# Using Cerebrovascular Response to Hyperoxia for Assessing Treatment Resonse in Glioblastoma

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## INTRODUCTION:

Understanding the oxygenation status of cells in tumors is important for predicting therapeutic response to treatment [1]. Breathing pure oxygen (i.e. 100% $O_2$) is one way of probing (and potentially modifying) tumor oxygenation. Hyperoxia increases the amount of dissolved $O_2$ in plasma, provides more $O_2$ at the capillary level and increases its diffusion into chronically hypoxic regions. High temporal and spatial resolution Blood Oxygenation Level Dependent (BOLD) measurements can be used to monitor these changes in tumor as well as in normal tissue. This method is sensitive to the changes in deoxyhemoglobin concentration through NMR relaxation rate R2*. As the oxygenation of hemoglobin is proportional to blood $pO_2$, and thus it is in equilibrium with tissue pO2, R2* is a sensitive indicator of tissue oxygenation [2]. In this study, we quantitatively investigated BOLD responses to 100% $O_2$ in glioblastoma (GBM) throughout the course of the treatment with chemoradiation and an anti-angiogenic drug.

## METHODS:

**Patients:** Eight GBM patients that received a daily oral dose of cediranib (45 mg) in addition to standard chemoradiation, were included in this study. All the subjects were scanned using a 3T Siemens MRI scanner with a 32-channel head coil at the following time points during their treatment: -5 to -3, -1, 1 days and once a week subsequently.

**Data Acquisition:** A simultaneous BOLD-pulsed ASL sequence (single-shot, gradient echo echo planar imaging acquisition with a 64×64 matrix) was used.. Eight-slice images with 8mm thickness were acquired using TE and TR optimized for BOLD (TR/TE=2000/19 ms, FOV = 220mm, 6/8 partial Fourier). The breathing paradigm was as follows: room air for two minutes, 100% $O_2$ for four minutes, and then again room air for four minutes. A custom-made breathing mask was used to administer 100% $O_2$ at a 45L/min flow rate. Post-contrast (gadolinium-DTPA) T1-weighted anatomical data were also acquired.

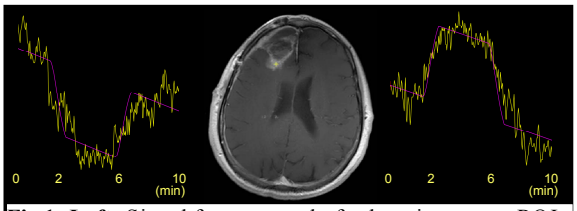


**Fig 1. Left:** Signal from a voxel of enhancing tumor ROI **Middle:** T1-weighted post-contrast image of a representative GBM patient **Right:** Signal from a voxel of contralateral normal tissue ROI

**Data Analysis:** The data processing consisted of motion correction, summation of the paired images to obtain BOLD data, and general linear modeling (GLM) using the Neurolens software. The percent changes in BOLD signal were analyzed in two ROIs – enhancing tumor (ET) and normal tissue on the contralateral side (cNT), as delineated on the T1 post-contrast images. Only the statistically significant (Student's t-test, $p<0.05$) output values were analyzed. **Figure 1** shows measured signals (yellow lines) and the fitted curves (purple lines) for two representative voxels from ET (Left) and from cNT (Right).

## RESULTS AND DISCUSSION:

The corresponding serial T1 and BOLD images for a representative GBM patient are shown in **Figure 2a-b.** In **Figure 2c** the percent signal changes in BOLD for all eight patients is shown. The pattern of BOLD response in cNT was similar to that observed in normal brain (i.e. signal increase primarily in GM), while either a decrease or a higher increase in signal were observed in the ET. BOLD signal changes dropped significantly at the beginning of the treatment in ET and gradually recovered afterwards. Conversely, in cNT a slight increase was observed at the early time points. Interestingly, no difference was observed between values in the ET and the cNT after 35 days.

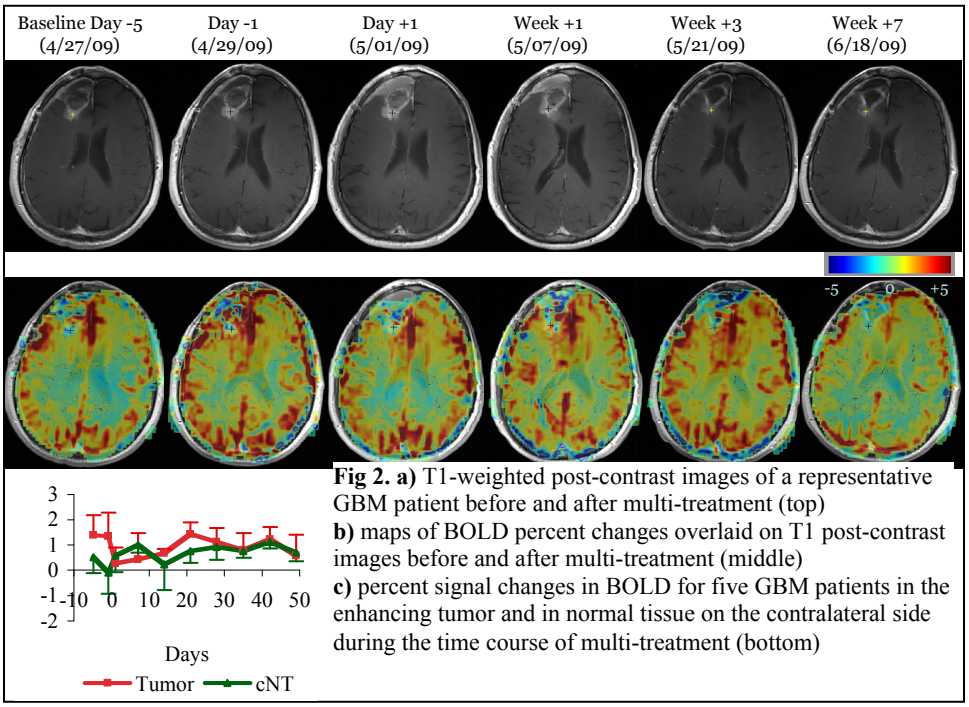


**Fig 2. a)** T1-weighted post-contrast images of a representative GBM patient before and after multi-treatment (top) **b)** maps of BOLD percent changes overlaid on T1 post-contrast images before and after multi-treatment (middle) **c)** percent signal changes in BOLD for five GBM patients in the enhancing tumor and in normal tissue on the contralateral side during the time course of multi-treatment (bottom)

Although the changes in BOLD signal were subtle, our preliminary findings warrant further investigation. A possible interpretation for the time course changes is that tumor vessels were destroyed during the treatment (an expected effect for an anti-angiogenic agent) and this has caused a decrease in the BOLD response. Despite our efforts to exclude the post-surgical cavities when defining the ET ROIs, partial volume effects might still confound our findings, and they could explain the variability observed in our measurements.

**CONCLUSION:** Our preliminary findings suggest that assessing the oxygenation status before and after treatment might be useful in GBM patients. Non-invasive R2* measurements based on BOLD signal changes could more accurately map the heterogeneous distribution of tumor oxygenation. Therefore, using hyperoxia as a probe for both prognostic and diagnostic assessment of tumors during treatment has great potential.

**REFERENCES:** [1] Horsman MR. Int J Radiat Oncol Biol Phys 42:701– 4 (1998) [2] Robinson SP et al., MRI 19:161–166 (2001)