Assessment of angiogenesis-induced hemodynamic abnormalities in brain tumors using intravoxel transit time distributions

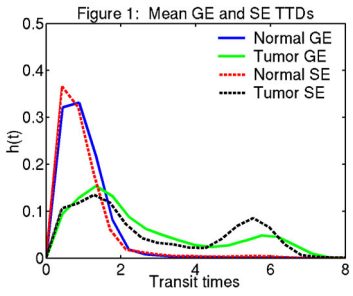
C. C. Quarles[1], D. Ward[1], K. M. Schmainda[1,2]

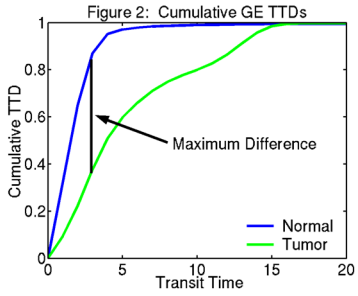
[1]Biophysics, Medical College of Wisconsin, Milwaukee, WI, United States, [2]Radiology, Medical College of Wisconsin, Milwaukee, Wisconsin, United States

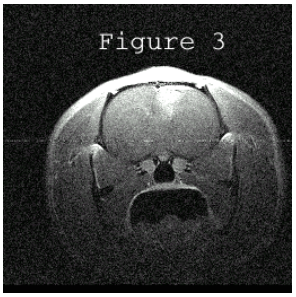
INTRODUCTION With the advent of numerous angiogenic inhibitors noninvasive methods to evaluate the morphological and functional changes in the tumor vasculature are crucial. To this end, DSC (dynamic susceptibility contrast) perfusion weighted MRI is playing an important role in the assessment of tumor angiogenesis providing high resolution information about the tumor blood volume, flow, mean vessel diameter, and mean transit time. Recently, it was shown that the analysis of tissue residue functions, normally used to compute blood flow, could be used to determine intravoxel transit time distributions (TTDs) and flow heterogeneity (1). Comparison of the flow heterogeneity between normal tissue and tissue at risk in stroke patients has shown to be useful in predicting the tissue viability (2). However, calculation of flow heterogeneity requires the assumption that the capillaries in a given voxel are all the same length. While tumor flow heterogeneity measurements would be extremely valuable, this assumption isn't valid in tumor tissue given the chaotic nature of the vasculature. However, the computation of TTDs requires no such assumption and they are easily calculated from tissue residue functions. The objective of this study was to determine if TTDs could be useful in the evaluation of tumor neovascularization using a rat brain tumor model.

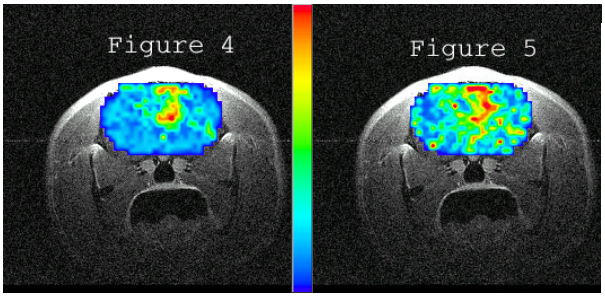
METHODS Five Fisher rats were inoculated with 9L gliosarcoma brain tumors. A 2 min simultaneous GE/SE EPI pulse sequence (64x64, TR = 1s, GE[TE] = 10.3ms, SE[TE] = 76.6ms, 3 slices, slice = 2mm, 3.5cm FOV) was used for the DSC perfusion scan. At 1 min, a 0.25 mg/kg bolus of iron oxide contrast agent (MION; MGH Contrast Media Laboratory, Charlestown, MA) was administered i.v. To determine the enhancing tumor volume, T1-weighted SE images (256x256, TR = 450ms, TE = 15 ms, slice = 2mm, 3 slices, 3.5cm FOV) were acquired following the administration of 0.2 mmol/kg dose of Omniscan (Nycomed). The tissue tracer concentration time curve, C(t), was deconvolved with the arterial input function, Ca(t), on a voxel-wise basis using Singular Value Decomposition (SVD) to compute the tissue response function (2): $\mathbf{C(t) = CBF*[Ca(t) \otimes R(t)]}$. Intravoxel transit time distributions (TTDs) were calculated from the negative derivative of the residue function (1): $\mathbf{TTD \Rightarrow h(t) = - dR(t)/dt}$. The maximum difference between the normal (averaged over a normal ROI) and a voxel's cumulative TTD is also computed. The maximum difference is used to quantify the differences between normal and tumor TTDs. This maximum difference is what is used in the Kolmogorov-Smirnov Test (KS-test), to test for the equivalency of distributions.

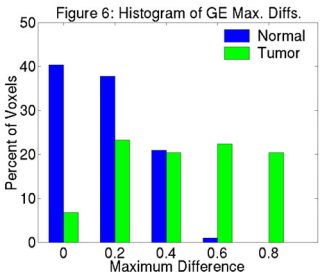
RESULTS Figure 1 shows the differences between the mean normal and mean tumor TTDs (normalized to the contralateral MTT for display purposes) for both GE and SE. The maximum difference between the normal and a given voxel's cumulative TTDs were calculated as shown by the GE example in Figure 2. Figure 3 shows a typical post-Gd T1 weighted cross-sectional image of a rat brain with a 9L brain tumor. The enhancing area is taken to be the primary tumor mass. Figures 4 and 5 are the GE and SE maximum difference maps for this rat. Substantial differences both within and around the primary tumor mass, outside of the enhancing area, can be seen. Histograms of all the tumor and normal maximum differences taken from all rats for GE and SE are shown in Figures 6 and 7. These figures demonstrate large differences between normal and tumor transit time distributions.

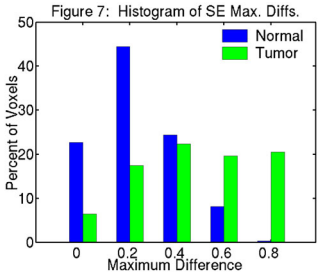












DISCUSSION To our knowledge this is the first use of intravoxel transit time distributions to evaluate the degree of angiogenesis-induced hemodynamic abnormalities. The substantial differences between the mean normal and tumor TTDs and the spatial differences seen in the maximum difference maps indicate that TTDs are sensitive to the abnormal tumor hemodynamics. The maximum difference maps were substantially different than MTT maps thus providing additional information about the spatial tumor perfusion efficiency. In addition, analysis of TTDs around the periphery of the tumor demonstrated their potential to detect the onset of angiogenic activity (data not shown). The sensitivity of TTDs to tissue hemodynamics suggest a possible role in the optimization and evaluation of novel anti-angiogenic therapies.

REFERENCES:

1. Ostergaard L., et al., J. Cereb Blood Flow Metab, 1999: 690-699, 1999.
2. Ostergaard, L., et al., MRM 36: 715-725, 1996.

ACKNOWLEDGEMENTS: NIH/NCI RO1 CA 82500.