Is T2* Enough to Assess Oxygenation? A Quantitative Blood-Oxygen Level Dependent Analysis in Brain Tumors.

T. Christen[1], B. Lemasson[2,3], N. Pannetier[3,4], R. Farion[3,4], C. Remy[3,4], G. Zaharchuk[1], and E. L. Barbier[3,4]
[1]Department of radiology, Stanford University, Stanford, California, United States, [2]Departments of Radiology, University of Michigan, Center for Molecular Imaging, Ann Arbor, Michigan, United States, [3]Grenoble Institut des Neurosciences, Grenoble, France, [4]U836, INSERM, Grenoble, France

Introduction

The availability of a technique to image tissue hypoxia in vivo is of considerable interest. Such tools may improve brain tumor diagnosis, therapeutic orientation, or detection of tumor recurrence. Several studies of oxygenation using MR BOLD have relied solely on evaluation of baseline T2* values [1-2]. Yet, T2*, while sensitive to oxygenation, also depends on several other hemodynamic parameters that can affect the measurements. The transverse relaxation time T2 is linked to the T2* according to the formula 1/T2*=1/T2+1/T2'. Also, macroscopic field inhomogeneities (ΔB0), which may originate from magnet imperfections, poor shimming, tissue-air interfaces, etc. affect the MR signal evolution and lead to erroneous underestimation of the true tissue T2*. Lastly, T2* is sensitive to the total amount of deoxyhemoglobin present in the voxel, and for this reason, knowledge of the blood volume fraction (BVf) is of tantamount importance. Recently it has been shown that these factors can be combined according to a mathematical model (quantitative BOLD or qBOLD) to obtain quantitative estimates of blood oxygen saturation (SO2). This approach has shown encouraging results in healthy rat brain [3]. The aim of this study was to analyze the impact of these additional measurements on tumor oxygenation measurement and to compare to results that would be obtained with T2* alone. In a rat brain tumor model, we analyzed the contribution of T2, BVf, and T2* corrected from macroscopic field variations (denoted T2*B0) to BOLD-based SO2 measurements.

Material and methods

The study design was approved by the local committee for animal care and use. 9LGS tumor cells were implanted in the brain of 8 Fisher rats (120-150g, Charles River, France). 15 days later, MR experiments were performed at 4.7 T to obtain quantitative estimates of T2*, T2, BVf, and T2*B0 (i.e. T2* corrected from ΔB0):
The following sequences were obtained:
-MSME (T2 map): Multi spin-echo 2D sequence (TR = 1500ms; 20 spin-echoes; ΔTE = 12 ms; voxel size = 234x234x1000 µm3; 3 min 40 sec).
-MGE3D (T2*B0 map): Multi gradient echo 3D sequence (TR = 100 ms; 15 gradient echoes; ΔTE = 4 ms; voxel size = 117x117x200 µm3; 12 min 48 sec).
-MGESE (T2*, BVf map): Multi gradient echo and spin-echo MRI sequence (TR = 6000 ms, 8 evenly spaced gradient-echoes =4 ms, 1 spin-echo = 60 ms, FOV 234x234x1000 µm3; 12min). This last scan was performed before and after administration of ultra small superparamagnetic iron oxide (USPIO) via the tail vein (200 µmol Fe/kg) (Sinerem®, Guerbet, Roissy, France; Combidex®, AMAG Pharmaceuticals, Inc, MA, USA).
T2 was computed by fitting a non-linear exponential fit of the MSME data. **T2*** was obtained using a non-linear exponential fit of the gradient echo signal of the MGESE sequence. To remove macroscopic inhomogeneities and determine **T2*B0**, the MGE3D sequence was used [3]. Each of the thin slices (200 µm) were averaged to form the same 1000 µm slice thickness as for the MGESE sequence. Exponential fit of this signal evolution was used to obtain the corrected T2*B0. **T2'** (**T2'B0**) were computed as 1/T2*-1/T2 (1/T2*B0-1/T2) respectively. BVf was estimated using the MGESE sequence and the steady-state approach described in [4]. MR estimates of local blood oxygenation (SO2) were derived by combining all the parameters according to the qBOLD approach described in [3].
T2* data with and without additional qBOLD analysis were compared to identify any correlates between the parameters. Tumor and contralateral regions-of-interest (ROIs) were manually delineated on the T2-weighted images. Paired Student t tests were used to compare the tumoral to the contralateral region. Values were considered significantly different when $p<0.05$.

Results

Fig1: MR estimates of T2 as a function of T2, T2*B0 , BVf and SO2 measured in the tumor region (squares) or contralateral region (circles) in one rat. Linear regression curves as well as corresponding equations and correlation coefficients are given for each scatter plot.*

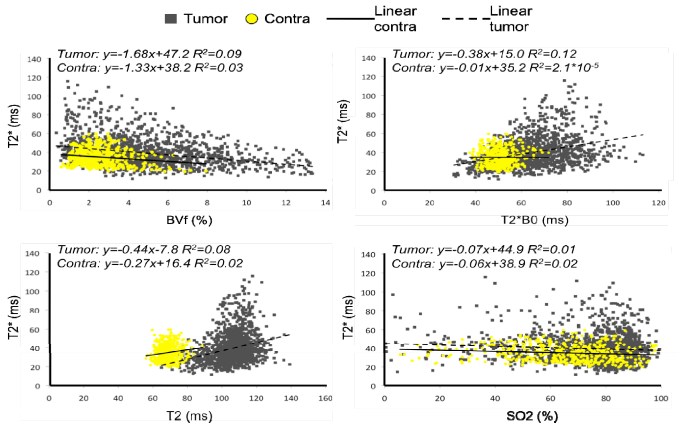
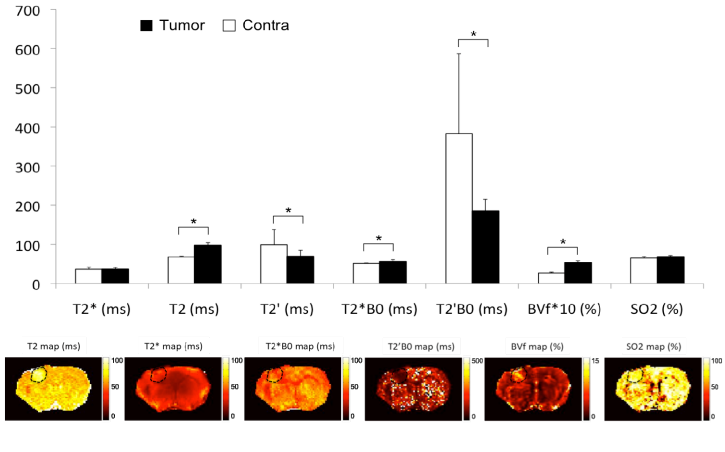


Fig2: Mean and standard deviation of the MR parameters averaged over the 8 rats in the tumor and contralateral region. (: P<0.005) and corresponding parametric maps from one animal.*



No significant correlations were found between T2* and all other parameters in both tumor and healthy tissues (Fig1). Tumor and contralateral T2* were found to be equivalent suggesting similar oxygenation (Fig2). Adding T2 information alone leads to apparent hypo-oxygenation of the tumor while incorporating BVf alone leads to apparent hyper-oxygenation. Complete qBOLD analysis measurement of SO2, although not correlated to the T2* values, suggests normal oxygenation within the tumors. The values of contralateral brain SO2 (~65%) agree with values previously reported [3].

Conclusion: In conclusion, we confirmed recent observations pointing out the importance of additional measurements such as T2, T2*B0, and BVf to accurately assess tissue oxygenation using MR-based BOLD T2* methods [5]. A lack of inclusion of any of these parameters may lead to incorrect conclusions about tumor oxygenation. Given that it is minimally invasive, the T2*-based qBOLD approach could be also extended to study other tumor models or acute pathologies, such as trauma or stroke.

References: [1] Rodrigues et al, JMRI, 2004. [2] Chopra et al, int J radiat Biol, 2009. [3] T Christen et al, NMR biomed, 2010. [4] I Troprès et al, Magn Reson Med, 2001. [5] A Padhani, Radiology, 2010.