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Diffusion Compensated Tofts-Model Suggests Contrast Leakage through Aneurysm Wall

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Abstract

Purpose—The purpose of this study was to investigate the diffusional transport of contrast agent and its effects on kinetic modeling of Dynamic Contrast Enhanced (DCE) images.

Methods—We performed simulations of our diffusion-compensated model and compared these results to human intracranial aneurysms (IAs). We derive an easy to use parameterization of diffusional effects that can provide an accurate estimate of diffusion corrected contrast agent leakage rates (k^{trans}). Finally, we performed re-analysis of an existing dataset to determine if diffusion-corrected kinetic parameters improve the identification of high-risk IAs, thereby providing a new MRI-based imaging metric of IA stability based on wall integrity.

Results—Probability distributions of simulated vs. measured data show contrast leakage away from the aneurysm wall. Parameterization of diffusional effects on k^{trans} showed high correlation with long-chain methods in both surrounding tissue and near the aneurysm wall ($r^2 = 0.91$ and $r^2 = 0.90$ respectively). Finally, size, k^{trans} , and $(k^{trans} - k^{trans}_{DC})$ showed significant univariate relationships with rupture risk ($p < 0.05$).

Conclusions—We report the first evidence of diffusion-compensated permeability-modeling in intracranial aneurysms and propose a parameterization of diffusional effects on k^{trans} . Furthermore, a comparison of measured against simulated data suggests contrast leakage occurs across the aneurysm wall.

Keywords

Tofts Model; Aneurysm; Rupture Risk; Contrast Leakage

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Introduction

The leakage of gadolinium based contrast agents has long been used as a clinical tool that reflects pathophysiology in cancers. The Standard Tofts model (1,2) applied to Dynamic Contrast Enhanced (DCE) MRI describes the transport of contrast from the intravascular to extravascular space that is reflective of microstructural tissue changes. In particular, Tofts modelling has been shown to reflect angiogenesis (3–7). Clinical translation of the Tofts model has been wildly successful and yields actionable information in tumor aggressiveness and response to anti-angiogenic chemotherapies (6,8,9). However, kinetic modelling of DCE images can yield anomalously high values of the fractional volume of extravascular extracellular space (v_e) and contrast agent permeability rate (k^{trans}) in some cases (10). This has prompted study by several researchers to improve upon the standard Tofts Model. For example, incorporating intravascular signal (2) and diffusional transport of contrast agent (10,11) have been developed and show significantly altered calculated parameters.

Unfortunately, the computational complexity of diffusion correcting k^{trans} is costly. Some direct models take between 1 minute and up to several hours per pixel of computing time (10). One goal of this work is to compare the accuracy of optimized, long chain diffusion correction with a parameterization of diffusion leakage derived from simulations. The development of an easily implementable approximation to the Pellerin model (11) has the potential to allow more widespread use of the proposed improvements on the Tofts model.

In this study, we evaluate the diffusional transport term in the modified Tofts model in a unique application, that of intracranial aneurysm (IA). The Tofts model has been shown to be clinically significant a predictor of rupture risk in intracranial aneurysms and is currently being evaluated as a metrics where by k^{trans} reflects the thickness of an aneurysm wall (12). For the purpose of understanding diffusional transport corrections to the Tofts model, brain aneurysms represent an ideal physiologic milieu: the aneurysm wall serves as a single distinct source of contrast through surface extravasation at the aneurysm dome, the leakage occurs directly into tissue which is characterized by low background leakage due to the presence of an intact blood brain barrier, and local diffusion of the brain parenchyma is well understood through extensive study of Apparent Diffusion Coefficient (ADC). These three factors allow us to separate diffusion transport from nominal k^{trans} “leakage” and to study these two effects separately *in vivo*.

Previous work by Fluckiger (10) and Pellerin (11) demonstrated that estimating kinetic parameters in the presence of passive contrast diffusion improved physiologic representation and reduced the likelihood of returning unphysical v_e values. We apply a diffusion compensated Tofts model (DC-Tofts) to analyze contrast kinetics at the surface of an IA wall. By incorporating the effects of passive diffusion within the parenchyma, the DC-Tofts model may more accurately represent contrast kinetics at the surface of an IA wall, and the macroscopic phenomena of contrast agent leakage into or through it. The purpose of this study was to quantify diffusion compensated IA wall permeability, and develop a rapid method to determine diffusional effects using parameterization based on easily accessible ADC values, which may preclude the need for iterative diffusion-compensated fitting.

Methods

We performed a mathematical simulation of our diffusion compensated Tofts model in the setting of an IA which we model as a local source of contrast. Next, we compared diffusion-corrected to uncorrected values in a study of human IAs. We then propose a parameterization of the diffusion corrected rate constant (k^{trans}_{DC}) as a function of tissue specific diffusion rate (D), k^{trans} and fractional plasma volume (v_p). Finally, we perform a re-analysis of an existing dataset (first reported in (12)) to determine if diffusion corrected kinetic parameters improve the risk identification of aneurysms. This investigation was HIPAA (Health Insurance Portability and Accountability Act) compliant and IRB (Institutional Review Board) approved. All subjects provided written informed consent.

Theory

Permeability Modeling—The Tofts Model is well known and used frequently in a variety of research and clinical settings. It describes the vascular delivery and distribution of a tracer into the extracellular volume and has been used to quantify contrast leakage in solid tumors with notoriously leaky vasculature (neovascularity). Since an intact blood brain barrier (within healthy brain tissue) restricts the distribution of contrast, the Tofts model can be used to quantify the leakage rate through a compromised blood brain barrier (4,5,8,13). While pathological tissue enhancement is adequately explained by leakage of tumor neovascularity, the presence of contrast enhancement in necrotic centers which lack a blood supply is less understood.

A similar problem arises when applying the Tofts model to contrast uptake into and across the aneurysm wall. In IA patients, their vasculature (barring the aneurysm) is largely unaffected—suggesting the blood brain barrier is intact and thus contrast enhancement should be minimal. However, as was previously shown (12), contrast can be readily observed beyond the compromised and thinned IA walls. Consequently, we have applied the DC-Tofts model to account for contrast extravasation through the vascular lumen and aneurysm wall into the CSF as well as diffusion from higher concentrated regions towards lower concentrations.

The permeability-limited Modified-Tofts Model (2) quantifies the kinetics of a tracer leaking through a semi-permeable membrane with the following relationship:

$$C(t) = k^{trans} \int_0^t e^{-k_{ep}(t-\tau)} C_p(\tau) d\tau + v_p C_p(t) \quad \text{Equation 1}$$

with k^{trans} dictating the tracer transfer rate from the intravascular into the extracellular extravascular space with units of min^{-1} , $k_{ep} = k^{trans}/v_e$ in units (min^{-1}) describing the ratio of the transfer rate (k^{trans}) to the fractional volume of tracer (v_e), $C_p(t)$ the intravascular tracer concentration, that is, the Arterial Input Function (*AIF*), $C(t)$ is the voxel tracer concentration and v_p the fractional plasma volume.

The diffusion-corrected model improves on the Tofts model by including a diffusion term when calculating the changes in concentration as a function of time (10,11). In this study,

since IAs are surrounded by the pial surface of the cerebral cortex, remote from white matter, we are able to reduce the computational complexity by approximating the diffusion rate (D) to be uniform in the extravascular space (Equation 2)

$$C_{DC}(t) = k^{trans} \int_0^t e^{-k_{ep}(t-\tau)} C_p(\tau) d\tau + v_p C_p(t) + \int_0^t \sum_N \frac{D}{a^2} \left(\frac{C_N(\tau)}{v_{eN}} - \frac{C_i(\tau)}{v_{ei}} \right) d\tau \quad \text{Equation 2}$$

where C_{DC} is the diffusion compensated tracer concentration, a is the in plane voxel length, D is the voxel specific diffusion constant, and C is the measured concentration. The subscript i refers to the voxel of interest while N refers to the adjacent neighbors (a total of 4 neighbors are included along the 2D plane). Note that Equation 2 is same as Equation 1, but includes an added “diffusion term” defined as the 3rd term (**Bolded**).

Simulation

To examine the effects of partial volume averaging and contrast diffusivity on contrast kinetics, we performed a 2D computer simulation. A single slice was used for simulations because the slice thickness in the DCE-MRI patient experiments was four times greater than in-plane resolution. Consequently, we estimated the inter-plane diffusion of contrast to be negligible compared to in-plane diffusion.

The simulated aneurysm model consisted of 3 different compartments—intravascular blood, vessel wall, and interstitial tissue (Figure 1a–b). The concentration of contrast in the blood was modeled with a population-averaged *AIF* derived from clinically collected aneurysm patient information (shown in Figure 1d). Simulated vessel wall and tissue compartment permeability parameters (k^{trans}_{true} , v_{true} , v_{pture}), distribution volumes (wall thickness), and diffusion rates (D_{true}) were allowed to vary within known physiologically realistic ranges (10,12) (Table 1). With the known kinetic parameters and the population averaged *AIF*, we generated a 512×512 parametric image of contrast concentration which was allowed to evolve over time, $C(x,y,t)$. The concentration time courses were convolved with a 2D Gaussian kernel (full width half maximum (FWHM) = 2.73 mm) and resampled onto 64 × 64 matrix to match the in-plane experimental imaging resolution 0.58 mm × 0.58 mm, where the vessel wall width was estimated to be 50–550 microns (14–16). Next we converted concentration curves into signal intensities (17) then added Rician noise to the signal time courses to create a uniform signal-to-noise ratio of SNR ~ 6.0. Finally, signal curves were converted back to concentration time course which were then fit to determine k^{trans} , v_e , and v_p values for both the Tofts model and the DC-Tofts model (examples shown in Figure 1e).

To examine how inputs parameters affected each model, k^{trans} and k^{trans}_{DC} were studied at varying distances from the vessel wall. Model variations are also shown in histograms of $k^{trans} - k^{trans}_{DC}$.

Patient Data

All *in vivo* data in this study were collected prospectively between July 2011 and July 2013 on consecutive patients with unruptured IAs reporting for neurointerventional consultation. These collected data were initially published in (12). Major exclusion criteria included:

pregnancy, contrast allergy, renal insufficiency, presence of MR incompatible implants, and prior IA treatment. In total, 26 unruptured aneurysms ($n_{\text{fusiform}} = 3$, $n_{\text{saccular}} = 23$) in 22 patients ($\langle \text{age} \rangle = 58.4 \pm 11.3$ years, age range 30–82 years), 13 women ($\langle \text{age} \rangle = 58.8 \pm 12.9$ years, range 30–76) and 9 men ($\langle \text{age} \rangle = 59.3 \pm 8.9$, range 39–82) were included in this study. There was no significant difference between men and women in age ($p=0.92$) or IA size ($p=0.20$).

Imaging Protocol—Patients were imaged on a 3T (Trio, Siemens) MR scanner. To determine IA location, a 3D time of flight (TOF) MRA was used. DCE-MRI was performed using a single dose (0.1 mmol/kg) bolus injection of T_1 -shortening contrast agent (Magnevist, Berlex; Wayne, NJ). The following image parameters were used for the DCE sequence: TR/TE=2.84 ms/0.8 ms, Partial Fourier = 0.5, matrix = $128 \times 128 - 384 \times 384$, FOV = 190–220 mm, and 12–24 partitions placed to adequately cover the IA, resulting in voxel dimensions between $0.58 \times 0.58 \times 2.0$ mm and $1.48 \times 1.48 \times 5.0$ mm. T_1 weighted images were acquired using a standard multi-phase 3D-gradient recalled echo (GRE) pulse sequence every 5 seconds for approximately 8 minutes. Pre-contrast T_1 values ($T_{1,0}$) of the tissue, used to estimate contrast concentrations, were found by varying the flip angle ($\alpha=5^\circ, 10, 12, 15, 20, 25$) and solving the spoiled gradient echo equation (12,18,19).

Post Processing

All permeability modeling and post-processing analyses were performed using in-house software developed in MATLAB (Mathworks, Natick, Massachusetts). Using a Dell XPS 8500 (16 GB of RAM, Intel i7-3770 CPU @ 3.4 GHz) computational time for contrast kinetic parameters was less than 10 minutes per slice.

Tofts Modeling—Kinetic modelling was performed in manually drawn large ROIs which contained the IA, a segment of the parent artery and the adjacent parenchyma. For every voxel within the ROI (including intra-vascular voxels) a Levenberg-Marquardt curve fit was utilized to find the k^{trans} , v_e , and v_p in Equation 1 that best fit the measured signal $C(t)$.

Diffusion-Compensated Modeling—Direct voxel-by-voxel diffusion correction of the Tofts model is heavily dependent on neighborhood values and thus any direct solution requires iterative fitting of diffusion coefficient, D and kinetic parameters, k^{trans} , v_e , and v_p for each voxel location. It has been previously shown that for even relatively small coverage, any direct solution becomes too computationally expensive (11). Consequently, we constrain the solution set to allow for faster implementation. First, as in previous work, D is not used as a free parameter (11). We instead assume a constant value for the diffusion rate ($D = 1.0 \times 10^{-3} \text{ mm}^2/\text{s}$ for all model comparisons and risk analyses) across the whole brain. By assuming a constant diffusion rate, we can first solve for the diffusion term in Equation 2 and subsequently solve for the kinetic terms using a Levenberg-Marquardt algorithm with the diffusion term fixed at the value determined above. D was fixed at $1.0 \times 10^{-3} \text{ mm}^2/\text{s}$ to be slightly higher than white and grey matter values (0.7 and 0.9 respectively (20)). This was done because large vessels of the brain are surrounded by cerebral spinal fluid (CSF) which on a whole will increase the diffusion coefficient of the voxel. We examined the fidelity of

this assumption by re-calculating *in vivo* data varying D from 0.2 to $2.5 \times 10^{-3} \text{ mm}^2/\text{s}$ (discussed below).

Concentration maps at each time point are allowed to diffuse in increments of time. Because the image temporal resolution is roughly 5 secs, we use 5 “diffusion steps”, enabling us to compute diffusion every $t = 1$ second (similar to (11)). During the diffusion calculations, v_e for each voxel was estimated as standard Tofts modelling, v_e . For each voxel and time point t we subtract the diffusion term from each side of Equation 2 and generate diffusion-compensated concentration curves. We then utilized the same Levenberg-Marquardt algorithm described above to solve for diffusion corrected kinetic parameters, k^{trans}_{DC} , v_{e-DC} , and v_{p-DC} . A schematic of the work flow is shown in Figure 1c.

Contrast Leakage through Aneurysm Wall

To investigate contrast leakage through the IA wall versus uptake and retention of contrast within the IA wall, we compared the probability density function (PDF) and cumulative density function (CDF) of $(k^{trans} - k^{trans}_{DC})$ between simulated and patient data. Simulated data were created over a wide range of D_{true} (Table 1). Best and worst fitting distributions were determined based on the Sum Square Error (SSE) between simulated and patient CDFs.

Model Comparisons

Several methods were used to compare the Tofts model with the diffusion compensated model using different regions of interests (ROIs). To remove any bias introduced by user-defined selection, ROIs were automatically selected to include only voxels with corresponding v_p smaller than 0.8 ($v_p < 0.8$). This approach ensures that voxels with DCE signal of greater than 80% from partial volume averaging between the parenchymal signal and intravascular signal (i.e. inside the parent artery and/or IA) are removed. Furthermore, due to the effect of partial volume averaging and blurring associated with the acquisition point spread function, we found near the vessel wall (0 to $\sim 4\text{mm}$; $0 < v_p < 0.9$) v_p correlated linearly with distance from the wall as: $distance = -4.64 v_p + 4.13$ ($r^2=0.9778$). Consequently, v_p was used as a surrogate for distance.

For all direct voxel-by-voxel comparisons of k^{trans} and v_e values, a large ROI was placed on a single slice containing the IA. The ROI was placed in a manner to fully encompass the aneurysm as well as all surrounding healthy vasculature. To examine how k^{trans} and v_e differed at the IA wall only, voxels within the large ROI with v_p values between 0.5 and 0.8 were used ($0.5 < v_p < 0.8$). Surrounding tissue was classified by v_p values between 0.01 and 0.5 ($0.01 < v_p < 0.5$). In each case, we utilized a linear model to determine the r^2 and p -value between the DCE-parameters (k^{trans} , v_e) of each model. Furthermore, to investigate model discrepancies as a function of distance from the aneurysm wall, we binned permeability parameters (k^{trans} and v_e) based on distance from the wall and calculated and analyzed means and standard deviations of each bin.

Mean k^{trans} , v_e , and v_p values were also measured adjacent to the wall of a healthy parent artery and compared against mean values adjacent to the aneurysm wall. For both the healthy artery and the IA wall, ROIs were 5 voxels wide surrounding and outside the

structure of interest. Average k^{trans} and v_e measurements from the aneurysm wall were compared with the parent artery values (which served as internal controls (i.e. non-disease values)) using a paired t -test to determine if the DCE measurements were significantly different. Average permeability parameters were also compared on an inter-model basis using a paired t -test. In all cases, statistical significance was defined at the 5% level.

DC Model Analysis and Parameterization—To dramatically reduce post-processing time, we utilized a homogeneous constant $D = 1.0 \times 10^{-3} \text{ mm}^2/\text{s}$. To examine the fidelity of this assumption, we re-analyzed *in vivo* data varying D from 0.2 to $2.5 \times 10^{-3} \text{ mm}^2/\text{s}$. For each D , mean k^{trans}_{DC} and v_{eDC} values were calculated adjacent to the aneurysm wall ($0.5 < v_p < 0.8$). k^{trans}_{DC} and v_{eDC} were then fit as functions of diffusion constant, D , and k^{trans} .

We next investigated parameterizing k^{trans}_{DC} as a function of tissue specific D , k^{trans} and v_p . To do this we used the large ROI including both surrounding tissue and the aneurysm wall and fit Equation 3 for parameters a , b , c and d , by minimizing the sum square difference between the long chain k^{trans}_{DC} and the parameterized $\hat{k}^{trans}_{Corr}$

$$\hat{k}^{trans}_{Corr} = k^{trans} + a(v_p - b)^2 + c\sqrt{D} + dv_p D \quad \text{Equation 3}$$

To analyze the predictive value of k^{trans}_{DC} parameterization, while preventing over-fitting, we performed a Leave One Out Cross Validation (LOOCV) study. In the LOOCV analysis, patient specific constants (a_i , b_i , c_i and d_i) were fit using Equation 4.

$$[a_i, b_i, c_i, d_i] = \underset{[a,b,c,d]}{\operatorname{argmin}} \sum_{n \neq i} (k^{trans}_{DC} - \hat{k}^{trans}_{Corr})^2 \quad \text{Equation 4}$$

For example, because this study included 23 saccular aneurysms, patient specific constants (a_i , b_i , c_i and d_i) were fit using data from the other 22 aneurysms. For each patient, we then calculated $\hat{k}^{trans}_{Corr}$ and compared it to the long-chain k^{trans}_{DC} with a linear model. Correlation and Bland Altman graphs for both surrounding tissue and the aneurysm wall were generated.

Clinical Consequence of Diffusion Compensation

To determine the clinical benefits of the DC-Tofts model, rupture risk was evaluated using mean values of DCE permeability parameters calculated in automatically drawn ROIs containing voxels adjacent to the aneurysm wall. ROIs were placed on a single slice containing the aneurysm where the highest k^{trans} values were observed. Aneurysm wall was defined as regions with v_p values between 0.5 and 0.8 ($0.5 < v_p < 0.8$). To examine only the regions of highest k^{trans} , the ROI was refined to only include the highest 25% of wall values.

Statistical Analysis and Risk Classification—Using previous published methodology (12), IAs were classified into high-risk and low-risk categories using two size-independent risk assessment paradigms. In clinical risk paradigm A, high-risk aneurysms were those that presented with neurological symptoms relevant to the aneurysm's location (headaches, mass

effect, cranial neuropathy); asymptomatic aneurysms were low risk. In risk paradigm B, high-risk aneurysms harbored one of the following three imaging/anatomic properties: (1) multilobulated dome or blebs, (2) presentation with multiple IAs, or (3) posterior circulation location; all others were defined as low-risk. Size indices were not used to define the risk profile for any aneurysm in Group A or B.

Univariate regression analyses were performed for groups A, B and AB (which was defined as A or B). High and low risk groups were compared against patient age, sex, aneurysm size, k^{trans} , and $(k^{trans} - k^{trans}_{DC})$. Multivariable logistic regression analysis was also performed to evaluate independent predictors of risk in the aforementioned risk paradigms/groups. In all risk analyses, only saccular aneurysms ($n = 23$) were examined. Significance was defined as <0.05 in all statistical tests.

Results

Simulations

Simulations (Figure 2) were performed comparing Tofts model results versus diffusion compensated results with respect to environmental diffusion constant D_{true} , wall thickness, and v_e . Diffusion compensation tended to increase k^{trans} values close to the wall (within two voxels), while slightly reducing them further from the wall. Both close to the wall and in the surrounding tissue, k^{trans}_{DC} was closer to true simulated k^{trans}_{true} (represented by the black line). The bottom row shows probability distributions of $(k^{trans} - k^{trans}_{DC})$ in the 1000 simulations which clearly show that the diffusion constant D_{true} has a dramatic effect in $(k^{trans} - k^{trans}_{DC})$, while both width and v_e have little effect. A larger diffusion constant means that contrast will diffuse faster and further away from the wall. Without correcting for this effect the Tofts model will underestimate the amount of contrast near the source (aneurysm wall), and overestimate it in healthy tissue.

Contrast Leakage through Aneurysm Wall

Figure 3 shows probability (a–c) and cumulative (d–e) distribution functions of $(k^{trans} - k^{trans}_{DC})$ for measured (represented in blue) and simulated data. Simulated data was done over a wide range of values for D_{true} . Three distributions are shown, red represents simulation results from $D_{true} = 2.0 \times 10^{-3} \text{ mm}^2/\text{s}$ (best fit with $\text{SSE}=0.128$), orange from $D_{true} = 1.0 \times 10^{-3} \text{ mm}^2/\text{s}$ (second best fit with $\text{SSE}=0.1473$), and green represents simulation data from $D_{true} = 0.01 \times 10^{-3} \text{ mm}^2/\text{s}$ (worst fit with $\text{SSE}=1.440$). Considering, previously published data show diffusion coefficients within the brain vary from approximately 0.6 to $2.7 \times 10^{-3} \text{ mm}^2/\text{s}$ (white matter to CSF) (20), these results taken in concert suggest contrast is actively leaking through the aneurysm wall and diffusing outward.

Model comparisons

Correlation between voxel-wise DCE parameters of both models are high. Measured k^{trans} and v_e values from both models are shown to be highly correlated. (k^{trans} : $r^2 = 0.821$, slope = 1.02, intercept = 0.009, $p < 0.0001$; v_e : $r^2 = 0.723$, slope = 0.797, intercept = 0.014, $p < 0.0001$). Figure 4a and 4d show correlation between models in surrounding tissue. (k^{trans} : $r^2 = 0.851$, slope = 1.00, intercept = 0.008, $p < 0.0001$; v_e : $r^2 = 0.718$, slope = 0.827, intercept

= 0.012, $p < 0.0001$). Figure 4b and 4e show measured k^{trans} and v_e values from both models adjacent to the aneurysm wall. We see a divergence at the wall between the models, but correlation remains high (k^{trans} : $r^2 = 0.761$, slope = 1.067, intercept = 0.0165, $p < 0.0001$; v_e : $r^2 = 0.717$ slope = 0.682, intercept = 0.013, $p < 0.0001$).

Figure 4c and 4f, show model divergences as a function of distance from aneurysm wall. Error bars show standard deviation around mean binned values. Though noisy, $k^{trans} - k^{trans}_{DC}$ clearly shows divergence near the wall. Though more subdued, $v_e - v_{eDC}$ also shows a clear trend decreasing from 0.011 at the wall to -0.002 in healthy tissue.

Figure 5 shows a comparison between k^{trans} values in Tofts and DC-Tofts models from healthy vessels and aneurysm walls, p-values were generated with a paired t-test. In both models, the healthy vessels show minimal k^{trans} divergence (Tofts vs DC-Tofts), 0.0284 ± 0.018 vs 0.0224 ± 0.015 , ($p = 0.1907$). Near the aneurysm wall however, DC-Tofts was significantly higher (Tofts vs DC-Tofts), 0.127 ± 0.053 , 0.183 ± 0.064 , ($p = 0.0011$). In each model, the difference between k^{trans} near the healthy vessel wall and aneurysm wall was significant ($p < 0.001$). Similarly, v_e showed minimal divergence near healthy vessels but significant change near the IA wall (Tofts vs DC-Tofts, Healthy: 0.0230 ± 0.0106 vs 0.0242 ± 0.0115 , $p = 0.7147$; IA wall: 0.1216 ± 0.0191 vs 0.0975 ± 0.0174 , $p < 0.0001$). Conversely, v_p showed minimal divergence in all cases (Tofts vs DC-Tofts, Healthy: 0.5766 ± 0.0503 vs 0.5815 ± 0.0616 , $p = 0.7690$, IA wall: 0.5906 ± 0.0525 vs 0.5837 ± 0.0771 , $p = 0.7245$).

Figure 6 shows representative images from patients with small, medium, and large aneurysms. Images were chosen to demonstrate the broad range of wall permeability values, both among subjects and within a single IA. Figure 6a, b, c, d, e, and f represent k^{trans} , k^{trans}_{DC} , ($k^{trans} - k^{trans}_{DC}$), v_e , v_{eDC} , and ($v_e - v_{eDC}$), respectively.

DC Model Analysis and Parameterization

Diffusion constant, D , used in the DC-Tofts model affects k^{trans}_{DC} values near the aneurysm wall, with $k^{trans}_{DC} = k^{trans} + 0.0511 \cdot D$ (95% CI 0.0453 – 0.0568), Figure 7a. Consequently, previous studies may have under estimated absolute k^{trans} , when a contrast point source is present (i.e. aneurysm wall, leaky tumor vs. necrotic core, etc.). While D affected measured k^{trans}_{DC} , it did not affect the univariate significance of k^{trans}_{DC} in determining risk—Group A show no significance for all D tested ($p > 0.05$), while Groups AB and B remained significant ($p < 0.05$). Figure 7b shows v_{eDC} near the aneurysm wall varies linearly with D , $v_{eDC} = v_e - 0.0107 \cdot D$ (95% CI 0.0088 – 0.0127).

Figure 8 shows the results of the LOOCV analysis. Figure 8a, shows $k^{trans}_{DC} - k^{trans}$ as a function of v_p and D . The dots shown are binned means and the surface shown is the fit generated by Equation 3 where ($a = 0.2511$, $b = 0.333$, $c = 0.01428$ and $d = 0.02364$). As seen before the two models tend to diverge near the aneurysm wall (high v_p) and as D increases k^{trans}_{DC} tends to be higher near the wall but lower in the surrounding tissue. Figures 8b through 8e show correlation and Bland Altman analysis between $\hat{k}^{trans}_{Corr}$ and k^{trans}_{DC} both in the surrounding tissue and near the aneurysm wall. $\hat{k}^{trans}_{Corr}$ shows very

high correlation with k^{trans}_{DC} (surrounding tissue: $r^2 = 0.911$, slope = 0.96149, intercept = 0.01445; wall: $r^2 = 0.899$, slope = 1.0573, intercept = 0.0031).

Association with Rupture Risk

Table 2 shows the results of the logistic regression comparing patient age, sex, aneurysm size as well as k^{trans} and $(k^{trans} - k^{trans}_{DC})$ in their ability to predict high risk saccular IAs in Group A, B, and AB (A or B). Size, k^{trans} , and $(k^{trans} - k^{trans}_{DC})$ showed significant univariate relationships ($p < 0.05$). While k^{trans} was closer to significance in Group A, $(k^{trans} - k^{trans}_{DC})$ was more significant in Group B and Group AB.

Discussion

We found that in DCE-MR permeability examination of IAs, the inclusion of a diffusion term in the Tofts model significantly changes the calculation of contrast kinetics when compared to more common Tofts modelling. Through simulation we presented evidence of contrast agent leakage through the IA wall. Finally, we have shown that a simple estimation of diffusion effects based on readily available ADC tissue values provide a computationally efficient estimate of diffusional transport in MRI (i.e. of k^{trans}_{DC} as a function of tissue specific D , k^{trans} and v_p).

Globally, both Tofts and DC-Tofts models generate highly correlated k^{trans} and v_e values. However, we see that near the aneurysm wall, the two models diverge. In Figure 4, we noted the greatest difference between the methods as the diffusion compensated model tended to generate higher values for k^{trans}_{DC} near the aneurysm, while away from the wall k^{trans}_{DC} tended to be slightly lower than Toft's model estimates. This phenomenon is a direct consequence of contrast diffusing away from the aneurysm wall into the extra cellular matrix. It should be noted here, that our reported "healthy" values appear high when compared with previously reported k^{trans} values for healthy tissue (12,13). This discrepancy is a direct result of our methodology used to investigate diffusional effects at the vessel wall. In previous studies, healthy tissue was remote from any vasculature. However, in our study, because we were interested in contrast leakage through the IA wall, ROIs were drawn immediately adjacent to the vessel of interest – causing partial volume averaging which may have artificially increased k^{trans} values. As a cross check we used methodology similar to (12) and found k^{trans} in line with previously reported ($k^{trans} = 0.0078 \pm 0.00088$, $k^{trans}_{DC} = 0.0075 \pm 0.00079$).

Because the original Tofts model does not address contrast extravasation through the aneurysm wall, the resulting kinetic parameters may reflect both contrast uptake into an inflamed aneurysm wall and the passive diffusion of contrast through a pathologically thinned wall into the CSF. Without the spatial resolution required to directly image the IA wall, typically 20–100 microns, an alternative approach to modeling the signal changes associated with pharmacokinetics of the aneurysm wall is required. Previous work hypothesized that thinner IA walls showed higher DCE-MRI wall permeability (12). In that study, however, k^{trans} and v_e were derived from the standard Tofts model, preventing the authors from addressing whether contrast was taken up within the wall or if the contrast was leaking through the wall and in turn diffusing away. We examined uptake versus diffusion in

Figure 3. Visually, it is very clear that data simulated with negligible diffusion does not match our patient data. Conversely, however, there is clearly a strong association between measured and simulated data using $D = 1.0$ and $2.0 \times 10^{-3} \text{ mm}^2/\text{s}$. Because the addition of diffusion improves association between simulated and measured data, these results imply that in addition to contrast uptake within the wall, some portion of the contrast must also diffuse through the compromised vasculature and vessel wall.

The regression models, show $(k^{trans} - k^{trans}_{DC})$ to be an independent indicator of rupture risk, as defined by imaging/anatomic metrics (Group B and AB). Interestingly, $(k^{trans} - k^{trans}_{DC})$ did not show significance in distinguishing risk groups in symptomatic patients (Group A). This may be because symptomatic patients are more likely to have active inflammation in the aneurysm wall due to wall remodeling. Active inflammation will result in more contrast uptake within the wall, and possibly less leakage through the wall, which may explain why symptomatic presentations correlated more highly with k^{trans} than with $(k^{trans} - k^{trans}_{DC})$.

Taken in concert, our results suggest that the difference between the common and DC models may quantify contrast leakage through the wall, implying that $(k^{trans} - k^{trans}_{DC})$ may be a more accurate measure of wall thickness than k^{trans} alone. Consequently, any future study investigating IA remodeling and wall thickness should include both k^{trans} and k^{trans}_{DC} as potential markers.

Finally, we present a simple estimation of k^{trans}_{DC} based on readily available ADC tissue values. This parameterization may preclude the need for time consuming iterative diffusion-compensated fitting, as well as, provide a method to retrospectively update k^{trans} where ADC imaging is available. In this study, we investigated parameterization near the aneurysm wall because IAs serve as a single distinct source of contrast. Consequently, future work is needed to confirm the effectiveness of the proposed parameterization in other disorders, specifically in tumors with multiple contrast source locations (from a damaged blood brain barrier).

Limitations

Several limitations were identified in this study. First, in order to reduce computation we estimated a homogenous diffusion constant D . Though we analyzed the effects of different D estimates, we did not investigate a spatially varying diffusion constant (more representative of tissue heterogeneity). The proposed parameterization of the diffusional effect might allow for the use of ADC values to represent the tissue heterogeneity, however, the D used in our parameterization may differ from ADC values measured using diffusion weighted imaging. Moreover, ADC values can vary based on imaging parameters; consequently, future work is still required to investigate the use of ADC directly. Secondly, we were limited to a relatively small sample size and a single institution. Finally, unlike true tissue perfusion and luminal arterial measurements, no readily available reference standard existed for k^{trans} that were within the scope for this work.

Conclusion

In this pilot study, we present the first evidence of diffusion compensated DCE-MRI modeling of contrast permeability in IAs and propose a parameterization of diffusional effects on k^{trans} . A comparison of measured against simulated data suggests contrast leakage occurs across the pathologically compromised aneurysm wall into the CSF. Finally, we show that the diffusion compensated wall permeability ($k^{trans} - k^{trans}_{DC}$) may provide an additional bioimaging marker to characterize the rupture risk of IAs.

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Figure 1.

(A) Schematic of leakage out of aneurysm and diffusion out toward areas of low concentrations. Regions of darker green represent higher concentrations (B) Schematic of simulated environment. (C) Flow chart of diffusion compensated method. Blue outline represents the typical Toft's method. The Green outline highlights diffusion compensation. addition. Red outline is complete proposed method. (D) Patient averaged AIF used in simulations. (E) Simulated concentration curves for a single voxel ($k_{true}^{trans} = 0.020$, $D_{true} = 1.0 \times 10^{-3} \text{ mm}^2/\text{sec}$, $v_{e_true} = 0.10$, $v_{p_true} = 0.10$). Dots represent noisy data, lines represent

model fits. Blue represents standard Tofts model ($k^{trans} = 0.029$, $v_e = 0.212$, $v_p = 0.11$), while Red represents DC-Tofts ($k^{trans}_{DC} = 0.031$, $v_{eDC} = 0.130$, $v_{pDC} = 0.11$).

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Figure 2.

Simulations show k^{trans} is predominately affected by diffusion constant D_{true} while minimally affected by V_{e_true} and wall thickness. The top row represents, k^{trans} values on the y-axis vs distance from vessel wall on the x-axis. Square root values are shown to better show distinction between lower k^{trans} values. The solid blue lines represent Tofts model results, while the dotted red lines are diffusion compensated results. The dots shown are mean k^{trans} from 1000 simulations. Black lines show k^{trans}_{true} values. Notice diffusion compensation tends to increase k^{trans} values close to the wall, while slightly reducing them further from the wall. In both cases moving k^{trans}_{DC} closer to true values. The bottom row shows the probability distributions in $(k^{trans} - k^{trans}_{DC})$ in the 1000 simulations. Note diffusion constant D_{true} has a drastic effect in $(k^{trans} - k^{trans}_{DC})$ while wall thickness and V_{e_true} have little effect.

Figure 3.

Simulated data suggests contrast leakage through the aneurysm wall. Probability (A–C) and cumulative (D–F) distribution functions of $(k^{\text{trans}} - k^{\text{trans}}_{\text{DC}})$ for measured data (represented in blue) and simulated data. Red and orange represent simulation results from $D_{\text{true}} = 2.0 \times 10^{-3} \text{ mm}^2/\text{s}$ and $D_{\text{true}} = 1.0 \times 10^{-3} \text{ mm}^2/\text{s}$ respectively. Green represents simulation data from $D_{\text{true}} = 0.01 \times 10^{-3} \text{ mm}^2/\text{s}$.

Figure 4.

A comparison of Tofts and DC-Tofts models shows high correlation between the models. Divergence between methods tended to occur near aneurysm wall. All images show the line of unity for visual purposes. The reported correlation coefficients (r^2) are from a linear regression (line not shown.) (A and D) pixels from surrounding tissue. (B and E) show pixel comparisons near the aneurysm wall. (C and F) show model divergence as a function of distance from the wall.

Figure 5.

Paired t -test comparison of DCE values in DC-Tofts and Tofts models. K^{trans}_{DC} shows a statistically significant increase near the aneurysm wall, while K^{trans}_{DC} near healthy vessels is slightly reduced though not significant.

Figure 6.

Permeability images demonstrate a broad distribution of kinetic values, both among subjects and within a single IA. Representative images chosen from patients with small, medium, and large aneurysms. (A, B, and C) show k^{trans} , k^{trans}_{DC} , and $(k^{trans} - k^{trans}_{DC})$ respectively. (D, E, and F) show v_e , v_{eDC} , and $(v_e - v_{eDC})$.

Figure 7. Permeability parameters vary with post-processing constant D . k_{DC}^{trans} near the aneurysm wall grows with D with $k_{DC}^{trans} = k^{trans} + 0.0511 * D$. (B) Shows v_{eDC} varies linearly near the aneurysm wall, $v_{eDC} = v_e - 0.0107 * D$.

Figure 8.

LOOCV shows the DC model parameterization is highly correlated with long chain, k^{trans}_{DC} . (A) Shows $k^{trans}_{DC} - k^{trans}$ as a function of v_p and D . Dots shown are binned means and the surface shown is the fit generated by Equation 3. (B and C) Show high correlation between $\hat{k}^{trans}_{Corr}$ and k^{trans}_{DC} both in the surrounding tissue and near the aneurysm wall. (D and E) Bland Altman analysis comparing $\hat{k}^{trans}_{Corr}$ and k^{trans}_{DC} in surrounding tissue and at the wall.

Table 1

Simulation value ranges.

	Intravascular	Vessel Wall	Interstitial Tissue
$K_{\text{true}}^{\text{trans}} (\text{min}^{-1})$	0.0	0.8	0.02
$v_{\text{e_true}} (\%)$	0.0	10	1.0 – 20
$v_{\text{p_true}} (\%)$	1.0	0.0	5.0
$D_{\text{true}} (10^{-3} \text{ mm}^2/\text{s})$		5.0	0.01 – 10

Table 2

Results of univariate and multivariate risk analysis.

Parameter	Group A (high risk = 6, low risk = 17)			Group B (high risk = 14, low risk = 9)			Group AB (high risk = 16, low risk = 7)		
	p-value	coefficient	std error	p-value	coefficient	std error	p-value	coefficient	std error
Univariate Analysis									
Sex	0.2132	-1.4917	1.1984	0.6486	0.4055	0.8898	0.8088	-0.2231	0.9220
Age	0.2226	-0.0533	0.0437	0.221	0.0507	0.0415	0.8393	-0.0084	0.0416
IA Size	0.0317	0.2739	0.1275	0.6257	-0.0374	0.0767	0.5614	0.0538	0.0927
K _{trans}	0.0531	17.4574	9.0259	0.0303	23.0784	10.6546	0.0304	36.3299	16.7791
K _{trans} _K _{trans} _{DC}	0.7139	-1.1696	3.1897	0.0237	-19.5151	8.5979	0.0171	-27.2100	11.6847
Multivariate Analysis									
IA Size	0.0406	0.2395	0.1169	0.1466	-0.1629	0.1122	0.4429	-0.0817	0.1064
K _{trans}	0.1417	18.1565	12.3555	0.0302	32.5074	14.9936	0.0367	42.8838	20.5280
IA Size	0.0258	0.2871	0.1288	0.8161	0.0221	0.0950	0.0867	0.3573	0.2086
K _{trans} _K _{trans} _{DC}	0.3961	-2.8846	3.3989	0.0252	-20.0533	8.9583	0.0147	-46.7818	19.1829
K _{trans}	0.0499	18.8892	9.6332	0.0671	24.2707	13.2557	0.0053	83.1078	29.8091
K _{trans} _K _{trans} _{DC}	0.6547	1.6235	3.6297	0.0319	-21.3202	9.9363	0.0022	-57.9266	18.8849
IA Size	0.0428	0.2426	0.1197	0.648	-0.0478	0.1046	0.1523	0.2858	0.1997
K _{trans}	0.1739	17.6657	12.9905	0.0681	26.002	14.2534	0.0110	56.0028	22.0384
K _{trans} _K _{trans} _{DC}	0.8971	-0.5023	3.8828	0.0655	-19.4838	10.5783	0.0016	-66.5703	21.0455