Brain tumors are characterized by abnormal, poorly constructed vasculature that is often permeable, making them identifiable on contrast-enhanced MR images. With dynamic contrast-enhanced (DCE)–MR imaging methods, contrast agent (CA) wash-in and extravasation alter the tissue T1 relaxation time, and kinetic analysis of the associated signal change permits the computation of the CA volume transfer constant (Ktrans), which reflects vascular permeability and perfusion. In dynamic susceptibility contrast MR imaging studies, CA flowing through blood vessels decreases tissue T2', and the acquired signal changes can be used to estimate tumor blood volume. However, CA extravasation has been shown to confound measurements of tissue perfusion (eg, underestimation of blood volume), particularly in high-grade brain tumors. When corrected for CA leakage effects, DSC–MR imaging measures of blood volume correlate with brain tumor grade and may be useful for monitoring treatment response.

CA extravasation leads to simultaneous and competing T1 and T2* leakage effects and TE dependency on these parameters. These effects, DSC–MR imaging measures of blood volume correlate with brain tumor grade and may be useful for monitoring treatment response.

On the Use of DSC-MRI for Measuring Vascular Permeability

J.T. Skinner, P.L. Moots, G.D. Ayers, and C.C. Quarles

ABSTRACT

BACKGROUND AND PURPOSE: Contrast agent extravasation has been shown to confound brain tumor perfusion measurements with DSC–MR imaging, necessitating the use of correction techniques (eg, Weisskoff, Bjornerud). Leakage parameters (Ktrans and Kep) postulated to reflect vessel permeability can be extracted from these correction methods; however, the biophysical interpretation of these parameters and their relationship to commonly used MR imaging measures of vascular permeability (eg, contrast agent volume transfer constant, Ktrans) remain unclear. Given that vascular density, as assessed by blood volume, and vascular permeability, as reflected by Ktrans (and potentially Kep), report on unique and clinically informative vascular characteristics, there is a compelling interest to simultaneously assess these features.

MATERIALS AND METHODS: We acquired multiecho DSC–MR imaging data, allowing the simultaneous computation and voxelwise comparison of single- and dual-echo derived measures of Ktrans, Kep, and Ktrans in patients with glioma. This acquisition enabled the investigation of competing T1 and T2* leakage effects and TE dependency on these parameters.

RESULTS: Ktrans and Kep displayed nonsignificant (P = .150 and P = .060, respectively) voxelwise linear correlations with Ktrans, while a significant (P < .001) inverse relationship was observed between Ktrans and Kep (coefficient of determination [r^2] = 0.466–0.984). Significantly different (P < .005) mean estimates were found between voxels exhibiting predominately T1 and T2* effects for Ktrans and Kep, Ktrans, however, was observed to be similar between these voxels (0.109 versus 0.092 minutes^-1). Significant differences (P < .001) in extracellular-extravascular volume fraction (V_e) (0.285 versus 0.167) were also observed between cohorts. Additionally, Ktrans and Kep were found to have a significant quadratic relationship (P = .031 and P = .005, respectively) with V_e.

CONCLUSIONS: Estimates of vascular permeability in brain tumors may be simultaneously acquired from multiple-echo DSC–MR imaging via Ktrans; however, caution should be used in assuming a similar relationship for Kep and Ktrans.

ABBREVIATIONS: CA = contrast agent; DCE = dynamic contrast-enhanced; Gd = gadolinium; Kapp = apparent transfer constant; Ktrans = leakage parameter; Ktrans = volume transfer constant; R1 = longitudinal relaxation rate; R2 = transverse relaxation rate; V_e = extracellular extravascular volume fraction; R2* = effective transverse relaxation rate
T2\textsuperscript{\textdagger} effects that can substantially alter the temporal dynamics of DSC–MR imaging signals\(^\text{6-8}\) and necessitate the use of correction techniques. One such technique, developed by Weisskoff et al\(^\text{7}\) and Boxerman et al\(^\text{9}\) incorporates knowledge of the average signal time course across the brain in nonenhancing voxels to model and correct time courses in tumor voxels. As a result, a leakage parameter termed “\(K_2\text{trans}\)” can be extracted and reflects the degree of CA extravasation. Although initially developed to correct T1 leakage effects, the Weisskoff method has been adapted to also account for T2\textsuperscript{\textdagger} leakage effects.\(^\text{6,7}\) A known limitation of this method, however, is that it assumes that the mean transit times of both healthy and diseased tissue are equal; this has been observed to not be true in gliomas.\(^\text{9}\) To address this issue, Bjørnerud et al\(^\text{10}\) recently developed an MTT-insensitive approach for correcting both T1 and T2\textsuperscript{\textdagger} leakage effects on DSC–MR imaging signals.\(^\text{11}\) In this method, the tissue residue function, which describes the CA passage through a voxel, is separated into an intravascular and an extravascular component, from which an apparent transfer constant “\(K_2\text{trans}\)” (similar to \(K_2\)) can be estimated. A third technique aims to remove T1-based CA leakage effects through the use of multiple gradient-echo acquisitions.\(^\text{12-14}\) A feature of this approach is that dynamic T1-weighted information can be separated and quantified.\(^\text{15-17}\) Traditional pharmacokinetic modeling\(^\text{18,19}\) can then be applied to these data to extract a measure of \(K_2\text{trans}\) in a manner similar to that in DCE–MR imaging. This approach has been validated in animal brain tumor models and has been recently applied in patients with high-grade gliomas.\(^\text{16,17,20}\) For one to collect both DCE–MR imaging and DSC–MR imaging datasets, an alternative strategy is to acquire traditional DCE–MR imaging data during a preload injection of contrast agent, which is a technique also commonly used to reduce T1 leakage effects in single-echo-based DSC–MR imaging data.\(^\text{21-23}\)

In the case of brain tumors, \(K_2\text{trans}\) is largely considered to reflect vascular permeability\(^\text{19}\) and has demonstrated promise in tumor grading\(^\text{21,22}\) and identifying disease progression and treatment response.\(^\text{23-26}\) It has been postulated that measures of \(K_2\) and \(K_0\) may also directly report on vascular permeability; however, their relationship with imaging biomarkers such as \(K_2\text{trans}\) is not entirely clear and may be dependent on CA kinetics, tissue microstructure, and imaging parameters. Preliminary studies have also investigated the use of \(K_2\) and \(K_0\) for assessing tumor type,\(^\text{27}\) grade,\(^\text{28,29}\) and treatment response.\(^\text{11}\)

Inherent to the aforementioned DSC–MR imaging correction techniques, estimates of \(K_2\) and \(K_0\) may assume positive or negative values depending on whether T1 (\(+K_0,+K_2\)) or T2\textsuperscript{\textdagger} (\(-K_0,-K_2\)) leakage effects are the dominating source of signal error. Unlike \(K_2\) and \(K_0\), estimates of \(K_2\text{trans}\) assume the use of a “purely” T1-weighted signal and, therefore, presume insensitivity to competing T1 and T2\textsuperscript{\textdagger} leakage effects. In this regard, a previous simulation study reported a non-linear relationship between \(K_0\) and \(K_2\text{trans}\) when large flip angles (\(>70^\circ\)) were used.\(^\text{15}\) In a follow-up in vivo study,\(^\text{11}\) a positive quadratic relationship between \(K_2\) and \(K_2\text{trans}\) was observed. A more recent study found a positive linear correlation between \(K_2\) and \(K_2\text{trans}\) when comparing maximum whole-tumor values across patients.\(^\text{30}\) These studies, however, were limited to ROI-based estimates and measures of \(K_2\text{trans}\) acquired from separate DCE–MR imaging acquisition and did not take into consideration the dominating CA leakage effect.

As suggested by previous works, the presence of simultaneous T1 and T2\textsuperscript{\textdagger} leakage effects within a tumor may influence the magnitude and interpretation of \(K_2\) and \(K_0\). The overarching goal of this study, therefore, was to investigate the contribution of both T1 and T2\textsuperscript{\textdagger} effects on \(K_2\) and \(K_0\), while evaluating these parameters as imaging biomarkers of vascular permeability in brain tumors. This goal was achieved through voxelwise comparisons of DSC–MR imaging–derived measures of \(K_2\), \(K_0\), and \(K_2\text{trans}\) using the previously described methods. The multiecho nature of this study allowed simultaneous measurement of these parameters from the same dataset, permitting a more accurate comparison free of registration errors and/or sequence-specific differences. In addition, the multiecho data allowed further exploration of potential TE dependencies of both Weisskoff and Bjørnerud correction techniques.

### MATERIALS AND METHODS

MR imaging data were acquired in patients with high-grade gliomas (\(n = 7\), Table 1) under Vanderbilt University Institutional Review Board guidelines at 3T (Achieva; Philips Healthcare, Best, the Netherlands) using a 32-channel head coil. Multiple flip angle data (\(TR = 7.6\) ms, \(TE = 4.6\) ms, flip angle = \(20^\circ\)-\(20^\circ\), in 2° increments) were acquired to compute precontrast longitudinal relaxation rate (\(R_{10}\)) maps. Dual-echo DSC–MR imaging data were then acquired by using either a dual gradient-echo EPI or spin- and gradient-echo EPI protocol\(^\text{17,31}\) with the following parameters: \(TR = 1.5\) seconds (dual gradient-echo) or 1.8 seconds (spin- and gradient-echo), \(TE_1/TE_2 = 7.0/31.0\) ms (dual gradient-echo) or 8.3/25 ms (spin- and gradient-echo), sensitivity encoding = 2, \(FOV = 240 \times 240\) mm\(^2\), reconstructed voxel size = \(2.5 \times 2.5 \times 5.0\) mm\(^3\), and sections = 15. For spin- and gradient-echo data, only the first 2 echoes were used in the analysis. Measurements were made before, during, and after administration of Gd-DTPA (0.1 mmol/kg, 4-mL/s infusion rate followed by a 20-mL saline flush). The scan duration was 7.5 minutes, including 80 seconds of prebolus baseline data. A high-resolution T1-weighted dataset was collected following the DSC–MR imaging experiment. Dynamic estimates of \(\Delta R_2\) were computed for each echo (\(\Delta R_{2,TE1}\) and \(\Delta R_{2,TE2}\)) and for the dual-echo data (\(\Delta R_{2,DE}\)) as previously described.\(^\text{12,13}\)
allows the extraction of $K_2$ from Equation 1,

$$\Delta \bar{R}_2(t) = K_2 \times \Delta \bar{R}_2(t) \times \int_{0}^{t} \Delta \bar{R}_2(t') dt'$$

where $\Delta \bar{R}_2$ is the average $\Delta R_2^*$ from a mask of nonenhancing brain voxels and $\Delta \bar{R}_2^*$ is the leakage affected estimate of $\Delta R_2^*$. A voxelwise least squares fit to Equation 1 was performed to extract $K_2$ by using 80 seconds of prebolus baseline data and 70 seconds of postbolus data (2.5 minutes total), consistent with previous reports.\textsuperscript{2,3,29}

$K_2$ Computation

In the presence of CA extravasation, the tissue concentration time course, $C_t(t)$, can be represented as

$$C_t(t) = \int_{0}^{t} R(t) \times C_p(t - \tau) d\tau + K_2 \int_{T_c}^{t} C_p(t - \tau) \times \exp(-K_a(t - T_c)/v_e) d\tau,$$

where $f$ is proportional to tissue blood flow, $R(t)$ is defined as the tissue-specific residue function, $T_c$ is the capillary transit time of the CA, $v_e$ is the extracellular extravascular volume fraction ($v_e$), and $C_p$ is the CA concentration in plasma (computed from an arterial input function extracted from the dual-echo data by using an automated selection process\textsuperscript{32,33}). In DSC–MR imaging, $C_p(t)$ is estimated in relative terms through measurements of $\Delta R_2^*$, where $\Delta R_2^* \times C_t(t)$ and $\Delta R_2^*$ is the effective transverse relaxation. Circular deconvolution of Equation 2 with the arterial input function (during the same time course used in the Weisskoff correction) results in a composite residue function $H(t)$ described by an early vascular phase ($0 \leq t < T_c$) and an extravasation phase ($t \geq T_c$):\textsuperscript{10}

$$H(t) = f \times R(t) \times \exp(-K_a(t - T_c)/v_e) \quad 0 \leq t < T_c,$$

$$H(t) = K_a \times \exp(-K_a(t - T_c)/v_e) \quad t \geq T_c.$$  

In the context of a single-echo DSC–MR imaging acquisition, $H(t) \approx K_a$ for $t \gg T_c$. In this study, $K_a$ was estimated as the mean value from $H(t = T_c)$, where $T_c$ is equal to 1.5 $\times$ the mean transit time, to $H(t = 60$ seconds).

$K_2$ Computation

The method proposed by Weisskoff et al\textsuperscript{7} allows the extraction of $K_2$ from Equation 1,

$$\Delta \bar{R}_2(t) = K_2 \times \Delta \bar{R}_2(t) - K_2 \int_{0}^{t} \Delta \bar{R}_2(t') dt',$$

where $\Delta \bar{R}_2$ is the average $\Delta R_2^*$ from a mask of nonenhancing brain voxels and $\Delta \bar{R}_2^*$ is the leakage affected estimate of $\Delta R_2^*$. A voxelwise least squares fit to Equation 1 was performed to extract $K_2$ by using 80 seconds of prebolus baseline data and 70 seconds of postbolus data (2.5 minutes total), consistent with previous reports.\textsuperscript{2,3,29}

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where $f$ is proportional to tissue blood flow, $R(t)$ is defined as the tissue-specific residue function, $T_c$ is the capillary transit time of the CA, $v_e$ is the extracellular extravascular volume fraction ($v_e$), and $C_p$ is the CA concentration in plasma (computed from an arterial input function extracted from the dual-echo data by using an automated selection process\textsuperscript{32,33}). In DSC–MR imaging, $C_p(t)$ is estimated in relative terms through measurements of $\Delta R_2^*$, where $\Delta R_2^* \times C_t(t)$ and $\Delta R_2^*$ is the effective transverse relaxation. Circular deconvolution of Equation 2 with the arterial input function (during the same time course used in the Weisskoff correction) results in a composite residue function $H(t)$ described by an early vascular phase ($0 \leq t < T_c$) and an extravasation phase ($t \geq T_c$):\textsuperscript{10}

$$H(t) = f \times R(t) \times \exp(-K_a(t - T_c)/v_e) \quad 0 \leq t < T_c,$$

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In the context of a single-echo DSC–MR imaging acquisition, $H(t) \approx K_a$ for $t \gg T_c$. In this study, $K_a$ was estimated as the mean value from $H(t = T_c)$, where $T_c$ is equal to 1.5 $\times$ the mean transit time, to $H(t = 60$ seconds).

$K_{\text{trans}}$ Computation

To compute an estimate of $K_{\text{trans}}$ from multiecho DSC–MR imaging data, a T1-weighted signal time course $[S_{T_1W}(t)]$ was first extracted from dual-echo data via Equation 4.\textsuperscript{15,16,38}

$$S_{T_1W}(t) = S_{T_1}(t) \times e^{(\frac{S_{T_1W}(t) - S_{T_1}(t)}{T_1}) \times (\frac{T_1}{T_2 - T_1})},$$

A $R_{1\beta}$ map was combined with the $S_{T_1W}(t)$ data to produce dynamic longitudinal relaxation rate time courses $[R_{1\beta}(t)]$ for each voxel.\textsuperscript{36,37} $K_{\text{trans}}$ and $v_e$ were estimated by fitting $R_{1\beta}(t)$ and $C_p(t)$ (arterial input function) with the standard Tofts model.\textsuperscript{18,19}

Voxel Selection

Voxels selected for this analysis were obtained from enhancing regions on the postgadolinium (Gd) T1-weighted images, determined using a 50% signal threshold (based on the maximum signal intensity in tumor-containing sections) over a manually drawn tumor ROI. These voxels were further categorized by the predominant leakage effect (T1 or T2) exhibited in their dynamic $\Delta R_2^*$ time course. In this study, “T2” voxels were defined by a positive mean $\Delta R_2^*$ during the last 20 seconds of the time course used for computation of $K_a$ and $K_2$. “T1 voxels” were defined as those in which this estimate was negative.

Statistical Analysis

Voxelwise measures of $K_2$ and $K_a$ were compared with $K_{\text{trans}}$ and $v_e$ to examine the relationship between these parameters. Associations between the aforementioned parameters were first analyzed on an individual basis by using simple linear regression and reported using the $r^2$ statistic (coefficient of determination). Unless otherwise noted, group voxelwise comparisons were conducted using analysis of covariance in a generalized linear model for repeated measures. Generalized estimating equations were used with an exchangeable covariance structure to model the correlation among voxels across patients.

RESULTS

Figure 1A shows a representative uncorrected tumor $\Delta R_2^*$ time course for each TE and the dual-echo signal, along with the associated Weisskoff model fit. Figure 1B shows the corresponding tissue residue functions used to compute $K_a$ from the same patient. The computed $K_{\text{trans}}$, $K_a$, and $K_2$ maps (overlaid on post-Gd T1-weighted images) for this patient (at TE2) can be seen in Figure 2B–D, respectively, along with the corresponding post-Gd T1-weighted image (Fig 2A). Figure 3A–B shows a sample voxelwise comparison of $K_2$ and $K_a$ (computed at TE2) with the parameter $K_{\text{trans}}$. The range of correlations at TE2 were $r^2 = 0.014–0.430$ for $K_2$ and $r^2 = 0.0001–0.403$ for $K_a$. Across patients, both $K_2$ and $K_a$ were found to have nonsignificant ($P = .150$ and $P = .060$, respectively) linear correlations with $K_{\text{trans}}$. A significant ($P < .001$) inverse relationship was observed (Fig 3C), however, between $K_2$.
and $K_a$ ($r^2 = 0.466–0.984$). To help elucidate these observed relationships, further analysis was performed.

With the availability of multiecho data, the effect of TE on $K_2$ and $K_a$ was investigated. Figure 4 shows boxplots using the median values of $K_2$ and $K_a$ across all patients. A statistically significant difference (Mann-Whitney $U$ test) was observed between $K_2$ at TE1 and TE2 ($P < .001$), $K_2$ at TE1 and dual-echo ($P < .001$), and $K_2$ at TE2 and dual-echo ($P < .01$) acquisitions. Similar differences were observed for $K_a$. For TE1, voxelwise estimates of $K_2$ were observed to be predominately positive for high-grade gliomas, whereas $K_a$ was predominately negative. A decrease in TE1 resulted in a broader voxelwise distribution of values across patients, with estimates of $K_2$ becoming increasingly positive and $K_a$ becoming increasingly negative. The computation of $K_2$ using the $\Delta R_2,DE$ time course resulted in a negative shift in the distribution of values, with an increase in the number of voxels near $K_2 = 0$. A similar shift in the distribution toward positive values was observed for $K_a$.

Figure 5 shows the contribution of both T1 and T2* leakage effects on the relaxation rate time courses. Figure 5A shows the mean $\Delta R_2,t$ time course (TE1) for a tumor ROI from patient 2. The resulting $\Delta R_2,t$ time course from the same tumor can be seen in Fig 5B. Although the $\Delta R_2,t$ time course appears to show no appreciable signs of CA leakage, the $\Delta R_1,t$ time course exhibits large changes in $R_1$ with bolus passage. This indicates CA extravasation and results in a moderate estimate of $K_\text{trans}$. Similarly, focusing on the smallest 10% of all voxels (based on the magnitude of $K_a$) in a given patient results in $K_a = -0.043 \pm 0.050$ minutes$^{-1}$, $K_2 = 0.113 \pm 0.553$ minutes$^{-1}$, and $K_\text{trans} = 0.060 \pm 0.099$ minutes$^{-1}$ (weighted mean $\pm$ pooled standard deviation). Figure 5C-D shows mean $\Delta R_2,t$ and $\Delta R_1,t$ time courses from the same tumor with voxels separated by predominate T1 or T2* leakage effects. Note that in Fig 5C-D, voxels from the same tumor exhibited positive and negative values of $K_2$ and $K_a$, while $K_\text{trans}$ was observed to be almost identical between the 2 cohorts.

Table 2 displays the mean estimates of $K_2$, $K_a$, and $K_\text{trans}$ (separated by T1 and T2* voxels) across all patients. On average, 63% of voxels in the high-grade gliomas were found to predominately exhibit T1 leakage effects. In addition, a significant difference ($P < .005$, paired $t$ test) was observed across patients between mean estimates from T1 and T2* voxel cohorts for both $K_2$ and $K_a$. While the difference between T1 and T2* cohorts for $K_\text{trans}$ trended toward significance ($P = .05$), the weighted mean for each cohort across patients was similar ($0.109$ minutes$^{-1}$ versus $0.092$ minutes$^{-1}$). In all voxels across patients, we observed $v = 0.241 \pm 0.207$. When separated by leakage effect, a significant difference ($P < .001$, paired $t$ test) in mean estimates of $v$ was also observed. Additionally, both $K_2$ and $K_a$ were found

*Fig 2. A, T1-weighted post-Gd anatomic image showing a high-grade brain tumor. Sample computed permeability maps (units in minute$^{-1}$), $K_\text{trans}$ (B), $K_2$ (C), and $K_a$ (D).

*Fig 3. A, Sample voxelwise comparison between $K_2$ at TE2 and $K_\text{trans}$. B, Sample voxelwise comparison between $K_a$ at TE2 and $K_\text{trans}$. C, Voxelwise comparison between $K_2$ (y-axis) and $K_a$ (x-axis). Linear regression line shown in black.
to have a significant quadratic relationship \((P = .031\) and \(P = .005\), respectively) with \(v_e\).

**DISCUSSION**

DCE–MR imaging estimates of vascular permeability, often reported via \(K^{\text{trans}}\), have been shown to be helpful in deciphering brain tumor grade\(^{23}\) and in predicting disease prognosis.\(^{25,38}\) Unlike DCE–MR imaging, DSC–MR imaging acquisitions can actually be confounded by the increased vascular permeability present in brain tumors, requiring strategies for leakage correction of the MR imaging signal time courses. Rate constants \((K_2\) and \(K_a)\) computed from these correction techniques have been suggested to reflect vessel permeability.\(^{27,28}\) To evaluate this relationship, we performed a simultaneous comparison between \(K^{\text{trans}}\) and the parameters \(K_2\) and \(K_a\) using multiecho DSC–MR imaging. In general, the range of \(K_2\) and \(K_a\) estimates in this study was observed to be larger than that of \(K^{\text{trans}}\), though they were consistent with previous measures in brain tumors.\(^{8,10,28}\) Voxelwise linear relationships between \(K_2\) and \(K_a\) and the parameter \(K^{\text{trans}}\) were found to be non-significant when computed from the same dataset. Although a nonlinear relationship between \(K_a\) and \(K^{\text{trans}}\) was previously presented in simulations,\(^{10}\) this work provides additional in vivo confirmation. The individual correlations observed here between \(K_2\) and \(K^{\text{trans}}\) in gliomas were similar to those observed by Bonekamp et al\(^{10}\) using maximum \(K^{\text{trans}}\) and \(K_a\) values from whole-tumor ROIs. Although the lack of a strong linear correlation with \(K^{\text{trans}}\) suggests potential limitations with extracting permeability estimates from DSC–MR imaging correction methods themselves, it should not, however, be interpreted as a failure of these techniques to reliably correct CBV measures for CA leakage.

The effect of TE on \(K_2\) and \(K_a\) was also studied. From Fig 4, we observed a significant increase (decrease) in estimates of \(K_2\) (\(K_a\) with a shorter TE. This is due, in part, to the decrease in \(T_2^*\) weighting with decreasing TE and subsequent dominance of \(T_1\) leakage effects. Liu et al\(^{38}\) previously explored the effect of TE on \(K_2\) in numeric simula-

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**FIG 4.** Boxplots of median parameter estimates (from all patients) calculated at various TEs for \(K_a\) (A) and \(K_2\) (B). Boxplots display the median, 25th, and 75th percentiles (edges of box) and extreme data points (whiskers). Outliers are plotted individually (plus sign). Significance was determined by the Mann-Whitney U test. * indicates \(P < .01\), ** \(P < .001\). Note: Positive outlier for \(K_a\) at TE not pictured.

**FIG 5.** Sample mean \(\Delta R_1\) time course (TE = 31 ms) for a tumor ROI (A) and the resulting \(\Delta R_1\) time course (B). Mean \(\Delta R_1\) of (C) and \(\Delta R_1\) of (D) time courses from the same tumor with voxels separated by whether they predominantly exhibit \(T_2^*\), leakage effects (\(T_2^*\) voxels) or \(T_1\) leakage effects (\(T_1\) voxels).

**Table 2: Patient-specific estimates of DSC-MRI and DCE-MRI parameters separated by the predominant leakage effect**

| Patient No. | No. of Voxels (%) | \(K_a\) (min\(^{-1}\)) | \(K_2\) (min\(^{-1}\)) | \(K^{\text{trans}}\) (min\(^{-1}\)) | \(v_e\) |
|-------------|-------------------|-------------------------|-------------------------|---------------------------------|-------|
| 1           | 44 (79%)          | 1.807                   | -0.373                  | 0.223                           | 0.221 |
| 2           | 12 (21%)          | -0.250                 | 0.066                   | 0.072                           |       |
| 3           | 126 (67%)         | 1.229                   | -0.342                  | 0.169                           | 0.359 |
| 4           | 79 (59%)          | 0.815                   | 0.026                   | 0.228                           | 0.050 |
| 5           | 374 (53%)         | 2.374                   | -0.372                  | 0.328                           | 0.138 |
| 6           | 176 (36%)         | 0.822                   | -0.372                  | 0.328                           | 0.138 |
| 7           | 16 (64%)          | 2.591                   | -0.418                  | 0.200                           | 0.203 |
| Mean        |                   | 2.627                   | -0.329                  | 0.109                           | 0.285 |

Note: Mean indicates weighted mean.

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tions and noted that changes in the actual vascular permeability should not affect the polarity of \( K_2 \), though changes in imaging parameters (e.g., TE) could. Before the current study, a similar analysis with \( K_v \) had not yet been performed, to our knowledge.

In addition to TE, the intrinsic presence of competing and simultaneous T1 and T2' leakage effects, within a given voxel, were integral in determining the value of \( K_d \) and \( K_v \). As shown in Fig 5, competing T1 and T2' leakage effects can produce a \( \Delta R_1 \) time course that paradoxically appears to be free of CA extravasation effects. This is misleading because the dynamic \( \Delta R_1 \) information reveals appreciable CA leakage, resulting in moderate estimates of \( K^{\text{trans}} \). As noted by Bjornerud et al., the presence of both T1 and T2' relaxation effects in the extracellular extravascular space may drive \( K_v \) (and \( K_d \)) toward zero, resulting in artifactually low estimates. As an example, in the smallest 10% of all voxels (based on the magnitude of \( K_d \)), the mean \( K^{\text{trans}} \) was observed to be 50% larger than \( K_v \). Conversely, the magnitude of the mean \( K_v \) was \( \approx 3 \times 10^9 \) larger than \( K^{\text{trans}} \) when computed using all voxels. Additionally, the mean value of \( K_2 \) and \( K_v \), computed from the aforementioned subset of voxels (smallest 10%), was almost an order of magnitude smaller than the respective mean \( K_1 \) and \( K_d \), computed using all voxels. These findings clearly have implications for the reliability of these parameters as measures of vascular permeability.

In general, the relationship of \( K_1 \) and \( K_v \) with \( K^{\text{trans}} \) may indicate an inaccurate assumption that these parameters solely reflect vessel permeability in brain tumors. When separated into T1 and T2' voxel cohorts, the mean values of \( K_d \) and \( K_v \) across patients were found to be significantly different from one another (Table 4). The same was true for \( v_c \). Similar to the previous observation between \( K_d \) and \( K^{\text{trans}} \) in vivo, a significant quadratic relationship was observed between \( K_v \) and \( v_c \) across all patients. To this end, a recent theoretic study by Liu et al demonstrated a potential relationship between \( v_c \) and the ratio of the parameters \( K_1 \) and \( K_2 \) from the Weisskoff correction method. These results indicate that \( K_1 \) and \( K_v \) may also be influenced by the extravasation space of the CA.

The data in Table 2 also revealed that T1 voxels demonstrated larger \( v_c \) values than those found in T2' voxels. This result likely originates from the underlying biophysical basis of T1 and T2' leakage effects. As in DCE–MR imaging, T1 leakage effects result from the direct interaction of CA with the extracellular extravascular water. Accordingly, the physiologic factors that drive the tissue CA concentration (compartmental volume fractions, perfusion, and vascular permeability) and physical properties (CA T1 relaxivity, precontrast T1) and pulse sequence parameters (TR, flip angle) all influence the shape and magnitude of T1 leakage effects on DSC–MR imaging signals. In addition to physiologic factors and imaging parameters, T2' leakage effects are influenced by intravoxel susceptibility differences created by the spatial distribution of the CA within a voxel. Recently, Semminhe et al demonstrated that these effects are predominantly influenced by cellular properties, including density, size, distribution, and shape. Consistent with the results presented herein, stronger T2' leakage effects were observed for tissues with higher cell density (or lower \( v_c \)). In general, the dependency of T2' leakage effects on tumor cellularity manifests as changes in the effective T2' relaxivity of the CA. So unlike T1 leakage effects, where the T1 relaxivity of the CA is essentially constant within and across tumors, the T2' relaxivity may vary from voxel to voxel as the cellular properties change.

The variable CA T2' relaxivity also has important implications for the interpretation of the extracted \( K_d \) and \( K_v \) parameters. Although voxels were designated as predominantly exhibiting either T1 or T2' leakage effects, the signal of each voxel is the summation of these competing effects, as previously discussed. In the limiting case in which T2' leakage effects are absent and the signals only reflect T1 leakage effects, the \( K_d \) and \( K_v \) parameters are primarily driven by the underlying CA kinetics and the assumptions built into the correction models and can be understood accordingly. However, when there are competing T1 and T2' effects, \( K_d \) and \( K_v \) represent a complex balance between the CA kinetics and the tissue microstructure. Practically, this implies that a positive and negative estimate of \( K_d \) or \( K_v \) of the same absolute value may not reflect the same combination of vascular permeability, tissue compartment size, or microstructural geometry. Similarly, \( K_2 \) and \( K_v \) values that are equivalent within or across tumors may not reflect the same underlying physiologic environment because they could originate from unique combinations of competing T1 and T2' effects. This observation may help further explain the discrepancies in using \( K_d \) and \( K_v \) to evaluate tumor grade and to assess treatment response. Computational studies that account for the underlying biophysical basis of the DSC–MR imaging signal could be used to systematically investigate and provide insight into the complex interaction between T1 and T2' leakage effects and the derived \( K_v \) and \( K_v \) values.

The use of multiecho DSC–MR imaging in this study enabled measures of DCE–MR imaging signals and, subsequently, computation of the associated \( K^{\text{trans}} \) maps. As mentioned above, an alternative approach to collect both datasets in the same examination is to acquire DCE–MR imaging data during a preload of CA. This step enables the use of traditional DCE–MR imaging pulse sequences, ones that typically have higher spatial (and lower temporal) resolution. For the purpose of the study, this approach would have enabled the comparison of more conventionally derived \( K^{\text{trans}} \) values with \( K_d \) and \( K_v \). However, the addition of a preload to this study would have reduced T1 leakage effects and increased T2' leakage effects. It is unclear how this change would influence the correlation among \( K^{\text{trans}} \), \( K_d \), and \( K_v \). Another limitation of this study is the small sample size. While the findings are likely to hold in a larger population of patients with gliomas, it would be valuable to expand the tumor types considered (e.g., primary central nervous system lymphoma and brain metastasis) as different histologic subtypes have been shown to express varying degrees of T1 and T2' leakage effects.

**CONCLUSIONS**

This study investigated the use of DSC–MR imaging for estimating vascular permeability in brain tumors. Implementation of common DSC–MR imaging leakage-correction techniques afforded the computation of rate constants \( (K_d \) and \( K_v) \) postulated to report on vessel permeability. Additionally, the acquisition of multiecho data allowed the computation of the DCE–MR imaging pharmacokinetic parameter \( K^{\text{trans}} \). A voxelwise comparison among the parameters \( K_d \), \( K_v \), and \( K^{\text{trans}} \) revealed nonsignificant linear correlations that may be attributed, in part, to competing
T1 and T2’ leakage effects and the effect of TE on \( K_2 \) and \( K_\rho \). Further investigation also revealed a significant quadratic relationship between \( K_2 \) and \( K_\rho \) and the DCE–MR imaging parameter \( T(1) \). On the basis of these findings, caution should be used in assuming a direct relationship between \( \rho_0 \) and \( K_\rho \) and vascular permeability in brain tumors. Furthermore, the acquisition of \( K_{\text{trans}} \) from multiecho DSC–MR imaging data may provide a convenient method for simultaneously measuring vascular permeability and perfusion in brain tumors.

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