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Bidirectional Contrast Agent Leakage Correction of Dynamic Susceptibility Contrast (DSC)-MRI Improves Cerebral Blood Volume Estimation and Survival Prediction in Recurrent Glioblastoma Treated With Bevacizumab

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Purpose: To evaluate a leakage correction algorithm for T_1 and T_2^* artifacts arising from contrast agent extravasation in dynamic susceptibility contrast magnetic resonance imaging (DSC-MRI) that accounts for bidirectional contrast agent flux and compare relative cerebral blood volume (CBV) estimates and overall survival (OS) stratification from this model to those made with the unidirectional and uncorrected models in patients with recurrent glioblastoma (GBM).

Materials and Methods: We determined median rCBV within contrast-enhancing tumor before and after bevacizumab treatment in patients (75 scans on 1.5T, 19 scans on 3.0T) with recurrent GBM without leakage correction and with application of the unidirectional and bidirectional leakage correction algorithms to determine whether rCBV stratifies OS.

Results: Decreased post-bevacizumab rCBV from baseline using the bidirectional leakage correction algorithm significantly correlated with longer OS (Cox, $P = 0.01$), whereas rCBV change using the unidirectional model ($P = 0.43$) or the uncorrected rCBV values ($P = 0.28$) did not. Estimates of rCBV computed with the two leakage correction algorithms differed on average by 14.9%.

Conclusion: Accounting for T_1 and T_2^* leakage contamination in DSC-MRI using a two-compartment, bidirectional rather than unidirectional exchange model might improve post-bevacizumab survival stratification in patients with recurrent GBM.

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Glioblastoma (GBM) is the most common primary malignant brain tumor in adults, with 10,000 new cases arising per year in the United States.¹ Median overall survival is ~12–15 months with surgery and radiochemotherapy.^{2,3} GBMs are among the most angiogenic of

malignant tumors,⁴ with hallmark features including cooption of existing vasculature and induction of new blood vessel growth via vascular endothelial growth factor (VEGF). Currently, bevacizumab, a humanized monoclonal antibody specifically targeting VEGF, is US Food and

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Drug Administration (FDA)-approved for the treatment of recurrent GBM.

Because antiangiogenic therapy may decrease the contrast-enhancing lesion volume on conventional T_1 -weighted postcontrast MRI, despite the absence of cytotoxic effect,^{5,6} there is growing interest in using perfusion magnetic resonance imaging (MRI) to evaluate changes in blood volume as a noninvasive method of assessing the efficacy of anti-VEGF therapies.^{7–9} In particular, relative cerebral blood volume (rCBV), a parameter computed by integrating the dynamic susceptibility contrast (DSC)-MRI relaxivity–time curve following the principles of indicator dilution theory,¹⁰ is the most common MRI-based perfusion measurement used in neurooncology.¹¹ It is generally accepted that rCBV is elevated in tumors and decreases with successful chemoradiation-induced reduction in tumor-area blood vessels.

Since DSC-MRI is based on the indicator dilution theory,^{10,12} the main assumption is that the injected contrast agent remains solely in the intravascular compartment. However, contrast agent extravasates into the extravascular, extracellular space (EES) during dynamic imaging of high-grade gliomas characterized by blood–brain barrier disruption,¹³ causing artifactual T_1 or T_2^* effects that increase and decrease, respectively, the measured relaxivity–time curve, thereby impacting computed rCBV.¹⁴ A popular leakage correction algorithm models unidirectional flux of contrast agent from the intravascular to the EES.^{13,15} It operates by modeling the relaxivity–time curve from the DSC-MRI measurements as the sum of two terms: one derived from the average relaxivity in nonenhancing tissues, where contrast agent does not leak, and the other that models contrast agent flux in a unidirectional manner. However, contrast agent exchange is in principle bidirectional,¹⁶ and a two-compartment bidirectional model could potentially improve the accuracy of rCBV estimates.

In the current study we aimed to determine the impact of accounting for bidirectional contrast agent exchange on rCBV estimates, as compared to unidirectional model-based rCBV estimates, and whether the association between early post-bevacizumab changes in rCBV compared to pretreatment baseline and overall survival (OS) significantly differed using the two models. We hypothesized that changes in posttreatment rCBV using the bidirectional leakage correction algorithm will better stratify GBM patients treated with bevacizumab therapy according to overall survival when compared with the unidirectional model.

Materials and Methods

Patients

All patients provided informed written consent to have their information stored in an Institutional Review Board (IRB)-approved neurooncology database for use in future investigations. Forty-seven sequential recurrent GBM (WHO grade IV) patients treated with bevacizumab who had DSC-MRI and outcome data available

were retrospectively enrolled (35 men; mean age 57 years, range 28–75). Anatomic and DSC-MRI were acquired within 1 month before (4.1 ± 7.0 days; mean $\pm$ standard deviation) and 2 months (28.2 ± 11.0 days) after the start of bevacizumab therapy (10 mg/kg IV every 2 weeks).

MRI

Studies were performed at either 1.5T (Siemens Avanto or Sonata, Erlangen, Germany) or 3T (Siemens Trio, Verio, or Skyra). Precontrast standard anatomical images were acquired, including T_1 -weighted, T_2 -weighted, and fluid-attenuated inversion recovery (FLAIR). For DSC-MRI, a total of 0.1 mmol/kg dose of gadopentate dimeglumine (Gd-DTPA; Magnevist, Bayer Schering Pharma, Leverkusen, Germany) was administered, 0.025 mmol/kg for preload dosage to mitigate T_1 -based leakage contamination¹⁷ and the remaining 0.075 mmol/kg for dynamic bolus administration. A 2-minute gap was placed between the preload dose and the start of baseline imaging of the DSC-MRI. The range of DSC-MRI acquisition parameters included: TE/TR = 23–41/1250–1400 msec, flip angle = 35°, matrix size = 80 $\times$ 96–128 $\times$ 128, slice thickness = 4–6 mm with an interslice gap of 0–1 mm, number of slices = 6–25, number of baseline acquisitions before contrast agent injection = 10–25, and number of timepoints = 40–120. Conventional postcontrast T_1 -weighted images ($T_1 + C$) were subsequently acquired.

Image Analysis

Tumor regions of interest (ROIs) were defined by abnormal hyperintensity on T_1 -weighted postcontrast images using semiautomated segmentation techniques, followed by manual inspection and adjustment of the resulting contour as described previously.¹⁸ All DSC-MRI studies completely covered the spatial extent of contrast-enhancing tumor. DSC-MRI images were motion-corrected on the scanner and processed via in-house custom scripts in MatLab (MathWorks, Natick, MA). All simulations and calculations were performed in MatLab using custom scripts. Uncorrected rCBV was calculated using trapezoidal integration of the original DSC-MRI relaxivity–time curve, $\Delta R_2^*(t)$. The whole-brain average relaxivity, derived from the nonenhancing voxels, was used for both the original unidirectional “Boxerman-Weisskoff” model¹³ (Unidir-model) and the newly proposed bidirectional exchange model (Bidir-model). (Details regarding the Bidir-model are described in the Appendix.) Linear least-squares optimization was used to determine the free parameters for both the Bidir-model and the Unidir-model algorithms. The rCBV maps were manually registered to the corresponding posttreatment $T_1 + C$ images using *tkregister2* (Freesurfer, surfer.nmr.mgh.harvard.edu; Massachusetts General Hospital, Harvard Medical School, Cambridge, MA).

Statistical Analysis

Median rCBV was calculated from segmented tumor at baseline (pretreatment) and 6-week posttreatment timepoints for all patients. All rCBV values were normalized to median rCBV within a circular ROI drawn in the contralateral normal-appearing white matter. Histograms of rCBV were generated via GraphPad Prism 6 (La Jolla, CA) with a bin width of 0.5. We used the absolute value of percentage difference to compare the leakage correction methods because rCBV tends to increase in the presence of T_1 leakage

(between correction methods) and decrease in the presence of T_2^* leakage. The absolute difference between the two techniques was calculated as the absolute value of the difference between the two methods divided by the average of the two methods for each patient and each MRI scan.

A multivariate Cox regression model was used to determine whether pretreatment rCBV, posttreatment rCBV, change in rCBV between pre- and posttreatment timepoints, age at time of diagnosis, tumor volume, Karnofsky Performance Status (KPS), and MR field strength stratified patients according to OS. Nineteen of the 94 total pre- and posttreatment scans were acquired at 3.0T, and the remaining 75 were acquired at 1.5T, with 10 in the pretreatment group, and 9 in the posttreatment group. No significant difference, using an unpaired two-tailed t -test, was found between the rCBV values computed using the 3.0T scanner data and the 1.5T scanner data in either the pretreatment group ($P=0.63$) or the posttreatment group ($P=0.14$). Nevertheless, to guard against potential biases with regard to field strength, the pre- and posttreatment field strength as separate covariates.

Results

As described in the Appendix and as illustrated in Fig. 1, the observed DSC-MRI signal includes both the desired signal-time curve, which reflects the change in magnetic susceptibility caused by the contrast agent bolus, and the artifact caused by contrast agent extravasation. The Unidir-model (dotted blue and red curves in Fig. 1) can only fit T_1 or T_2^* leakage scenarios, where contrast agent extravasates from the intravascular space to the EES without back-flux. By comparison, the Bidir-model can fit relaxivity-time curves with a wider range of behavior. Most notably, the Bidir-model can more accurately model the late postbolus timepoints by accounting for variable rates of contrast agent backflow that can exist within different regions of a tumor and within different tumor types.

Figure 2 highlights the difference in the model fits and resulting relaxivity-time curves between the two different leakage correction algorithms in a sample tumor. The extra parameter used for the Bidir-model allows for a better fit to the raw DSC-MRI data than the Unidir-model with respect to residual errors. Both model fits can then be broken down into their respective T_1 leakage and rCBV curve components. The T_1 leakage from the Unidir-model rises almost linearly over time. On the other hand, the Bidir-model rises faster initially, but corrects the T_1 leakage curve such that the curve eventually slows down, a trend that is more reflective of what is often observed on dynamic contrast enhancing (DCE)-MRI. Whereas in the simulation the different curves arose from the same “true” rCBV curve, in experimental data the differences in leakage correction algorithms result in distinct corrected rCBV curves. Most noticeably, the primary change in rCBV comes from the first-pass curve, the difference arising from the more rapid rise in the bidirectional T_1 -leakage curve. In the T_1 leakage

FIGURE 1: Sample simulation of DSC-MRI relaxivity-time curves. (A) The black curve reflects absence of contrast agent leakage. The blue and red curves include contrast extravasation with dominant T_2^* (overestimation of rCBV) and T_1 (underestimation of rCBV) artifact, respectively, both without (dotted) and with (dashed) inclusion of bidirectional contrast flux. The Unidir-model is limited to fitting the dotted curves (with different magnitudes), whereas the Bidir-model can fit a greater range of all leakage-contaminated curves. The raw leakage-contaminated DSC-MRI curves in (A) are a summation of the “true” relaxivity-time curve (solid black line) and the leakage contamination curves (B).

case, there is a trend of increasing rCBV from the uncorrected version to the Bidir-model.

Figure 3 illustrates a case where the mean tumor rCBV increased following bevacizumab therapy. Individual tumor rCBV values notably increased when employing more accurate leakage correction strategies, exemplified by the progressive rightward shift of the uncorrected, Unidir-model and Bidir-model rCBV histograms. The uncorrected rCBV map contained a high percentage of negative rCBV values within tumor, averaging -0.09 pretreatment and 0.29 posttreatment, highlighting the inaccuracies of uncorrected rCBV estimates. Mean tumor rCBV substantially increased when using the Unidir-model (1.72 pretreatment and 2.33 posttreatment) and increased further when using the Bidir-model (2.24 pretreatment and 2.69 posttreatment).

Next, we evaluated whether a change in rCBV from baseline to 2 months measured using the various leakage correction strategies could stratify the 47 recurrent GBM

FIGURE 2: Leakage correction model comparison in tumor voxel. (A) T_1 -weighted postcontrast image of a sample case of recurrent GBM and selected voxel. (B) Comparison of Bidir-model (red) and Unidir-model (blue) fits to the raw relaxivity-time data. (C) The T_1 leakage contamination curve computed with the Bidir-model is less steep than that observed with the Unidir-model and demonstrates approach towards equilibrium that is not seen on the Unidir-model curve. (D) The Bidir-model and Unidir-model corrected relaxivity-time curves differ notably in the first-pass, and both are substantially different from the raw relaxivity-time data.

patients treated with bevacizumab according to OS. In particular, we tested whether patients with decreased rCBV following bevacizumab ($\Delta rCBV < 0$) had significantly longer OS compared to patients with increased rCBV ($\Delta rCBV > 0$) after accounting for age, KPS, enhancing tumor size, and MRI field strength. Figure 4 demonstrates that both uncorrected $\Delta rCBV$ and Unidir-model $\Delta rCBV$ did not stratify patients according to OS (Cox regression; $P = 0.28$ and 0.43 , respectively) in a statistically significant manner, whereas the Bidir-model $\Delta rCBV$ significantly stratified patients into long and short OS based on the change in rCBV ($P = 0.01$). Median OS for the patients whose rCBV estimated with the Bidir-model decreased following bevacizumab treatment was 358 days, versus 183 days for those with increasing rCBV. Table 1 illustrates detailed results from the Cox proportional hazards model, including effects of age, change in tumor volume, field strength at the pretreatment and posttreatment timepoints, and KPS.

The mean rCBV with the Bidir-model had a $13.9 \pm 10.3\%$ absolute difference from the Unidir-model prior to therapy and a

$16.0 \pm 17.6\%$ absolute difference in rCBV after treatment over all 47 patients. Over all 94 scan sessions, there was a $14.9 \pm 14.4\%$ difference between mean leakage-corrected whole-tumor rCBV computed with the Bidir-model and Unidir-model. Interestingly, when $\Delta rCBV$ was used to characterize “responders” ($\Delta rCBV < 0$) and “nonresponders” ($\Delta rCBV > 0$), 11 of the 47 cases (23%) had different classifications using the two leakage correction algorithms. We then characterize the “responders” and “nonresponders” according to whether they had a survival time less than the median (222 days), “short-term survival,” or greater than the median, “long-term survival.” We considered a “correct classification” to be either a nonresponder with short-term survival or a responder with long-term survival. Among the four “nonresponders” classified by the Bidir-model, three had “short-term survival” (75%), and among the seven “responders,” five had long-term survival (71%). Figure 5 illustrates one case where the bidirectional leakage correction algorithm demonstrated a decrease in rCBV in a long-term survivor, whereas the unidirectional and uncorrected rCBV did not. Posttreatment rCBV based on the uncorrected model more than doubles from pretreatment baseline, with equivalent pre- and

FIGURE 3: (A) Sample rCBV maps for a recurrent GBM, both pre- and post-bevacizumab treatment. Mean pre- and posttreatment tumor rCBV progressively increase when using the uncorrected, Unidir-model and Bidir-model postprocessing strategies. **(B)** There is a progressive rightward shift of the uncorrected, Unidir-model and Bidir-model rCBV histograms, demonstrating that the increase in mean rCBV is due to increased rCBV in the entire population of voxels, not just a few, as expected in a T_1 -leakage scenario.

FIGURE 4: Kaplan-Meier survival plots for $\Delta rCBV$, with patients stratified according to whether rCBV increased or decreased using (A) uncorrected rCBV, (B) Unidir-model rCBV, and (C) Bidir-model rCBV.

TABLE 1.

<i>Variable</i>	<i>Hazard Ratio</i>	<i>Standard Error</i>	<i>p-value</i>	<i>95% C.I.</i>
$\Delta rCBV > 0$ (<i>Uncorrected</i>)	0.64	0.41	0.28	0.29, 1.42
Age at recurrence	1.02	0.02	0.25	0.98, 1.06
Change in tumor volume	1.00	0.01	0.98	0.97, 1.03
Field Strength (Pre-tx)	0.65	0.33	0.19	0.34, 1.24
Field Strength (Post-tx)	1.97	0.57	0.24	0.64, 3.02
KPS	0.99	0.02	0.41	0.95, 1.02
$\Delta rCBV > 0$ (<i>Unidirectional</i>)	1.33	0.36	0.43	0.66, 2.67
Age at recurrence	1.02	0.02	0.28	0.98, 1.06
Change in tumor volume	1.00	0.01	0.79	0.98, 1.03
Field Strength (Pre-tx)	0.68	0.34	0.25	0.35, 1.31
Field Strength (Post-tx)	1.66	0.36	0.16	0.82, 3.34
KPS	0.99	0.02	0.55	0.95, 1.03
$\Delta rCBV > 0$ (<i>Bidirectional</i>)	3.12	0.42	0.01*	1.37, 7.10
Age at recurrence	1.01	0.02	0.65	0.97, 1.05
Change in tumor volume	0.99	0.01	0.64	0.97, 1.02
Field Strength (Pre-tx)	0.67	0.34	0.36	0.35, 1.30
Field Strength (Post-tx)	2.43	0.38	0.02	1.14, 5.18
KPS	0.98	0.02	0.36	0.95, 1.02

posttreatment rCBV using the Unidir-model. However, the Bidir-model yields a substantial decrease from pretreatment to posttreatment rCBV, which is concordant with the long OS in this patient (1149 days). The rightward shifts of the rCBV histograms illustrate that differences in mean tumor rCBV are not merely reflecting a large change for few voxels, but rather a global change over the entire tumor.

Discussion

The results from this study support the hypothesis that DSC-MRI leakage correction accounting for bidirectional contrast agent exchange may yield significantly different estimates of tumor rCBV compared with the standard “Boxerman-Weisskoff” unidirectional model and the uncorrected model. We found that early changes in rCBV estimated using the Bidir-model better stratify bevacizumab-treated recurrent GBM patients according to OS as compared to estimates using the Unidir-model. In accordance with the notion that efficacious therapy works by reducing tumor vascularity, this supports the hypothesis that bidirectional contrast agent exchange using a two-compartment model similar to DCE-MRI more accurately represents contrast agent pharmacokinetics within tumor vasculature.

In this study the direction of change from baseline in rCBV using the Bidir-model stratified patients according to

OS. However, in contrast to recent studies by Schmainda et al¹⁹ and Kickingereder et al,²⁰ using absolute measures of pre- and posttreatment rCBV did not achieve statistical significance. This could potentially be attributed to differences in methodology, as the current study normalized rCBV to the contralateral, normal-appearing white matter. By comparison, Schmainda et al¹⁹ used a standardized rCBV, where the white matter is controlled to be within a certain range of intensities, and Kickingereder et al²⁰ normalized rCBV by the arterial input function using a *k*-means cluster algorithm.

When introduced, the standard Unidir-model significantly improved rCBV estimates compared to those made without leakage correction.¹³ The addition of a preload or incubation dose to Unidir-model postprocessing leakage correction further reduced T_1 -leakage effects by increasing EES contrast agent concentration prior to dynamic bolus injection, yielding greater improvement in rCBV measurements obtained without leakage correction.^{14,21} However, the lack of a contrast agent backflow term may lead to an incomplete elimination of the T_1 or T_2^* leakage artifact, especially in the presence of a preload because the total contrast agent concentration in the EES is no longer negligible (which ensures the concentration gradient is purely unidirectional), even with short DSC-MRI acquisition times. This is likely a factor contributing to the observed 14.9% difference in

FIGURE 5: (A) Comparison of rCBV maps of recurrent GBM based on uncorrected, Unidir-model, and Bidir-model methodologies in a patient with long-term survival (1149 days). Whereas the Bidir-model demonstrates a substantial decrease in rCBV posttreatment, in accordance with favorable OS, the uncorrected and Unidir-model estimates of increasing or stable rCBV misclassify the patient as having poor prognosis. **(B)** rCBV histograms demonstrate a rightward shift of the Uncorrected and Unidir-model in the post-treatment setting as compared to the pre-treatment setting, whereas the Bidir-model had a leftward shift, demonstrating global rCBV changes in opposite directions after treatment rather than in just a few voxels.

rCBV between the different leakage correction algorithms, since we used a preload in the current study. It is important to note that this magnitude of difference in rCBV between the Bidir-model and Unidir-model may be clinically meaningful and could potentially impact clinical decision-making.

This study has certain notable limitations. First, the DSC-MRI protocols had variable TEs and TRs, with a varying number of slices, slice thicknesses, and field strengths. Although this permitted generalization of our results across a variety of acquisition schemes and MRI platforms, it is unclear whether the same magnitude of differences between the leakage correction algorithms would be maintained in a trial with a single standardized acquisition protocol. Additionally, the time between the MR scans and treatments

varied slightly between patients, which may have reduced our ability to assess treatment response. In a clinical trial, these would ideally be more standardized throughout the patient cohort. Given the relatively small sample size and retrospective nature, which includes biases inherent to such retrospective studies, this investigation was exploratory and larger studies are needed to evaluate the potential impact of the leakage correction algorithms on clinical decision-making. Furthermore, a scanning protocol might be useful to develop in order to provide a more standardized approach for DSC-MRI, even for clinical use in the future.

Furthermore, this study assumes the use of a gadolinium-based contrast agent, which often leaks into the extravascular space when vascular permeability is disrupted.

Currently, pure intravascular contrast agents, such as ferumoxytol, are not approved for central nervous system (CNS) imaging, although it is approved for MR angiography. The main advantage of using intravascular contrast agents for perfusion imaging is the lack of extravasation into the extravascular space, eliminating the need for leakage correction algorithms or preload injection.²² On the other hand, because it is a blood pool agent, the enhancement pattern of biological tissues may differ as compared with gadolinium-based contrast agents, with the possibility of susceptibility artifacts arising.²³ Furthermore, there is potentially a requirement of 2 consecutive days of imaging to obtain relatively intracellular-weighted or interstitial-weighted images, the scans that would be more analogous to the gadolinium-based anatomical scans.²⁴

The use of a bidirectional leakage correction model changed the estimated rCBV values significantly compared to both the standard unidirectional leakage correction model and rCBV measured without leakage correction, despite relatively short DSC-MRI acquisition times. The change from pretreatment baseline in rCBV estimated using the Bidir-model 2 months after bevacizumab therapy in recurrent GBM stratified patients according OS, whereas uncorrected and standard Unidir-model estimates of change in rCBV did not.

Appendix

Following eq. A6 of Boxerman et al.,¹³ the leakage-contaminated DSC-MRI relaxation rate-time curve, $\Delta\hat{R}_2^*(t)$ equals intravascular contrast-driven transverse relaxation rate change, $\Delta R_2^*(t)$, plus $\Delta R_{2,E}^*(t)$, a tissue leakage term describing the simultaneous T_1 and T_2^* relaxation effects resulting from gadolinium extravasation:

$$\Delta\hat{R}_2^*(t) = \Delta R_2^*(t) + \Delta R_{2,E}^*(t) = \Delta R_2^*(t) + \left[r_{2,E}^* - \frac{TR}{TE} \cdot \left(\frac{E_1}{1-E_1} \right) \cdot r_1 \right] C_E(t) \quad (1)$$

where $E_1 = e^{-TR/T_{1o}}$, T_{1o} is the precontrast tissue T_1 , r_1 is the T_1 relaxivity of gadolinium, $C_E(t)$ is the concentration of gadolinium in the extravascular, extracellular space, and $r_{2,E}^*$ represents the T_2^* relaxation effects of gadolinium extravasation, as described by Quarles et al.²⁵ and Schmiedeskamp et al.²⁶ From the original Tofts model describing bidirectional contrast agent flux between the intravascular and extravascular compartments¹⁶:

$$C_E(t) = k_{trans} \cdot \left(C_p(t) * e^{-k_{ep}t} \right) \quad (2)$$

where k_{trans} and k_{ep} are the transfer coefficients for intra- to extravascular and extra- to intravascular contrast flux, respectively, and $C_p(t)$ is the plasma contrast concentration. $C_p(t)$ and $\Delta R_2^*(t)$ can be defined as scaled versions of the whole-brain average relaxation rate in nonenhancing voxels, $\Delta\bar{R}_2^*(t)$ ¹³:

$$C_p(t) = k \cdot \Delta\bar{R}_2^*(t) \quad (3)$$

$$\Delta R_2^*(t) = K_1 \cdot \Delta\bar{R}_2^*(t) \quad (4)$$

Combining Eqs. (1)–4 yields:

$$\Delta\hat{R}_2^*(t) = K_1 \cdot \Delta\bar{R}_2^*(t) - K_2 \int_0^t \Delta\bar{R}_2^*(\tau) \cdot e^{-k_{ep}(t-\tau)} d\tau \quad (5)$$

where

$$K_2 = \left[r_{2,E}^* - \frac{TR}{TE} \cdot \left(\frac{E_1}{1-E_1} \right) \cdot r_1 \right] \cdot k_{trans} \cdot k \quad (6)$$

K_1 , K_2 , and k_{ep} (units of sec^{-1}) are the free parameters of Eq. (5). In general, K_1 depends on CBV, vessel size, and other physiologic factors, while K_2 is related to vascular permeability. Substituting $k_{ep} = 0$, which occurs with no backflow of extravasated contrast agent, yields the original Weisskoff-Boxerman leakage correction algorithm, where K_1 and K_2 are solved by linear least-squares fit to $\Delta\hat{R}_2^*(t)$.¹³ For the Bidir-model correction method, a linear least-squares fit to K_1 , K_2 , and k_{ep} can be employed using the methodology of Murase,²⁷ as described by the following equation:

$$\Delta\hat{R}_2^*(t) = (K_2 + k_{ep} \cdot K_1) \int_0^{t_k} \Delta\hat{R}_2^*(\tau) d\tau - k_{ep} \cdot \int_0^{t_k} \Delta\hat{R}_2^*(\tau) d\tau + K_1 \cdot \Delta\hat{R}_2^*(t) \quad (7)$$

Integrating the corrected relaxation rate-time curve yields leakage-corrected rCBV:

$$rCBV_{corr} = rCBV + K_2 \int_0^T \int_0^t \Delta\hat{R}_2^*(\tau) \cdot e^{-k_{ep}(t-\tau)} d\tau dt \quad (8)$$

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