Evaluation of relative CMRO2 from BOLD and CBF changes in hyperoxia: Significant increase of oxygen consumption rate in glioblastoma

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INTRODUCTION: There is renewed interest in tumor oxygenation metabolism particularly in glioblastoma (GBM), where mutations in metabolic pathways have been recently identified, prompting a re-examination of the Warburg effect. To identify metabolic changes in tumor oxygenation, simultaneous BOLD and ASL technique can be used to quantify hemodynamic parameters with excellent structural resolution[1]. The specific goal of this study was to evaluate relative $CMRO_2$ in GBM in response to hyperoxia.

METHODS:

Data Acquisition: Ten healthy volunteers and ten GBM patients were scanned using the simultaneous BOLD and ASL sequence developed based on pulsed ASL sequence with QUIPSS II technique and PICORE tagging followed by single-shot, 64×64 matrix GE-EPI acquisition. Specific imaging parameters used: TI1/TI2 =700/1400ms, 11-slices, 8mm thickness, TR/TE=2000/19ms, FOV=220mm. The breathing paradigm consisted of baseline room air (2min), followed by 100% O_2 (4min) and then washout room air (4min) with 40L/min flow rate. T2-weighted images for healthy volunteers and T1-weighted images after an injection of contrast for GBM patients were acquired to provide anatomical details.

Data Analysis: The preprocessing of the raw data included motion correction, subtraction (CBF) and addition (BOLD) of the paired images, spatial smoothing, and general linear modeling using Neurolens software. For healthy volunteers, two ROIs (i.e. gray matter (GM) and white matter (WM)) and for GBM patients, four ROIs - enhanced tumor (ET) and normal tissue on the contralateral side (cNT) as well as normal appearing gray matter and white matter were defined on the anatomical images. BOLD and CBF signal change maps were analyzed using in house developed code to estimate relative $CMRO_2$ according to Davis' formula[2].

RESULTS and DISCUSSION:

Healthy Subjects: The images of T2, BOLD and CBF signal change maps are shown in **Fig.1a**. BOLD and CBF effects were detected primarily in gray matter (increased BOLD and decreased CBF responses). The signal percentage changes (ΔS) averaging all subjects are shown in **Fig.1b**. BOLD signal change in GM was approximately twice than in WM (2% vs 0.9%). CBF signal change in GM was also larger than that in WM (34% vs 21%). These measurements agreed with previously published preclinical data[3].

GBM Patients: The corresponding images for a GBM patient and graphs averaging all patients are shown in **Fig.2a-c.** In the enhanced tumor, there was an increase (1.4%) in BOLD signal and a decrease (12%) in CBF signal. Normal tissue on the contralateral side showed an increase (0.8%) in BOLD and a decrease (5%) in CBF. Normal-appearing gray matter showed a higher increase (2.7%) in BOLD and a lower decrease (13%) in CBF than those in healthy subjects. Normal-appearing white matter reflected less increase (0.2%) in BOLD and decrease (17%) in CBF. These values in normal-appearing gray and white matter are adequately matched to Davis's model[2]. They have traditionally been interpreted as enhanced oxygenation of the blood supply (BOLD) and a vasocontrictive effect (CBF), and might be mediated by tumor.

Post-contrast T1, the relative $CMRO_2$ map, and the graph of relative $CMRO_2$ in GBM patients normalized by relative $CMRO_2$ in healthy brains are shown in **Figure 3a-b.** Notably, it shows 59% increased response of $CMRO_2$ at oxygen in enhanced tumor(ET), 27% in peritumoral tissue(PT), and subtle changes in contralateral normal tissue(cNT) for GBM patients compared to relative $CMRO_2$ in healthy volunteers' gray matter(GM). It might indicate that hyperbaric oxygen administration manipulates the oxygenation metabolism in cancer cells.

CONCLUSION: Our findings, if confirmed in detailed studies, could identify the mechanism of tumor oxygenation and potentially help the effective therapeutic options such as oxygen treatments.

REFERENCES: [1] Wong EC et al. NMR Biomed 1997; [2] Davis TL et al. PNAS 1998; [3] Lu et al. NeuroImage 2009

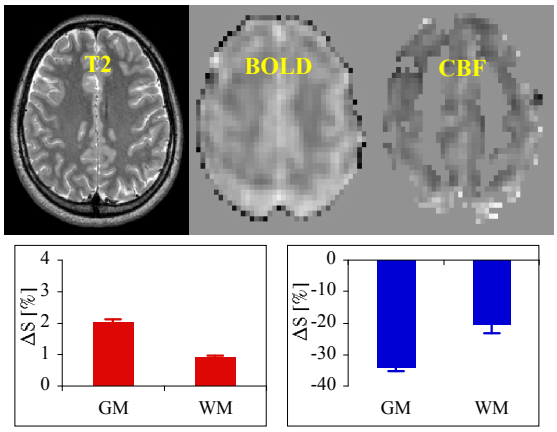

Fig1. a) top: T2-weighted, and relative BOLD and CBF maps for a representative healthy subject
b) bottom: graphs for signal changes in BOLD (red) and in CBF (blue)

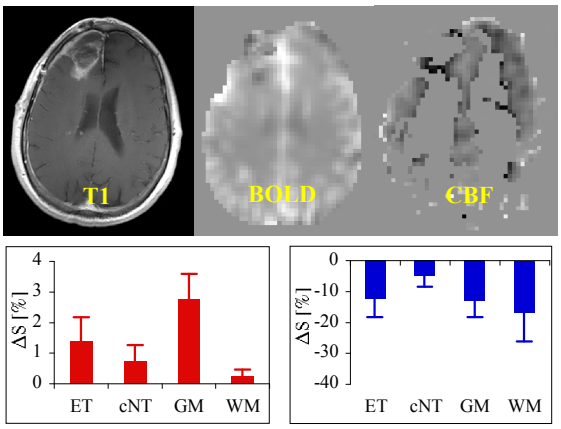

Fig2. a) top: post-Gd T1-weighted, and relative BOLD and CBF maps for a representative GBM patient
b) bottom: graphs for signal changes in BOLD (red) and in CBF (blue)

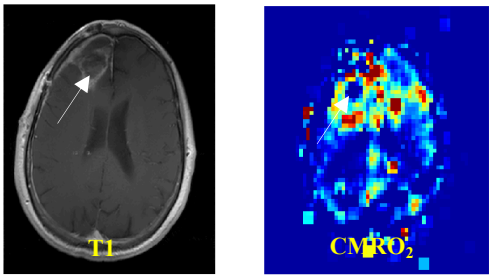

Fig3. a) top: post-Gd T1-weighted image & relative $CMRO_2$ map
b) bottom: graph for relative $CMRO_2$ averaging 10 patients
* White arrows indicate tumor region