Brain tumor oxygen saturation mapping with magnetic resonance imaging corrected by a local hematocrit mapping assessed by nuclear imaging

Benjamin Lemasson[1,2], Alexis Broisat[3,4], Pauline Busieau[1,2], Régine Farion[1,2], Mitra Ahmadi[3,4], Sandrine Bacot[3,4], Catherine Ghezzi[3,4], Chantal Rémy[1,2], and Emmanuel Barbier[1,2]

[1]U836, Inserm, GRENOBLE, France, [2]Grenoble Institut des Neurosciences, Université Joseph Fourier, GRENOBLE, France, [3]U1039, Inserm, GRENOBLE, France, [4]Radiopharmaceutiques Biocliniques, Université Joseph Fourier, GRENOBLE, France

Purpose: Brain oxygenation level is of physiological interest in numerous cerebral pathologies. A few MRI techniques are available to quantify oxygen-level parameters (e.g. partial pressure of oxygen, oxygen extraction fraction...)[1]. Recently, Christen *et al*. proposed an *in vivo* MR approach – multiparametric quantitative BOLD – to map tissular oxygen saturation (StO_2) [2]. This approach is robust enough to monitor change in oxygenation during tumor growth under anti-angiogenic treatment [3]. However, in that study, the StO_2 maps were computed considering a constant hematocrit level (Hct). In this study, we evaluate the impact of Hct on the StO_2 estimates measured in tumors by comparing 2 approaches: 1) use a constant Hct and 2) use a Hct map obtained from the autoradiography of two different isotopes.

Material and methods: Eight Wistar rats were orthotopically injected with 10^5 C6 glioma cells. Twenty days post-implantation, the animals were imaged at 4.7T on a Bruker Avance 3 console using a volume/surface cross coil configuration. All data were acquired with the same geometry (5 contiguous, 800µm-thick slices, FOV=30x30mm; matrix=128x128), except for B0 mapping (3D GE sequence, FOV=30x30mm, matrix=256x256x26, TR=100ms, TEs: n=15 [4-67ms]). Acquisition protocol was: brain shimming, B_0 mapping, T_2 mapping (TR=2000ms, 26 spin-echoes, ΔTE=12ms), T2* mapping (TR=4000ms, 32 gradient echoes, ΔTEGE=23.3ms, TESE = 60ms, multiple gradient-echoes spin-echo sequence), before and 3min after injection of 200µmol/kg of iron oxide particles (USPIO: P904, Guerbet). The entire MRI protocol lasted 40 min per animal. Systemic Hct was assessed by a blood gas analysis. Thereafter the animals were transferred in nuclear medicine facility for autoradiography to map the Hct. Briefly, brains were excised 15 minutes following i.v. injection of a mixture of ^{99m}Tc-labelled red blood cells (RBCs) (37MBq) and ^{125}I-labelled albumin (3.7MBq). Two autoradiographic images were then successively performed on several 100µm-thick slices using a phosphor-imager (Fuji BASS 5000) to first map ^{99m}Tc+^{125}I and, after ^{99M}Tc decay, ^{125}I only one week later. Fractional RBCs, plasmatic volumes, and eventually Hct were then derived. The *ex-vivo* Hct maps were then co-registered to the corresponding MR images. Finally, 2 StO_2 maps were computed, 1) using Hct = 37.5% (StO_2-c) and 2) using for each voxel the Hct value obtained by autoradiography (StO_2-corr-Hct). Data, averaged across rats, are presented for 2 regions of interest: the whole tumor and the contralateral healthy striatum. Paired student t-tests were used to assess differences between tumor and healthy tissues and between StO_2-c and StO_2-corr-Hct, respectively.

Results: The C6 tumors appeared well vascularized with a CBV similar to that of healthy striatum (3.4±0.8% *vs*. 3.5±0.5%, respectively). Similarly, StO_2-c values in the tumor and in the healthy striatum were comparable (62±9% *vs*. 65±10%, respectively). Tumor Hct level was however significantly decreased as compared to the healthy striatum (15.2±2.1% *vs*. 29.5±2.1%, respectively, p<0.01). We also observed that the systemic Hct, assessed by blood gas analysis, was significantly higher as compared to the healthy striatum (42.5±0.8% *vs*. 29.5±2.1%, respectively, p<0.01). Using the measured Hct value (and not a constant value) to compute the StO_2 map voxel-wise (StO_2-corr-Hct) led to a significant reduction in tumor oxygenation in comparison to that of the healthy striatum (46.2±4.6% *vs*. 57.2±7.8%, respectively, p<0.01).

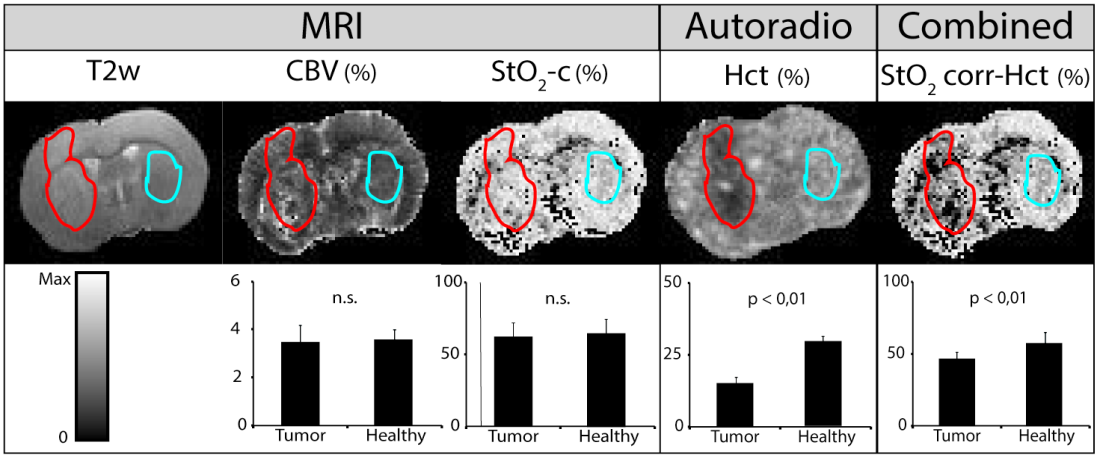

Figure 1: (***Top***) Representative T2w image and maps of CBV, StO_2-c, Hct, and StO_2-corr-Hct. (***Bottom***) Data, averaged across rats (mean ± SD), are presented for 2 regions of interest: whole tumor (red) and contralateral healthy striatum (blue). Color bar: black=0, white=maximum: CBV=15% and StO_2-c, Hct and StO_2corr-Hct = 100%.

Discussion:

Our study presents a new molecular imaging protocol to map the local hematocrit level into the brain. The Hct measured in the healthy contralateral striatum corresponds to the values already published [3]. This new mapping allows us to study the impact of the Hct values (constant or measured) on the final StO_2 maps. Similar StO_2c values were found in the tumor and healthy contralateral striatum (p = n.s). The use of Hct maps did not change the StO_2 estimate in the healthy striatum but led to a significant 14.6% decrease in the tumor (p<0.01). Although the Hct mapping technique needs further investigations to control for a potential extravasation of ^{125}I-labelled albumin in the tumor, our results indicate that change in Hct should not be overlooked when assessing oxygenation in brain tumors or in other brain diseases. Spatial and temporal variations of Hct could furthermore impact fMRI studies and need further investigations.

References: [1] Yablonskiy et al. NMR in Biomed 2013 [2] Christen et al. Radiology 2011; [3] Lasher et al. Circulation Research 1956