Estimation of vascular functionality in two separate mammary carcinoma tumors during growth and exposure to carbogen using an interleaved DGE/DSE acquisition

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Introduction

Analysis of tumor vascular function and maturation has been proven to be difficult using a variety of MRI techniques. We present the use of an interleaved Double Gradient echo (DGE) and Double spin echo (DSE) acquisition for the subsequent estimation of R2*, R2, and R2' as a basis for this analysis. R2* is the total transverse relaxation rate, R2 the irreversible relaxation rate and R2' the rate due only to susceptibility where R2' = R2*-R2. This analysis was performed on data collected from mammary carcinoma tumors of different volumes in mice exposed to the gas carbogen (95%O2/5%CO2). There have been similar investigations performed using blood oxygen level dependent (BOLD) contrast to analyze different treatment paradigms and growth [1,2].

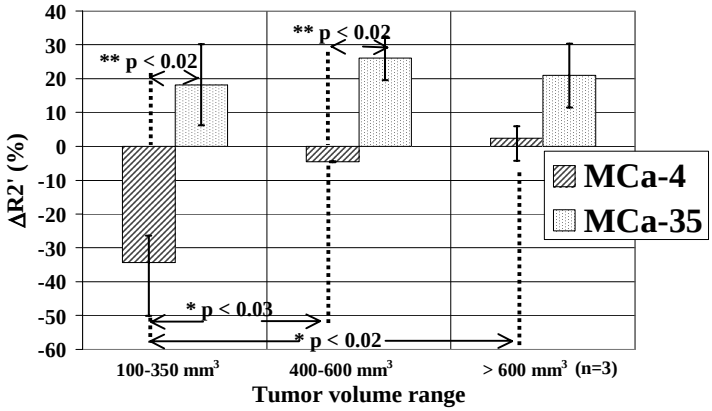
Methods

MCa-4 and MCa-35 murine mammary carcinoma cells were injected into the hind limbs of C3H mice (8 mice total). Mice were exposed to carbogen (2L/min) through a mask with scavenger. Individual experiments were performed over a 10-day period of tumor growth. Control acquisitions were performed with room air at 2L/min. DGE/DSE imaging was performed on a 9.4 T scanner (GE Omega) using a 1.5 cm surface coil. The imaging parameters for DGE images were TE1/TE2/TR =3.3ms/12ms/200ms, flip angle= 15°, NEX 4, and for DSE images TE1/TE2/TR = 6.5ms/18ms/1s, NEX 2. For both imaging protocols, matrix size 128x64, slice thickness=0.75 mm, 8 slices, and FOV= 25mm. Region of interest (ROIs) were selected from a DW image (b=660 sec/mm^2) of the same slice orientation and thickness as with the DGE/DSE. A single diffusion gradient was applied parallel to the muscle fiber direction in the leg. Image analysis was performed using MATLAB (Mathworks, Natick, Ma.). Data sets with substantial motion artifacts were removed. Statistical comparisons were performed using Student's t-test.

Results

To verify consistency of signal acquisition, a series of 4 DGE/DSE images were taken of each tumor for air- baseline, carbogen, and return to air. The acquisition time for each set of 4 image pairs was 12 minutes (i.e., 4 baseline-4 carbogen-4 return). Mice were given 2 minutes between gas changes to reach equilibrium. Percent changes in R2*, R2 and R2', following carbogen exposure were calculated for each slice for individual tumors. The bar graph in Figure 1 shows the relative changes in R2' when gas is switched from air to carbogen for three different ranges of tumor volumes for MCa-4 and MCa-35 tumors. A total of 3 separate tumors were analyzed for each volume group. Consistent decreases were observed in R2' following carbogen exposure in the small (100-350mm^3) and medium (400-600 mm^3) MCa-4 tumor volume groups. Also, significant differences were noted in the relative change of R2' during carbogen exposure between the MCa-4 small tumor group and both the medium group and the large group(> 600mm^3, $p<0.03$) The opposite effect was seen in MCa-35 tumors where R2' increased in all three size groups. This opposing difference is significantly different in the small and medium tumor groups($p < 0.02$).

Figure 1 - Relative Percentage Change in R2' vs. tumor volume



Discussion

Alterations in R2' should correspond to changes in blood oxygen levels assuming that no changes in tumor blood volume. The low flip angle of 15° reduces any potential effect due to in-flow. We present the changes in relaxation rates in two different mammary carcinoma cell lines of varying vasculature in mice exposed to carbogen. As expected, these results show that there is a relative decrease in R2' following carbogen exposure in Mca-4 tumors. Unexpectedly the results show a relative increase in R2' in MCa-35 tumors following carbogen exposure. The vasculature in the MCa-35 tumors has a different structure than that seen in MCa-4 tumors, where the MCa-4 vessels are much larger and contain a greater number of sinusoids. It is hypothesized that the increase in R2' is due to the vasodilatory effect of the CO_2 in carbogen resulting in an increased tumor blood volume of MCa-35 tumors. This increase in blood volume results in an increased relative deoxyhemoglobin concentration within the tumor. Additionally, the difference between the R2' of the two groups was shown to be insignificant when tumor volume is large, suggesting that as tumors pass a specific growth stage, the relative amount of functional vasculature is reduced. These results will be further explored by performing steady state contrast enhanced imaging in these two tumor types during carbogen exposure. The DGE/DSE acquisition during a vasomodulatory stimulus may present a non-invasive, non contrast-enhanced method to evaluate the functionality of the microcirculation in tumors.

References

[1] Abramovitch et al., 1999. *Cancer Res*, **59**:5012-5016

[2] Thomas et al., 2003. *MRM*, **50,** 522-530