The steroid, Dexamethasone, normalizes brain tumor hemodynamics in a rat tumor model as indicated by DSC-MRI perfusion parameters

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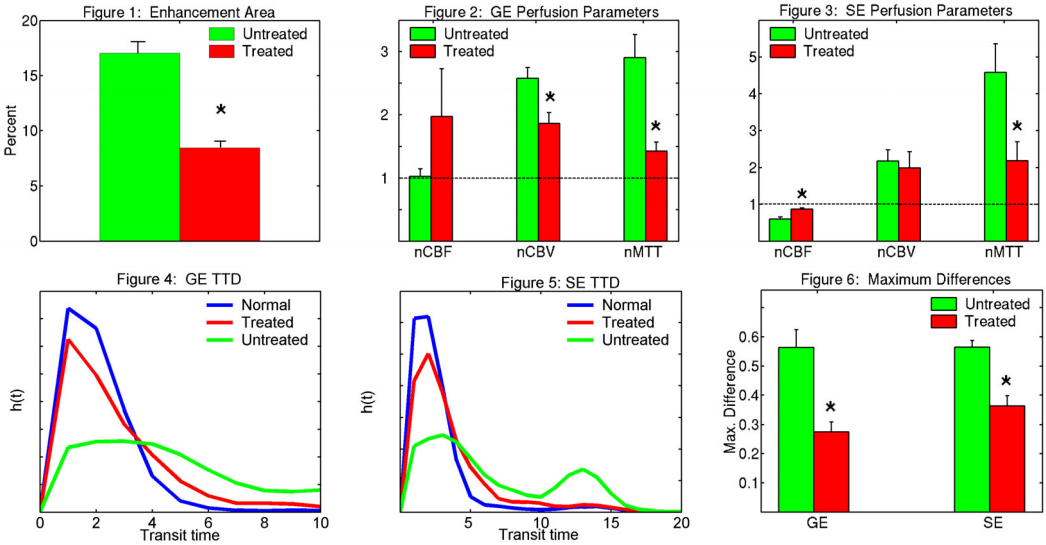
INTRODUCTION In the rat 9L gliosarcoma model dexamethasone has a therapeutic effect that may be related to the inhibition of tumor-associated angiogenesis (1). Specifically, it has been shown that dexamethasone decreases the expression of vascular endothelial growth factor (VEGF) in 9L and C6 tumor cells (2). In a previous study, we demonstrated that a simultaneous GE/SE EPI DSC (dynamic susceptibility contrast) method could be used to evaluate the changes in blood volume and vascular morphology following dexamethasone treatment (3). A significant decrease was found in total CBV and mVD (as measured by $\Delta R2^*/\Delta R2$). To further investigate the observed treatment effects on the rat 9L tumor model we now extend the analysis to include measurements of nCBF and nMTT. In addition, we demonstrate the feasibility and usefulness of computing tumor transit time distributions (TTDs) for the evaluation of brain tumors and their response to therapy.

METHODS Twenty-four Fisher rats were inoculated with 10^5 9L gliosarcoma brain tumor cells. Of these, fifteen were treated with 3 mg/kg of dexamethasone (i.p.) and 9 served as (untreated) controls. All MR experiments were performed on a 3T Bruker system 14 days post-inoculation. Just prior to the perfusion scan, a 0.05mmole/kg loading dose of Omniscan (Nycomed) was administered to diminish T1 leakage effects that may occur during the subsequent perfusion scan (Dex reference). Next, a 2 min simultaneous GE/SE EPI pulse sequence (64x64, TR = 1s, GE[TE] = 20ms, SE[TE] = 96ms, 3 slices, slice = 2mm, 3.5cm FOV, partial NEX) was used for the DSC perfusion scan. At 1 min, a 0.2-mmol/kg bolus of Omniscan, was administered via the femoral vein. To determine the enhancing tumor area T1-weighted SE images (256x256, TR = 450ms, TE = 15 ms, slice = 2mm, 3 slices, 3.5cm FOV) were acquired after the DSC perfusion scan. Due to low contrast to noise of some of the SE data, the SE perfusion parameters could only be determined from data collected from 8 of 15 treated and 2 of 9 control rats. Consequently, studies were performed on 5 additional untreated rats using 0.25 mg/kg of the long-lived iron oxide contrast agent MION (MGH Contrast Media Laboratory, Charlestown MA), administered as a bolus 1 minute into the perfusion scanning. This contrast agent has a larger susceptibility effect and does not extravasate as does Omniscan, thereby giving acceptable SE data. Comparison of the MION and Omniscan results in normal brain were the same, and therefore the MION and Omniscan data are pooled for the SE control (untreated) rats. GE and SE CBF, CBV, and MTT maps were created using the SVD approach (4). Intravoxel transit time distributions (TTDs) were calculated from the negative derivative of the residue function (5). The maximum difference between a voxel's cumulative TTD and a normal cumulative TTD (averaged over a normal ROI) were also computed. Unpaired two-tailed *t*-tests were used to compare t he effects of treatment, using an α=0.05 level of significance.

RESULTS Figure 1 demonstrates a significant decrease in tumor volume following dexamethasone treatment. Figures 2-3 show the normalized (to contralateral brain) GE and SE perfusion results. The GE nCBF doubled (not significantly) while the GE nCBV and nMTT decreased significantly with treatment. The SE nCBF (Fig. 3) increased while the nMTT decreased, both significantly. Figures 4 and 5 are the mean untreated and treated TTDs for GE and SE, respectively. Following treatment the tumor TTD appeared more like normal brain tissue. As Figure 6 shows, there is a significant change between the treated and untreated maximum differences for normal and tumor cumulative TTD.



DISCUSSION In addition to the previously reported decreases in nCBV and mVD (3) we now show that these morphological changes in the tumor vasculature, following dexamethasone treatment, are accompanied by functional changes in the tumor hemodynamics. The normalization of nMTT following treatment may indicate an increased perfusion efficiency, so that it is more like that of normal tissue. Given that dexamethasone has been shown to inhibit VEGF expression, it is possible that the effect observed here results from the normalization of the balance of angiogenic factors, followed by a re-normalization of the vascular morphology. Thus, the simultaneous GE/SE DSC methods and analysis described here can provide more specific information about a tumor's vascular response to therapy, thus aiding in the optimization and evaluation of novel anti-angiogenic therapies.

REFERENCES and ACKNOWLEDGEMENTS: NIH/NCI RO1 CA 82500.

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