

Integrated MRI approaches to interrogate tumor oxygenation and vascular perfusion of orthotopic brain tumors in a mouse model

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Introduction

It is recognized that tumor microcirculation and oxygenation play important roles in malignant progression and metastasis, as well as response to various therapies (1). There is little knowledge about *in situ, in vivo*, tumor hypoxia during intracranial development of malignant brain tumors because of lack of efficient means to monitor it. Blood Oxygenation Level Dependent (BOLD) MRI based on T_2^* contrast induced by deoxyhemoglobin, is sensitive to tumor vascular oxygenation and blood flow. Recently, studies have suggested a possibility of assessing tissue oxygenation (TOLD) based on the shortening of the tissue water T_1 due to oxygen (2). Here, we are investigating differences in T_1 - and T_2^* -weighted signal intensity in response to oxygen breathing, as well as their correlation with tumor perfusion assessed by using dynamic susceptibility contrast (DSC) MRI.

Materials and Methods

Human glioma U87 cells were transfected to stably express firefly luciferase (U87-luc). 5×10^4 U87-luc cells were injected directly into the right caudal nucleus of mouse brain ($n = 6$). Bioluminescent imaging (BLI) was initiated 2 weeks after implantation and repeated weekly. Once BLI signal was detected, MR measurements were performed on a 4.7 T Varian system. Anatomic T_2 -weighted and T_1 -weighted contrast enhanced MRI were used to evaluate tumor volume. Functional BOLD and TOLD MRI was acquired with an interleaved T_2^* -weighted (TR = 150 ms, TE = 20 ms) and T_1 -weighted (TR = 30 ms, TE = 5 ms) gradient-echo sequence during air baseline and transition to oxygen breathing. Finally, T_2 -weighted gradient echo DSC MRI (acquisition time = 1s) was acquired after i.v infusion of contrast agent Gd-DTPA-BMA via a tail vein catheter. Data analysis of BOLD and TOLD MRI was carried out on a voxel-by-voxel basis. Vascular perfusion was evaluated in both tumor and contralateral normal brain based on DSC MRI signal drop during the first pass and a ratio of tumor versus contralateral normal brain (TNR) was calculated (3).

Results

There was a strong correlation between BLI signal intensity of intracranial tumors and MRI measured tumor volume. In response to oxygen breathing, significant increase in BOLD signal intensity (SI) was observed in the intracranial tumors (mean = 5.2 ± 2.2 %), while much less change was seen in the contralateral normal brain (mean = 2.3 ± 1.1 %). In a good agreement, TOLD SI of glioma increased significantly with respect to oxygen (mean = 5.4 ± 1.7 %). There was a positive correlation between BOLD and TOLD ΔSI ($r > 0.7$). DSC MRI showed intratumoral heterogeneity in tumor perfusion. Significantly higher perfusion was found in the tumors than the contralateral normal brain. Spatial comparison revealed a good correlation between BOLD ΔSI and perfusion, whereas a lack of correlation between TOLD and perfusion.

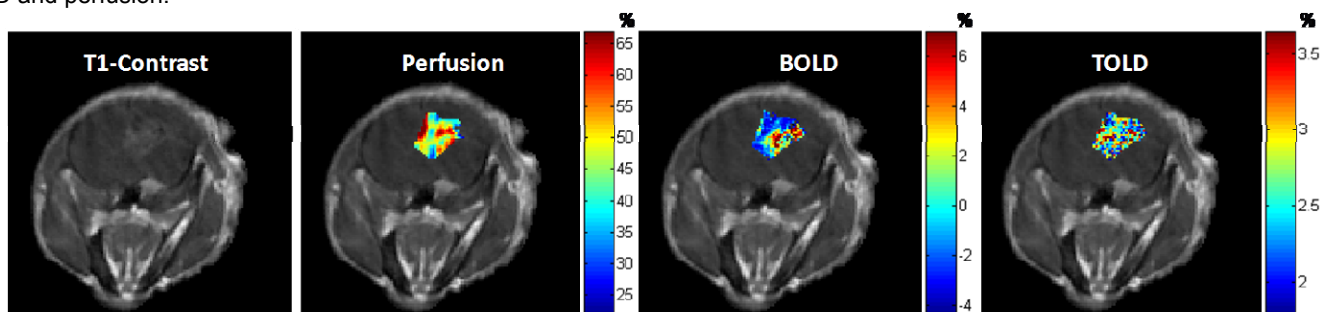


Fig. T_1 -weighted contrast enhanced MR image shows high signal intensity of the tumor region. Maximum ΔSI maps for tumor region were obtained for perfusion, BOLD and TOLD and overlaid on the T_1 -weighted contrast enhanced MR image as shown above.

Discussion

Breathing hyperoxic gas significantly improved blood and tissue oxygenation of orthotopic U87 glioma although it could result in decreased blood flow due to vasoconstrictive effect. Lack of correlation between TOLD and tumor perfusion may implicate that tissue oxygenation depends upon both vascular supply and consumption.

Reference

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