An Exploration of the Relation between Angiogenic Status and Susceptibility Contrast in Brain Tumors

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INTRODUCTION: Recently, we and others showed that microvessel geometry is a significant determinant of susceptibility-based contrast [1, 2]. This is especially relevant when imaging tumors with their characteristically anomalous vascular trees. We also demonstrated that in such cases, the traditional cylindrical perturber approximations employed by most susceptibility models may be inadequate, and proposed a novel simulation methodology called the *finite perturber model* (FPM) [3]. This new approach enables us to study susceptibility-induced contrast arising from *arbitrary* microvascular geometries in 3D, such as those typically observed during tumor angiogenesis. It was also demonstrated by Holash et al. that in contrast to the prevailing view that most brain tumors began as avascular masses, some tumors initially grew by co-opting existing host vessels [4]. We call this angiogenic *Stage-1,* wherein the tumor microvessel density (MVD) and caliber are comparable to that in the contralateral brain (**Fig. 1a**). This co-opted host vasculature does not immediately undergo angiogenesis, but instead initially regresses and is accompanied by vessel dilation. We call this angiogenic *Stage-2* wherein the tumor vessel density decreases and vessel caliber increases (**Fig. 1b**). This stage is then followed by robust angiogenesis or what we call angiogenic *Stage-3*, wherein the tumor vessel density and caliber both increase (**Fig. 1c**). In this study, we employed the FPM in conjunction with computer-generated "*in silico*" 3D tumor microvasculature that conforms to the three stages of angiogenesis, with the goal of exploring the relation between angiogenic status and susceptibility-based MR contrast in brain tumors.

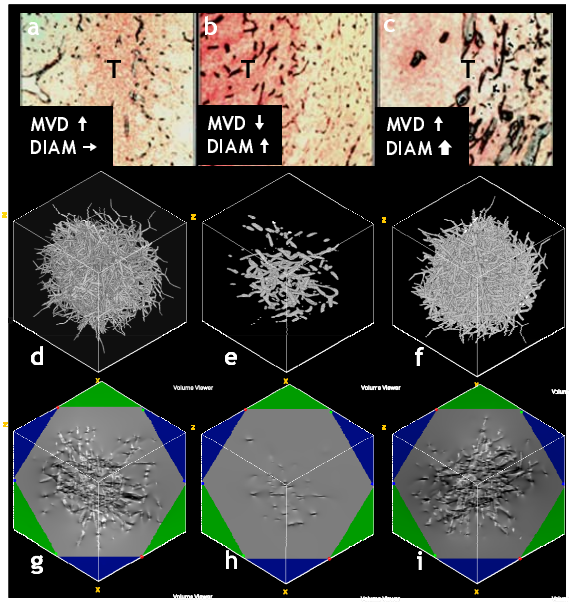

Fig. 1: (a-c) Stages of brain tumor angiogenesis. Adapted from [4]. (d-f) "In silico" microvascular architecture corresponding to the stages (a-c). (g-i) 3D normalized field maps for the microvascular substrates shown in (d-f).

METHODS: Using the *finite perturber model* (FPM) we conducted a series of simulations to determine the effect of angiogenesis-induced vascular remodeling on the gradient-echo (GE) and spin-echo (SE) signals. In the FPM approach, the underlying vessel geometry is divided into minute "perturbers". To calculate the field shift at a given point, the shift due to each perturber is calculated independently. The total field shift is then calculated as the sum of the field shifts from all the perturbers. The field shift arising from the entire vascular structure is computed in the Fourier domain, details of which can be found in [3]. To simulate the different stages of angiogenesis, a digitized 3D representation of a cerebrocortical capillary network was subjected to a series of morphological operations such as dilation, erosion and superposition until the desired microvascular architecture was obtained. **Fig. 1d-f** demonstrates the "*in silico*" versions of the three angiogenic stages: the first exhibits elevated MVD but unchanged caliber (FV~4%), the second exhibits reduced MVD but dilated vessels (FV~1%), and the final stage shows both, elevated MVD and radius (FV~6%). The biophysical parameters for the simulations were: B_0=1.5T, $\Delta\chi$=1×10-7 (~3.6mM Gd-DTPA), GETE=60ms, SETE=60ms, *dt*=0.1ms, unrestricted diffusion coefficient=1.0 μm^2/ms, with 10000 protons randomly placed in the simulation universe.

RESULTS: **Fig. 1g-h** demonstrates a slice through the magnetic field perturbation map ($\Delta B_{normalized}=\Delta B/\Delta\chi B_0$) for each angiogenic substrate. **Fig. 2** illustrates the effect of angiogenesis-induced changes in MVD and vessel caliber on the GE and SE signals, respectively. One can clearly see that the MR signal in both cases is profoundly affected by the angiogenic status of the underlying tumor.

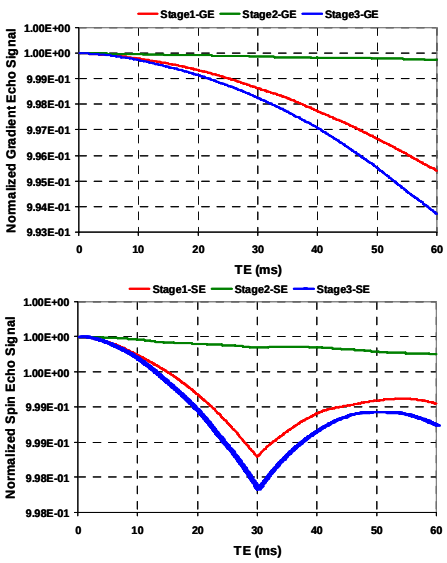

Fig. 2: Plots of the normalized (a) gradient-echo (GE), and (b) spin-echo (SE) signals demonstrating their dependence on the angiogenic stages of the brain tumor.

DISCUSSION: The data presented in **Fig. 2** indicate that during a typical susceptibility-based imaging protocol, one would measure drastically different MR signals depending on the angiogenic status of the tumor. These effects appear to be more pronounced for the GE signal. This is not surprising since Monte Carlo simulations have demonstrated the sensitivity of the GE signal to vessels of all sizes [5]. However, further simulations are warranted to explore the dependence of the relaxation rates ($\Delta R2$, $\Delta R2^*$) on the underlying vessel geometry, and the relative vessel distributions. Currently, these efforts are underway in our laboratory alongside efforts to obtain the "de facto" tumor microvascular geometry at different angiogenic stages in a human brain tumor model.

CONCLUSIONS: These simulations indicate that the grossly different vascular morphologies of brain tumors at different angiogenic stages can profoundly influence susceptibility-induced MR contrast, and the FPM is a powerful new tool for investigating the biophysics of such phenomena.

REFERERENCES: **1.** Pathak et al., *JMRI*, 18(4):2003. **2.** Kiselev *MRM*, 46(6):2001. **3.** Pathak et al., ISMRM, 34:2006; **4.** Holash, et al. *Science*, 284:1999. **5.** Boxerman et al., *MRM*, 34(4):1995.

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