Tumour leakage characterized using a novel dynamic susceptibility contrast MRI model correlates with tumour interstitial space

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Introduction: Quantification of cerebral perfusion parameters using T2-weighted dynamic susceptibility-contrast MRI (DSC-MRI) is confounded by the extravasation of contrast agent through disrupted (i.e. leaky) blood brain barrier in aberrant brain tissues. An empirical DSC-MRI model that includes first-pass, re-circulation and leakage components was recently presented [1] and was shown to be capable of characterising DSC-MRI curve features in both leaky and non-leaky tissues. Leakage effects can be minimised at the time of data acquisition by pre-dosing. Furthermore, T1-weighted dynamic-contrast enhanced MRI (DCE-MRI) can be performed whilst pre-dosing which can provide additional vascular information. In this study, we evaluate this novel DSC-MRI model on brain tumour datasets which have been pre-dosed. We aim to establish relationships between kinetic parameters derived from DCE-MRI and DSC-MRI studies.

Materials and methods: Imaging was performed at seven different time points, after temozolomide (TMZ) chemotherapy (Ex1-Ex4) and after TMZ and bevacizumab (BEV) (Ex5-Ex7), on a patient with glioblastoma multiforme (GBM) on a 1.5T Siemens, Symphony scanner. T1-weighted DCE-MRI sequences (3D GE, TE 1.41ms, TR 4.41ms, α 2°/24°, 256x256 matrix, dynamic duration 7 min) and DSC-MRI sequences (2D GE, TE 20ms, TR 48ms, α 40°, 128x128 matrix, 60 dynamic measurements, total imaging time 2 min) were performed using 0.1mmol/kg and 0.2 mmol/kg body weight of Gd-DTPA respectively. Post-contrast T1-weighted anatomical sequence (2D SE, TE 17ms, TR 305ms, 256x156 matrix) was performed at the end of the imaging session. During post-processing, the matrix of the DCE-MRI data was down-sampled to 128x128 to match that of the DSC-MRI data. Dynamic DCE- and DSC-signal intensities were converted to Gd-DTPA concentrations on a per pixel basis by calculating dynamic T1s and R2*s, respectively. The extended Tofts' model was fitted to the DCE-MRI concentration curves with a population-averaged arterial input function [2] DCE-MRI parameters obtained were: Ktrans, ve, kep, vp and IAUGC60. An empirical model [1] was fitted to the DSC-MRI concentration curves and the following parameters were obtained: BV, BF, MTT and the amplitude and rate constants of the tertiary phase, a3 and m3, respectively. These tertiary phase parameters characterize the equilibrium phase (where BBB is intact) or leakage (where BBB is disrupted). Regions-of-interest were drawn to encompass the solid tumour component whilst avoiding the cystic core. Median ROI values were used to explore relationships between the parameters via linear regression analyses and by computing the Pearson correlation coefficients and corresponding significance levels.

Results: The disease was found to progress during the course of treatment with TMZ (Ex1-Ex4). Pseudo-response was observed during treatment with TMZ and BEV (Ex5-Ex7). Contrast agent concentration curves from a tumour pixel measured using DCE- and DSC-MRI studies are shown in figure 1 together with their respective model fits. The DCE-MRI concentration curve depicted is characteristic of a slowly enhancing tumour and the corresponding DSC-MRI concentration curve shows significant leakage. These prominent leakage features, despite pre-dosing, were seen at most of the imaging time-points. Parameters with correlation coefficients $r^2 > 0.80$ and $p < 0.05$ are summarized in table 1. In addition to strong correlations between DCE-parameters such as ve and IAUGC60 ($r^2 = 0.901$, $p = 0.003$), the DSC-parameter, a3 and DCE-parameter, ve were found to strongly correlate ($r^2 = 0.837$, $p = 0.015$). These relationships were maintained despite the treatment status. A linear regression plot for ve and a3 is shown in figure 2. Example DSC- and DCE-parametric maps (BV, a3 and ve) from two separate imaging time-points are shown in figure 3 with the corresponding post-contrast T1w anatomical images. For parametric map a3, pixels with m3 = 0 are displayed in black as these correspond to cystic regions. A large degree of spatial agreement can be seen between the a3 and ve maps as well as with the post-contrast T1w image. BV, a parameter widely used in DSC-MRI studies, did not demonstrate obvious spatial agreement with any of the DCE-maps nor did it correlate strongly with other parameters.

Discussion and conclusions: It was found that pre-dosing did not completely remove leakage effects in our DSC-MRI data. This is likely to be due to the large interstitial spaces (ve) within the tumour. The strong correlation found between DCE-parameter, ve and DSC-parameter, a3 provides further support for this finding. Results from this study have highlighted the value of the novel empirical DSC-MRI model which characterizes the tertiary phase of the contrast uptake. Results suggest it may be possible to obtain information on tumour interstitial space, in addition to BV, BF and MTT, from a single DSC-MRI measurement by employing this novel model. This is beneficial because DSC-MRI measurements are shorter than DCE-MRI measurements. Further work will be carried out to evaluate the model in different tumour types (both intra- and extra-cranial tumours) and in different clinical trial settings to evaluate the potential of the tertiary amplitude in assessing response to treatment.

References: [1] Orton MR. et al. In Proc ISMRM 2012. 5059. [2] Parker G. et al, MRM. 2006. 56:993-1000
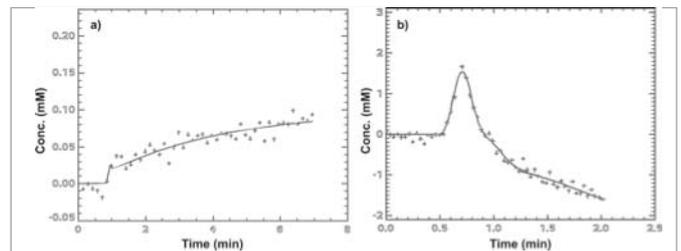
Figure 1: Concentration curves from a tumour pixel measured using a) DCE- and b) DSC-MRI studies together with their respective model fits. DSC-MRI concentration curve shows significant leakage despite pre-dosing

Param. 1	Param. 2	Correlation coefficient, r2
ve (DCE)	IAUGC60 (DCE)	0.901 (p = 0.003)
vp (DCE)	kep (DCE)	0.826 (p = 0.019)
ve (DCE)	a3 (DSC)	0.837 (p = 0.015)

Table 1: Pairs of kinetic parameters with Pearson correlation coefficients $r^2 > 0.80$ and $p < 0.05$

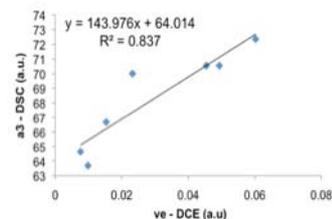

Figure 2: Linear regression plot of a3 vs. ve for all 7 examinations. A strong correlation ($r^2 = 0.837$, $p = 0.015$) between these DSC- and DCE-derived parameters were found.
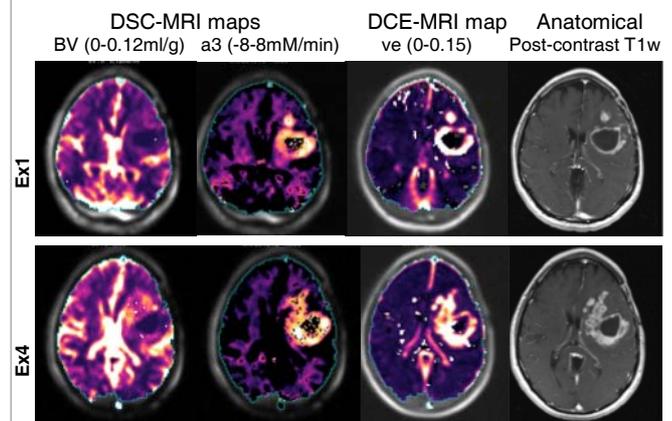

Figure 3: Example DSC- and DCE-parametric maps (BV, a3 and ve) with the corresponding post-contrast T1w anatomical images acquired at Ex1 and Ex4.