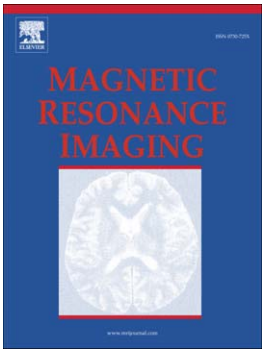

Optimization of DCE-MRI protocol for the assessment of patients with brain tumors

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Optimization of DCE-MRI protocol for the assessment of patients with brain tumors

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ABSTRACT

The interstitium-to-plasma rate constant (k_{ep}), extracted from dynamic contrast enhancement (DCE-MRI) MRI data, seems to have an important role in the assessment of patients with brain tumors. This parameter is affected by the slow behavior of the system, and thus is expected to be highly dependent on acquisition duration. The aim of this study was to optimize the scan duration and protocol of DCE-MRI for accurate estimation of the k_{ep} parameter in patients with high grade brain tumors. The effects of DCE-MRI scan duration and protocol design (continuous vs integrated scanning) on the estimated pharmacokinetic (PK) parameters and on model selection, were studied using both simulated and patient data. Scan duration varied, up to 60 minutes for simulated data, and up to 25 minutes in 25 MRI scans obtained from patients with high grade brain tumors, with continuous and integrated scanning protocols.

Converging results were obtained from simulated and real data. Significant effect of scan duration was detected on k_{ep}. Scan duration of nine minutes, with integrated protocol in which the data is acquired continuously for 5 minutes, and additional volumes at 7 and 9 minutes, was sufficient for accurate estimation of even low k_{ep} values, with an average error of 3%. Over-estimation of the PK parameters was detected for scan duration >12 minutes, being more pronounced at low k_{ep} values ($<0.1 min^{-1}$). For the model selection maps, significantly lower percentage of the full extended-Tofts-model (ETM) was selected in patients at scan duration of 5 minutes compared to >12 minutes. An integrated protocol of nine minutes is suggested as optimal for clinical use in patients with high grade brain tumors. Lower acquisition time may result in over-estimation of k_{ep} when using ETM, and therefore care should be taken using model selection.

Keywords: Dynamic Contrast Enhanced MRI (DCE-MRI), Pharmacokinetic parameters (PK), Interstitium to plasma rate constant (k_{ep}); Model Selection; Brain Tumors

1. Introduction

Dynamic contrast enhanced T_1 weighted magnetic resonance imaging (DCE-MRI) is increasingly being used for the characterization of tumor microvasculature and therapy response assessment in patients with high grade brain tumors [1, 2]. DCE-MRI is acquired using dynamic T_1 weighted images, during bolus injection of a contrast agent. When applying a pharmacokinetic (PK) model, such as the commonly used extended-Tofts-model (ETM), several pharmacokinetic parameters can be extracted, including the volume transfer constant (k^{trans}), extravascular extracellular space (v_e), interstitium to plasma rate constant ($k_{ep;}\ k_{ep}=k^{trans}/v_e$) and plasma volume ($v_p$) [3, 4]. In recent years there has been an effort to establish the use of DCE-MRI as a quantitative endpoint biomarker for patient assessment, and in particular for the assessment of antiangiogenic therapies, targeting the tumor blood supply [5].

k_{ep} represents the wash-out phase, i.e. the re-entrance of the contrast agent into the blood vessel. This parameter was shown to have a clinically important role in patient assessment and prognosis. Several studies in patients with high grade brain tumors [6, 7], rectal [8] and breast [9] cancer have reported significant high correlations between k_{ep} and several markers of tumor angiogenesis and aggressiveness (such as microvessel density), demonstrating the role of k_{ep} in differentiating between radiation necrosis and recurrent tumor. These studies suggest k_{ep} as a potential imaging biomarker for patient evaluation and prognosis [6, 7].

The estimation of DCE PK parameters is highly dependent on acquisition parameters and particularly temporal resolution and scan duration [10-12]. A systematic review performed on the existing literature on DCE-MRI up to February 2014 concluded that scan duration varied widely in pathologies of intracranial neoplasms, with median scan duration of 5.5 minutes and median temporal resolution of 5.3 seconds [13]. Higher temporal resolution (<2 seconds) is recommended in order to extract the perfusion parameters (including cerebral blood flow) and to increase the estimation accuracy of the parameters [11, 14-16], however this requirement is less applicable in current clinical practice due to the demand for sufficient brain coverage and high signal to noise ratio.

Regarding scan duration, the total scan time should be long enough to capture PK parameters with slow rate such as k_{ep} [11, 12, 17]. This implies a long scan duration in the order of $1/k_{ep}$ that may reach dozens of minutes, which is not practical in clinical settings. Several works have previously studied the effect of scan duration on the accuracy and precision of the estimated DCE-MRI PK parameters. Aerts et al. [12] studied the effect of scan duration on the precision of PK parameters in a simulation study, concluding that for accurate estimation of k^{trans} and v_e scan duration should be above 2 minutes, whereas durations of more than 7 minutes do not further

improve parameter estimation. Cramer et al. [11], studied simulated data, healthy volunteers and patients with multiple sclerosis, and reported that long acquisition duration (15 minutes) improved accuracy of tissue permeability assessment (compared to 5 minutes) with over-estimation detected at 5 minutes using the extended Tofts method. Larsson et al. [16], investigating the effect of scan duration (up to 15 minutes) on the estimations of k^{trans}, k_{ep}, v_e and v_p in patients with high grade brain tumors, found that scan duration should be at least 5 minutes for this patient group and that scan duration <5 minutes results with in -estimation of k^{trans} and k_{ep} and under-estimation of v_p and v_e.

The choice of the pharmacokinetic model was also shown to affect the accuracy of the PK parameter estimation. Nested models, in which a model is selected based on voxels, which better represent the system behavior in order to avoid over fitting, have been previously shown to improve the accuracy of DCE-MRI PK parameter estimation in animal models and in patients with glioblastoma [18, 19]. However, the effect of scan duration on the model selected has not been fully investigated.

In this work we further optimized the DCE-MRI protocol in relation to scan duration and acquisition design taking into account clinical constraints, focusing mainly on k_{ep} estimation, using both simulated data and real data obtained from patients with high grade brain tumors.

2. Materials and methods

2.1 Simulated data

Simulated data was generated based on the ETM with three free parameters: k^{trans}, k_{ep} and v_p; population-averaged arterial input function (AIF) was simulated using [20] and convolved with 1000 impulse response functions (IRFs). The IRFs were built using ETM and the convolution results were set to be the concentration time curves (CTCs). The simulated AIF and CTCs were generated with high temporal resolution, 1 millisecond intervals, to accurately simulate the continuous process, and then down-sampled to a temporal resolution of 6 seconds, to reflect the temporal resolution usually performed in clinical settings. A Gaussian noise with a realistic contrast to noise ratio (CNR) of 15, was added to both AIF and CTC. A broad range of clinically relevant PK values from patients with brain tumors, previously used in other simulation studies [12, 21], was used, with varying values of: k^{trans} = 0.05-0.5 min^{-1}, v_p = 0.01-0.3 and k_{ep} = 0.01-0.30 min^{-1}; PK parameters were extracted from different scan durations, 5, 12, 20, 30 and 60 minutes. The effect of the scan duration on different values of k_{ep} (0.03, 0.08, 0.12, 0.18, 0.23, 0.27 min^{-1}) was studied.

2.2 Real data

2.2.1 Subjects

Twenty-five MRI scans obtained from nineteen patients with high grade brain tumors (17 patients with glioblastoma and two patients with anaplastic astrocytoma grade 3) were included in this study (thirteen males, age range 19-71 years old). Inclusion criteria were: (1) patients with biopsy-proven high grade glioma, (2) patients with enhanced region on conventional contrast enhancement T_1 weighted images, (3) normal glomerular filtration rate, and no contraindication to MRI scan. The study was approved by the hospital review board, and written informed consent was obtained from all subjects.

2.2.2 MRI protocol

Scans were performed on a 3.0 Tesla MRI scanner. 13 scans were performed on a GE system (Signa EXCITE, Milwaukee, USA) using an eight channel head coil, and 12 scans were performed on a Siemens system (MAGNETOM Prisma, Germany) using a twenty channel head coil. The protocol included conventional imaging: high-resolution T_1 weighted imaging performed before and after contrast agent injection (Gadolinium Dotarem); and fluid attenuated inversion recovery (FLAIR) images. The DCE data was acquired using multi-phase 3D T_1 weighted SPGR/ FLASH imaging before and during contrast agent injection, field of view FOV= 250mm; matrix 256x256/256x184, slice thickness of 5mm, repetition time (TR) / echo time (TE) ≈ 5 / 2.2 millisecond, and flip angle (FA) = 20°. For the T_1 maps, variable flip angle (VFA) SPGR/ FLASH data was acquired with nominal FAs = 3/5/10/15/20/30°. All data was acquired with temporal resolution of 6 seconds. 20 data sets were acquired with a continues protocol of 6 minutes (with 50 seconds of baseline before contrast agent injection), and additional volumes acquired at 13 and 24 minutes following injection, maintaining the same parameters and calibrations throughout the entire scan, with anatomical scans acquired in between. Five data sets were acquired with continuous protocol of at least nine minutes (following the simulation results). A power injector (MEDRAD, Solaris) was used to infuse single dose - 0.2cc/kg of contrast agent, followed by a flush of 20cc saline, both at a constant rate of 5cc/sec. 14-20 slices were centered on the tumor area as identified in the conventional images, providing brain coverage of 70-100mm;

2.2.3 Estimation of the DCE-MRI PK parameters

k^{trans}, v_e, k_{ep} and v_p were calculated using DUSTER, an in-house code written in MATLAB for DCE Up Sampled Temporal Resolution based on the ETM [3, 4], incorporating correction for bolus arrival time (BAT) [22, 23]. The analysis pipeline included baseline T_1 maps calculated from the variable flip angle SPGR (VFA-SPGR) using DESPOT1 [24] analyzed with correction for FA deviations [22]; motion correction on the 4D data using SPM8b' rigid-body co-registration; brain

extraction using FMRIB Software Library (FSL) [25]; identification and compensation for noisy time-points; raw-signal-to-T_1-to-concentration time curves (CTC) conversion; B_1 inhomogeneity correction; semi-automatic artery localization; AIF extraction at temporal super-resolution. Fitting of the contrast agent CTCs to the PK model was done using Murase's method [26].

Model selection was performed in a manner similar to [18], by analyzing each voxel's CTC with four nested models, with the BAT parameter added to three of the four following models, enabling extraction of v_p, k^{trans}, v_e and k_{ep}; where model #1= empty model; model #2= no leakage (BAT and v_p only); model #3= leakage from the microvasculature, with negligible re-entrance (BAT, v_p and k^{trans}), and model #4= leakage and re-entrance (the full ETM model: BAT, v_p, k^{trans} and k_{ep}).

2.2.4 Calculating/assessing the effect of scan duration and protocol design on the estimated DCE-MRI PK parameters

The enhanced tumor area was extracted from the raw DCE data using independent components analysis (ICA) as previously reported [7]. The effect of scan duration on model selection was studied by comparing the percentage of areas detected as the full ETM model within the tumor area between the different scan durations.

Mean and standard error of the mean (SEM) values of the PK parameters within the enhanced tumor areas were compared for the different scan durations. Further, in order to study the effect of scan duration on the different k_{ep} ranges, the tumor area was segmented into three areas: low [$k_{ep} \leq 0.05$ min^{-1}]; intermediate [$0.05 < k_{ep} < 0.3$ min^{-1}] and high [$k_{ep} > 0.3$ min^{-1}]. The three areas were defined based on the long scan duration maps (>24 minutes), and mean and SEM values of the PK parameters were compared in the three areas for the different scan durations.

In order to further optimize the scanning protocol, continuous vs. integrated scanning protocols were compared, in five patients who had continuous protocol. Differences, in percentages, within the enhanced tumor area were calculated between the protocols for the k_{ep}, k^{trans} and v_p maps.

2.2.5 Statistical analysis

One way ANOVA (SPSS, Chicago, IL, USA) with Bonferroni correction for multiple comparisons was used to study the effect of scan duration on the PK parameters.

3. Results

3.1 Simulated data

3.1.1 The effect of scan duration on the accuracy of the estimated k_{ep}, k^{trans} and v_p

Figure 1 shows the relative errors (in absolute values) for the PK parameters for different scan durations. Scan duration had significant effect only on the k_{ep} estimation ($p<0.001$, corrected for

multiple comparison), with over-estimation for scan duration <12 minutes. In addition, larger error and standard deviations were detected for scan duration <12 minutes, with mean relative errors of 38±65% and 12±18% for 3 and 5 minutes respectively. For scan durations ≥12 minutes, the average mean relative errors reduced to 2±2%. For k^{trans} and v_p, an error of 10±3% and 12±9% were detected for all scan durations with no significant effect of scan duration.

3.1.2 The effect of scan duration for different k_{ep} values

Mean and SEM of the estimated k_{ep} values for the different scan durations and k_{ep} values, are given in Table 1. Significant differences were detected between the estimated k_{ep} obtained for scan duration of 3 and 5 minutes and the true values (p<0.001 corrected for multiple comparison), for all k_{ep} ranges. Over-estimation of k_{ep} was detected mainly in the low range (k_{ep} = 0.03 min^{-1}) and larger SEM were detected for short scan durations for all k_{ep} values. Relative errors reached 167% and 133%, for k_{ep} =0.03 min^{-1} for scan durations of 3 and 5 minutes, respectively.

Figure 2 shows the simulation results for scan duration of 3-15 minutes. Over-estimation of k_{ep} was detected for short scan durations, being more pronounced for low k_{ep} values. Scan duration of 9 minutes was found to suffice for accurate k_{ep} estimation, even for low k_{ep} values (k_{ep}=0.03min^{-1}), with estimated error of <5% for all tested k_{ep} values.

Table 1: Simulated data - mean and standard error of the mean (SEM) of the estimated k_{ep} parameter for the different scan durations.

True k_{ep}	Estimated k_{ep} [min^{-1}] (mean, SEM)					
[min^{-1}]	3min	5min	12min	20min	30min	60min
0.03	0.05±0.05	0.04±0.02	0.03±0.01	0.03±0.01	0.03±0.01	0.03±0.01
0.08	0.08±0.04	0.08±0.03	0.08±0.01	0.08±0.01	0.08±0.01	0.08±0.01
0.12	0.13±0.05	0.12±0.03	0.12±0.01	0.12±0.01	0.12±0.01	0.13±0.01
0.18	0.18±0.06	0.18±0.03	0.18±0.02	0.18±0.01	0.18±0.01	0.18±0.01
0.23	0.24±0.06	0.23±0.03	0.23±0.02	0.23±0.01	0.23±0.01	0.23±0.01
0.27	0.28±0.07	0.28±0.03	0.27±0.02	0.27±0.02	0.27±0.01	0.27±0.01

SEM = standard error of the mean

3.2 Real data

3.2.1 The effect of scan duration on the selected models

Using model selection, significant differences ($p \leq 0.05$, corrected for multiple comparison) were detected between the percentage of area defined as the full ETM (i.e. exhibiting leakage and re-entrance, non-zero v_p, k^{trans} and k_{ep}) within the tumor area, for scan duration of 5 minutes compared to 12 and 20 minutes. Smaller areas were detected as the full ETM for the short scan duration compared to the longer durations: 5 minutes= 44±21%; 13 minutes = 65±22%; and 24 minutes=77±18% (relative to the total enhanced tumor volume). Figure 3 shows model selection maps obtained from a 53 year old patient, based on DCE-MRI data, analyzed 5, 12 and 22 minutes following contrast agent injection. In this case, the model selection identified the full model (#4, red) in 83% of the tumor area for scan duration of 20 minutes, in 64% for scan duration of 12 minutes, and only 37% for scan duration of 5 minutes.

3.2.2 The effect of scan duration on the accuracy of the estimated k_{ep}, k^{trans} and v_p parameters within the enhanced tumor area

Since significant differences were detected in model selection maps between the different scan durations, comparison between the PK parameter estimations were performed for the mean values obtained from the enhanced lesion areas for the full ETM, without model selection. Significantly higher k_{ep} values (33%) were detected for the short scan duration (5 min) in comparison to the 12 and 20 minute scans. No significant differences were detected for the k_{ep} values between 12 and 20 minutes, or for the k^{trans} and v_p between the different scan durations. Figure 4 shows the mean and SEM values of the PK parameters within the enhanced tumor areas for the different scan durations.

3.2.3 The effect of the scan duration for different k_{ep} ranges

Significantly higher values were detected for low (350% increase, $k_{ep}>0.05$ min^{-1}) and intermediate (45% increase, $0.05<k_{ep}<0.3$ min^{-1}) ranges with scan duration of 5 minutes compared to scan durations of 12 and 20 minutes. No significant differences were detected for the different scan durations for the high k_{ep} range ($k_{ep}>0.3$ min^{-1}). Figure 5 shows the mean and the SEM of the PK values obtained from the various scan durations, for the different k_{ep} ranges.

3.2.4 Continuous vs. integrated scanning protocol

Based on results obtained from simulated and real data, a scanning duration of 9 minutes was set as optimal and sufficient for accurate estimation of k_{ep} even for low values with less than 5% error. In five patients two integrated protocols were tested: the first, with continuous acquisition of 5 minutes and two additional volumes acquired at 9 minutes, and the second with continuous acquisition of 5

minutes and two additional volumes acquired at 7 and at 9 minutes, both were compared with continuous protocol of 9 minutes acquisition. Small differences were detected for all PK parameters between the protocols, with mean absolute percent differences of 6±4% for $k_{ep,}$ 1±3%, for the v_p, and 4±6% for k^{trans} for the first integrated protocol, and 3±2% for $k_{ep,}$ 0±2%, for the v_p, and 3±5% for k^{trans} for the second integrated protocol, both compared to the continuous protocol of 9 minutes. The integrated protocols require less scanning time and enable the acquisition of anatomical sequences in between.

4. Discussion

In this study, the effect of scan duration on the accuracy of the estimated PK parameters obtained from DCE-MRI data was investigated, focusing on k_{ep}. Recent studies have shown the importance of the k_{ep} parameter in several clinical applications in patients with brain tumors [6, 7]. Therefore, identification of the areas with k_{ep} values and accurate estimation of this parameter, are of high clinical importance. Converging results from simulated and real data were obtained showing a significant effect of scan duration on the accuracy of k_{ep}. Using the ETM, over-estimation of the k_{ep} values was detected for scan duration <9 minutes, being more pronounced for low k_{ep} values. Using real data, significant differences were detected between model selection maps for the different scan durations, with significantly lower percentage of the full ETM detected for shorter scan durations. This study suggests an optimal protocol for DCE-MRI in patients with brain tumor, applicable in and optimized for clinical settings. An integrated protocol is proposed, with a total scan duration of 9 minutes following contrast agent injection, consisting of continuous acquisition for 5 minutes (temporal resolution of 6 seconds), and additional volumes acquired at 7 and 9 minutes, providing accurate estimation of k_{ep} values with an average error of 3%.

DCE-MRI has proven valuable in the assessment of many pathologies within the brain including intracranial neoplasms, stroke and cerebrovascular disease and Alzheimer's disease [13]. Applications of DCE in the assessment of patients with brain tumors are varied [1, 6-9, 27] and include differentiation and grading of brain lesions, early evaluation of responses to anti-cancer treatment and differentiation between radiation necrosis and recurrent tumor. The scan duration of DCE-MRI in patients with brain tumors varies widely between studies with a median imaging duration of 5.5 minutes [13]. The Radiological Society of North America (RSNA) DCE-MRI technical committee recently published a recommendation indicating that scan duration of 5 minutes post injection is sufficient for the assessment of the k^{trans} and blood normalized initial area under the gadolinium concentration curve (IAUGC) [5]. However, accurate estimation of the PK

parameters requires scan durations of $1/k_{ep}$ value, meaning a scan time up to dozens of minuets for the parameters with low frequency features such as $k_{ep,}$ clearly not applicable in clinical settings.

This study showed converging results from simulated and real data demonstrating that 9 minutes of acquisition is sufficient to reliably detect low k_{ep} values. The study provides an optimal scan duration long enough to obtain accurate PK parameters, yet short enough for clinical patients. Previous DCE-MRI studies in brain tumors demonstrated that long scan duration is required [11, 16], yet it was suggested that increasing scan duration beyond 5 minutes would increase the probability of severe patient motion [16]. In order to comply with the need for long scan duration while minimizing patient motion, integrated protocols were tested, which also minimize the actual scan duration dedicated to/used by DCE. The recommended protocol enables estimation of low k_{ep} values with 3% error (relative to continuous protocol of 9 minutes).

The accuracy of the PK parameters is highly dependent on the pharmacokinetic model used. Several models have been previously proposed [3]. For accurate estimation of the perfusion, data with high temporal resolution is needed [3, 11], however, with the currently available technology, this usually comes at the expense of spatial resolution and brain coverage, rendering it less suitable for clinical needs. The current study aimed to optimize DCE–MRI protocol in routine clinical practice, which is usually acquired with relatively low temporal resolution (6 seconds), and therefore was limited to models with up to three parameters. In brain pathologies with relatively low permeability values such as multiple sclerosis, the Patlak model was recommended [11]. However, in brain tumors the PK values can have a wide range and k_{ep} is an important parameter; therefore, the ETM is most widely used and has proven useful in a variety of clinical applications, in particular in intracranial neoplasms [3, 28].

Model selection has been proposed to improve curve fitting and the accuracy of the estimated PK parameters [18, 19]. However it should be noted that using model selection, a lower percentage of areas were detected as the full ETM within the enhanced lesion area for short scan durations. Those areas that were detected as the full ETM were mainly with high k_{ep}, which were over-estimated. Our results of over-estimation of k_{ep} using the ETM for short scan duration, is in line with previous studies [11, 16]. In short scan durations there is less information to allow for accurate estimation of k_{ep} specifically in the low range, often resulting in the mis-selection of a model with only two parameters (k^{trans} and v_p). Although nested models have been shown to be useful in animal studies and in patients with glioblastoma [18, 19], this study emphasizes that longer scan duration is necessary in order to benefit the use of model selection.

Recent studies have shown the importance of the k_{ep} parameter in several clinical applications in patients with brain tumors [6, 7]. Therefore, identification of the areas with k_{ep} values and accurate estimation of this parameter, are of high clinical importance.

Data in this study was acquired from two 3.0 Tesla MRI systems; GE (Signa EXCITE) and Siemens (MAGNETOM Prisma), showing similar results, thus demonstrating the robustness of these findings and the analysis method.

5. Conclusion

An optimized DCE-MRI protocol for patients with brain tumors is proposed, suitable for clinical settings. The recommended protocol includes an integrated protocol of nine minutes, using temporal resolution of 6 seconds for 5 minutes and additional volumes acquired at 7 and 9 minutes. This protocol provides accurate assessment of k_{ep} parameter, which has been suggested as a potential imaging biomarker for patient evaluation and prognosis.

Figure captions

Figure 1: Simulation Results showing the relative errors (Err, in percentages relative to the true value) for the estimated (a) k_{ep}; (b) k^{trans} and (c) v_p parameters for the different scan duration times.

Figure 2: Simulation Results showing the ratio between nominal and estimated k_{ep} values as a function of scan duration time total measurement time for different values of k_{ep} (in units of min^{-1})

Figure 3: (a) Post contrast T_1 weighted images and model selection maps obtained from a 53 year old patient based on DCE data, analyzed using the first (b) 5th, (c) 12th and (d) 22nd minutes following contrast agent injection.

Figure 4: Mean and standard errors of the (a) k_{ep}; (b) k^{trans} and (c) v_p values obtained for the different scan durations (5, 12 and 20 minutes); (d) k_{ep} values obtained for the different scan durations for the different k_{ep} (as defined based on long duration condition).

Figure 5: Representative k_{ep} and differences maps obtained from a patient with anaplastic astrocytoma grade 3, analyzed with scan duration of 5, 12 and 20 minutes.

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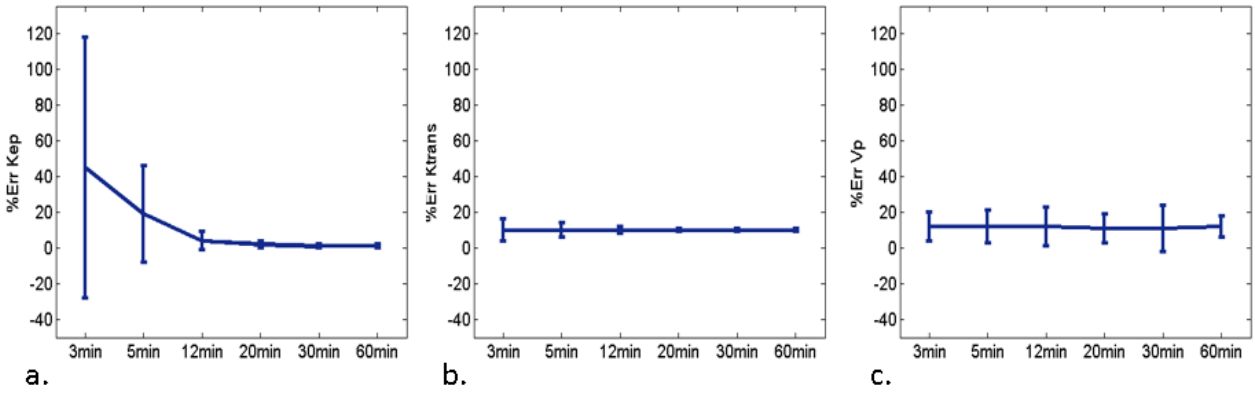

Figure 1

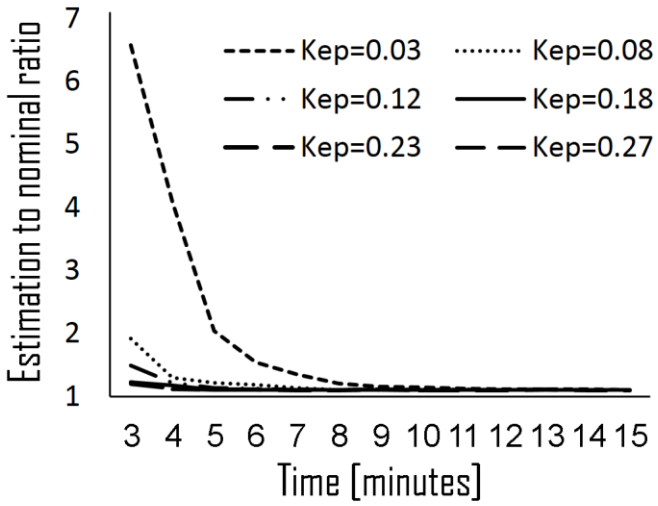

Figure 2

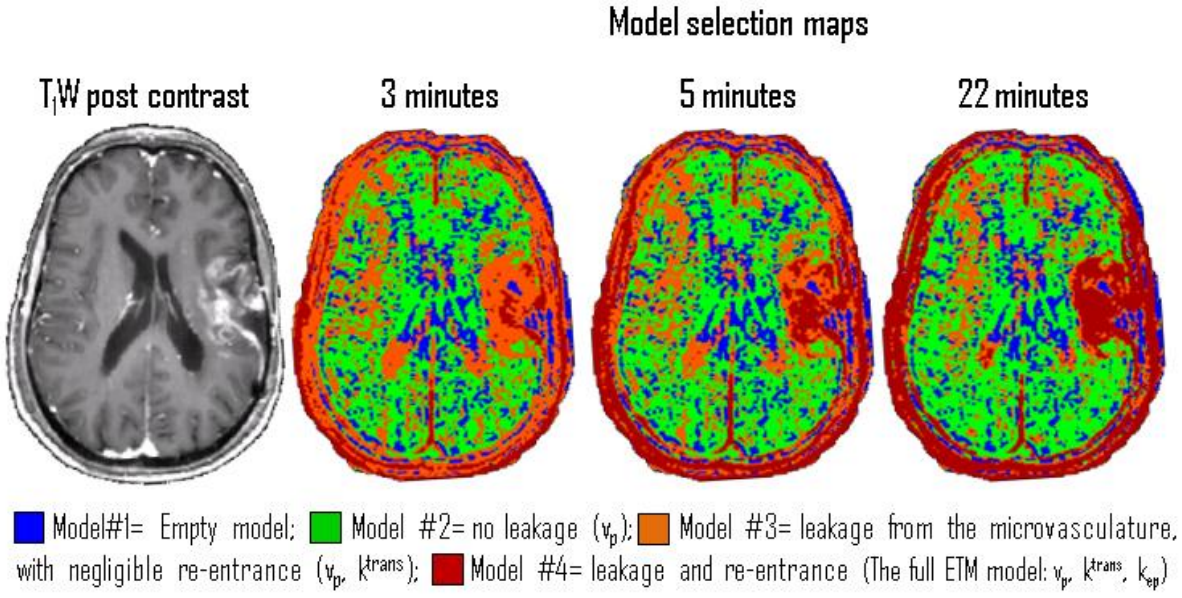

Figure 3

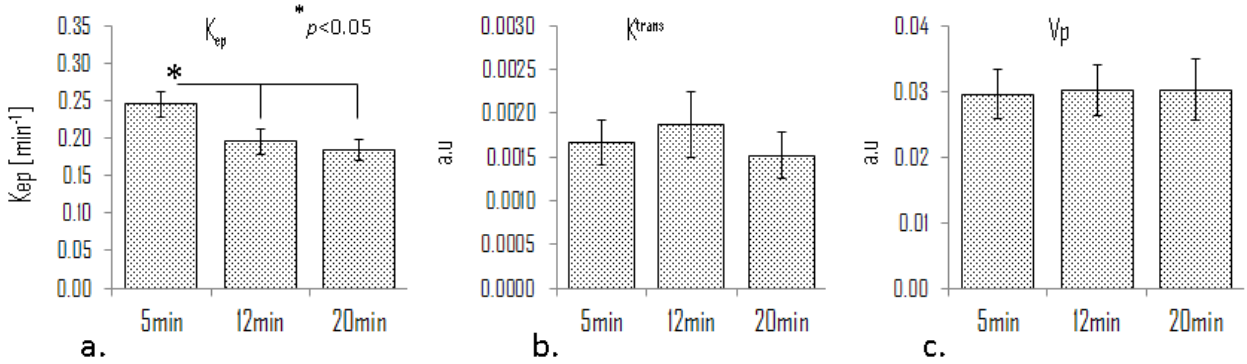

Figure 4

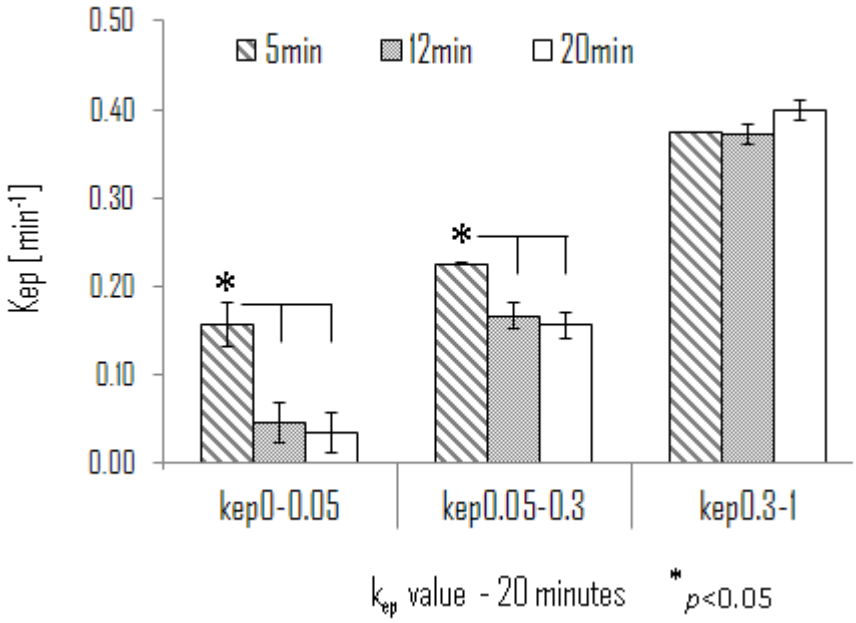

Figure 5