Combined analysis of perfusion and capillary permeability by parametric analysis of the tissue residue function from DCE-MRI

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Purpose: To test the utility of a novel method for analysis of tumor perfusion and capillary permeability from a single dynamic contrast enhanced (DCE) acquisition and compare the method to the established two-compartement method for analysis of capillary permeability.

Background: The standard two-compartement model commonly used for assessment of tumoral capillary permeability explicitly assumes that the tissue mean transit time (MTT) is short compared to the sampling interval (TR) of the dynamic sequence so that the contrast agent (CA) response in tissue and blood is related by a single scaling factor (proportional to tissue blood volume) in the absence of CA extravasation (1). High temporal resolution DCE sequences can readily be achieved on modern scanners, and the error introduced by MTT-effects thus have to be considered. Further, high temporal resolution scans also enables estimation of cerebral perfusion (CBF) and blood volume (CBV) from the first-pass DCE response and the kinetic models used to assess tissue perfusion in MRI generally assume that the CA is confied to the intravascular space and CA extravasation may lead to error in both CBV and CBF measurements (2). Recent models have been proposed which provides combined estimation of perfusion and permeability based on rather complex kinetic modeling (3). We here simpler model, originally developed for leakage correction in DSC perfusion imaging (4) which enables estimation of perfusion in the presence of extravasation and the measurement of permeability in the presence of elongated MTT values thereby providing multiple hemodynamic parameters reflecting both perfusion and capillary permeability from a single DCE acquisition.

Theory: A combined kinetic model incorporating both perfusion and permeability components can be expressed as:
$C_t(t) = \int_0^t \left[F \cdot R(t-\tau) + K^{trans} e^{-K^{trans}(t-\tau)/v_e}\right] C_p(\tau) d\tau$ (Eq. 1) where $C_p(t)$ is CA concentration in plasma, F is tissue flow, R(t) is the tissue residue function in absence of extravasation, K^{trans} is the transfer constant and v_e is CA distribution volume in the extravascular- extracellular space (EES). When MTT is short compare to TR, R(t) reduces to an delta function and Eq. 1 equals the standard two-compartement leakage model (1). Eq. (1) can be expressed in standard matrix notation and the *apparent* residue function is then given by: $\boldsymbol{r_a} = F[R(t_1), R(t_2)..R(t_N)]^T + K^{trans}\left[e^{-K^{trans}t_1/v_e}, e^{-K^{trans}t_2/v_e}, .., e^{-K^{trans}t_N/v_e}\right]^T$ (Eq. 2). The residue function thus contains an exponential 'tail' in the presence of extravasation and the initial height of the residue function is then given by F + K^{trans}. The respective volume fractions of the intravascular space and EES are then given by: $v_i = F\int_0^N R(t)dt$ and $v_e = K^{trans}\int_0^N e^{-K^{trans}t/v_e}dt$ (Eq. 3) and the total blood volume fraction in a voxel is given by $v_t = v_i + v_e$. F, K^{trans}, v_i and v_e can be estimated by approximating the non-leaky residue term by a Lorentzian and assuming a linear approximation to the leakage induced exponential tail so that the apparent residue function is fitted to the expression:
$\boldsymbol{r_a} = \frac{F}{1+\left(\frac{t}{MTT}\right)^2} + K^{trans}(1 - K^{trans}t/v_e)$ (Eq. 4)

Methods: DSE images were obtained longitudinally in three patients participating in an ongoing glioblastoma treatment response study, with a total of 13 separate scans included in the analysis. Imaging was performed at 3 T (Philips Achieva) using a 3D Saturation Recovery (SR) sequence (TR/TD/flip=3300 ms / 80 ms/ 90 deg). Deconvolution was performed using an iterative Tikhonov regularized SVD routine [3] in order to minimize oscillations in the resulting residue function. T_1-w post contrast images were coregistered to the parametric images and the tumor region of interest was semi-automatically segmented from the region of contrast enhancement. Identical AIF and tumoral ROIs were used for all analysis at each time-point. The resulting values of K^{trans}, v_i and v_e obtained with the residue function analysis (Method I) was correlated to the same values obtained using standard two-compartement analysis (Method II) by linear regression analysis. Image analysis was performed using nordicICE (NordicImagingLab, Bergen, Norway).

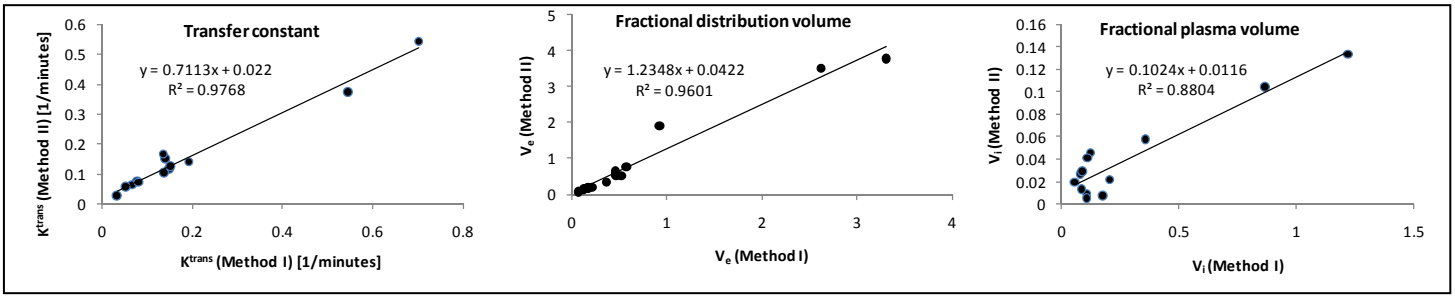

Figure 1.

Results: For all three hemodynamic parameters assessed by both models, a high correlation ($p<0.0001$) was obtained between the values obtained using Method I and Method II. Figure 1 shows the correlation obtained for K^{trans} (A), v_i (B) and v_e (C). Whereas K^{trans} and v_e were of the same magnitude for both models, v_i values obtained with Method I were systematically larger than those obtained with Method II and v_i also exhibited a lower correlation between the two models. Figure 2 shows a sample case with the resulting parametric maps for K^{trans}, CBF and MTT obtained with the combined model.

Discussion:
We propose a novel model to estimate both perfusion and permeability related parameters directly from the residue function. The transfer constants obtained with the model were in very good agreement with the values obtained using a standard two-compartement model and the model additionally enabled absolute estimates of tumor perfusion with good reproducibility. Although it is hypothesized that the proposed model is less sensitive to MTT effects, this could not be confirmed in this work due to limited sample size and lack of ground thruth. However the largest discrepancy between the two models was observed for the analysis of plasma volume (v_i), which is the parameter expected to be most sensitive to MTT effects. It is therefore concluded that the proposed model has merits as an alternative MTT insensitive approach for combined estimation of multiple perfusion and permeability related parameters in from high temporal resolution DCE-MRI acquisitions.

References:
1.Tofts et al. JMRI 1999 (10)
2. Boxerman et al. AJNR 2006 (27)
3. Larsson et al. MRM 2009 (62)
4. Bjornerud et al. Proc. ISMRM 2009

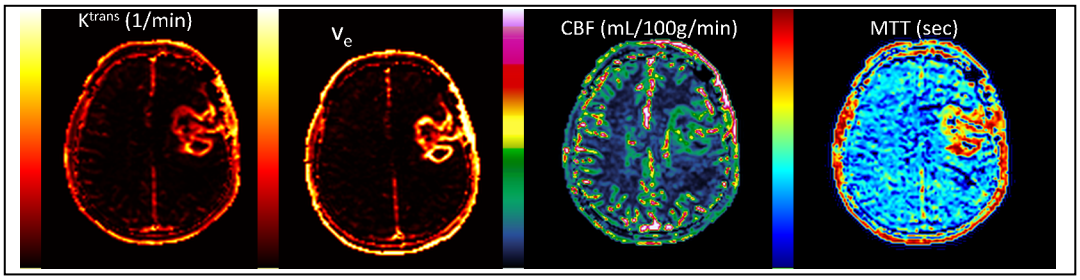

Figure 2.