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Pseudo Extravasation Rate Constant of Dynamic Susceptibility Contrast MRI Determined From Pharmacokinetic First Principles

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Abstract

Dynamic Susceptibility Contrast (DSC) Magnetic Resonance Imaging (MRI) is widely used to obtain informative perfusion imaging biomarkers like the relative cerebral blood volume (rCBV). The related post-processing software packages for DSC-MRI are available from major MRI instrument manufacturers and third-party vendors. One unique aspect of DSC-MRI with low molecular-weight Gadolinium (Gd) based contrast reagent (CR) is that CR molecules leak into the interstitium space and therefore confound the DSC signal detected. Several approaches to correct this leakage effect have been proposed throughout the years. Among the most popular is the Boxerman-Schmainda-Weisskoff (BSW) K_2 leakage-correction approach, where the K_2 pseudo first-order rate constant quantifies the leakage. In this work, we propose a new method for the BSW leakage correction approach. Based on the pharmacokinetic interpretation of the data, the commonly adopted R_2^* expression accounting for contributions from both intravascular and extravasating CR components is transformed using a method mathematically similar to Gjedde-Patlak linearization. Then, the leakage rate constant (K_L) can be determined as the slope from the linear portion of a plot of the transformed data. Using the high-molecular weight (~750 kDa) iron-based intravascular Ferumoxytol (Fe) DSC data, the pharmacokinetic interpretation of the new paradigm is empirically validated. The primary objective of this work is to empirically

demonstrate that a linear portion often exists in the graph of the transformed data. This linear portion provides a clear definition for Gd CR's pseudo leakage rate constant, which equals to the slope derived from the linear segment. A secondary objective is to demonstrate that transformed points from the initial transient period during the CR wash-in often deviate from the linear trend of the linearized graph. Including those points will negatively impact the leakage rate constant's accuracy, and even make it time-dependent.

Graphical Abstract

A new method similar to Gjedde-Patlak linearization is proposed to correct leakage effect of Gadolinium (Gd) based contrast agent in Dynamic Susceptibility Contrast MRI. Using the high-molecular weight iron-based intravascular Ferumoxytol (Fe) DSC data, the pharmacokinetic interpretation of the new paradigm is empirically validated. Compared to relative cerebral blood volume (rCBV) color map obtained with Fe (e), Gd rCBV without leakage correction often underestimates (b), current correction can slightly overestimates (c), and the new method shows improved result (d).

Keywords

relative cerebral blood volume; leakage correction; intravascular contrast reagent; Ferumoxytol; Gadolinium; Gjedde-Patlak transformation

INTRODUCTION

Dynamic susceptibility contrast (DSC) Magnetic Resonance Imaging (MRI) with Gadolinium (Gd) contrast reagent (CR) has become one of the imaging standards for the detection and depiction of brain tumors. Relative cerebral blood volume (rCBV) has been shown as a useful imaging biomarker for brain tumor diagnosis, prognosis, and treatment response monitoring (1–3). Software packages like Nordic ICE (4) with 510k clearance issued by the Food and Drug Administration (FDA) further facilitate DSC's clinical usage. Still, leakage of Gd CR into the brain tumor interstitium confounds rCBV quantification, and violates basic tenets of the indicator dilution theory upon which DSC analyses are based. Since the inception of the leakage correction approach for DSC-MRI (5) more than 20 years ago, extensive model based and model independent leakage correction methods have been proposed (6–17), and the model independent approach has been used the most (9, 14, 18). However, pharmacokinetic indication of the corrected “leakage rate constant”

remains to be clearly defined and the variable influence of the transient phase during the CR first pass often further complicates rCBV calculation. The latter could partially be a direct consequence of the non-linear dependence of R_2^* and [CR] at high CR concentration. Recent results also indicate that leakage correction can be software package dependent (19), demonstrating additional complexity in implementing even the Boxerman-Schmainda-Weisskoff (BSW) method (8), which simplifies the DSC rCBV quantification by eliminating pharmacokinetic modeling on CR intravasation. Furthermore, effects of mixed T_1/T_2^* weighting were particularly noticeable towards the tail of the DSC time-courses and may require additional corrections (9, 14). Thus, the optimal leakage correction approach remains to be identified for Gd CR.

In this study, we propose a linearization approach for leakage rate constant quantification. The mathematical steps were similar to that of the Gjedde-Patlak plot (20–23). However, the empirical nature in this approach is intended only to demonstrate a potentially simple and improved method for leakage correction. The graph of the transformed data generally shows a linear portion corresponding to the washout phase of the DSC data. This linear portion clarifies two aspects related to DSC leakage quantification: 1) the existence of a linear portion in the graph from the transformed data demonstrates that a pseudo first-order leakage rate constant exists in the short DSC acquisition time window (i.e., a pseudo first order rate constant can be defined for CR leakage); 2) the slope from the linear portion of the transformed data provides a “pharmacokinetic” definition of the pseudo first-order rate constant characterizing leakage of CR from plasma to interstitium. Using a low-molecular weight extracellular avid Gd contrast reagent (Gd; ~ 600 Da) and the high-molecular weight (750 kDa) iron-based intravascular Ferumoxytol (Fe), we demonstrate the efficacy of the linearization approach. Specifically, the advantages of the new approach include uniquely identifying the CR extravasation rate constant and effectively minimizing leakage correction steps.

MATERIALS AND METHODS

Human Subjects

Seventeen subjects with Glioblastoma multiforme (GBM) were prospectively studied on institutional review board approved protocols. Informed written consent was obtained from each subject. Subjects underwent MRI sessions consisting of two consecutive days of MRI scans. On the first day, pre- and post-contrast T_1 -weighted images and DSC-MRI were acquired using Gadoteridol (ProHance, Bracco Diagnostic Inc., Princeton, NJ). On the following day, the same MRI sequences were acquired using Ferumoxytol (provided by AMAG Pharmaceuticals, Inc., Cambridge, MA). No subject had any complications during the MRI examinations. All MRI sessions were conducted using a 3T whole-body MRI system (TIM TRIO, Siemens, Erlangen, Germany) with a body coil for RF transmitting and a 12-channel matrix head coil for signal receiving.

MRI Data Acquisition

For DSC-MRI, dynamic T_2^* -weighted images were acquired using a gradient-recalled echo-planar imaging pulse sequence (repetition time 1500 ms, echo time 20 ms, flip angle 45° ,

field of view 192×192 mm, matrix 64×64 , and 27 interleaved slices). After an initial baseline period of seven imaging volumes (11 s), a bolus of contrast reagent (Gd or Fe) was administered intravenously using a power injector (Spectris Solaris - MEDRAD Inc., Warrendale, PA) through an 18-gauge intravenous line at a rate of 3 mL/s, followed immediately by 20 mL of saline flush at the same rate. Including baseline, DSC data were collected up to 90 volumes (frames). Gadoteridol was injected at a dose of 0.1 mmol/kg of body weight. Ferumoxytol was first diluted with equal volume of saline (1:2 dilution). The dose administered was either 1 mg/kg, 2 mg/kg, or in a constant volume of 5.0 mL diluted Ferumoxytol solution (75 mg of element iron) regardless of body weight.

Imaging Analysis

All Gd and Fe DSC data were first motion corrected within each dynamic series and then between the series using FMRIB's Linear Image Registration Tool (FLIRT) within FMRIB Software Library (FSL). Based on pre- and post-CR T_1 -weighted and T_2 -weighted images, a radiologist drew one region of interest (ROI) on the co-registered DSC images from the enhanced area.

rCBV without leakage correction—Data processing was performed using in-house software written in Matlab (Mathwork, Natick, MA). Here, the standard approach (24) as shown in Eq. (1) was used for $\Delta R_2^*(t)$ calculation:

$$\Delta R_2^*(t) = - \frac{\ln(\frac{S(t)}{S_0})}{TE} \quad (1)$$

where $S(t)$ is the signal at time t , S_0 is the baseline signal (prior to CR), and TE is the imaging echo time. When no Gd CR leakage is assumed, Eq. (1) can be used to calculate ΔR_2^* for blood or tissue. Assuming that ΔR_2^* is predominately caused by the blood fraction within the voxel or region of interest (ROI), leakage-uncorrected rCBV, $rCBV_{un}$, can be determined from the ratio of post-contrast $\Delta R_2^*(t)$ integrals from the tissue to blood ROIs.

For DSC MRI data acquired with intravascular Ferumoxytol CR, Eq. (1) is suitable for $\Delta R_2^*(t)$ calculation of all tissue types in this study.

Common leakage correction approach—To correct for “leakage,” the BSW approach that was initially proposed more than 20 years ago (5, 8) has been adopted widely into commercially available packages for both research and clinical applications. In this approach, based on the simple assumption that the effective transverse relaxation rate constant (R_2^*) changes induced by extravasating and intravascular Gds can be linearly combined (8), the voxel $\Delta R_2^*(t)$ time-course accounting for an intravascular contribution and an extravasating component can be simplified to Eq. (2),

$$\Delta R_2^*(t) \approx K_1 \overline{\Delta R_2^*(t)} - K_2 \int_0^t \overline{\Delta R_2^*(t')} dt' \quad (2)$$

where $\Delta R_2^*(t)$ represents the voxel time-course for R_2^* change, and K_1 and K_2 are proportional constants for the intravascular and extravascular contributions to ΔR_2^* , respectively. $\overline{\Delta R_2^*}(t)$ is the time-course of R_2^* change, derived by combining signal changes from all non-leaking voxels (8) available within the imaging slice or volume. Following the basic DSC assumption that $\Delta R_2^*(t)$ change is proportional to blood volume fraction, $\overline{\Delta R_2^*}(t)$ represents a simple and robust way to estimate the relative blood ΔR_2^* time-course, the relative whole blood input function. Due to temporal resolution and signal-to-noise ratio (SNR) requirements, DSC measurements typically are carried out using a sequence with mixed T_1/T_2^* weighting, where both T_1 and T_2^* contribute to changes in DSC signal intensity time-course. Therefore, the negative sign in Eq. (2) reflects the MRI specific phenomenon that CR induced T_1 shortening will result in a *signal increase* post CR, opposing that of the signal reduction in a heavily T_2^* -weighted DSC sequence. The overall effect from both T_1 and T_2^* could be field dependent and the T_2^* relaxivity can become a dominant effect at high field (25). Furthermore, using water proton ΔR_2^* time-courses to estimate CR pharmacokinetics intrinsically assumes that the CR relaxivities remain unchanged under different CR concentrations and tissue compartmental geometries. Thus, K_2 is not a commonly defined pharmacokinetic rate constant, but rather a potential pseudo rate constant that reflects MRI signal weighting associated with CR extravasation. Although expressed as such in Eq. (2), it is not clear whether K_2 itself is actually a constant.

Improved leakage correction—From Eq. (2), if K_2 is a pseudo first-order rate constant mostly reflecting CR extravasation, its value can be readily identified through a linearization transformation mathematically similar to that of the Gjedde-Patlak plot (20–23) used in pharmacokinetic equations. From Eq. (2), we obtain:

$$\frac{\Delta R_2^*(t)}{\overline{\Delta R_2^*}(t)} = K_1 - K_L \frac{\int_0^t \overline{\Delta R_2^*}(t') dt'}{\overline{\Delta R_2^*}(t)} \quad (3)$$

where K_L (a pseudo first-order leakage rate constant) is used to differentiate it from K_2 and

the significance of their difference will become obvious later. From Eq. (3), if the $\frac{\Delta R_2^*(t)}{\overline{\Delta R_2^*}(t)}$

term is graphed as the ordinate vs. $\frac{\int_0^t \overline{\Delta R_2^*}(t') dt'}{\overline{\Delta R_2^*}(t)}$ as the abscissa, the concept from fundamental pharmacokinetic theorem predicts that there will be a linear portion (20–23) within the graph if K_L is truly a pseudo first order rate constant and the numerical value of K_L is given by the slope of the graph. With the integral expression similar to that of the pharmacokinetic expression for unidirectional contrast agent uptake (22), Eq. (2) doesn't include details for CR intravasation rate constant modeling which in turn boosts its robustness in rCBV quantification. Practically, K_L calculation with Eq. (3) should not include the transformed data points that deviate the linear trend toward the tail of the graphed data. Otherwise, it will make K_L time-dependent, which defeats the purpose for its quantification. Apart from other potential sources for this linearity departure toward the tail

of the graph data, the most likely reason for the deviation is that CR intravasation becomes appreciable.

rCBV with leakage corrections—Gd CR extravasating rate constant is calculated either with the Eq. (2) fitting approach to obtain K_2 , or from the linear portion of the graphed points using Eq. (3) to calculate the slope for K_L . For the latter, linear regression with Eq. (3) started at 40 s post CR injection to ensure minimal influence of CR transient period (period **i** in Fig. 1e and 1f) on K_L quantification. Leakage corrected rCBV is calculated from Eq. (4):

$$rCBV_{LC-2,L} = rCBV_{un} + K_{2,L} \int_0^T dt' \int_0^{t'} \overline{\Delta R_2^*}(t) dt \quad (4)$$

where $rCBV_{LC}$ is the leakage corrected rCBV, $rCBV_{un}$ stands for uncorrected rCBV, $K_{2,L}$ takes either K_2 or K_L leakage rate constant to correct for CR extravasation, which then lead to the leakage corrected rCBVs with the K_2 approach ($rCBV_{LC-2}$) or with the K_L approach ($rCBV_{LC-L}$), respectively. The last term of Eq. (4) estimates integrated ΔR_2^* introduced by CR extravasation (8).

Applying all three rCBV quantifications ($rCBV_{un}$, $rCBV_{LC-2}$, and $rCBV_{LC-L}$) to DSC data acquired with both extracellular Gd CR and with high-molecular weight (750 kDa) iron-based intravascular Ferumoxytol CR, the validity for the leakage-corrected rCBVs was empirically demonstrated.

Statistical Analysis

The Pearson's correlation coefficient was used to assess the linear relationship between Fe rCBVs and the three Gd rCBVs (uncorrected, K_2 corrected, and K_L corrected). The mean differences between Fe rCBVs and the three Gd rCBVs were evaluated using a linear mixed effects model while accounting for the correlation among the repeated measurements within the subject. Multiple comparisons were adjusted using the Dunnett-Hsu method. All analyses were conducted using SAS 9.4 (SAS Institute Inc., Cary, NC, USA.).

RESULTS

Representative co-registered pixel intensity time-courses from the enhancing lesion area for Gd and Fe CRs are shown in Figs. 1a and 1b, respectively. Insets in Figures 1a and 1b display corresponding to same frame (~ 19.5 s post-injection) co-registered dynamic images. While the 1b time-course shows a consistent signal reduction post Fe as expected in the predominately T_2^* -weighted DSC sequence, the signature “leakage effect” of signal to increase above baseline due to T_1 shorting post Gd is evident in Figure 1a. A direct calculation of ΔR_2^* (the change of R_2^*) using Eq. (1) finds that its time-course artificially dips below zero after the CR first pass (Fig. 1c), and the integration of ΔR_2^* time-course up to ~1.0 minute post injection (8) will result in an underestimation of rCBV value (partial cancellation of positive and negative shaded areas as well as underestimation of the positive peak), as illustrated in Figure 1c. For the nano-sized intravascular Fe CR, $\Delta R_2^* > 0$ at all

times throughout the CR passage and this returns consistent rCBV estimation as illustrated in Figure 1d (26).

The most common approach in leakage correction is using Eq. (2) to estimate the leakage rate constant by fitting post Gd CR data points with both K_1 and K_2 as fitting parameters. After all, CR's influence is throughout its passage. However, it is generally not obvious to evaluate whether K_2 is a constant from an expression like Eq. (2). In the remaining part of Figure 1, we illustrate this point using the Eq. (3) transformed data.

Figure 1e symbols show the same voxel data from Figure 1a after undergoing the Eq. (3) linearization. The solid line with a slope of K_L is from the linear regression of the transformed data points with abscissa numerical range from 100 to 140 on the Fig. 1e abscissa scale, reflecting a DSC time-course range from 40 s to 70 s post-CR injection. The dashed line has a slope of K_2 determined from fitting Eq. (2) post CR points, which involves all data points up to 70 s post CR injection. The plot can be roughly divided into three periods: **i**) transient period of CR first pass; **ii**) pseudo equilibrium period where linearity obtains; and **iii**) intravasation/linearity deviation period, where data show evidence of deviation from the linear trend established in period **ii**, most likely due to CR intravasation. Within a DSC acquisition of ~ 1.5 minutes, a period **iii** with a clear departure of linearity is uncommon. In fact, K_L quantification in the Fig 1e data won't be greatly affected even if we include all points towards the tail end of the DSC- time-course. The vast majority of the plot actually look like that shown in Figure 4, which doesn't show a period **iii**. With no measurable CR extravasation and roughly a 5X more sensitive scale, the linearization transformed plot of the intravascular Fe CR in Fig. 1f shows no departure from the linear trend even towards the end of the DSC time-course (no appreciable Fe intravasation when there is no Fe in interstitium space). Not surprising, we can only define periods **(i)** and **(ii)** for the Fe data of the same pixel. The apparent numerical range difference in the abscissas of Fig. 1e and 1d is due to the linearization approach, which has an expression associated to the K_L term in Eq. (3). In addition, a uniformly spaced temporal resolution in the DSC data does not necessarily result in evenly spaced data points along the 1e and 1f abscissas.

To demonstrate the spatial correlation of the current approach, Figure 2a shows a T_1 -weighted image slice post Gd injection. The enhancing lesion is indicated with the arrow. Figure 2b–2e shows rCBV maps zoomed to the bottom part of the Figure 2a brain slice: Figure 2b, Gd rCBV map without leakage correction; Figure 2c, leakage corrected Gd rCBV map, leakage correction using leakage rate constant K_2 derived from fitting Eq. (2); Figure 2d, leakage corrected rCBV with leakage rate constant equals K_L , the slope of the linear portion of the Eq. (3) transformed data; Figure 2e, Fe rCBV map. Compared with Figure 2e, rCBV in lesion area (arrow) is substantially underestimated without leakage correction (Fig. 2b) and could be overestimated using the Eq. (2) fitting approach (Fig. 2c). With leakage rate constant defined as K_L , Figure 2d represents the best agreement between the Fe and leakage corrected Gd rCBV maps.

Figure 3 plots the three Gd rCBVs vs. Fe rCBVs (solid line) for lesion regions of interest (ROIs) of all 17 subjects included in the study: Gd without leakage correction (►); with Eq. (1) fitted K_2 leakage correction (◆); and with K_L , the slope of the linear portion of the Eq.

(2) graph, leakage correction (●). Comparing to Fe rCBV, while the uncorrected Gd method likely under-estimates rCBVs, the K_2 corrected method likely overestimates rCBVs. The relatively more evenly distributed rCBVs with K_L correction around the solid line suggests better agreement with Fe rCBVs. Compared with Fe rCBV, the mean uncorrected Gd rCBV is 0.33 lower than the mean Fe rCBV (95% CI, -1.01 to 0.36; $P = 0.50$), and the mean K_2 corrected rCBV is 0.45 higher (95% CI, -0.03 to 0.94; $P = 0.07$), though none of the differences is statistically significant after multiple comparison adjustment. The mean K_L corrected rCBV and the mean Fe rCBV are similar with a difference of 0.09 (95% CI, -0.38 to 0.55; $P = 0.93$). The correlation coefficients between Fe rCBVs and 1) uncorrected Gd rCBVs, 2) K_2 corrected Gd rCBVs, and 3) K_L corrected Gd rCBVs are 0.78 (95% CI, 0.46 to 0.91; $P < 0.0001$), 0.87 (95% CI, 0.66 to 0.95; $P < 0.0001$), 0.89 (95% CI, 0.70 to 0.96; $P < 0.0001$), respectively.

Although a fixed DSC range of 40 s – 70 s post CR injection was used for K_L quantification due to the image voxels' variable SNR, the linear portion in the graph of the transformed data could be determined from the data directly with sufficient SNR. One approach to find the proper linear range is to perform a series of linear regressions with an increased number of transformed data points included and compare the coefficient of determination (R^2) to figure out the optimal linear range. Figure 4 shows an attempt using a three-step approach from the transformed Gd DSC ROI data of one subject: 1) start an initial regression using data points within the linear portion of the graph from the transformed data (11 black squares indicated in Fig. 4a, representing time frames 27–37 acquired from ~ 40 to 55 seconds post CR), and calculate R^2 value; 2) perform a serial linear regression and calculate the associated R^2 values, with each subsequent fitting involving an additional data point from the next time-frame. For the above example, the first added point is from time frame 38, and the regression includes 12 transformed points from time frames 27–38. The process is repeated until reaching the last point of the time-course. Fig. 4b (right bottom panel) plots the R^2 values from these regressions, and the black filled circle represents the largest R^2 when moving in this direction. Essentially, when tail end of the data is concerned, all points after frame 27 except the last time frame can be included in calculating K_L in this case; 3) perform similar linear regressions as in step 2), but this time each subsequent regression adds one time frame immediately prior to the segment (*i.e.*, in reverse time order and moving towards the left when adding frames). Again using the above example, the first regression in this step includes time frames 26–71, where 71 is the next to last time-frame obtained from step 2 (4b) processes. The solid circle in Figure 4c (left bottom panel) marks the regression producing the largest R^2 , which includes three additional points to the left (the rightmost diamond corresponds to the leftmost black square, frame 27, in Figure 4a). Thus, a range from points 24–71 in the DSC time-course can be used for K_L quantification in this ROI time-course. Besides extra time needed for these calculations, this R^2 approach requires relatively good SNR for all pixel data. This remains a challenge for our current data. Thus, we only reported the K_L results from a fixed data range (40–70 sec) for all pixel data. This may lead to slightly poorer K_L precision. For the 17 ROI data, the R^2 values ranged from 0.452 to 0.995 with a median value of 0.903 (correlation coefficient, $r = 0.95$), suggesting good linearity. The R^2 mean $\pm$ SD for the whole group is 0.833 ± 0.174 . The plot of the

transformed data from the smallest R^2 value (0.452, $r = 0.672$) of the group has a noticeable scatter due to its poor SNR.

To further test whether there was residual autocorrelation in our linear regression results and the validity of residual independence assumption inherent to the linear regression approach, Durbin–Watson (DW) statistics were calculated along the abscissa (i.e., the so-called “stretch time”) direction for the linear segments of the 17 transformed ROI data. The DW values ranged from 1.51 to 2.79 (2.06 ± 0.41), indicating no statistically significant “autocorrelation” in any of our 17 ROI data.

DISCUSSION

Using concepts from pharmacokinetic first principles, we demonstrated a new and simple way to correct for brain lesion Gd CR leakage in DSC MRI. The original linearization approach described by the Gjedde–Patlak plot (20–23) transforms pharmacokinetic expressions mathematically similar to Eq. (2), with the primary difference being a negative sign before the second term in the DSC leakage-correction equation. Therefore, the linearization provides a straightforward interpretation for the pseudo first order CR leakage rate constant under mixed T_1/T_2^* signal weighting. Here, a linear portion of the graph from the transformed data often can be observed, demonstrating that a constant leakage rate (vs. time-dependent) exists, and its numerical value equals the slope of the linear segment (K_L , Figs. 1e,f). This K_L rate is unique and its validity is further supported by our Fe DSC results obtained from the same individuals. Ferumoxytol is an intravascular CR and its corresponding post-CR DSC signal time-course is consistently below baseline, and the slope of the linear portion from the graph is close to zero (1f).

In this work, a DSC time window of 40 to 70 seconds post-CR injection was adopted for K_L calculation. This selection is based on our data and other results already available in literature. Twenty-thirty seconds typically is required for CR to reach the brain after intravenous injection, and blood mean transit time (MTT) values are predominately determined to be less than 8 seconds for healthy brain (27) and for high grade glioma (28). An initial value of 40 seconds is thus on the relatively conservative side for ensuring that the transient period of Gd passage (Fig. 1e, period i) is over. It is interesting to point out that in our data, it is extremely rare ($\ll 0.1\%$) to observe voxels with appreciable linearity departure (period iii) in Gd CR data when using the Fig. 1e approach, even though post CR T_1 shortening caused signal increase above baseline like that shown in Figure 1a is relatively more common. This indicates intravasation may not be a noticeable confounder for DSC time-courses with a less than 70 s post CR injection data-acquisition window. Our simulations based on expressions in reference (8) accounting for CR transport from interstitium back to blood pool also show that the effect due to CR intravasation is small for the short period (< 1.2 min) post CR injection.

As the original empirical correction fundamentally relies on K_2 to be a time-invariant constant, the concept from that of the Gjedde–Patlak plot was borrowed in this work to identify the linear portion of the transformed data. However, since Eq. (2) is not a pharmacokinetic equation like that in the original Gjedde–Patlak approach, the current work

only empirically demonstrates the feasibility for the popular BSW leakage correction approach with a potentially time-invariant K_L . Since R^2 is a good measure for overall goodness of fitting data points to linear models, we explored the R^2 approach for a rough quantification of linearity of the transformed data segments. Given the slow-varying nature of the integral term of Eq. (2) after the first pass, it is expected that the transformed data associated with K_L will also be slow varying in general. This provides additional assurance that high R^2 values (median value of 0.903 for the 17 ROI data) validly represent linear behaviors. Furthermore, no residual autocorrelation was detected using the Durbin–Watson statistics. Future work may include steps to empirically identifying a R^2 low bound to achieve optimum results for the automated linear region determination under good SNR.

Given that Fe and Gd CRs have different susceptibility and bio-distribution *in vivo*, the rCBVs obtained with intravascular Ferumoxytol may not be a perfect “gold standard” for Gd rCBVs, particularly at low rCBV. Results from the correlation coefficients between the rCBVs partially demonstrated this issue. It shows good agreement of the two methods measuring the same parameter. However, the sample size of our data is too small to establish a clear conclusion. This is somewhat reflected by the non-statistically significant findings between the mean values of any of the Gd rCBV groups with the Fe rCBV group, even though CR leakage results in systematic errors in both the uncorrected Gd rCBVs and the K_2 corrected rCBVs. Larger sample sizes with clinical outcomes as the gold standard are the next step to investigate K_L as an improved Gd DSC leakage correction approach.

Our current approach builds on the robustness of the original method (4, 8), which doesn’t include pharmacokinetic modeling, and can be potentially faster and easier compared to the original approach. With the pharmacokinetic interpretation of the data clearly defined, it also adds insight to the already robust and rapid DSC MRI quantification (4, 8) for translational research as well as clinical application.

Limitations of this current study include the fact that fixed cutoff time points (40 s and 70 s in the DSC time-course for the start and the end points, respectively) are used for the linear portion slope calculation. This could affect the numerical K_L value slightly, especially for noisy data. With multi-band and improved coil arrays available in MRI, SNR is expected to improve. This could enable future DSC data for the R^2 based range determination approach.

Conclusion

Using a linearization approach similar to that of the Gjedde–Patlak plot, this study demonstrated that a pseudo rate constant generally exists in the most commonly used leakage correction expression. By performing linear regressions on the linear portion of the transformed data, the proposed approach can potentially be faster.

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Abbreviations used

CR	contrast reagent
DSC	Dynamic Susceptibility Contrast
GBM	Glioblastoma multiforme
rCBV	relative cerebral blood volume
ROI	region of interest

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Figure 1.

An illustration of time-courses in DSC MRI and associated leakage rate quantification for extracellular or intravascular CRs. **1a** and **1b** show co-registered same pixel intensity time-courses from enhancing lesion area for Gd and Fe CRs, respectively. Insets in **1a** and **1b** display corresponding same frame co-registered post-injection dynamic images. With intravascular Fe CR, **1b** shows a consistent signal reduction time-course post CR. The signature “leakage effect” of post CR signal increase to above baseline due to T_1 shorting is evident in **1a** Gd time-course. **1c** shows calculated ΔR_2^* from **1a** time-course resulting in an artificial dipping of ΔR_2^* below zero after CR first pass. Shaded area illustrates numerical

integration of ΔR_2^* underestimates rCBV value. This is not seen with nano-sized intravascular Fe CR in **1d**. Figure **1e** symbols show the same pixel data from **1a** underwent the Eq. (3) linearization and plotted with respective coordinates as labeled. The solid line is from a linear regression of the transformed data points from 100 to 140 on Fig. **1e** abscissa scale, reflecting a range of 40 s –70 s post-CR on DSC time-course. The dashed line is with the slope equals to K_2 determined from fitting Eq. (2) with all data points up to 70 s post CR injection. The plot can be roughly divided into three regions: i, transient period of CR first pass; ii, pseudo equilibrium period where linearity obtains; iii, intravasation (linearity deviation) period, where graphed data points deviate from the linear trend, most likely due to intravasation. With no CR extravasation, plot of the intravascular Fe data after the linearization transformation in **1f** shows no departure from the nearly horizontal linear trend after its establishment even towards the end of the DSC time-course. Here, there is no visible period iii for intravasation.

Figure 2.

rCBV maps for extracellular and intravascular CRs. 2a shows a T_1 -weighted image slice post Gd injection. The enhancing lesion is indicated with an orange arrow. 2b–2e show rCBV maps zoomed to the bottom part of the 2a brain slice: 2b, Gd rCBV map without leakage correction; 2c, Gd rCBV map with K_2 rate constant leakage correction; 2d, Gd rCBV map with K_L rate constant leakage correction; 2e, Fe rCBV map. Compared with 2e, lesion (arrow) rCBV is generally underestimated without leakage correction (2b) and could be overestimated using the K_2 Eq. (2) fitting approach (2c). 2d presents the best agreement between Fe and leakage corrected Gd rCBV maps.

Figure 3.

A summary of ROI rCBVs for all subjects. The three Gd rCBVs were plotted against Fe rCBVs (solid line, unit slope) for all 17 subjects included in the study: rCBVs from Gd without leakage correction ($\blacktriangleright$); leakage corrected rCBVs using Eq. (2) fitted K_2 leakage rate constant ($\blacklozenge$); and leakage corrected rCBVs using the K_L leakage rate constant derived from the linear portion of the Eq. (3) graphed data($\bullet$). While the uncorrected Gd rCBVs underestimate, the Eq. (2) fitted K_2 could overestimate. The relatively more evenly distributed rCBVs with K_L leakage correction around the solid line empirically demonstrate the approach's better performance.

Figure 4.

Using R^2 to determine the linear range of the transformed data. **4a.** shows the initial linear regression with data points from the linear portion of the transformed data (black squares), representing time frames 27–37 acquired from ~ 40 to 55 seconds post-CR injection. **4b** plots R^2 values from a series of linear regressions, each subsequent fitting with the next time-frame added to the regression (first added point is thus from time frame 38) till the process reaching the last point of the time-course. The largest R^2 from these regressions is indicated with the black filled circle. **4c** shows a process similar to **4b**, except each subsequent regression is performed with an additional time frame immediately prior to the

previous segment (*i.e.*, in reverse time order). The first of this set of regressions includes time frames 26–71, where 71 is the next to last time-frame obtained in **4b**. The black filled circle in **4c** marks the regression producing the largest R^2 , which includes three additional points to the left of time frame 27 (right most diamond in **4c**). Thus, a range from points 24–71 can be used for K_L fitting for this data set.