The Transfer Constant K^{trans} in Glioblastomas is Limited by Permeability and not Perfusion

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TARGET AUDIENCE: Clinicians, physicists and researchers involved in DSC imaging studies and in the interpretation of DSC-derived brain tumor perfusion data.

PURPOSE: Tumor perfusion (CBF) and capillary permeability transfer constant (K^{trans}) have been proposed as sensitive biomarkers to monitor the effect of vascular-targeting and anti-angiogenic agents[1,4]. However, these two metrics are not physiologically independent parameters which may complicate their interpretation in clinical data. Changes in K^{trans} may represent change in permeability surface area (PS) product, change in CBF or a combination of the two[2]. Given the increasing interest of using these metrics as target biomarkers for clinical anti-angiogenic studies in patients with glioblastomas, any interaction between K^{trans} and CBF should be established.

METHODS: Both K^{trans} and CBF were estimated directly from the tissue residue function derived from dynamic contrast susceptibility (DSC) MRI, as previously described [3]. From this, the initial voxel-wise contrast agent extraction fraction, $E=K^{trans}/CBF = 1-exp(-PS/CBF)$ was estimated. The tumor value of E thus provides a direct estimate of the inter-dependence of K^{trans} and CBF because $K^{trans} \approx CBF$ when $E \to 1$ and $K^{trans} \approx PS$ when $E \ll 1$. Independence of K^{trans} and CBF thus requires $E \ll 1$. In this retrospective study, we included 30 patients with recurrent glioblastomas enrolled in a Phase II clinical trial of cediranib (clinicaltrials.gov, NCT00305656), an orally administered [45mg/kg/day] pan-VEGF receptor tyrosine kinase inhibitor[5] Gadolinium-based (Gd) DSC MRI was performed at 3 T (Siemens Magnetom Trio) prior to therapy onset (days -5 and -1) and repeated at days +1, +28, +56 and +112, as previously reported[4]. Tumor regions-of-interests were outlined on the post-contrast axial T1-weighted images by an experienced neuroradiologist and co-registered to DSC space using Statistical Parametric Mapping (SPM8). Values of E, CBF and K^{trans} at baseline (averaged over days -5 and -1) were compared using Spearman correlation (ρ). The kinetic analysis was performed in nordicICE (NordicNeuroLab AS, Bergen, Norway).

RESULTS AND DISCUSSION: By visual inspection, values of E before cediranib therapy were regionally and spatially different from CBF and K^{trans} (Fig. 1a-d). The average (±SD) whole tumor E was 6% (±3.5%). E was negatively correlated with tumor CBF ($\rho = -0.51$; $P < 0.01$; Fig. 1e) and positively correlated with tumor K^{trans} ($\rho = 0.45$; $P < 0.05$; Fig. 1f). There was no correlation between K^{trans} and CBF ($\rho = 0.15$), indicating that K^{trans} is not perfusion limited in glioblastomas.

During cediranib therapy, the temporal progression of whole tumor E was found to follow the same trend as for K^{trans} and with no difference between patients with different CBF trajectories (Fig. 1g-h). This observation confirms that E is dependent on the cediranib-induced decrease in vascular permeability regardless of perfusion.

CONCLUSION: We find the initial contrast agent extraction fraction in glioblastomas using conventional gadolinium chelates to be on average below 10% suggesting contrast agent extravasation is limited by permeability and not perfusion. K^{trans} and CBF derived from DSC MRI can be considered independent parameters in glioblastomas.

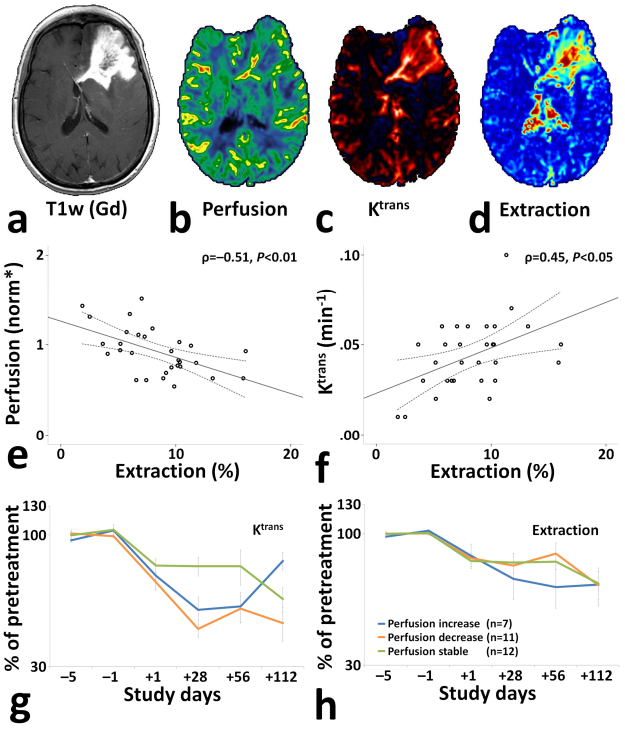

Figure 1: *Contrast-enhanced MRI (**a**), CBF (**b**), K^{trans} (**c**) and extraction fraction (**d**) of a therapy-naïve glioblastoma patient. Extraction fraction in tumor was negatively correlated with perfusion (**e**) and positively correlated with K^{trans} (**f**). Both K^{trans} (**g**) and extraction (**h**) were reduced following cediranib therapy regardless of perfusion status. (*perfusion values in tumor normalized to reference tissue).*

References

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