The assessment of cellular packing heterogeneity in brain tumors using DSC-MRI

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Introduction: The use of DSC-MRI in brain tumors is known to be confounded by the leakage of contrast agent, which can result in additional extravascular T_1 and T_2* effects well after the contrast agent (CA) initial bolus has passed through tissue [1]. By separating and quantifying these T_1 and T_2* effects in the period of time after the CA's first pass we proposed that a new metric, termed the extravascular susceptibility calibration factor (K_e), could be derived [2,3]. Our theoretical simulations have shown that this factor, which relates the change in the tissue T_2* to the extravascular extracellular (EES) CA concentration, is related to cellular spacing and their spatial distribution within tissue [3]. The goal of this study was to compare K_e in two brain tumor animal models with varying perfusion, permeability and cellular characteristics.

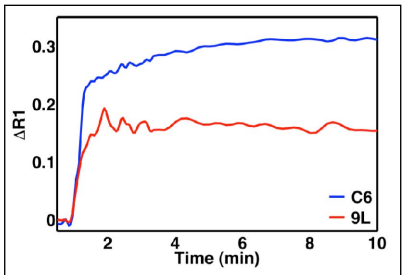

Figure 1: Example ΔR1 time curves in C6 and 9L tumors

Methods: Using a 4.7T MRI system, dual-echo DSC-MRI data was acquired for ten minutes in rats bearing C6 (n = 9) and 9L (n = 9) brain tumors. Such data can be used to reliably compute ΔR2* time curves free of T_1-effects, and, when combined with a pre-contrast T_1-map, ΔR1 time curves free of T_2*-effects, as we have previously shown [3]. Following the initial bolus passage of CA through tissue, the ΔR2* for each voxel can be approximated as $\Delta R2^* = K_e v_e C_e(t)$, which is reasonable given the length of the DSC-MRI scan. Our previous computational studies also support a linear relationship between ΔR2* and cell volume fraction for fractions greater than 50%. The last two minutes of the DSC-MRI data was used to compute K_e maps for each animal. Standard H&E and DAPI immunohistochemistry was then used to assess tumor cellularity.

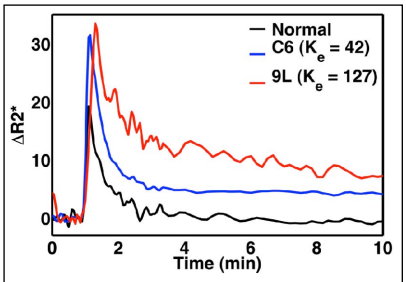

Figure 2: Example ΔR2* time curves in C6 and 9L tumors.

Results: As shown in **Figure 1**, 9L and C6 tumors exhibited dissimilar CA kinetics through the extravascular space, with C6 tumors consistently showing higher ΔR1 time curves. Despite having a lower $v_e C_e(t)$ (as derived from ΔR1), the 9L tumors exhibited post-first pass ΔR2* values greater than those found in C6 tumors (**Figure 2**), thus yielding higher K_e values. Note that the ΔR2* values remained elevated in both tumor models even after 10 minutes supporting the idea that compartmentalization of CA within the extravascular space creates additional T_2* effects. Such effects are not seen in normal tissue where the blood brain barrier is intact. **Figure 3** shows example v_e maps, K_e maps and H&E staining in the C6 and 9L tumors. The 9L tumors had lower v_e values and higher K_e values as compared to C6 tumors. The K_e maps were heterogeneous and not simply the inverse of the v_e maps, indicating that while v_e is related to cellular density, K_e is reflecting other cellular features such as (for example) their spacing. Consistent with the v_e results, H&E staining revealed that 9L tumors had higher cellular density than C6 tumors. On average, K_e values in 9L tumors across all animals were twice as high as those found in C6 tumors as shown in **Figure 4**.

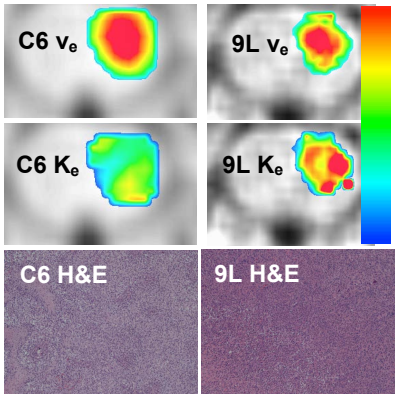

Figure 3: Representative v_e maps, K_e maps and histology in C6 and 9L tumors. Note that the color scale bar was individualized for the v_e maps to enhance contrast, where red indicates v_e values ~0.2 for the C6 tumor and ~0.1 for the 9L tumor. The scale bar for the K_e maps are the same.

Discussion: The *in vivo* results support the hypothesis that DSC measurements acquired in tumors with permeable blood vessels are highly sensitive to variations in tumor cellular features. Taken together the results indicate that the higher cell density found in the 9L tumors created a more heterogeneous compartmentalization of the CA in the extravascular space and therefore more heterogeneous field perturbations and larger ΔR2* changes. That K_e values were so dissimilar between the tumor types indicate that it could potentially serve as a new metric with which to evaluate tumor cellularity and treatment response. Future studies will focus on specifically identifying what cellular features impact K_e by looking at micro structural features of the cells within tissue. These studies also serve to demonstrate the advantage of acquiring DSC-MRI data in tumors using dual-echo pulse sequences along with a pre-contrast T_1 map [5]. While such metrics as the "percent signal recovery" may reflect the elevated ΔR2* observed in 9L tumors, it cannot account for variations in local CA concentration and v_e, which is critical for the proper interpretation of such results.

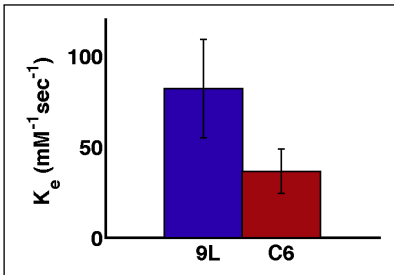

Figure 4: A comparison of K_e values in C6 and 9L tumors.

References: [1] Quarles CC, et al, Phys Med Biol, 2009. [2] Quarles CC, et al ISMRM 2010. [4] Semmineh, N et al, ISMRM 2010. [5] Quarles, CC, et al, ISMRM 2007.

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