Does DSC-derived CA extravasation correlate with DCE $K_{\text{trans}}$?

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Purpose: A ‘byproduct’ of the contrast agent (CA) DSC leakage correction method proposed by Weisskoff and colleagues2 is the $K_2$ term reflecting estimated CA extravasation into the interstitial space. If the $K_2$ parameter really reflects tumor permeability, DSC imaging could potentially provide estimates similar to that of DCE $K_{\text{trans}}$, thereby providing a powerful and time-efficient tool for monitoring of treatment response to anti-VEGF therapy3. In our study, we explore the relationship between CA extravasation from DSC and DCE both in simulations and patient data.

Methods and Materials: First, a simulation was performed by modeling an arterial input function (AIF) as a gamma variate function with an additional exponential term to model steady state effects. From this, a $K_{\text{trans}}$-like leakage constant (denoted ‘$K_{\text{leak}}$’) was determined by incorporating a CA leakage term in the tissue residue function4. A corresponding $K_{\text{trans}}$ parameter was derived using a standard two compartment model. $K_a$ was compared to $K_{\text{trans}}$ over a relevant range of $K_{\text{trans}}$ values by including the T1-term in the equation for signal intensity change due to CA induced increase in relaxation rates:

$$\frac{1}{TE} \left[ \ln \left( \frac{SI(0)}{SI(C)} \right) \right] = \Delta R2^* (C) - \frac{1}{TE} \ln \left( \frac{E1(C)}{E1(0)} \right) = \Delta R2_{\text{app}}^* (C)$$

where $\Delta R2^*$ is change in T2* relaxation rate, C is CA concentration, $\Delta R2_{\text{app}}^*$ is the measured apparent change in $\Delta R2^*$ including T1-effects and E1(C) $\geq$ E1(0). The following parameters were fixed for all simulations: TR/TE=1500ms/45ms, CBF=100mL/100g/min and MTT=5s. Second, $K_a$ values from DSC (TE=34ms) and $K_{\text{trans}}$ values from DCE were derived from baseline scans part of a retrospective study of 30 patients with recurrent glioblastomas5 and tumor pixel-by-pixel $K_a$ and $K_{\text{trans}}$ values were compared by deriving median $K_a$ values for increasing $K_{\text{trans}}$ cohorts similar to the simulations.

Results: Figure 1 shows the results of the comparisons between $K_a$ and $K_{\text{trans}}$. By including a pre-dose in the simulation similar to the patient data (0.1mmol/kg), a T2*-dominant leakage effect and a positive relationship between $K_a$ and $K_{\text{trans}}$ was observed for high flip angles (90º; as used in the patient data) and varying extravascular transverse relaxivity ($r2_{\text{ev}}$). For the patient data, linear mixed model analysis showed a significant increase in median $K_a$ values for increasing $K_{\text{trans}}$ cohorts ($P<0.001$) and a higher goodness of fit was observed when fitting a quadratic function to the data compared to using a linear fit (adjusted $R^2=0.68$, vs. adjusted $R^2=0.65$, respectively).

Conclusion: Although good correlation between permeability markers from DCE and DSC have been previously shown in gliomas6, the exact relationship between the two parameters has not received much attention. Results from both simulations and patient data clearly suggest that the CA leakage constant estimated from DSC is non-linearly correlated to the underlying permeability surface area product, even when extravasation is permeability limited. The lack of a simple linear correlation is due to the complex relationship between CA concentration in tissue and the measured change signal intensity and corresponding transformation to apparent transverse relaxation rates. Nevertheless, for the ranges of $K_{\text{trans}}$ values usually found in enhancing tumor tissue, for high $r2_{\text{ev}}$ values (>20mM⁻¹s⁻¹), or by assuming a quadratic relationship between $K_a$ and $K_{\text{trans}}$ over a larger range of $K_{\text{trans}}$ values, a DSC-derived permeability marker could form the basis for a pseudo-leakage parameter in tumor monitoring by MR.

Figure 1: A: Simulations showing the $K_a$ and $K_{\text{trans}}$ relationship for varying extravascular transverse relaxivity ($r2_{\text{ev}}$). B: Box plot with 75% confidence intervals of median $K_a$ values as a function of $K_{\text{trans}}$ cohorts across all patients. Although the median values across patients have large confidence intervals, results of the linear mixed model analysis showed that $K_a$ increased significantly for increasing $K_{\text{trans}}$.