 13 rats (69%) had a low rCBV (mean, 0.83 ± 0.15) and four (31%) had a high rCBV (mean, 2.67 ± 0.28). After single-dose gadodiamide preload, the rCBV became elevated in all 13 rats (mean, 4.82 ± 0.45 ; $P < .001$) and was even higher after the double-dose preload (mean, 6.4 ± 0.49 ; $P < .001$) (Fig 4). With gadodiamide, the rCBV increased 3.5 times after single-dose preload and 4.6 times after double-dose preload compared with no contrast agent preload ($P < .001$). There was a significant monotonic relationship between gadodiamide preload dose and rCBV ($P < .0001$).

In all nine rats imaged with ferumoxytol, the mean rCBVs on three consecu-

tive DSC MR acquisitions were high and values were similar (2.56 ± 0.22 without preload, 2.54 ± 0.23 with single-dose preload, and 2.49 ± 0.24 with double-dose preload; $P > .05$) (Figs 2, 4).

The differences between rCBVs with gadodiamide and ferumoxytol were significant for all three sequential measurements ($P < .05$ without preload, $P < .005$ with single-dose preload, and $P < .0005$ with double-dose preload) (Fig 4).

Monitoring Antiangiogenic Therapy Efficacy

Six rats underwent MR imaging with both contrast agents before and after bevacizumab treatment. At imaging with use of gadodiamide performed 48 hours after bevacizumab administration, the rCBV decreased compared with corresponding pretreatment values in all rats; however, apparent rCBV was highly dependent on the preload contrast agent

dose, with mean values of 0.27 ± 0.05 without preload, 2.88 ± 0.44 with single-dose preload, and 4.03 ± 0.5 with double-dose preload (Figs 2, 4). Differences between rCBVs were significant ($P < .001$), with linear preload dose dependence ($P < .0001$). At imaging with use of ferumoxytol performed 72 hours after bevacizumab treatment, rCBV was diminished relative to pretreatment values in all rats and remained constant ($P > .05$) in three consecutive perfusions (mean, 1.18 ± 0.12 , 1.16 ± 0.1 , and 1.15 ± 0.1 , respectively) (Figs 2, 4).

The differences between rCBVs obtained after treatment with use of gadodiamide and ferumoxytol were significant ($P < .009$) in all three sequential perfusions (Fig 4).

A large percentage decrease in rCBV was seen with gadodiamide after antiangiogenic therapy on all three sequential DSC MR acquisitions (mean, $68.79\% \pm 8.81$ without preload, $42.83\% \pm 9.73$ with single-dose preload, and $43.96\% \pm 5.3$ with double-dose preload), with significant differences between values obtained without preload and with single- or double-dose preload ($P < .001$). However, the magnitude of changes varied unpredictably in three consecutive perfusions in individual rats (Fig 5). Ferumoxytol also revealed a large percentage decrease in rCBV (mean, $45.89\% \pm 6.37$ without preload, $46.08\% \pm 6.64$ with single-dose preload, and $45.01\% \pm 6.7$ with double-dose preload), but the magnitude of decrease was the same at all three consecutive DSC MR acquisitions (Fig 5).

Figure 6

Figure 6: Relationship between accuracy of tumor rCBV obtained with gadodiamide and tumor vasculature permeability. Intracerebral U87 glioma has high signal intensity on T2-weighted MR images (*T2W*) and shows enhancement on gadodiamide-enhanced T1-weighted MR images (*T1W+Gd*). Hematoxylin (*Htx*)-stained histologic slices are also shown. *A*, Tumor with a high permeability coefficient (K^{trans}) and distribution volume (v_e) has low rCBV without preload. There is a large difference between rCBVs with single-dose (*s.d.*) and double-dose (*d.d.*) preload. *B*, Tumor with a lower permeability coefficient (K^{trans}) and distribution volume (v_e) (relative to the tumor in *a*) has high rCBV without preload; the difference between rCBVs obtained with single-dose (*s.d.*) and double-dose (*d.d.*) preload is small.

Influence of Blood–Tumor Barrier Condition on rCBV Estimation

Figure 6 compares three sequential rCBVs obtained with gadodiamide in two tumors with different K^{trans} and v_e parameters. The tumor with the higher K^{trans} (more permeable) and larger v_e (larger extravascular-extracellular space) (Fig 6a) had a low rCBV, whereas the tumor with the lower K^{trans} and smaller v_e had a higher rCBV when there was no contrast agent preload (Fig 6b). Moreover, the relative difference between rCBVs with single- and double-dose preload was smaller in the tumor with the lower K^{trans} and smaller v_e than in the tumor with the higher K^{trans} and larger v_e .

Discussion

We tested the contrast agent preload method, one of the most common extravasation correction techniques, comparing the GBCA gadodiamide versus the ultrasmall superparamagnetic iron oxide ferumoxytol before and after antiangiogenic therapy. We demonstrated

that the rCBV of highly vascularized tumors with a disrupted BBB is significantly underestimated with GBCA without the use of preload and is dose dependent with the preload method. Conversely, ferumoxytol, as a true intravascular agent, provides consistent assessment of tumor rCBV and antiangiogenic therapy efficacy regardless of the permeability of the tumor vasculature and independent of contrast agent preload. As such, the magnitude of antiangiogenic therapy efficacy is better estimated with ferumoxytol rather than GBCA.

The results of this study are in agreement with those of our previous clinical imaging study (19), where five of 11 patients with viable glioblastoma multiforme who underwent DSC MR imaging showed low rCBV (≤ 1.75) with gadoteridol; all 11 patients showed high rCBV (> 1.75) with ferumoxytol. Hu et al (27) had similar results, performing six consecutive perfusion MR image acquisitions with use of GBCA and correlating rCBVs with histopathologic findings in patients with high-grade glioma after

chemoradiotherapy. They showed that rCBV was underestimated in biopsy-verified tumors and dependent on contrast agent preload dose. Our findings provide additional information to that provided by those previous studies because we assessed the preload method before and after antiangiogenic therapy by using standard GBCA in comparison to ferumoxytol.

In addition to blood volume measurements, we characterized brain tumor vasculature permeability and extravascular-extracellular volume modeled from DCE MR imaging to provide further insights into DSC MR imaging with GBCA in two animals. The dose of preload contrast reagent necessary to saturate interstitial T1 varies depending on both K^{trans} and v_e . Because bevacizumab treatment can cause variable effects on both K^{trans} and v_e in each tumor, the dose of preload contrast agent necessary to saturate interstitial T1 will not be the same before and after treatment. We suggest that the difference in K^{trans} and v_e was a major reason for the variability

in apparent tumor treatment response assessment when gadodiamide was used for DSC MR imaging along with the preload method. Conversely, ferumoxytol showed the same magnitude of treatment response regardless of preload status in perfusion MR imaging, suggesting negligible influence of vascular permeability and extravascular-extracellular space on the rCBV measurement when the blood pool agent is used.

There are several potential limitations to this study. First, mathematical contrast agent extravasation correction was not applied during postprocessing. Because it is well known that rCBV is underestimated with GBCA, a number of mathematical algorithms have been proposed to minimize artifacts from contrast agent extravasation. However, these methods require sophisticated postprocessing and suffer from a lack of consistency. These problems were shown by Paulson and Schmainda (23), who compared five different mathematical correction algorithms in the same patients and demonstrated variability in tumor rCBV depending on choice of method of analysis. Perfusion MR imaging provides a measurement of tumor blood volume as a ratio compared with normal-appearing parenchyma rather than as an absolute measurement of tumor vasculature as a percentage of tumor volume. There is no reference standard for conversion of rCBV to actual vascular density. In our study, we compared the blood pool agent ferumoxytol with low-molecular-weight GBCA in tumors with leaky vasculature; future studies might evaluate blood pool high-molecular-weight GBCAs. Second, there are differences in the number of animals per group owing to tumor burden and anesthesia difficulties; however, all groups had a minimum of six rats, which was sufficient for statistical evaluation. The final limitation of the study is that the animal model does not adequately reflect the heterogeneity of human brain tumors; therefore, this study should be repeated in a clinical study.

Practical application: Underestimation of tumor rCBV may lead to incorrect diagnosis and treatment strategy, as in the case of differentiation of tumor pro-

gression from pseudoprogression. The preload method improves the estimation of tumor rCBV when GBCA is used; however, rCBVs are dependent on the dose of contrast agent preload. Our findings suggest that using ferumoxytol for DSC MR imaging provides more consistent rCBV estimation than GBCA regardless of the permeability of the tumor vasculature.

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