# Evaluating anti-angiogenic therapy response in patients with GBM using Homodynamic Response Imaging.

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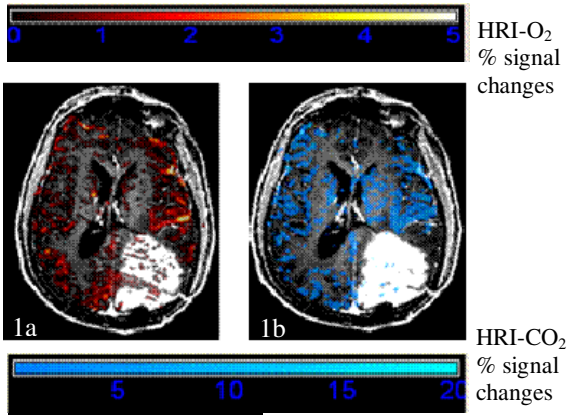
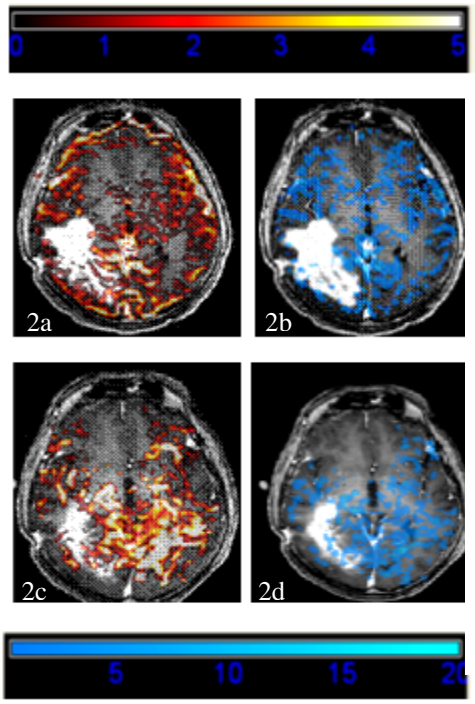
**Background / Aims:** One of the main characteristics of malignant phenotype of a lesion is the formation of new and abnormal blood vessels (angiogenesis). The close correlation between angiogenic processes and poorer prognosis have led, during recent years, to new strategies utilizing combinations of antiangiogenic and chemotherapies. Yet, methods for monitoring vascalature changes under such therapies are limited. We have previously presented a novel fMRI method (hemodynamic response imaging - HRI), using hyperoxia and hypercapnia for the detection of vascular functionality and maturation, both in animal models as well as in human brain tumors [1,2]. This method has been shown to facilitate detection of mature vessels resistant to anti-angiogenic therapy in animal models [3], and to differentiate between various tissue types with high sensitivity in humans[2]. The ***aim*** of this study was to evaluate the sensitivity of HRI to assess therapy response in patients with glioblastoma multiforme (GBM) during the course of the antiangiogenic therapy.




**Methods:** Three patients with recurrent GBM treated with a combination of anti VEGF and cytotoxic chemotherapy were scanned several times during the course of therapy with conventional MRI methods and the proposed method -HRI, at intervals of 2-8 weeks (total of 10 MR examinations). MRI was performed on a 3T GE magnet. For the HRI method, gradient-echo EPI sequence was used with TR=5000msec and TE=35msec. Two separated scans were performed, each using a block design paradigm with inhalation of either 95%O2 + 5%CO2 or 95%air + 5%CO2 and 100% air. Statistical maps of the signal intensity changes were analyzed and realigned to the contrast enhanced 3D images using Matlab package SPM5.

**Results:** Figures 1a-b show representative HRI-$O_2$ (a) and HRI-$CO_2$ (b) maps, superimposed on the contrast enhanced images, from a 54 year-old patient with recurrent GBM. Blood vessels are present within the enhanced tissue, as shown by response to $O_2$. However, the lack of response to $CO_2$, in the enhanced tissue, indicates the absence of smooth muscle cells on these vessels suggestive of new immature blood vessels.

Figure 2 demonstrates results from a 74 year-old patient obtained at: baseline (a,b) and two weeks after the beginning of antiangiogenic therapy (c,d). HRI-$O_2$ (a,c) and HRI-$CO_2$ (b,d) maps are superimposed on the contrast enhanced images. At baseline scan (before therapy), HRI demonstrates areas that respond to $O_2$ (2a) within the enhanced lesion and show no response to $CO_2$ (2b). After two weeks of therapy, partial response, (MacDonald criteria), was detected using $T_1$ weighted images post-Gadolinum correlating with the patient's clinical improvement. Using the HRI method, a response to $CO_2$ became visible within the enhanced tumor area (2d). This vascular response to $CO_2$ might indicate the existence of smooth muscle coverage on these blood vessels, demonstrating a process of "vessel normalization" as a result of antiangiogenic therapy. Such mechanism has been previously proposed to occur with anti-VEGF therapies[4]. Similar results were obtained in the other two patients, demonstrating "normalization" of blood vessels during the first 2-8 weeks of therapy, correlating with the clinical improvement of these patients.




**Conclusion:** HRI is a novel non-invasive method for vascular assessment which provides additional information regarding vessel permeability and maturation. This method shows high sensitivity for evaluating therapy response and might have added value in clinical management especially in anti-angiogenic therapies..

**References:** [1]Abramovitch R, *et al*, Neoplasia 6:480-489 2004, [2]Ben Bashat D *et al.*, 13th meeting of the ISMRM, 2005, [3]Abramovitch R, *et al,* Cancer Res 9:5012-5016, 1999. [4]Jain, RK *et al,* Nat Rev Neurosci 8:610-622, 2007.