Low Dose T1W DCE-MRI for Early Time Points (ET) Perfusion Measurement in Patients with Intra-Cranial Tumors: A Pilot Study Applying the Microsphere Model to Measure Absolute Cerebral Blood Flow

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Tumors: A Pilot Study Applying the Microsphere Model to
Measure Absolute Cerebral Blood Flow**

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**Low Dose T1W DCE-MRI for Early Time Points (ET) Perfusion Measurement in
Patients with Intra-Cranial Tumors: A Pilot Study Applying the Microsphere
Model to Measure Absolute Cerebral Blood Flow**

Abstract

BACKGROUND:

Previous studies have measured cerebral blood flow (CBF) with DSC-MRI using an “early time points” (ET) method based on microsphere theory.

PURPOSE:

To develop and assess a new ET method for absolute CBF estimation using low-dose high-temporal (LDHT) T1W-DCE-MRI.

STUDY TYPE:

Retrospective cohort study

SUBJECTS:

Seven patients with sporadic vestibular schwannoma (VS) who underwent test-retest imaging; one patient with glioblastoma multiforme (GBM) imaged pre-treatment; and twelve neurofibromatosis type 2 (NF2) patients undergoing bevacuzimab treatment, imaged pre- and 90 days post-treatment.

FIELD STRENGTH/SEQUENCE,

LDHT-DCE-MRI was performed at 1.5 and 3.0T, using 3D spoiled gradient echo with phase cycling. DSC-MRI performed in one patient, using 3D echo-shifted multi-shot echo-planar imaging (PRESTO) at 3T.

ASSESSMENT:

Through Monte Carlo simulations, CBF estimation using three newly developed average contrast agent concentration (AC) based methods (ACrPK, ACrMG, ACcomb), was compared against conventional maximum gradient (MG) approaches, at varying Rician noise levels. Reproducibility and applicability of the ACcomb method was assessed in our sporadic-VS/GBM/NF2 patient cohort respectively.

STATISTICAL TESTS:

Reproducibility was measured using test-retest coefficient of variation (CoV). Pre- and post-treatment CBF values were compared using paired t-test with Bonferroni correction.

RESULTS:

Monte Carlo stimulations demonstrated that AC-based methods, particularly ACcomb, offered superior accuracy to conventional MG approaches. Overall test-retest CoV using the ACcomb method was 5.76 in normal-appearing white matter (NAWM). The new ACcomb method produced GM/WM CBF estimates in the NF2 patient cohort of $55.9 \pm 13.9 / 25.8 \pm 3.5$ on day 0; compared to $155.6 \pm 17.2 / 128.4 \pm 29.1$ for the classical MG method. There was a moderate (10% using ACcomb and ACrpk) increase in CBF of

NAWM 90 days post therapy ($P = 0.03$ and 0.005).

DATA CONCLUSION:

Our new AC based method of CBF estimation offers excellent reproducibility, and displays more accuracy in both Monte Carlo analysis and clinical data application, than conventional MG based approaches.

Keywords: Low dose gadolinium based contrast agent, cerebral blood flow, dynamic susceptibility contrast-enhanced MRI, dynamic contrast enhanced MRI, early time points, intra-cranial tumor

INTRODUCTION

The microsphere method is a classic technique for blood flow quantification, based on the principle that injected labelled particles, which are too big to fit through the capillaries, are delivered to each tissue element in proportion to the local blood flow, and remain trapped there for subsequent counting. While the classical microsphere method is restricted to animal studies, the microsphere model¹⁻³ has become the basis for blood flow quantification in both computed tomography (CT)³⁻⁵, and perfusion MRI⁶⁻⁹.

The maximum gradient (MG) method for calculation of cerebral blood flow (CBF) is based on the microsphere model and has been widely applied in perfusion CT^{3,10}. Recently, Kwong et al^{7,11,12} proposed a technique utilizing the early data points of the contrast agent (CA) bolus for relative CBF (rCBF) calculation with dynamic susceptibility contrast (DSC) MRI. They used measurement from early time points before the gadolinium based contrast agent (GBCA) has left the tissue, i.e. the time window which meets the microsphere prerequisite. They named the region of the time course curve that meets the requirements of the microsphere model the “early time points window (ETW)” and the analysis technique the “early time points” (ET) method. They proposed that as long as the microsphere prerequisite is satisfied, different ways of manipulating the early rising bolus concentration time course would theoretically yield the same rCBF result, but that one method could prove superior to another under specific noise conditions, and that measurement of absolute blood flow could be achieved with sampling of arterial blood from appropriate arteries^{7,11,12}.

The MG method has however, not been broadly accepted in T1 weighted (T1W) dynamic contrast enhanced (DCE) MRI evaluation of CBF¹³. There are two main reasons for this: Firstly, the use of the MG method in DCE-MRI data requires that the microsphere prerequisite is met⁷ which depends on various factors, including: contrast bolus volume, injection rate and the patient's cardiac output¹⁰. Secondly, the MG method requires good enhancement-to-noise ratio (ENR, maximal signal change divided by the standard deviation of the baseline of the DCE-MRI), which may not always be met in early time-point DCE MRI images used to calculate perfusion. The aim of the current study was to therefore develop and assess a new methodology for absolute CBF estimation which uses data derived from a low dose whole brain 3D coverage T1W DCE MRI acquisition, and is based on the microsphere and ET strategies.

MATERIALS AND METHODS

Patients

We retrospectively analyzed MRI data from twenty patients, which had been prospectively collected for a previous study using the same T1W DCE MRI protocol. Twelve patients with type 2 neurofibromatosis (NF2), seven patients with sporadic vestibular schwannomas (VS), and one patient with histologically proven glioblastoma multiforme (GBM) were recruited into the study. Ethical approval was in place for the study (NHS Health Research Authority; NRES committee North West 13/NW/0131) and all participants had previously consented for later data analysis of their MRI data. Amongst the twelve NF2 patient cohort there were 21 vestibular schwannomas and 11

meningiomas. All twelve patients with NF2 were undergoing treatment with the anti-Vascular Endothelial Growth Factor antibody, bevacizumab, and underwent imaging on two occasions: pre-treatment (day0) and 3 months (day90) following treatment. The seven patients with sporadic VS cohort were imaged on two separate occasions 4 days apart.

MRI

The 12 Patients with NF2 and seven patients with sporadic VS were imaged on a 1.5T scanner (Philips Achieva, Best, Netherlands) using an 8-channel head coil. The patient with a GBM was imaged on a 3.0T scanner (Philips Achieva, 3.0TX).

The following scanning protocols were employed: 1) Higher spatial resolution morphological MRI, e.g. high spatial resolution non-enhanced (C-) 3D T1-weighted (T1W) MRI to support tissue segmentation, and contrast enhanced (C+) T1W gradient echo for extracting tumor enhanced volume. 2) DCE-MRI. Low GBCA dose, high temporal resolution (LDHT) DCE-MRI data were collected as the first part of the dual temporal resolution technique, an improved coverage and spatial resolution—using Dual Injection dynamic Contrast-Enhanced (ICR-DICE), as described previously¹⁴. Variable flip angle ($\alpha = 2^\circ, 8^\circ, 15^\circ$ and 20°) acquisitions were performed prior to the LDHT-DCE series for native longitudinal relaxation rate (R_{1N}) mapping. The LDHT-DCE MRI uses the same 3D GRE sequence with a flip angle of 20° , with an FOV of 240 x 240 mm, image matrix of 96 x 96 x 22 voxels, sense acceleration factor of 1.8, and temporal

resolution of $\Delta t = 1.0$ s ($n = 300$) (Fig. 1a). A low dose (fixed volume of 3 ml, 0.02 mmol/kg depending on body weight) of macrocyclic GBCA (gadoterate meglumine; Dotarem, Geurbet, Roissy, France) was administered by power injector as an intravenous bolus at a rate of 3 ml/s, followed by a chaser of 20 mls of 0.9% saline administered at the same rate. This LDHT acquisition was then followed by a full GBCA dose (0.1 mmol/kg), high-spatial resolution (matrix size of $240 \times 240 \times 70$) acquisition (FDHS) DCE MRI. As the name of ICR-DICE indicates, a large acquisition volume covering the whole brain is used in order to eliminate unsaturated flowing spins enter the imaging slab, which can cause undesirable signal enhancement and generate image artifacts. To obtain satisfactory elimination of in-flow artifacts, it is paramount important that (1) the volume coverage of 3D slab is large enough to incorporate the top of the brain, the circle of Willis and the terminations of the internal carotid arteries bilaterally (Fig 1b); (2) The read gradient of the 3D slab is orientated in parallel to the vessels for the maximum saturation of the out slab upstream. 3) For the GBM patient, following the T1W-DCE MRI acquisition, a dynamic susceptibility contrast enhancement imaging (DSC) series was undertaken, using a 3D echo-shifted multi-shot echo-planar imaging (3D PRESTO)¹⁵. The PRESTO series used scan parameters of TR/TE/flip angle of 20 ms/26.5 ms/10°. The contrast bolus administered for the T1W-DCE MRI acquisitions was used as the preload for leakage correction, and a third injection of 0.1 mmol/kg of Dotarem followed by a saline flush was administered at the 5th dynamic frame of the 3D PRESTO-DSC. The DSC has an image matrix of $128 \times 128 \times 30$ and Δt of 1.5 s.

Image Co-registration and Segmentation

SPM¹⁶ was used for image co-registration and segmentation of the MRI data into GM, WM, and CSF. Three probability maps representing GM, WM and CSF, segmented from the 3D T1W images, were re-aligned and re-sliced to the space of the 3D individual volumes of the DCE-MRI of the subject. WM and GM masks were generated using a probability cutoff of 0.975, and these masks were then used for subsequent quantitative analysis. Figure 1b shows the segmented GM, WM, and tumor mask overlaid on the aligned last frame of the 3D LDHT and FDHS.

Measurement of Vascular Input Function (VIF)

Estimation of absolute CBF requires identification of a suitable AIF, and for practical purposes, a good approximation may be achieved by measuring the input function in the superior sagittal sinus (SSS)^{3,17}. Our VIF measurement method for the T1W LDHT data has been previously described and utilizes a semi-automatic extraction method, to identify voxels within the SSS that display maximum enhancement during the first pass of the CA bolus¹⁸.

In order to investigate variations in the shape of VIFs from individually measured $C_b(t)$ curves we retrospectively inspected VIFs from all previous LDHT T1W DCE MRI studies performed in our laboratory that used the same injection protocol. In total 55 VIFs from 55 visits of 36 patients with NF2 (n = 20), sporadic VS (n = 7), and GBM (n = 9) were analyzed. All participants had consented for later retrospective analysis of their data.

We examined variations in the VIF to identify the range in the number of measurement points that can be identified in the early time points window.

Data from the T2*W DSC acquisition was processed using the commercially available software tool (MISar, Apollo Medical Imaging, Melbourne, Australia), which incorporates an automated AIF detection algorithm. This algorithm performs pixelwise calculation of bolus arrival time, height, width and area under curve (AUC) of the $\Delta R2^*$ signal, and identifies the AIF as the cluster of pixels which show early arrival, large AUC, high peak height and narrow peak width.

The Microsphere Model

A prerequisite for the application of the microsphere theory is “sufficient organ retention”³. In fact, for a time period less than the minimum intravascular transit time, any indicator behaves like a microsphere, in that no indicator that has arrived in an organ will have yet left it. During this time, the organ ‘collects’ counts, i.e. performs a ‘biological’ integration of the arterial counts. ‘Mathematical’ integration of the arterial counts, i.e. a running sum of the frame-by-frame counts, therefore generates a curve which has the same shape as the organ curve². Mathematically, the microsphere model can be written as:

$$C_t(t) = f \cdot \int_0^t C_b(t') dt' \quad \text{with } t \in ETW, \quad [1]$$

where the tissue GBCA concentration, $C_t(t)$, is equal to the amount of GBCA delivered to 1 ml of tissue by time t , f is the perfusion term (usually expressed as $\text{ml minute}^{-1} \text{ ml}^{-1}$)² and $C_b(t)$ is the arterial blood concentration (input function).

Then, according to the fundamental theorem of calculus, we have

$$\frac{dC_t(t)}{dt} = f \cdot C_b(t), \quad [2]$$

and

$$\max\left(\frac{dC_t(t)}{dt}\right) = f \cdot \max(C_b(t)). \quad [3]$$

Eq. 3 implies that the maximum gradient of the upslope of the first-pass $C_t(t)$ is reached at the same time as the regional arterial peak under the microsphere prerequisite:

$$t_{MG} = t_{AIF_peak} \quad \text{with } t \in ETW, \quad [4]$$

where t_{MG} and t_{AIF_peak} are the time to the maximum gradient of $C_t(t)$ and the time to the peak of arterial input function (AIF), respectively.

The MG method for blood flow derivation is then expressed as:

$$f = \max\left(\frac{dC_t(t)}{dt}\right) / \max(C_b(t)). \quad [5]$$

The New T1W-ET Methods For Absolute CBF Estimation

The new T1W-ET methods are based on the following two hypotheses:

- I) With a low dose compact bolus, the whole upslope segment prior to the first pass peak of the tissue concentration-time curves can be taken as the early time window (ETW), and the working data range for the CBF measurement.
- II) When the effects of noise are considerable, an averaged concentration (AC) based method, especially when applied on data points located in a segment with higher ENR, is superior to a MG based method.

To assess the validity of our low dose T1W DCE MRI protocol for CBF evaluation using the microsphere model, i.e. whether Eq. 1 does hold true for our data, we tested whether the integrated input curve (INT_{aif}) could be scaled so that it paralleled (or aligned after time shifting) the rising bolus time course of the tissue uptake curve, and if the required scaling factor was within the expected range of the cerebral blood flow (f) for the type of the tissue tested.

The first step of the T1W-ET methods is to identify the first pass peak point of the tissue concentration-time curve, which is the point of maximum enhancement within the 30 s time period following the bolus arrival time of the global AIF. The two consecutive data points which display the greatest difference in tissue enhancement within the time segment between the AIF bolus arrival and the first pass peak point, are then found. Five different ways of manipulating the rising bolus concentration time course were compared for absolute CBF evaluation:

- 1) The classical maximum gradient (MGclassical) method - the two consecutive data points which display the greatest difference in tissue enhancement on the rising bolus time course are identified. The maximum gradient is calculated as $(\Delta C_t(t))_{\max} / \Delta t$, and used in Eq [5] to determine CBF.
- 2) The upslope method (the slope method) - the two data points, i and $i+1$, displaying the greatest difference in enhancement are identified and the slope over these two points and two adjacent points $[i-1, i, i+1, i+2]$ is estimated by linear regression. This slope is then used as the numerator in Eq. [5] for calculating CBF.

The next two methods use the running average of three consecutive data points as the value of $C_t(t)$ in Eq. [1] for CBF evaluation. Both methods choose a reference time point (t_{ref}) other than the time of bolus arrival (TOA), and identify data points located on the upper part of the rising bolus time course (a segment with higher ENR).

- 3) Averaged concentration referencing t_{MG} (the ACrMG method), where $t_{\text{MG}} = (t_i + t_{i+1})/2$. The running average of three data points $[i+1, i+2, i+3]$ was used as the value of $C_t(t)$, therefore $t = t_{i+2} = t_{\text{MG}} + 1.5 \cdot (\Delta t) = t_{\text{AIF_peak}} + 1.5 \cdot (\Delta t)$ in Eq. [1]. The value of $t_{\text{AIF_peak}}$ was found from the gamma variant fit of the $C_b(t)$.
- 4) Averaged concentration referencing t_{peak} (the ACrPK method), where t_{peak} was the tissue peak time. If the time point for the tissue peak was i_{peak} , the running average of three data points $[i_{\text{peak}}-1, i_{\text{peak}}-2, i_{\text{peak}}-3]$ was used as the value of $C_t(t)$. For

convenience, we used $t = t_{\text{AIF_peak}} + 1.5 \cdot (\Delta t)$ as the upper time limit in integration of AIF, as same as in the ACrMG method.

- 5) Finally, based on the results from Monte Carlo error analysis of the above four methods, we developed a new method for calculation of the averaged concentration. The new method takes the average of the CBF values obtained from the ACrMG and ACrPK methods. We called the combined method the ACcomb method.

We denoted the absolute CBF estimated using the five methods as T1W-CBF_{ET} which comprises CBF_{ACrMG}, CBF_{ACrPK}, CBF_{ACcomb}, CBF_{MGclassical}, and CBF_{slope}, respectively.

Monte Carlo Simulation For Error Analysis

Monte Carlo simulation was used to investigate the effects of noise on the CBF values estimated with the five T1W-ET methods. The WM and GM GBCA concentration curves were simulated based on the microsphere model and the hypothesis that the ETW (i.e., the working data range for the CBF measurement) is the whole upslope segment prior to the first pass peak of the tissue concentration-time curves.

The synthesized WM and GM contrast agent concentration curves (see below), with ‘true’ CBF_{WM} = 25 ml/min/100ml and ‘true’ CBF_{GM} = 60 ml/min/100ml respectively, were converted back into SI-time curves based on the in vivo mean baseline SI, the pre-contrast T1 relaxation time (T_{10}), and a literature value of longitudinal relaxivity (4.39

$\text{mM}^{-1} \text{s}^{-1})^{19}$. The generated SI-time courses were sampled with a temporal resolution of 1.0 second, and Rician white noise with noise level (= standard deviation/ mean baseline signal) of 1%, 2%, 3%, 4% and 5% respectively was added to the simulated SI-time curves. Absolute CBF values were calculated using the synthetic data sets to produce the so-called ‘measured’ values with the five estimation methods respectively. Percent deviations (PD) of the ‘measured’ values from the ‘true’ values were calculated as: $\text{PD} = (\text{measured} - \text{true})/\text{true} \cdot 100\%$. 20000 repetitions were performed for each method to produce mean and standard deviation (SD) of PD for each CBF estimates.

In Vivo Data Processing

T1W-CBF_{ET} images were calculated for the 12 NF2 patients, the 7 sporadic VS patients, and for the one patient with a GBM. For the GBM patient, maps of T2*W-CBF and T2*W-CBV were generated from the DSC MRI using MISTar and the singular value decomposition (SVD) deconvolution method of Ostergaard et al²⁰. Previous authors have attempted to use model free deconvolution to analyse T1W DCE data²¹. We therefore also analysed the LDHT DCE-MRI data from our GBM patient using a model free SVD deconvolution approach and compared these derived values with values obtained using the T1W-CBF_{ET} and T2*W-CBF approaches.

We also carried out a tracer kinetic analysis on the T1W-DCE MRI data using the extended Tofts model (ETM)^{22,23}, to yield fractional plasma volume (v_p) and other physiological parameters such as the transfer constant K^{trans} . Figure 1c shows representative CBF_{ACcomb} images of a patient with NF2 alongside maps of v_p and K^{trans}

derived using the LDHT and FDHS acquisitions of the ICR-DICE¹⁴. As can be seen from Fig 1c, the LDHT derived K^{trans} map is free from vessel artifacts, whereas the K^{trans} map derived from the FDHS showed greater tumor heterogeneity detail thanks to the higher spatial resolution but at the expense of vessel artifacts due to overestimation of K^{trans} in areas of high v_p resulting from the low temporal resolution ($\Delta t = 10$ s).

For direct comparison between various parametric matrices, a data processing pipeline was constructed using SPM scripts¹⁶ to allow intra-subject spatial alignment between various MR images and derived parametric maps. Segmented tissue masks (WM, GM, CSF, and tumor respectively) were then applied onto parametric maps for generating ROI mean values, or for pixel-by-pixel comparison between multi-parametric maps. For repeated studies, longitudinal spatial alignment was also performed using the ending frame, i.e. the last 3D volume of the LDHT or FDHS DCE series acquired on day 0 as the destiny of the co-registration for all other images of the patient at day0 or day90. The comprehensive image spatial alignment between the T2*W-DSC and T1W-DCE images facilitated more convenient visual inspection and pixel-by-pixel comparison of T2*W-CBF and T1W-CBF_{ET} maps.

Statistical Analysis

The accuracy and precision of the five methods were compared by Monte Carlo simulation of the mean and SD of percent deviations for CBF estimates at varying levels of Rician noise.

Using the LDHT T1W DCE and T2*W DSC-MRI data from the patient with a GBM, we investigated the concordance in the relationships of T2*W-CBF vs. T2*W-CBV and T1W-CBF_{ACcomb} vs. v_p in tumor on a pixel-by-pixel basis. Pixel scatter plots and linear regression analysis were further used to assess concordance of intratumoral T1W-CBF_{ET} and T2*W-CBF estimates and to assess the intratumoral pixelwise relationship of T2*W-CBF compared to T2*W-CBV, and T1W-CBF_{ACcomb} compared to v_p . Pixelwise concordance between the derived T1W(SVD)-CBF estimates and T1W-CBF_{ET} and T2*W-CBF data is shown in supplementary data.

In order to assess the reproducibility of the ACcomb method, mean GM and WM CBF values were calculated from each MRI scan, for the 7 sporadic VS patients who underwent two consecutive DCE-MRI acquisitions. The reproducibility of each pairwise comparison was then assessed using the test–retest coefficient of variation (CoV). For each subject, i , the CoV is the standard deviation, σ_i , for the two measurements on that subject, divided by the mean, μ_i , for the subject. The overall test–retest CoV for a group of N subjects is then ^{24,25}

$$\sqrt{\sum_i (\sigma_i / \mu_i)^2 / N}.$$

To compare the pre- and post-treatment values of CBF in patients with NF2, the average CBF values of GM, WM, and tumor (VS) over the whole-volume ROIs were calculated for each visit of each patient, using the five T1W-ET methods respectively. A paired t-test was used to compare the group mean values on day0 and day90. To reduce the potential for Type I errors through multiple comparisons using the five T1W-ET

methods, the standard significance level of $P = 0.05$ was adjusted using the Bonferroni correction ($C=5$) to achieve a family-wise error rate (FEWR) of no more than 5%.

RESULTS

The VIF and the Tissue Concentration Curves Within the ETW (Hypothesis 1) From the LDHT TIW-DCE MRI Fulfills the Requirements of the Microsphere Model

Figure 2 shows variation in the shape of $C_b(t)$ curves measured from the superior sagittal sinus (SSS) of different individuals, when using the power injector with the same GBCA dose and injection rate. Of the 55 MRI exams studied 92.7%, had either 5 (43.6%), 6 (38.2%), or 7 (10.9%) data points on the upslope segment prior to the first pass peak of the measured $C_b(t)$ curves.

For a study using the microsphere model, the validity of the technical acquisition needs to be checked by ensuring that the integrated input curve, multiplied by the tissue blood flow, parallels to that of the tissue time-density curve, thus fulfilling one of the requirements of the model¹⁻³. Figures 3a and 3b demonstrate an example of this. INT_{aif} was calculated by integration of the gamma variant fit of the $C_b(t)$; the measured WM and GM curves were averaged concentration-time curves from the whole-volume ROIs, which were automatically defined from the WM and GM masks respectively. In Fig. 3a, the INT_{aif} was time-shifted and scaled to align with the rising bolus time course of the WM concentration curve, resulting in a calculated f_{wm} of 25 ml/min/100ml. In Fig. 3b, the

INT_{aif} was time-shifted and scaled to align with the rising bolus time course of the GM concentration curve, resulting in a calculated f_{gm} of 60 ml/min/100ml.

Figures 3c and 3d show a simulation of the tissue concentration curves based on the microsphere model. The flow-scaled INT_{aif} and ROI-averaged WM and GM concentration curves used in the simulation were the same as in Figs. 3a and 3b. The upslope part of the theoretical tissue curve (the working data range, ETW, for CBF measurement) was sampled from the flow-scaled INT_{aif}, while keeping the downslope part, starting from and including the tissue peak time point, of the measured tissue curve.

Averaged Concentration Methods Performed Better Than Upslope or Maximum

Gradient Methods on Monte Carlo Simulations

Figure 4 compares percent deviation (mean and SD) in CBF_{WM} and CBF_{GM} derived from ACrMG, ACrPK, ACcomb, upslope, and the traditional MG methods, using various noise levels. The traditional MG method yielded poor accuracy and precision even at small noise levels for simulated WM and GM curves. The upslope method showed better accuracy and precision than the MG method but poorer precision than the averaged-concentration methods, especially at noise levels higher than 3%. For noise levels higher than 2%, the CBF_{WM} estimates obtained from the ACrMG and the ACrPK methods behaved oppositely: the ACrMG analysis (green line) overestimates while the ACrPK (blue line) underestimates CBF_{WM}. The ACcomb method, which is the average of the ACrMG and ACrPK values, estimates CBF_{WM} more accurately, and reduces the SD of

PD in CBF_{WM} estimation (Figures 4a and 4b). The CBF_{GM} estimates (Figures 4c and 4d), showed much less variation in the three averaged-concentration methods, which may be due to the more than twofold greater ENR in the GM uptake curves relative to the WM curves for the same noise level. The overall performance of the ACcomb method was better than the other two averaged-concentration methods (ACrMG and ACrPK) at a noise level of 4% or higher, but consistently underestimated CBF_{GM} by about 5%. For noise levels $< 4\%$, the accuracy of CBF_{ACrPK} became close to, or better than that of CBF_{ACcomb} . Furthermore, comparing Fig. 4a with 4c revealed that CBF_{GM}/CBF_{WM} obtained by ACcomb would be on average around 5% lower than the ‘true’ CBF_{GM}/CBF_{WM} , while CBF_{GM}/CBF_{WM} obtained by ACrPK would be on average [2%, 5%, 11%, 14%, 15%] higher than the ‘true’ CBF_{GM}/CBF_{WM} with the error increasing with increasing noise level (0.01, 0.02, 0.03, 0.04, 0.05, respectively). This was because, although ACrPK underestimated both CBF_{GM} and CBF_{WM} , the size of the negative PD of CBF_{WM} was larger than that of CBF_{GM} .

Noise Levels For the In Vivo Pixel SI Curves Are Consistent With the Noise Levels Employed In the Simulation

Figure 5 shows in vivo signal intensity (SI) curves for GM and WM derived from individual voxels (Fig 5a and 5b) and ROIs placed within the GM and WM respectively (see Fig 5d and 5e), whereas Fig 5f shows the vascular input function. The SI baseline mean, standard deviation, noise level (= SI baseline SD/mean), ENR and the estimated CBF values are shown on the panel for each of the tissue pixel/ROI SI curves. As can be

seen, the noise levels for the pixel SI curves acquired from a 1.5T scanner show around 4% or less, consistent with the noise levels employed in the simulation.

Averaged Concentration Methods Provide More Accurate Estimation of In Vivo CBF Values Than Classical Maximum Gradient (MG)/ Upslope Methods

Figure 6a shows the CBF images derived using the LDHT T1W DCE-MRI (the left five columns) and the T2*W DSC-MRI (the right column) acquired at 3T from a patient with a right sided GBM. The left hand panel shows representative axial section taken from the acquired whole brain 3D CBF_{ACcomb} images. Using the ACcomb method, the calculated mean CBF value was 75.3 ml/min/100ml for GM and 32.3 ml/min/100ml for WM, giving a CBF_{GM}/CBF_{WM} ratio of 2.33. The derived CBF maps using the ACrMG and ACrPK methods are visually similar to the ACcomb method, but as shown in Figure 6a there is over-estimation of the mean CBF values of GM and WM when using the classical MG and the upslope methods. The mean ROI CBF values of the GM, WM and tumor derived from the five methods are listed in Table 1. Spatial alignment of the T2*W DSC-MRI to their T1W counterparts (see Figure 6a), showed expected differences in appearances of the vasculature within both the ‘normal’ brain and the tumor itself due to the susceptibility effects of intravascular contrast in T2*W images. The mean values of the T2*W-CBF and those of T1W-CBF_{ET} derived by the AC-based methods for both GM and WM are globally compatible, however, as shown in Table 1.

Close Intratumoral Pixel-by-Pixel Correlation Between T1W-CBF_{ACcomb} and Estimates of v_p Derived From Extended Tofts Model

Figure 6b shows the central slice of the 3D v_p and T2*W-CBV maps from the patient with a GBM. The depicted tumor and brain vasculature on the v_p map are visually very similar to the T1W-CBF_{ACcomb}. This is in concordance with the similarity observed between the T2*W-CBV and T2*W-CBF maps. Figure 6b also displays the scatter plots of pixel values of v_p vs T1W-CBF_{ACcomb} and T2*W-CBV vs T2*W-CBF from the tumor ROI. Visual inspection supported the use of a simple linear regression model, which showed a close correlation between T1W-CBF_{ACcomb} and v_p ($R^2 = 0.934$). A similar relationship was found between T2*W-CBV and T2*W-CBF ($R^2 = 0.853$). Nevertheless, the scatterplot of tumor voxels of maps of T1W-CBF_{ACcomb} vs. T2*W-CBF and their linear regression displayed a much weaker relationship ($R^2 = 0.263$).

CBF Estimation Using T1W(SVD) Approach Overestimates Tumor CBF

As can be seen in Table 1, when using an ROI analysis with parametric maps, T1W (SVD) methods gave mean CBF values for WM and GM compatible with the T2*W-SVD and our T1W-CBF-ET method, but overestimated CBF in the tumor itself. Our pixelwise analysis is shown in supplementary data, and showed a close pixelwise correlation between the T1W(SVD) T1W-CBF_{ACcomb} estimates for both GM and WM.

Good Reproducibility of the ACcomb Method Reported In Terms of CoVs

Table 2 details the test-retest CoV for $\text{CBF}_{\text{ACcomb}}$ obtained from the seven patients with sporadic VSs. As can be seen the overall test-retest CoV was 5.76 and 8.51 for NAWM and NAGM respectively, showing overall good reproducibility of the $\text{CBF}_{\text{ACcomb}}$ measurements and better reproducibility for NAWM measurements.

Average Concentration ET Methods Show Post-Treatment Increases In Normal Appearing WM CBF In NF2 Patients Treated With Bevacizumab

Figure 7 shows CBF (top row) maps derived from a NF2 patient with a large left sided vestibular schwannoma and four meningiomas. The v_p images derived using the ETM are also displayed for comparison in the bottom row. Slices from three levels of the 3D parametric images are shown. As can be seen there is some reduction of CBF and v_p within the VS at 90 days and the appearances of the T1W- $\text{CBF}_{\text{ACcomb}}$ maps and v_p maps are very similar at each time-point.

Table 3 lists the group mean values ($\pm$ SD) of CBF for GM, WM, and $\text{CBF}_{\text{GM}}/\text{CBF}_{\text{WM}}$ respectively for the 12 patients with NF2 treated with bevacizumab. Estimated mean values on day0 and day90 using the five different ET methods, are listed. The ACcomb produced mean CBF_{GM} of 55.9 ± 13.9 mL/100g/min. CBF_{WM} of 25.8 ± 3.45 mL/100g/min on day0, CBF_{GM} of 61.0 ± 8.28 mL/100g/min.

CBF_{WM} of 28.4 ± 3.43 mL/100g/min on day90. The ACcomb and ACrPK methods produced the highest CBF_{GM}/CBF_{WM} ratios (2.15 – 2.34), and the least intra-group SD for GM (8.04 – 13.92), and WM (3.06 – 3.45) respectively. With a paired t-test, both the AC-based methods, ACcomb and ACrPK, show a moderate increase in the group mean value of CBF in NAWM after treatment (Adjusted p values 0.03 and 0.005 respectively). Interestingly, neither the classical MG nor upslope method, show such changes in WM and GM CBF after treatment.

DISCUSSION

We present a new method based on the microsphere principle, for estimation of absolute CBF using a low dose high temporal T1W DCE MRI acquisition. This new method allows a more accurate and reliable estimation of absolute CBF, as instead of using a conventional MG-based algorithm, an averaged contrast agent concentration based method is used, which utilizes data points located in a higher ENR segment of the rising bolus time course.

Monte Carlo simulations demonstrated that these AC-based T1W-CBF_{ET} methods provided more accurate estimates of CBF compared to the MG and slope methods, especially when the ENR is low, such as within normal appearing white matter. The mean CBF of GM was, however, underestimated when using the ACrPK and ACcomb methods. The observed 5% underestimation in CBF_{GM} values using this new combined

method is, however, in alignment with published simulation results, such as those of Wu et al. using deconvolution²⁶, and those of Kwong et al. using the ET in DSC MRI⁷.

In vivo evaluation of this new T1W-CBF_{ET} algorithm in 20 patients showed that the MG method produced the poorest CBF estimates (CBF_{GM}/CBF_{WM} ratio less than 1.5) whilst the ACcomb and ACrPK methods produced a more reasonable CBF_{GM}/CBF_{WM} ratio (average 2.15 – 2.52). The CBF_{WM} calculated by ACrPK was lower than that produced by ACcomb; and the CBF_{GM} calculated by ACrPK was lower than that by ACcomb for DCE MRI 1.5T data, but higher than that by ACcomb for DCE MRI for 3T data. The CBF_{GM}/CBF_{WM} ratio produced by ACrPK (2.52 and 2.30 for 3.0T and 1.5T data respectively) was higher than that from ACcomb (2.33 and 2.15 for 3.0T and 1.5T data respectively). These in vivo observations were consistent with the Monte Carlo simulations, and can be attributed to the lower ENR on 1.5T compared with 3.0T¹³.

A correlation between CBF and CBV in both normal brain tissue^{21,27} and gliomas²⁸ has been previously reported using both a simple linear model and the Grubb formula²⁹. In our study we compared the relationships between T2*W-CBF and T2*W-CBV and between T1W-CBF_{ACcomb} and v_p on a pixel-by-pixel basis within a high grade glioma. Both pairs were highly correlated, consistent with previous results²⁸. On the other hand, there was a weak pixel wise correlation between the ET derived T1W-CBF and deconvolution derived T2*W-CBF maps. This discrepancy may be due in part to the fundamental differences in mechanism between T1 relaxivity and T2* susceptibility contrast effects³⁰. Alternatively image distortion due to magnetic susceptibility effects,

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3 especially when using fast T2*W- DSC imaging techniques may limit accurate
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5 coregistration of T1W-DCE and T2*W-DSC images thereby adversely affecting
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7 pixelwise correlations^{31,32 33}. Indeed the relatively good concordance between AC based
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9 T1W-CBF_{ET} and deconvolution derived T2*W-CBF values when using a ROI analysis
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11 suggests that this may be the case.
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17 In addition to providing more accurate reliable estimates of CBF, the reproducibility of
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19 this new AC based method was established by test re-test analysis. The overall coefficient
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21 of variation (CoV) for absolute CBF measured using the ACcomb method compared
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23 favourably with a recent study utilising both H₂O¹⁵ PET and contrast-enhanced perfusion
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31 Some authors have advocated the use of model free singular value decomposition
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33 approaches for CBF derivation from DCE-MRI data. There are, however, distinct
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35 advantages to the use of ET methods over SVD approaches. Firstly, T1W(SVD) can not
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37 distinguish signal contributions from intra- and extra-vascular space, and is thereby more
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39 affected by vessel leakage than the CBF-ET methods. In our study SVD methods applied
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41 to T1 data gave mean CBF values for WM and GM comparable to those acquired with
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43 T2*W-SVD and T1W-CBF-ET method. However, in tumors, there was overestimation of
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45 CBF, an effect we hypothesize is due to BBB breakdown and contrast leakage. In
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47 addition, perfusion calculation by deconvolution is critically dependant on the data ENR⁷.
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51 In the work by Larsson et al¹³, T1W-DCE MRI data was acquired on a 3T scanner with a
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53 GBCA dose of 0.05 mmol/kg to ensure sufficient ENR for pixelwise calculation of CBF
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using Tikhonov's procedure of deconvolution. Despite this, the authors commented that the relatively poor ENR at 1.5T prevented the calculation of CBF maps using the deconvolution approach.³⁵ Through using data points located in a higher ENR segment of the rising bolus time course, however, our ET methods suffer less from this limitation.

The CBF increases demonstrated using the ACcom and ACrPK method in normal appearing WM (NAWM) at 90 days post bevacizumab treatment were statistically significant, and exceeded our demonstrated reproducibility threshold for WM CBF measurements. This suggests that these changes are genuine rather than due to reproducibility variation, and, whilst this is a preliminary study of only 12 patients, these findings are biologically plausible, as the therapeutic effect of bevacizumab in this group is believed to result from alleviation of intracranial pressure due to reduction in intratumoural oedema³⁶. Larger studies will, however, be needed, to further investigate bevacizumab treatment related changes in microcirculatory parameters of normal-appearing brain tissues.

The key advantages of our new AC-based T1W-ET methods can be outlined as below:

- 1) *Application of T1W-ET in leaky tissue.* The T1W-ET method is less vulnerable to confounding resulting from leakage, re-circulation, and back flux^{7,11}.
- 2) *Improved robustness to low signal to noise ratio.* Through use of data points located in a higher ENR segment of the rising bolus time course, the AC-based T1W-ET method allows pixel-by-pixel calculation of CBF using T1W-DCE MRI

- acquired at both 1.5T and 3T scanners, with a GBCA dose as low as 0.02 mmol/kg.
- 3) *Simplified data processing.* When using the AC-based T1W-ET methodology there is no need to measure TOA, de-noise data, or correct for leakage and re-circulation.
- 4) *Acquiring 3D DCE-MRI covering the whole brain.* A time resolution of 1 s was chosen in this study, allowing averaging of three GBCA concentration data points when using the new T1W-ET methods, whilst permitting acquisition of 3D DCE images covering the whole brain.
- 5) *No covariance error due to multi-parameter fitting procedure.* Calculation of CBF with ACcomb does not require multi-parametric fitting, which is prone to covariance errors and ‘salt-and-pepper’ noise³⁷. The generation of CBF_{ACcomb} maps does not require filtering, in contrast to the maps generated using the two-compartment exchange model³⁷.

Finally, one important advantage of the new method is that it allows a lower dose of GBCA to be used compared to other methods of determining CBF such as DSC-MRI. To successfully utilize the microsphere model in determining CBF, a low-dose compact contrast bolus injection is optimum to ensure there is no efflux of intravascular tracer before the first pass AIF peak and to enable better determination of the arterial input function peak²⁰. Reduced contrast dose is a pertinent clinical concern, as the potential nephrotoxicity of full dose GBCA is well recognized³⁸, and there is growing evidence that gadolinium deposition may occur in the brain following repeated exposures^{39,40}.

Patients with CNS tumors, especially more benign lesions, may receive many contrast enhanced MR scans throughout their lifetime. As such, an MR acquisition method, which permits derivation of accurate perfusion metrics using a lower dose of contrast agent, may be of high clinical utility.

There are some limitations in our study. Firstly, the new AC-based methods for CBF measurements were evaluated in only a small cohort of patients with intra-cranial tumors. Secondly, the 3D whole brain acquisition used in the study comes at the expense of lower spatial resolution than methods utilized by other authors, who acquired only 4-10 slices^{7, 21,37}. Finally, a uniform value of hematocrit was used in this study, despite expected inhomogeneities in intra- and inter-subject hematocrit. Because measurements of regional cerebral blood flow are dependent upon regional hematocrit, any alteration in this may produce errors in the calculation of regional blood flow.

In conclusion, we have developed and assessed a new early time points (ET) method of estimating absolute CBF using low dose high temporal (LDHT) DCE MRI data. Monte Carlo analysis shows that this new method improves the accuracy of measured absolute CBF values at different noise levels. In vivo application of this new method showed that the acquired T1-CBF_{ET} maps displayed excellent gray-white matter flow contrast using a much smaller dose of GBCA than is used for conventional DSC experiments, and the measured values of WM and GM CBF using our new method matched perfusion values in literature. The typical test-retest coefficients of variation observed in this study suggest that T1W-ET measured CBF have sufficient reproducibility to be used in longitudinal

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3 studies, especially if large changes due to therapeutic intervention are expected, In a
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5 cohort of patients with NF2 undergoing treatment with bevacizumab, there was a
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7 moderate increase in CBF of normal-appearing white matter 90 days post therapy. Our
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9 new method offers advantages over currently used non-invasive methods of CBF
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11 measurement, and may have considerable future utility in clinical perfusion imaging.
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Appendix A. Supplementary Data

Supplementary data to this article can be found online at **DOI:** [10.17632/hg7vppf6g5.1](https://doi.org/10.17632/hg7vppf6g5.1)

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Glossary

Symbols	Interpretation	unit
AIF	Arterial input function	mmol/ml
$C_b(t)$	Blood CA concentration curve	mmol/ml
$C_t(t)$,	Tissue CA concentration curve	mmol/ml
CBF	Cerebral blood flow	ml/min/100ml
rCBF	Relative CBF	None
CBV	Cerebral blood volume	ml/100ml; ml/100g
CBF_{ET}	Absolute CBF measured by the Early time (ET) method	ml/min/100ml
CBF_{ACcomb}	CBF measured using average of the CBF values obtained from the ACrMG and ACrPK methods.	ml/min/100ml
CBF_{ACrMG}	CBV measured using averaged concentration referencing the time to maximum gradient	ml/min/100ml
$CBF_{MGclassical}$	CBF measured using classical Maximum Gradient method.	ml/min/100ml
CBF_{ACrPK}	CBF measured using averaged concentration referencing time to peak	ml/min/100ml
CBF_{slope}	CBF measured using upslope method	ml/min/100ml
Δt	Update time of DCE or DSC	s
DCE MRI	Dynamic contrast enhancement MRI	

DSC MRI	Dynamic susceptibility contrast enhancement MRI	
ENR	Enhancement-to-noise ratio	
ET	Early time method	
ETM	Extended Tofts model	
ETW	Early time window	
FDHS DCE MRI	Full dose high spatial resolution DCE MRI	
f_{gm} or CBF_{GM}	Blood flow of grey matter	ml/min/100ml
f_{wm} or CBF_{WM}	Blood flow of white matter	ml/min/100ml
GBCA	Gadolinium based contrast agent.	
GBM	Glioblastoma Multiforme (syn WHO grade IV glioma)	
HCT	Hematocrit.	none (%)
INT_{aif}	Integral of AIF	
LDHT DCE-MRI	Low dose high temporal resolution DCE MRI	
MG	Maximum Gradient	
NAWM	Normal-Appearing WM	
PD	Percentage deviation, $PD = (measured - true)/true \times 100\%$	
PRESTO	(3D) echo-shifted multi-shot echo planar imaging	
$R1_N$	Native longitudinal relaxation rate	s^{-1}

ROI	Region of interest	
SD	Standard deviation	
SSS	Superior sagittal sinus	
T1W	Longitudinal relaxation (T1) weighted (MR imaging)	
T2*W	Effective transverse relaxation (T2*) weighted	
$t_{\text{AIF_peak}}$	Time to peak of AIF	s
t_{mg}	Time to maximum gradient	s
TOA	Time of arrival of contrast bolus	s
t_{peak}	Time to peak	s
t_{ref}	Reference time point	s
TR/TE	Repetition time and echo time	ms/ms
VIF	Vascular input function	mmol/ml
v_p	Plasma volume fraction, $v_p = \text{CBV}(1 - \text{HCT})$	none (%)
VS	Vestibular Schwannoma	

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Table 1.
ROI mean values of CBF measured from the patient with GBM using different CBF calculation methods. MRI data were acquired on a 3.0T scanner.

acquisition	analysis method	CBF _{GM} (ml/min/100ml)	CBF _{WM} (ml/min/100ml)	CBF _{GM} /CBF _{WM}	CBF of tumor (ml/min/100ml)
T1W-DCE	ACcomb	75.3±64.6	32.3±22.8	2.33	96.0±52.9
	ACrMG	72.5±56.7	33.5±21.9	2.16	88.4±48.5
	ACrPK	78.2±66.2	31.1±24.9	2.52	103.7±39.5
	classicalMG.	180.1±64.6	128.9±22.8	1.39	194.4 ±52.9
	upslope	110.3±83.4	47.7±36.6	2.31	129.7±79.2
T2*W-DSC	SVD	71.5±66.6	36.7±26.9	1.95	111.0±75.6
T1W-DCE	SVD	76.3 ± 78.5	37.5 ± 27.1	2.01	130.7 ± 69.8

Table 2.

Reproducibility (CoV) of absolute CBF measured in NAWM and NAGM with the ACcomb method. Mean CBF values were calculated using ROIs at 1.5 T scanner.

Patient with sporadic VS			NAWM			NAGM		
No.	Age (y)	Sex	CBF (ml/min/100ml)			CBF (ml/min/100ml)		
			Visit 1	Visit 2	CoV	Visit 1	Visit 2	CoV
1	67	M	31.97	31.18	1.78	77.09	72.80	4.06
2	77	M	16.43	15.63	3.57	39.30	32.42	13.56
3	54	M	28.08	25.80	5.97	60.52	60.10	0.49
4	69	M	25.31	25.31	0.01	51.35	55.37	5.33
5	67	M	22.99	24.52	4.58	49.45	51.60	3.02
6	37	M	26.32	31.35	12.33	47.01	56.00	12.34
7	65	M	23.14	24.05	2.74	42.80	49.86	10.78
Mean CoV±SD			4.43±3.98			7.08±5.09		
Overall CoV			5.76			8.51		

Table 3.

Comparison of group mean CBF (ml/min/100ml) between day0 and day90 in GM, WM, and CBF_{GM}/CBF_{WM} in 12 patients with NF2, estimated using different methods. MRI data were acquired on a 1.5T scanner. *P*-values from paired two-tailed t-tests (df = 11) were listed for each paired data.

methods	tissue	CBF _{GM}			CBF _{WM}			CBF _{GM} /CBF _{WM}		
	CBF	day0	day90	<i>P</i> -value	day0	day90	<i>P</i> -value	day0	day90	<i>P</i> -value
ACcomb	mean	55.90	61.00	0.093	25.83	28.43	0.006*	2.15	2.15	0.978
	±SD	± 13.92	± 8.28		± 3.45	± 3.42		± 0.28	± 0.18	
ACrMG	mean	60.85	67.11	0.122	29.99	32.97	0.017	2.01	2.04	0.667
	±SD	± 17.13	± 9.37		± 4.36	± 4.13		± 0.31	± 0.17	
ACrPK	mean	50.94	54.88	0.094	21.67	23.90	0.001*	2.34	2.30	0.567
	±SD	± 11.51	± 8.04		± 3.06	± 3.17		± 0.28	± 0.24	
classicalMG	mean	155.56	159.50	0.726	128.35	124.08	0.721	1.25	1.32	0.198
	±SD	± 17.15	± 35.58		± 29.06	± 35.23		± 0.20	± 0.19	
upslope	mean	75.42	81.33	0.123	36.59	39.48	0.136	2.07	2.06	0.912
	±SD	± 16.60	± 16.56		± 4.45	± 6.18		± 0.38	± 0.24	

* Significant at *P* < 0.01 (with Bonferroni correction)

Figure Legends

Figure 1:

Figure 1a shows a diagram of 3D fast field echo (FFE) pulse sequence with $TR/TE/\alpha = 2.95\text{ms}/0.66\text{ms}/[2^\circ, 8^\circ, 15^\circ, 20^\circ]$, used for the LDHT-DCE-MRI. This short TR gradient recalled echo based pulse sequence is embedded with both gradient spoiler and phase cycling for the elimination of the net transverse magnetization. The gradient spoilers are applied along read and slab selection directions. The phase cycling has a phase increment angle of 117° . The 3D data block covers whole brain without use of a RF prepulse, such as the regional saturation technique (REST) by Philips to achieve minimum TR and maximum temporal resolution.

Figure 1b shows the last frame of a 3D FDHS-DCE ($T = 600$ s) acquisition (left column), in a patient with neurofibromatosis type 2 with a large right sided vestibular schwannoma (see overlaid tumor mask) and multiple meningiomas. The middle and right columns show the last frame of 3D LDHT-DCE ($T = 300$ s) overlaid with the segmented grey matter mask or segmented WM mask respectively.

Figure 1c shows maps of CBF_{ACcomb} (top left panel, in $\text{ml}/\text{min}/100\text{ml}$) and v_p derived from ETM (bottom left panel) in the same patient as shown in **Fig 1b**. The right column shows maps of K^{trans} (min^{-1}) from LDHT MRI (top) or FDHS MRI (bottom), both derived from the ETM. The LDHT derived K^{trans} map is free from vessel artifacts, whereas the K^{trans} map derived from the FDHS showed greater tumor heterogeneity detail thanks to

the higher spatial resolution but at the expense of vessel artifacts due to the low temporal resolution ($\Delta t = 10$ s).

Figure 2. a. Distribution of number of exams with various number of data points on the upslope segment prior to the first pass peak of the measured $C_b(t)$ curves. The bottom row shows the typical $C_b(t)$ curves with upslope data points of 4 (**b.** acquired from a 16-year old male of 85 kg body weight), 6 (**c.** acquired from a 16-year old female of 60 kg body weight), and 8 (**d.** acquired from a 25-year old male of 107 kg body weight).

Figure 3. Assessment of validity of LDHT-T1W DCE MRI for microsphere CBF analysis (a and b), and simulation of the ‘theoretical’ WM and GM curves for Monte Carlo error analysis (c and d). Fig. 3a shows the integrated input curve, multiplied by $f_{wm} = 25$ ml/min/100ml = 0.00417 ml/s/ml, and time-shifted to align with the rising bolus time course of the WM concentration curve. Fig. 3b shows the integrated input curve, multiplied by $f_{gm} = 60$ ml/min/100ml = 0.01 ml/s/ml, and time-shifted to align with the rising bolus time course of the GM concentration curve. Figures 3c and 3d showed the simulated WM and GM concentration curves respectively.

Figure 4. PD analysis for absolute CBF estimates using different methods. Mean (4a and 4c) and SD (4b and 4d) of percent deviations for CBF of WM (4a and 4b) and CBF of GM (4c and 4d) calculated from 20,000 Monte Carlo repetitions of fitting individual SI-time curves using the ACrMG (green), ACrPK (blue), ACcomb (red), upslope (black) and the traditional MG (purple) methods.

Figure 5. SI curves for representative voxels in GM and WM and for a ROI of a relevant size together with the vascular input function: a) a pixel GM SI-time curve; b) a pixel WM SI-time curve; c) GM (filled square) and WM (circle) ROIs; d) mean SI curve from the GM ROI; e) mean SI curve from the WM ROI; f) vascular input function measured from the superior sagittal sinus. The dashed line in each plot indicates the estimated time of bolus arrival for global AIF.

Figure 6. Figure 6a shows visual comparison of CBF images obtained from a patient with a glioblastoma multiforme on a 3T scanner. The left five columns show CBF images from the LDHT T1W DCE MRI calculated with the five ET methods. The right column shows CBF from T2*W DSC MRI calculated with a deconvolution method.

Figure 6b shows the v_p map derived from ETM (left panel), and the T2*W-CBV map (right panel) from the same patient. The 2nd panel from left shows the intratumoral pixel-by-pixel comparison of v_p and CBF_{ACcomb} , both obtained from the LDHT T1W-DCE MRI, while the 2nd panel from right shows the intratumoral pixel-by-pixel comparison of CBV and CBF derived by SVD-deconvolution, both from the T2*W-DSC MRI.

Figure 7. T1W- CBF_{ACcomb} (top row) and v_p maps (bottom row) derived using the extended Tofts model in an NF2 patient with a large left sided vestibular schwannoma and multiple meningiomas. These maps were derived from the low dose T1W DCE-MRI acquired on a 1.5T scanner, pre- and 90 days post- bevacizumab therapy. Slices from three levels of the 3D maps of CBF and v_p are displayed, which show: a vestibular

schwannoma within the left cerebellopontine angle (left two columns, white arrow); a representative slice at the level of the centrum semiovale (middle two columns); and a right sided occipitoparietal meningioma (right two columns, white arrow).

FOR PEER REVIEW ONLY

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8 **Low Dose T1W DCE-MRI for Early Time Points (ET) Perfusion Measurement in**
9 **Patients with Intra-Cranial Tumors: A Pilot Study Applying the Microsphere**
10 **Model to Measure Absolute Cerebral Blood Flow**
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17 **Abstract**

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19 **BACKGROUND:**

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21 Previous studies have measured cerebral blood flow (CBF) with DSC-MRI using an
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23 “early time points” (ET) method based on microsphere theory.
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27 **PURPOSE:**

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29 To develop and assess a new ET method for absolute CBF estimation using low-dose
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31 high-temporal (LDHT) T1W-DCE-MRI.
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34 **STUDY TYPE:**

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36 Retrospective cohort study
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40 **SUBJECTS:**

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42 Seven patients with sporadic vestibular schwannoma (VS) who underwent test-retest
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44 imaging; one patient with glioblastoma multiforme (GBM) imaged pre-treatment; and
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46 twelve neurofibromatosis type 2 (NF2) patients undergoing bevacuzimab treatment,
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48 imaged pre- and 90 days post-treatment.
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FIELD STRENGTH/SEQUENCE,

LDHT-DCE-MRI was performed at 1.5 and 3.0T, using 3D spoiled gradient echo with phase cycling. DSC-MRI performed in one patient, using 3D echo-shifted multi-shot echo-planar imaging (PRESTO) at 3T.

ASSESSMENT:

Through Monte Carlo simulations, CBF estimation using three newly developed average contrast agent concentration (AC) based methods (ACrPK, ACrMG, ACcomb), was compared against conventional maximum gradient (MG) approaches, at varying Rician noise levels. Reproducibility and applicability of the ACcomb method was assessed in our sporadic-VS/GBM/NF2 patient cohort respectively.

STATISTICAL TESTS:

Reproducibility was measured using test-retest coefficient of variation (CoV). Pre- and post-treatment CBF values were compared using paired t-test with Bonferroni correction.

RESULTS:

Monte Carlo stimulations demonstrated that AC-based methods, particularly ACcomb, offered superior accuracy to conventional MG approaches. Overall test-retest CoV using the ACcomb method was 5.76 in normal-appearing white matter (NAWM). The new ACcomb method produced GM/WM CBF estimates in the NF2 patient cohort of $55.9 \pm 13.9 / 25.8 \pm 3.5$ on day 0; compared to $155.6 \pm 17.2 / 128.4 \pm 29.1$ for the classical MG method. There was a moderate (10% using ACcomb and ACrpk) increase in CBF of

NAWM 90 days post therapy ($P = 0.03$ and 0.005).

DATA CONCLUSION:

Our new AC based method of CBF estimation offers excellent reproducibility, and displays more accuracy in both Monte Carlo analysis and clinical data application, than conventional MG based approaches.

Keywords: Low dose gadolinium based contrast agent, cerebral blood flow, dynamic susceptibility contrast-enhanced MRI, dynamic contrast enhanced MRI, early time points, intra-cranial tumor

INTRODUCTION

The microsphere method is a classic technique for blood flow quantification, based on the principle that injected labelled particles, which are too big to fit through the capillaries, are delivered to each tissue element in proportion to the local blood flow, and remain trapped there for subsequent counting. While the classical microsphere method is restricted to animal studies, the microsphere model¹⁻³ has become the basis for blood flow quantification in both computed tomography (CT)³⁻⁵, and perfusion MRI⁶⁻⁹.

The maximum gradient (MG) method for calculation of cerebral blood flow (CBF) is based on the microsphere model and has been widely applied in perfusion CT^{3,10}. Recently, Kwong et al^{7,11,12} proposed a technique utilizing the early data points of the contrast agent (CA) bolus for relative CBF (rCBF) calculation with dynamic susceptibility contrast (DSC) MRI. They used measurement from early time points before the gadolinium based contrast agent (GBCA) has left the tissue, i.e. the time window which meets the microsphere prerequisite. They named the region of the time course curve that meets the requirements of the microsphere model the “early time points window (ETW)” and the analysis technique the “early time points” (ET) method. They proposed that as long as the microsphere prerequisite is satisfied, different ways of manipulating the early rising bolus concentration time course would theoretically yield the same rCBF result, but that one method could prove superior to another under specific noise conditions, and that measurement of absolute blood flow could be achieved with sampling of arterial blood from appropriate arteries^{7,11,12}.

The MG method has however, not been broadly accepted in T1 weighted (T1W) dynamic contrast enhanced (DCE) MRI evaluation of CBF¹³. There are two main reasons for this: Firstly, the use of the MG method in DCE-MRI data requires that the microsphere prerequisite is met⁷ which depends on various factors, including: contrast bolus volume, injection rate and the patient's cardiac output¹⁰. Secondly, the MG method requires good enhancement-to-noise ratio (ENR, maximal signal change divided by the standard deviation of the baseline of the DCE-MRI), which may not always be met in early time-point DCE MRI images used to calculate perfusion. The aim of the current study was to therefore develop and assess a new methodology for absolute CBF estimation which uses data derived from a low dose whole brain 3D coverage T1W DCE MRI acquisition, and is based on the microsphere and ET strategies.

MATERIALS AND METHODS

Patients

We retrospectively analyzed MRI data from twenty patients, which had been prospectively collected for a previous study using the same T1W DCE MRI protocol. Twelve patients with type 2 neurofibromatosis (NF2), seven patients with sporadic vestibular schwannomas (VS), and one patient with histologically proven glioblastoma multiforme (GBM) were recruited into the study. Ethical approval was in place for the study (-NHS Health Research Authority; NRES committee North West 13/NW/0131) and all participants had previously consented for later data analysis of their MRI data. Amongst the twelve NF2 patient cohort there were 21 vestibular schwannomas and 11

meningiomas. All twelve patients with NF2 were undergoing treatment with the anti-Vascular Endothelial Growth Factor antibody, bevacizumab, and underwent imaging on two occasions: pre-treatment (day0) and 3 months (day90) following treatment. The seven patients with sporadic VS cohort were imaged on two separate occasions 4 days apart.

MRI

The 12 Patients with NF2 and seven patients with sporadic VS were imaged on a 1.5T scanner (Philips Achieva, Best, Netherlands) using an 8-channel head coil. The patient with a GBM was imaged on a 3.0T scanner (Philips Achieva, 3.0TX).

The following scanning protocols were employed: 1) Higher spatial resolution morphological MRI, e.g. high spatial resolution non-enhanced (C-) 3D T1-weighted (T1W) MRI to support tissue segmentation, and contrast enhanced (C+) T1W gradient echo for extracting tumor enhanced volume. 2) DCE-MRI. Low GBCA dose, high temporal resolution (LDHT) DCE-MRI data were collected as the first part of the dual temporal resolution technique, an improved coverage and spatial resolution—using Dual Injection dynamic Contrast-Enhanced (ICR-DICE), as described previously¹⁴. Variable flip angle ($\alpha = 2^\circ, 8^\circ, 15^\circ$ and 20°) acquisitions were performed prior to the LDHT-DCE series for native longitudinal relaxation rate ($R1_N$) mapping. The LDHT-DCE MRI uses the same 3D GRE sequence with a flip angle of 20° , with an FOV of 240 x 240 mm, image matrix of 96 x 96 x 22 voxels, sense acceleration factor of 1.8, and temporal

resolution of $\Delta t = 1.0$ s ($n = 300$) (Fig. 1a). A low dose (fixed volume of 3 ml, 0.02 mmol/kg depending on body weight) of macrocyclic GBCA (gadoterate meglumine; Dotarem, Geurbet, Roissy, France) was administered by power injector as an intravenous bolus at a rate of 3 ml/s, followed by a chaser of 20 mls of 0.9% saline administered at the same rate. This LDHT acquisition was then followed by a full GBCA dose (0.1 mmol/kg), high-spatial resolution (matrix size of $240 \times 240 \times 70$) acquisition (FDHS) DCE MRI. As the name of ICR-DICE indicates, a large acquisition volume covering the whole brain is used in order to eliminate unsaturated flowing spins enter the imaging slab, which can cause undesirable signal enhancement and generate image artifacts. To obtain satisfactory elimination of in-flow artifacts, it is paramount important that (1) the volume coverage of 3D slab is large enough to incorporate the top of the brain, the circle of Willis and the terminations of the internal carotid arteries bilaterally (Fig 1b); (2) The read gradient of the 3D slab is orientated in parallel to the vessels for the maximum saturation of the out slab upstream. 3) For the GBM patient, following the T1W-DCE MRI acquisition, a dynamic susceptibility contrast enhancement imaging (DSC) series was undertaken, using a 3D echo-shifted multi-shot echo-planar imaging (3D PRESTO)¹⁵. The PRESTO series used scan parameters of TR/TE/flip angle of 20 ms/26.5 ms/10°. The contrast bolus administered for the T1W-DCE MRI acquisitions was used as the preload for leakage correction, and a third injection of 0.1 mmol/kg of Dotarem followed by a saline flush was administered at the 5th dynamic frame of the 3D PRESTO-DSC. The DSC has an image matrix of $128 \times 128 \times 30$ and Δt of 1.5 s.

Image Co-registration and Segmentation

SPM¹⁶ was used for image co-registration and segmentation of the MRI data into GM, WM, and CSF. Three probability maps representing GM, WM and CSF, segmented from the 3D T1W images, were re-aligned and re-sliced to the space of the 3D individual volumes of the DCE-MRI of the subject. WM and GM masks were generated using a probability cutoff of 0.975, and these masks were then used for subsequent quantitative analysis. Figure 1b shows the segmented GM, WM, and tumor mask overlaid on the aligned last frame of the 3D LDHT and FDHS.

Measurement of Vascular Input Function (VIF)

Estimation of absolute CBF requires identification of a suitable AIF, and for practical purposes, a good approximation may be achieved by measuring the input function in the superior sagittal sinus (SSS)^{3,17}. Our VIF measurement method for the T1W LDHT data has been previously described and utilizes a semi-automatic extraction method, to identify voxels within the SSS that display maximum enhancement during the first pass of the CA bolus¹⁸.

In order to investigate variations in the shape of VIFs from individually measured $C_b(t)$ curves we retrospectively inspected VIFs from all previous LDHT T1W DCE MRI studies performed in our laboratory that used the same injection protocol. In total 55 VIFs from 55 visits of 36 patients with NF2 (n = 20), sporadic VS (n = 7), and GBM (n = 9) were analyzed. All participants had consented for later retrospective analysis of their data.

We examined variations in the VIF to identify the range in the number of measurement points that can be identified in the early time points window.

Data from the T2*W DSC acquisition was processed using the commercially available software tool (MISar, Apollo Medical Imaging, Melbourne, Australia), which incorporates an automated AIF detection algorithm. This algorithm performs pixelwise calculation of bolus arrival time, height, width and area under curve (AUC) of the $\Delta R2^*$ signal, and identifies the AIF as the cluster of pixels which show early arrival, large AUC, high peak height and narrow peak width.

The Microsphere Model

A prerequisite for the application of the microsphere theory is “sufficient organ retention”

³. In fact, for a time period less than the minimum intravascular transit time, any indicator behaves like a microsphere, in that no indicator that has arrived in an organ will have yet left it. During this time, the organ ‘collects’ counts, i.e. performs a ‘biological’ integration of the arterial counts. ‘Mathematical’ integration of the arterial counts, i.e. a running sum of the frame-by-frame counts, therefore generates a curve which has the same shape as the organ curve². Mathematically, the microsphere model can be written as:

$$C_i(t) = f \cdot \int_0^t C_b(t') dt' \quad \text{with } t \in ETW, \quad [1]$$

where the tissue GBCA concentration, $C_t(t)$, is equal to the amount of GBCA delivered to 1 ml of tissue by time t , f is the perfusion term (usually expressed as $\text{ml minute}^{-1} \text{ ml}^{-1}$) and $C_b(t)$ is the arterial blood concentration (input function).

Then, according to the fundamental theorem of calculus, we have

$$\frac{dC_t(t)}{dt} = f \cdot C_b(t), \quad [2]$$

and

$$\max\left(\frac{dC_t(t)}{dt}\right) = f \cdot \max(C_b(t)). \quad [3]$$

Eq. 3 implies that the maximum gradient of the upslope of the first-pass $C_t(t)$ is reached at the same time as the regional arterial peak under the microsphere prerequisite:

$$t_{MG} = t_{AIF_peak} \quad \text{with } t \in ETW, \quad [4]$$

where t_{MG} and t_{AIF_peak} are the time to the maximum gradient of $C_t(t)$ and the time to the peak of arterial input function (AIF), respectively.

The MG method for blood flow derivation is then expressed as:

$$f = \max\left(\frac{dC_t(t)}{dt}\right) / \max(C_b(t)). \quad [5]$$

The New T1W-ET Methods For Absolute CBF Estimation

The new T1W-ET methods are based on the following two hypotheses:

- I) With a low dose compact bolus, the whole upslope segment prior to the first pass peak of the tissue concentration-time curves can be taken as the early time window (ETW), and the working data range for the CBF measurement.
- II) When the effects of noise are considerable, an averaged concentration (AC) based method, especially when applied on data points located in a segment with higher ENR, is superior to a MG based method.

To assess the validity of our low dose T1W DCE MRI protocol for CBF evaluation using the microsphere model, i.e. whether Eq. 1 does hold true for our data, we tested whether the integrated input curve (INT_{aif}) could be scaled so that it paralleled (or aligned after time shifting) the rising bolus time course of the tissue uptake curve, and if the required scaling factor was within the expected range of the cerebral blood flow (f) for the type of the tissue tested.

The first step of the T1W-ET methods is to identify the first pass peak point of the tissue concentration-time curve, which is the point of maximum enhancement within the 30 s time period following the bolus arrival time of the global AIF. The two consecutive data points which display the greatest difference in tissue enhancement within the time segment between the AIF bolus arrival and the first pass peak point, are then found. Five different ways of manipulating the rising bolus concentration time course were compared for absolute CBF evaluation:

- 1) The classical maximum gradient (MGclassical) method - the two consecutive data points which display the greatest difference in tissue enhancement on the rising bolus time course are identified. The maximum gradient is calculated as $(\Delta C_t(t))_{\max} / \Delta t$, and used in Eq [5] to determine CBF.
- 2) The upslope method (the slope method) - the two data points, i and $i+1$, displaying the greatest difference in enhancement are identified and the slope over these two points and two adjacent points $[i-1, i, i+1, i+2]$ is estimated by linear regression. This slope is then used as the numerator in Eq. [5] for calculating CBF.

The next two methods use the running average of three consecutive data points as the value of $C_t(t)$ in Eq. [1] for CBF evaluation. Both methods choose a reference time point (t_{ref}) other than the time of bolus arrival (TOA), and identify data points located on the upper part of the rising bolus time course (a segment with higher ENR).

- 3) Averaged concentration referencing t_{MG} (the ACrMG method), where $t_{\text{MG}} = (t_i + t_{i+1})/2$. The running average of three data points $[i+1, i+2, i+3]$ was used as the value of $C_t(t)$, therefore $t = t_{i+2} = t_{\text{MG}} + 1.5 \cdot (\Delta t) = t_{\text{AIF_peak}} + 1.5 \cdot (\Delta t)$ in Eq. [1]. The value of $t_{\text{AIF_peak}}$ was found from the gamma variant fit of the $C_b(t)$.
- 4) Averaged concentration referencing t_{peak} (the ACrPK method), where t_{peak} was the tissue peak time. If the time point for the tissue peak was i_{peak} , the running average of three data points $[i_{\text{peak}}-1, i_{\text{peak}}-2, i_{\text{peak}}-3]$ was used as the value of $C_t(t)$. For

convenience, we used $t = t_{\text{AIF_peak}} + 1.5 \cdot (\Delta t)$ as the upper time limit in integration of AIF, as same as in the ACrMG method.

- 5) Finally, based on the results from Monte Carlo error analysis of the above four methods, we developed a new method for calculation of the averaged concentration. The new method takes the average of the CBF values obtained from the ACrMG and ACrPK methods. We called the combined method the ACcomb method.

We denoted the absolute CBF estimated using the five methods as T1W-CBF_{ET} which comprises CBF_{ACrMG}, CBF_{ACrPK}, CBF_{ACcomb}, CBF_{MGclassical}, and CBF_{slope}, respectively.

Monte Carlo Simulation For Error Analysis

Monte Carlo simulation was used to investigate the effects of noise on the CBF values estimated with the five T1W-ET methods. The WM and GM GBCA concentration curves were simulated based on the microsphere model and the hypothesis that the ETW (i.e., the working data range for the CBF measurement) is the whole upslope segment prior to the first pass peak of the tissue concentration-time curves.

The synthesized WM and GM contrast agent concentration curves (see below), with ‘true’ CBF_{WM} = 25 ml/min/100ml and ‘true’ CBF_{GM} = 60 ml/min/100ml respectively, were converted back into SI-time curves based on the in vivo mean baseline SI, the pre-contrast T1 relaxation time (T_{10}), and a literature value of longitudinal relaxivity (4.39

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$\text{mM}^{-1} \text{s}^{-1}$)¹⁹. The generated SI-time courses were sampled with a temporal resolution of 1.0 second, and Rician white noise with noise level (= standard deviation/ mean baseline signal) of 1%, 2%, 3%, 4% and 5% respectively was added to the simulated SI-time curves. Absolute CBF values were calculated using the synthetic data sets to produce the so-called ‘measured’ values with the five estimation methods respectively. Percent deviations (PD) of the ‘measured’ values from the ‘true’ values were calculated as: $\text{PD} = (\text{measured} - \text{true})/\text{true} \cdot 100\%$. 20000 repetitions were performed for each method to produce mean and standard deviation (SD) of PD for each CBF estimates.

In Vivo Data Processing

T1W-CBF_{ET} images were calculated for the 12 NF2 patients, the 7 sporadic VS patients, and for the one patient with a GBM. For the GBM patient, maps of T2*W-CBF and T2*W-CBV were generated from the DSC MRI using MISTar and the singular value decomposition (SVD) deconvolution method of Ostergaard et al²⁰. Previous authors have attempted to use model free deconvolution to analyse T1W DCE data²¹. We therefore also analysed the LDHT DCE-MRI data from our GBM patient using a model free SVD deconvolution approach and compared these derived values with values obtained using the T1W-CBF_{ET} and T2*W-CBF approaches.

We also carried out a tracer kinetic analysis on the T1W-DCE MRI data using the extended Tofts model (ETM)^{22,23}, to yield fractional plasma volume (v_p) and other physiological parameters such as the transfer constant K^{trans} . Figure 1c shows representative CBF_{ACcomb} images of a patient with NF2 alongside maps of v_p and K^{trans}

derived using the LDHT and FDHS acquisitions of the ICR-DICE¹⁴. As can be seen from Fig 1c, the LDHT derived K^{trans} map is free from vessel artifacts, whereas the K^{trans} map derived from the FDHS showed greater tumor heterogeneity detail thanks to the higher spatial resolution but at the expense of vessel artifacts due to overestimation of K^{trans} in areas of high v_p resulting from the low temporal resolution ($\Delta t = 10$ s).

For direct comparison between various parametric matrices, a data processing pipeline was constructed using SPM scripts¹⁶ to allow intra-subject spatial alignment between various MR images and derived parametric maps. Segmented tissue masks (WM, GM, CSF, and tumor respectively) were then applied onto parametric maps for generating ROI mean values, or for pixel-by-pixel comparison between multi-parametric maps. For repeated studies, longitudinal spatial alignment was also performed using the ending frame, i.e. the last 3D volume of the LDHT or FDHS DCE series acquired on day 0 as the destiny of the co-registration for all other images of the patient at day0 or day90. The comprehensive image spatial alignment between the T2*W-DSC and T1W-DCE images facilitated more convenient visual inspection and pixel-by-pixel comparison of T2*W-CBF and T1W-CBF_{ET} maps.

Statistical Analysis

The accuracy and precision of the five methods were compared by Monte Carlo simulation of the mean and SD of percent deviations for CBF estimates at varying levels of Rician noise.

Using the LDHT T1W DCE and T2*W DSC-MRI data from the patient with a GBM, we investigated the concordance in the relationships of T2*W-CBF vs. T2*W-CBV and T1W-CBF_{ACcomb} vs. v_p in tumor on a pixel-by-pixel basis. Pixel scatter plots and linear regression analysis were further used to assess concordance of intratumoral T1W-CBF_{ET} and T2*W-CBF estimates and to assess the intratumoral pixelwise relationship of T2*W-CBF compared to T2*W-CBV, and T1W-CBF_{ACcomb} compared to v_p . Pixelwise concordance between the derived T1W(SVD)-CBF estimates and T1W-CBF_{ET} and T2*W-CBF data is shown in supplementary data.

In order to assess the reproducibility of the ACcomb method, mean GM and WM CBF values were calculated from each MRI scan, for the 7 sporadic VS patients who underwent two consecutive DCE-MRI acquisitions. The reproducibility of each pairwise comparison was then assessed using the test-retest coefficient of variation (CoV). For each subject, i , the CoV is the standard deviation, σ_i , for the two measurements on that subject, divided by the mean-volume, μ_i , for the subject. The overall test-retest CoV for a group of N subjects is then [24,25](#)

$$\sqrt{\sum_i (\sigma_i / \mu_i)^2 / N}.$$

To compare the pre- and post-treatment values of CBF in patients with NF2, the average CBF values of GM, WM, and tumor (VS) over the whole-volume ROIs were calculated for each visit of each patient, using the five T1W-ET methods respectively. A paired t-test was used to compare the group mean values on day0 and day90. To reduce the potential for Type I errors through multiple comparisons using the five T1W-ET

methods, the standard significance level of $P = 0.05$ was adjusted using the Bonferroni correction ($C=5$) to achieve a family-wise error rate (FEWR) of no more than 5%.

RESULTS

The VIF and the Tissue Concentration Curves Within the ETW (Hypothesis 1) From the LDHT T1W-DCE MRI Fulfills the Requirements of the Microsphere Model

Figure 2 shows variation in the shape of $C_b(t)$ curves measured from the superior sagittal sinus (SSS) of different individuals, when using the power injector with the same GBCA dose and injection rate. Of the 55 MRI exams studied 92.7%, had either 5 (43.6%), 6 (38.2%), or 7 (10.9%) data points on the upslope segment prior to the first pass peak of the measured $C_b(t)$ curves.

For a study using the microsphere model, the validity of the technical acquisition needs to be checked by ensuring that the integrated input curve, multiplied by the tissue blood flow, parallels to that of the tissue time-density curve, thus fulfilling one of the requirements of the model¹⁻³. Figures 3a and 3b demonstrate an example of this. INT_{aif} was calculated by integration of the gamma variant fit of the $C_b(t)$; the measured WM and GM curves were averaged concentration-time curves from the whole-volume ROIs, which were automatically defined from the WM and GM masks respectively. In Fig. 3a, the INT_{aif} was time-shifted and scaled to align with the rising bolus time course of the WM concentration curve, resulting in a calculated f_{wm} of 25 ml/min/100ml. In Fig. 3b, the

INT_{aif} was time-shifted and scaled to align with the rising bolus time course of the GM concentration curve, resulting in a calculated f_{gm} of 60 ml/min/100ml.

Figures 3c and 3d show a simulation of the tissue concentration curves based on the microsphere model. The flow-scaled INT_{aif} and ROI-averaged WM and GM concentration curves used in the simulation were the same as in Figs. 3a and 3b. The upslope part of the theoretical tissue curve (the working data range, ETW, for CBF measurement) was sampled from the flow-scaled INT_{aif}, while keeping the downslope part, starting from and including the tissue peak time point, of the measured tissue curve.

Averaged Concentration Methods Performed Better Than Upslope or Maximum Gradient Methods on Monte Carlo Simulations

Figure 4 compares percent deviation (mean and SD) in CBF_{WM} and CBF_{GM} derived from ACrMG, ACrPK, ACcomb, upslope, and the traditional MG methods, using various noise levels. The traditional MG method yielded poor accuracy and precision even at small noise levels for simulated WM and GM curves. The upslope method showed better accuracy and precision than the MG method but poorer precision than the averaged-concentration methods, especially at noise levels higher than 3%. For noise levels higher than 2%, the CBF_{WM} estimates obtained from the ACrMG and the ACrPK methods behaved oppositely: the ACrMG analysis (green line) overestimates while the ACrPK (blue line) underestimates CBF_{WM}. The ACcomb method, which is the average of the ACrMG and ACrPK values, estimates CBF_{WM} more accurately, and reduces the SD of

PD in CBF_{WM} estimation (Figures 4a and 4b). The CBF_{GM} estimates (Figures 4c and 4d), showed much less variation in the three averaged-concentration methods, which may be due to the more than twofold greater ENR in the GM uptake curves relative to the WM curves for the same noise level. The overall performance of the ACcomb method was better than the other two averaged-concentration methods (ACrMG and ACrPK) at a noise level of 4% or higher, but consistently underestimated CBF_{GM} by about 5%. For noise levels < 4%, the accuracy of $\text{CBF}_{\text{ACrPK}}$ became close to, or better than that of $\text{CBF}_{\text{ACcomb}}$. Furthermore, comparing Fig. 4a with 4c revealed that $\text{CBF}_{\text{GM}}/\text{CBF}_{\text{WM}}$ obtained by ACcomb would be on average around 5% lower than the ‘true’ $\text{CBF}_{\text{GM}}/\text{CBF}_{\text{WM}}$, while $\text{CBF}_{\text{GM}}/\text{CBF}_{\text{WM}}$ obtained by ACrPK would be on average [2%, 5%, 11%, 14%, 15%] higher than the ‘true’ $\text{CBF}_{\text{GM}}/\text{CBF}_{\text{WM}}$ with the error increasing with increasing noise level [0.01, 0.02, 0.03, 0.04, 0.05, respectively]. This was because, although ACrPK underestimated both CBF_{GM} and CBF_{WM} , the size of the negative PD of CBF_{WM} was larger than that of CBF_{GM} .

Noise Levels For the In Vivo Pixel SI Curves Are Consistent With the Noise Levels Employed In the Simulation

Figure 5 shows in vivo signal intensity (SI) curves for GM and WM derived from individual voxels (Fig 5a and 5b) and ROIs placed within the GM and WM respectively (see Fig 5de and 5ef), whereas Fig 5f shows the vascular input function. The SI baseline mean, standard deviation, noise level (= SI baseline SD/mean), ENR and the estimated CBF values are shown on the panel for each of the tissue pixel/ROI SI curves. As can be

seen, the noise levels for the pixel SI curves acquired from a 1.5T scanner show around 4% or less, consistent with the noise levels employed in the simulation.

Averaged Concentration Methods Provide More Accurate Estimation of In Vivo CBF Values Than Classical Maximum Gradient (MG)/ Upslope Methods

Figure 6a shows the CBF images derived using the LDHT T1W DCE-MRI (the left five columns) and the T2*W DSC-MRI (the right column) acquired at 3T from a patient with a right sided GBM. The left hand panel shows representative axial section taken from the acquired whole brain 3D CBF_{ACcomb} images. Using the ACcomb method, the calculated mean CBF value was 75.3 ml/min/100ml for GM and 32.3 ml/min/100ml for WM, giving a CBF_{GM}/CBF_{WM} ratio of 2.33. The derived CBF maps using the ACrMG and ACrPK methods are visually similar to the ACcomb method, but as shown in Figure 6a there is over-estimation of the mean CBF values of GM and WM when using the classical MG and the upslope methods. The mean ROI CBF values of the GM, WM and tumor derived from the five methods are listed in Table 1. Spatial alignment of the T2*W DSC-MRI to their T1W counterparts (see Figure 6a), showed expected differences in appearances of the vasculature within both the ‘normal’ brain and the tumor itself due to the susceptibility effects of intravascular contrast in T2*W images. The mean values of the T2*W-CBF and those of T1W-CBF_{ET} derived by the AC-based methods for both GM and WM are globally compatible, however, as shown in Table 1.

Close Intratumoral Pixel-by-Pixel Correlation Between T1W-CBF_{ACcomb} and Estimates of v_p Derived From Extended Tofts Model

Figure 6b shows the central slice of the 3D v_p and T2*W-CBV maps from the patient with a GBM. The depicted tumor and brain vasculature on the v_p map are visually very similar to the T1W-CBF_{ACcomb}. This is in concordance with the similarity observed between the T2*W-CBV and T2*W-CBF maps. Figure 6b also displays the scatter plots of pixel values of v_p vs T1W-CBF_{ACcomb} and T2*W-CBV vs T2*W-CBF from the tumor ROI. Visual inspection supported the use of a simple linear regression model, which showed a close correlation between T1W-CBF_{ACcomb} and v_p ($R^2 = 0.934$). A similar relationship was found between T2*W-CBV and T2*W-CBF ($R^2 = 0.853$). Nevertheless, the scatterplot of tumor voxels of maps of T1W-CBF_{ACcomb} vs. T2*W-CBF and their linear regression displayed a much weaker relationship ($R^2 = 0.263$).

CBF Estimation Using T1W(SVD) Approach Overestimates Tumor CBF

As can be seen in Table 1, when using an ROI analysis with parametric maps, T1W (SVD) methods gave mean CBF values for WM and GM compatible with the T2*W-SVD and our T1W-CBF-ET method, but overestimated CBF in the tumor itself. Our pixelwise analysis is shown in supplementary data, and showed a close pixelwise correlation between the T1W(SVD) T1W-CBF_{ACcomb} estimates for both GM and WM.

Good Reproducibility of the ACcomb Method Reported In Terms of CoVs

Table 2 details the test-retest CoV for CBF_{ACcomb} obtained from the seven patients with sporadic VSs. As can be seen the overall test-retest CoV was 5.76 and 8.51 for NAWM and NAGM respectively, showing overall good reproducibility of the CBF_{ACcomb} measurements and better reproducibility for NAWM measurements.

Average Concentration ET Methods Show Post-Treatment Increases In Normal Appearing WM CBF In NF2 Patients Treated With Bevacizumab

Figure 7 shows CBF (top row) maps derived from a NF2 patient with a large left sided vestibular schwannoma and four meningiomas. The v_p images derived using the ETM are also displayed for comparison in the bottom row. Slices from three levels of the 3D parametric images are shown. As can be seen there is some reduction of CBF and v_p within the VS at 90 days and the appearances of the T1W- CBF_{ACcomb} maps and v_p maps are very similar at each time-point.

Table 3 lists the group mean values ($\pm$ SD) of CBF for GM, WM, and CBF_{GM}/CBF_{WM} respectively for the 12 patients with NF2 treated with bevacizumab. Estimated mean values on day0 and day90 using the five different ET methods, are listed. The ACcomb produced mean CBF_{GM} of 55.9 ± 13.9 mL/100g/min. CBF_{WM} of 25.8 ± 3.45 mL/100g/min on day0, CBF_{GM} of 61.0 ± 8.28 mL/100g/min.

CBF_{WM} of 28.4 ± 3.43 mL/100g/min on day90. The ACcomb and ACrPK methods produced the highest CBF_{GM}/CBF_{WM} ratios (2.15 – 2.34), and the least intra-group SD for GM (8.04 – 13.92), and WM (3.06 – 3.45) respectively. With a paired t-test, both the AC-based methods, ACcomb and ACrPK, show a moderate increase in the group mean value of CBF in NAWM after treatment (Adjusted p values 0.03 and 0.005 respectively). Interestingly, neither the classical MG nor upslope method, show such changes in WM and GM CBF after treatment.

DISCUSSION

We present a new method based on the microsphere principle, for estimation of absolute CBF using a low dose high temporal T1W DCE MRI acquisition. This new method allows a more accurate and reliable estimation of absolute CBF, as instead of using a conventional MG-based algorithm, an averaged contrast agent concentration based method is used, which utilizes data points located in a higher ENR segment of the rising bolus time course.

Monte Carlo simulations demonstrated that these AC-based T1W-CBF_{ET} methods provided more accurate estimates of CBF compared to the MG and slope methods, especially when the ENR is low, such as within normal appearing white matter. The mean CBF of GM was, however, underestimated when using the ACrPK and ACcomb methods. The observed 5% underestimation in CBF_{GM} values using this new combined

method is, however, in alignment with published simulation results, such as those of Wu et al. using deconvolution²⁶, and those of Kwong et al. using the ET in DSC MRI⁷.

In vivo evaluation of this new T1W-CBF_{ET} algorithm in 20 patients showed that the ~~AC-~~
~~based methods provided superior estimates of CBF compared to the MG and slope~~
~~methods, with the classical~~ MG method produced ~~the~~ the poorest CBF estimates
(CBF_{GM}/CBF_{WM} ratio less than 1.5) ~~whilst t-~~ Both the ACcomb and ACrPK methods ~~for~~
~~calculating T1W-CBF_{ET} produced the most a more realistic reasonable~~ CBF_{GM}/CBF_{WM}
ratio (average 2.15 – 2.52). The CBF_{WM} calculated by ACrPK was lower than that
~~produced~~ by ACcomb; and the CBF_{GM} calculated by ACrPK was lower than that by
ACcomb for DCE MRI ~~data acquired on a 1.5T scanner data (Table 3),~~ but higher than
that by ACcomb for DCE MRI ~~for 3T data acquired on a 3.0T scanner (Table 1).~~ The
CBF_{GM}/CBF_{WM} ratio produced by ACrPK (2.52 and 2.30 for ~~DCE data acquired on 3.0T~~
and 1.5T ~~scanner data~~ respectively) was higher than that ~~by from~~ ACcomb (2.33 and 2.15
~~for 3.0T and 1.5T data respectively for DCE data acquired on 3.0T and 1.5T scanner~~
~~respectively~~). These in vivo observations were consistent with the Monte Carlo
simulations, ~~and can be attributed to the considering the generally poorer lower~~ ENR on
1.5T compared with 3.0T ~~scanner~~¹³.

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A correlation between CBF and CBV in both normal brain tissue^{21,27} and gliomas²⁸ has
been previously reported using ~~a both a~~ simple linear model ~~or and~~ the Grubb formula²⁹.
In our study we compared the ~~relationships between~~ T2*W-CBF ~~vs and~~ T2*W-CBV
~~relationship and the between~~ T1W-CBF_{ACcomb} ~~vs and~~ v_p ~~relationship~~ on a pixel-by-pixel

basis within a high grade glioma. Both pairs were highly correlated, consistent with previous results²⁸. On the other hand, there was a weak pixel wise correlation between the ET derived T1W-CBF and deconvolution derived T2*W-CBF maps. This discrepancy may be due in part to the fundamental differences in mechanism between T1 relaxivity and T2* susceptibility contrast effects³⁰. Alternatively image distortion due to magnetic susceptibility effects, especially when using fast T2*W- DSC imaging techniques may limit accurate coregistration of T1W-DCE and T2*W-DSC images thereby adversely affecting pixelwise correlations^{31,32,33}. Indeed the relatively good concordance between AC based T1W-CBF_{ET} and deconvolution derived T2*W-CBF values when using a ROI analysis ~~shown in Table 1~~, suggests that this may be the case.

In addition to providing more accurate reliable estimates of CBF, the reproducibility of this new AC based method was ~~shown through a established by~~ test re-test analysis. ~~The~~ Overall coefficient of variation (CoV) for absolute CBF measured using the ACcomb method ~~was 5.76% in the NAWM, and 8.51% in the NAGM. Our measured CoV compares compared~~ favourably with a recent study utilising both H₂O¹⁵ PET and contrast-enhanced perfusion ~~MR imaging, where the CoV across two scans taken 2 days apart was 8% vs 30% for white matter, and 10% vs 40% for grey matter respectively³⁴.~~

Some authors have advocated the use of model free singular value decomposition approaches for CBF derivation from DCE-MRI data. There are, however, distinct advantages to the use of ET methods over SVD approaches. Firstly, T1W(SVD) can not distinguish signal contributions from intra- and extra-vascular space, and is thereby more

affected by vessel leakage than the CBF-ET methods. ~~As shown in our data (see table 1), whilst~~In our study SVD methods applied to T1 data gave mean CBF values for WM and GM ~~compatible, comparable with the~~to those acquired with T2*W-SVD and ~~our~~T1W-CBF-ET method. However, in tumors, there was ~~an~~overestimation of CBF ~~in tumors~~, an effect we ~~hypothesise~~hypothesize is due to BBB breakdown and contrast leakage. SecondlyIn addition, perfusion calculation by deconvolution is critically dependant on the data ENR ⁷. In the work by Larsson et al ¹³, T1W-DCE MRI data was acquired on a 3T scanner with a GBCA dose of 0.05 mmol/kg to ensure sufficient ENR for pixelwise calculation of CBF using Tikhonov’s procedure of deconvolution. Despite this, ~~and~~the authors commented that the relatively poor ENR at 1.5T prevented the calculation of CBF maps using ~~this the~~ deconvolution approach. ³⁵ Through using data points located in a higher ENR segment of the rising bolus time course, however, our ET method ~~does not~~ suffer less from this limitation.

The CBF increases demonstrated using the ACcom and ACrPK method in normal appearing WM (NAWM) at 90 days post ~~bevacuzimab~~bevacizumab treatment were statistically significant, and exceeded our demonstrated reproducibility threshold for WM CBF measurements. This suggests that these changes are genuine rather than due to reproducibility variation, and, whilst this is a preliminary study of only 12 patients, these findings are biologically plausible, as the therapeutic effect of bevacizumab in this group is believed to result from alleviation of intracranial pressure due to reduction in intra-tumoural oedema ³⁶. ~~as decreases in cerebral blood flow in “normal” appearing brain in patients with GBM undergoing bevacizumab treatment have been previously reported~~ ³⁶.

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Larger studies will, however, be needed, to further investigate bevacizumab treatment related changes in microcirculatory parameters of normal-appearing brain tissues.

The key advantages of our new AC-based T1W-ET methods can be outlined as below:

- 1) *Application of T1W-ET in leaky tissue.* The T1W-ET method is less vulnerable to confounding resulting from leakage, re-circulation, and back flux^{7,11}.
- 2) *Improved robustness to low signal to noise ratio.* Through use of data points located in a higher ENR segment of the rising bolus time course, the AC-based T1W-ET method allows pixel-by-pixel calculation of CBF using T1W-DCE MRI acquired at both 1.5T and 3T scanners, with a GBCA dose as low as 0.02 mmol/kg.
- 3) *Simplified data processing.* When using the AC-based T1W-ET methodology there is no need to measure TOA, de-noise data, or correct for leakage and re-circulation.
- 4) *Acquiring 3D DCE-MRI covering the whole brain.* A time resolution of 1 s was chosen in this study, allowing averaging of three GBCA concentration data points when using the new T1W-ET methods, whilst permitting acquisition of 3D DCE images covering the whole brain.
- 5) *No covariance error due to multi-parameter fitting procedure.* Calculation of CBF with ACcomb does not require multi-parametric fitting, which is prone to covariance errors and 'salt-and-pepper' noise³⁷. The generation of CBF_{ACcomb}

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maps does not require filtering, in contrast to the maps generated using the two-compartment exchange model³⁷.

Finally, one important advantage of the new method is that it allows a lower dose of GBCA to be used compared to other methods of determining CBF such as DSC-MRI. To successfully utilize the microsphere model in determining CBF, a low-dose compact contrast bolus injection is optimum to ensure there is no efflux of intravascular tracer before the first pass AIF peak and to enable better determination of the arterial input function peak²⁰. Reduced contrast dose is ~~also~~ a pertinent clinical concern, as the potential nephrotoxicity of full dose GBCA is well recognized³⁸, and there is growing evidence that gadolinium deposition may occur in the brain following repeated exposures^{39,40}. Patients with CNS tumors, especially more benign lesions, may receive many contrast enhanced MR scans throughout their lifetime. As such, an MR acquisition ~~method which permits derivation of accurate perfusion metrics using a lower dose of contrast agent~~ method, which permits derivation of accurate perfusion metrics using a lower dose of contrast agent, may be of high clinical utility.

There are some limitations in our study. Firstly, the new AC-based methods for CBF measurements were evaluated in only a small cohort of patients with NF2 and one patient with a GBM. Secondly, the 3D whole brain acquisition used in the study comes at the expense of lower spatial resolution than methods utilized by other authors, who acquired only 4-10 slices^{7, 21,37}. Finally, a uniform value of hematocrit was used in this study, despite expected inhomogeneities in intra- and inter-subject hematocrit. Because

measurements of regional cerebral blood flow are dependent upon regional hematocrit, any alteration in this may produce errors in the calculation of regional blood flow.

In conclusion, we have developed and assessed a new early time points (ET) method of estimating absolute CBF using low dose high temporal (LDHT) DCE MRI data. Monte Carlo analysis shows that this new method improves the accuracy of measured absolute CBF values at different noise levels. In vivo application of this new method showed that the acquired T1-CBF_{ET} maps displayed excellent gray-white matter flow contrast using a much smaller dose of GBCA than is used for conventional DSC experiments, and the measured values of WM and GM CBF using our new method matched perfusion values in literature. The typical test-retest coefficients of variation observed in this study suggest that T1W-ET measured CBF have sufficient reproducibility to be used in longitudinal studies, especially if large changes due to therapeutic intervention are expected. In a cohort of patients with NF2 undergoing treatment with bevacizumab, there was a moderate increase in CBF of normal-appearing white matter 90 days post therapy. Our new method offers advantages over currently used non-invasive methods of CBF measurement, and may have considerable future utility in clinical perfusion imaging.

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Appendix A. Supplementary Data

Supplementary data to this article can be found online at **DOI:** [10.17632/hg7vppf6g5.1](https://doi.org/10.17632/hg7vppf6g5.1)

FOR PEER REVIEW ONLY

Glossary

Symbols	Interpretation	unit
AIF	Arterial input function	mmol/ml
$C_b(t)$	Blood CA concentration curve	mmol/ml
$C_t(t)$,	Tissue CA concentration curve	mmol/ml
CBF	Absolute Cerebral blood flow	ml/min/100ml
rCBF	Relative CBF	None
CBV	Absolute Cerebral blood volume	ml/100ml; ml/100g
CBF_{ET}	Absolute CBF measured by the Early time (ET) method	ml/min/100ml
CBF_{ACcomb}	CBF measured using average of the CBF values obtained from the ACrMG and ACrPK methods.	ml/min/100ml
CBF_{ACrMG}	CBV measured using averaged concentration referencing the time to maximum gradient	ml/min/100ml
$CBF_{MGclassical}$	CBF measured using classical Maximum Gradient method.	ml/min/100ml
CBF_{ACrPK}	CBF measured using averaged concentration referencing time to peak	ml/min/100ml
CBF_{slope}	CBF measured using upslope method	ml/min/100ml
Δt	Update time of DCE or DSC	s
DCE MRI	Dynamic contrast enhancement MRI	

DSC MRI	Dynamic susceptibility contrast enhancement MRI	
ENR	Enhancement-to-noise ratio	
ET	Early time method	
ETM	Extended Tofts model	
ETW	Early time window	
FDHS DCE MRI	Full dose high spatial resolution DCE MRI	
f_{gm} or CBF_{GM}	Blood flow of grey matter	ml/min/100ml
f_{wm} or CBF_{WM}	Blood flow of white matter	ml/min/100ml
GBCA	Gadolinium based contrast agent.	
GBM	Glioblastoma Multiforme (syn WHO grade IV glioma)	
HCT	Hematocrit.	none (%)
INT_{aif}	Integral of AIF	
LDHT DCE-MRI	Low dose high temporal resolution DCE MRI	
MG	Maximum Gradient	
NAWM	Normal-Appearing WM	
PD	Percentage deviation, $PD = (measured - true)/true \times 100\%$	
PRESTO	(3D) echo-shifted multi-shot echo planar imaging	
$R1_N$	Native longitudinal relaxation rate	s^{-1}

ROI	Region of interest	
SD	Standard deviation	
SSS	Superior sagittal sinus	
T1W	Longitudinal relaxation (T1) weighted (MR imaging)	
T2*W	Effective transverse relaxation (T2*) weighted	
$t_{\text{AIF_peak}}$	Time to peak of AIF	s
t_{mg}	Time to maximum gradient	s
TOA	Time of arrival of contrast bolus	s
t_{peak}	Time to peak	s
t_{ref}	Reference time point	s
TR/TE	Repetition time and echo time	ms/ms
VIF	Vascular input function	mmol/ml
v_p	Plasma volume fraction, $v_p = \text{CBV}(1 - \text{HCT})$	none (%)
VS	Vestibular Schwannoma	

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Table 1.

ROI mean values of CBF measured from the patient with GBM using different CBF calculation methods. MRI data were acquired on a 3.0T scanner.

acquisition	analysis method	CBF _{GM} (ml/min/100ml)	CBF _{WM} (ml/min/100ml)	CBF _{GM} /CBF _{WM}	CBF of tumor (ml/min/100ml)
T1W-DCE	ACcom b	75.3±64.6	32.3±22.8	2.33	96.0±52.9
	ACrMG	72.5±56.7	33.5±21.9	2.16	88.4±48.5
	ACrPK	78.2±66.2	31.1±24.9	2.52	103.7±39.5
	classicalMG.	180.1±64.6	128.9±22.8	1.39	194.4 ±52.9
	upslope	110.3±83.4	47.7±36.6	2.31	129.7±79.2
T2*W-DSC	SVD	71.5±66.6	36.7±26.9	1.95	111.0±75.6
T1W-DCE	SVD	76.3 ± 78.5	37.5 ± 27.1	2.01	130.7 ± 69.8

Table 2.
Reproducibility (CoV) of absolute CBF measured in NAWM and NAGM with the ACcomb method. Mean CBF values were calculated using ROIs at 1.5 T scanner.

Patient with sporadic VS			NAWM			NAGM		
			CBF (ml/min/100ml)			CBF (ml/min/100ml)		
No.	Age (y)	Sex	Visit 1	Visit 2	CoV	Visit 1	Visit 2	CoV
1	67	M	31.97	31.18	1.78	77.09	72.80	4.06
2	77	M	16.43	15.63	3.57	39.30	32.42	13.56
3	54	M	28.08	25.80	5.97	60.52	60.10	0.49
4	69	M	25.31	25.31	0.01	51.35	55.37	5.33
5	67	M	22.99	24.52	4.58	49.45	51.60	3.02
6	37	M	26.32	31.35	12.33	47.01	56.00	12.34
7	65	M	23.14	24.05	2.74	42.80	49.86	10.78
Mean CoV±SD			4.43±3.98			7.08±5.09		
Overall CoV			5.76			8.51		

Table 3.

Comparison of group mean CBF (ml/min/100ml) between day0 and day90 in GM, WM, and CBF_{GM}/CBF_{WM} in 12 patients with NF2, estimated using different methods. MRI data were acquired on a 1.5T scanner. *P*-values from paired two-tailed t-tests (df = 11) were listed for each paired data.

methods	tissue CBF	CBF_{GM}			CBF_{WM}			CBF_{GM}/CBF_{WM}		
		day0	day90	<i>P</i> -value	day0	day90	<i>P</i> -value	day0	day90	<i>P</i> -value
ACcomb	mean	55.90	61.00	0.093	25.83	28.43	0.006*	2.15	2.15	0.978
	±SD	± 13.92	± 8.28		± 3.45	± 3.42		± 0.28	± 0.18	
ACrMG	mean	60.85	67.11	0.122	29.99	32.97	0.017	2.01	2.04	0.667
	±SD	± 17.13	± 9.37		± 4.36	± 4.13		± 0.31	± 0.17	
ACrPK	mean	50.94	54.88	0.094	21.67	23.90	0.001*	2.34	2.30	0.567
	±SD	± 11.51	± 8.04		± 3.06	± 3.17		± 0.28	± 0.24	
classicalMG	mean	155.56	159.50	0.726	128.35	124.08	0.721	1.25	1.32	0.198
	±SD	± 17.15	± 35.58		± 29.06	± 35.23		± 0.20	± 0.19	
upslope	mean	75.42	81.33	0.123	36.59	39.48	0.136	2.07	2.06	0.912
	±SD	± 16.60	± 16.56		± 4.45	± 6.18		± 0.38	± 0.24	

* Significant at $P < 0.01$ (with Bonferroni correction)

Figure Legends

Figure 1:

Figure 1a shows a diagram of 3D fast field echo (FFE) pulse sequence with $TR/TE/\alpha = 2.95\text{ms}/0.66\text{ms}/[2^\circ, 8^\circ, 15^\circ, 20^\circ]$, used for the LDHT-DCE-MRI. This short TR gradient recalled echo based pulse sequence is embedded with both gradient spoiler and phase cycling for the elimination of the net transverse magnetization. The gradient spoilers are applied along read and slab selection directions. The phase cycling has a phase increment angle of 117° . The 3D data block covers whole brain without use of a RF prepulse, such as the regional saturation technique (REST) by Philips to achieve minimum TR and maximum temporal resolution.

Figure 1b shows the last frame of a 3D FDHS-DCE ($T = 600\text{ s}$) acquisition (left column), in a patient with neurofibromatosis type 2 with a large right sided vestibular schwannoma (see overlaid tumor mask) and multiple meningiomas. The middle and right columns show the last frame of 3D LDHT-DCE ($T = 300\text{ s}$) overlaid with the segmented grey matter mask or segmented WM mask respectively.

Figure 1c shows maps of CBF_{ACcomb} (top left panel, in $\text{ml}/\text{min}/100\text{ml}$) and v_p derived from ETM (bottom left panel) in the same patient as shown in Figure 1b. The right column shows maps of K^{trans} (min^{-1}) from LDHT MRI (top) or FDHS MRI (bottom), both derived from the ETM. The LDHT derived K^{trans} map is free from vessel artifacts, whereas the K^{trans} map derived from the FDHS showed greater tumor heterogeneity detail thanks to

the higher spatial resolution but at the expense of vessel artifacts due to the low temporal resolution ($\Delta t = 10$ s).

Figure 2. a. Distribution of number of exams with various number of data points on the upslope segment prior to the first pass peak of the measured $C_b(t)$ curves. The bottom row shows the typical $C_b(t)$ curves with upslope data points of 4 (**b.** acquired from a 16-year old male of 85 kg body weight), 6 (**c.** acquired from a 16-year old female of 60 kg body weight), and 8 (**d.** acquired from a 25-year old male of 107 kg body weight).

Figure 3. Assessment of validity of LDHT-T1W DCE MRI for microsphere CBF analysis (a and b), and simulation of the ‘theoretical’ WM and GM curves for Monte Carlo error analysis (c and d). Fig. 3a shows the integrated input curve, multiplied by $f_{wm} = 25$ ml/min/100ml = 0.00417 ml/s/ml, and time-shifted to align with the rising bolus time course of the WM concentration curve. Fig. 3b shows the integrated input curve, multiplied by $f_{gm} = 60$ ml/min/100ml = 0.01 ml/s/ml, and time-shifted to align with the rising bolus time course of the GM concentration curve. Figures 3c and 3d showed the simulated WM and GM concentration curves respectively.

Figure 4. PD analysis for absolute CBF estimates using different methods. Mean (4a and 4c) and SD (4b and 4d) of percent deviations for CBF of WM (4a and 4b) and CBF of GM (4c and 4d) calculated from 20,000 Monte Carlo repetitions of fitting individual SI-time curves using the ACrMG (green), ACrPK (blue), ACcomb (red), upslope (black) and the traditional MG (purple) methods.

Figure 5. SI curves for representative voxels in GM and WM and for a ROI of a relevant size together with the vascular input function: a) a pixel GM SI-time curve; b) a pixel WM SI-time curve; c) GM (filled square) and WM (circle) ROIs; d) mean SI curve from the GM ROI; e) mean SI curve from the WM ROI; f) vascular input function measured from the superior sagittal sinus. The dashed line in each plot indicates the estimated time of bolus arrival for global AIF.

Figure 6. Figure 6a shows visual comparison of CBF images obtained-at 3T from a patient with a glioblastoma multiforme on a 3T scanner. The left five columns show CBF images from the LDHT T1W DCE MRI calculated with the five ET methods. The right column shows ~~3D~~-CBF from T2*W DSC MRI calculated with a deconvolution method. Figure 6b shows the v_p map derived from ETM (left panel), and the T2*W-CBV map (right panel) from the same patient. The 2nd panel from left shows the intratumoral pixel-by-pixel comparison of v_p and CBF_{ACcomb} , both obtained from the LDHT T1W-DCE MRI, while the 2nd panel from right shows the intratumoral pixel-by-pixel comparison of CBV and CBF derived by SVD-deconvolution, both from the T2*W-DSC MRI.

Figure 7. T1W- CBF_{ACcomb} (top row) and v_p maps (bottom row) derived using the extended Tofts model in an NF2 patient with a large left sided vestibular schwannoma and multiple meningiomas. These maps were derived from the low dose T1W DCE-MRI acquired on a 1.5T scanner, pre- and 90 days post- bevacizumab therapy. Slices from three levels of the 3D maps of CBF and v_p are displayed, which show: a vestibular

schwannoma within the left cerebellopontine angle (left two columns, white arrow); a representative slice at the level of the centrum semiovale (middle two columns); and a right sided occipitoparietal meningioma (right two columns, white arrow) ~~and the centrum semiovale (middle two columns).~~

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107x76mm (300 x 300 DPI)

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