Application of a modified quantitative BOLD approach to monitor local Blood Oxygen Saturation in two glioma models and a stroke model in rat

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Introduction

Brain oxygenation level is physiological information of interest in numerous cerebral pathologies. However, few MRI techniques for quantifying oxygen-level parameters (such as partial pressure of oxygen, oxygen extraction fraction…) are available. Recently, He and Yablonskiy proposed an *in vivo* MR approach – quantitative BOLD – to obtain local blood oxygen saturation (lSO_2) maps **[1] [2]**. In this study, we evaluate a modified version of the qBOLD technique in two cerebral diseases: stroke and tumor.

Theory

The gradient echo MR signal decay can be described by: $S(t)= Cte.\ F(t).\exp(-t.R_2).\exp(-t.R_2')$ (water diffusion neglected) **[Eq. 1]**

Where Cte is a proportionality constant, F(t) represents the contribution to signal attenuation caused by macroscopic field inhomogeneities **[1],** $R_2= 1/T_2$ and $R_2'= 1/T_2'= 4/3.\pi.\Delta\chi_0.Hct.(1-lSO_2).B_0.\gamma.BVf$. $\Delta\chi_0$ represents the change in magnetic susceptibility between oxy and deoxy-haemoglobin (0.264 ppm), Hct for hematocrit (%), and γ for magnetogyric ratio.

Material and methods

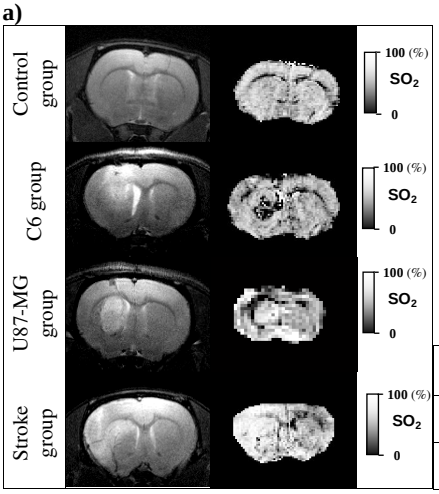
Animals (n=23) were anaesthetized using isoflurane (2%). The tail vein was equipped with a catheter. Four groups of animal were studied:

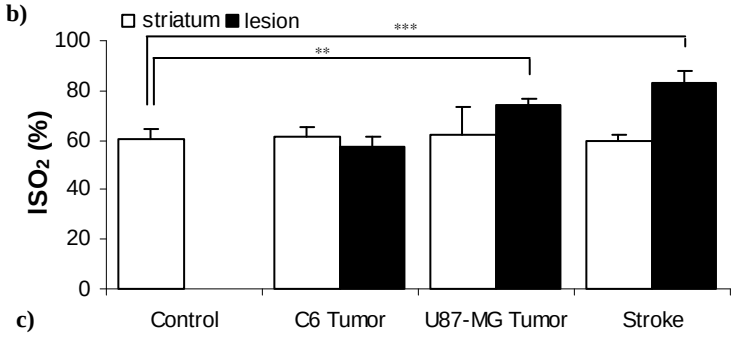
- *Control group:* male Wistar rats were used as control (n=12).
- *C6 group*: 10^5 C6 glioma cells were orthotopically implanted in the striatum of Wistar rats (n=4). Imaging was performed 18 days after tumor implantation.
- *U87-MG group*: 10^5 U87-MG glioma cells were orthotopically implanted in the striatum of male nude rats (n=4). Imaging was performed 34 days after tumor implantation.
- *Stroke group*: Transient (90min) focal brain ischemia was induced by occlusion of the right Middle Cerebral Artery using the intraluminal suture model **[3]** in male Sprague-Dawley rats (n=3). MRI was performed 2 days after ischemia.

MR imaging was performed at 4.7T on a Bruker Avance 3 console using volume/surface cross coil configuration. All data were acquired with the same geometry (7 contiguous, 1mm-thick slices, FOV=30x30mm; matrix=64x64 or 128x128), except for B_0 mapping (3D GE sequence, FOV=30x30mm, matrix=128x128x40, TR=100ms TEs=4 and 12ms). Acquisition protocol was: brain shimming, B_0 mapping, T_2 mapping (TR=1500ms, 20 spin-echoes, ΔTE=12ms), T_2* mapping (TR=1500ms, 30 gradient echoes, ΔTE=2.5ms), BVf/VSI mapping **[4]** (multiple gradient-echoes spin-echo sequence, before and 3min after injection of 200µmol/kg of iron oxide particles (USPIO: Combidex®/Sinerem®, Amag Pharmaceuticals/Guerbet): TR=6000ms; ΔTE_{GE}=3ms; TE_{SE}=60ms). The entire MRI protocol lasted 1h15 per animal.

Processing was performed with the Matlab environment and using home-made software. B_0 map was obtained by unwrapping the phase maps of the 3D GE sequence **[5]**. This B_0 map was used to compute F(t) in **[1]**. T_2 was computed using a non-linear fit algorithm and a two-parameter exponential decay. BVf and VSI were obtained with the formula given in **[4]** using 700µm²/s for the apparent diffusion coefficient and 0.28ppm for the increase in intravascular magnetic susceptibility due to the injection of USPIO **[4]**. To compute lSO_2 maps, **Eq [1]** was fitted to the MR gradient-echo data. Since maps of BVf, R_2, and F(t) are available, the fitted parameters were Cte and lSO_2. Data, averaged across rats in each group, are presented for 2 regions of interest (healthy striatum and tumor or stroke region). Student t-tests (after assessment of variance homogeneity) were used to assess differences (**:p<0.01, ***:p<0.001).

Results





	Control group (n=12)	C6 group (n=4)	U87-MG group (n=4)	Stroke group (n=3)
Striatum	**60.8±3.9%**	**61.6±3.6%**	**62.2±11.1%**	**59.4±2.5%**
Lesion		**57.2±4.3%**	**74.1±2.5%**	**83.0±4.5%**

Figure 1:
a) Representative T_{2w} images and lSO_2 maps in all groups. Black pixels in lSO_2 maps correspond to values outside the range of validity.
b) lSO_2 measurements in Control, C6, U87-MG and Stroke groups. Mean±SD **: p<0.01, ***: p<0.001.
c) Data, averaged across rats (mean±SD), are presented for the two regions of interest (lesion and contralateral striatum) and for each group.

lSO_2 estimates in contralateral striatum of lesioned groups did not differ from that in Control striatum value (61±1.2%; Fig. 1b-c). In the C6 tumor, lSO_2 did not differ from Control striatum (57.2±4.3%; Fig. 1b-c). In the U87MG tumor and in the infarcted region, lSO_2 was higher than in Control striatum (74.1±2.5 and 83.0±4.5% respectively; Fig. 1b-c). lSO_2 value in the infracted region is in good agreement with the reported luxury perfusion **[6]**.

Conclusion

Values of lSO_2 in the contralateral striatum of rats bearing a brain lesion or in healthy rats are consistent with the literature **[7]**. The small standard deviation suggests that the proposed lSO_2 measurement approach is reproducible. This study shows differences in lSO_2 values between two glioma models (C6 and U87-MG) and modification in case of focal brain ischemia model. Our results suggest that MRI measurement of lSO_2 might be an interesting biomarker to characterize brain lesion and improve therapeutical monitoring. Further insights on the physiological meaning of lSO_2 are thus required.

Reference

[1] He and Yablonskiy, *Magn Reson Med*, 2007.[2] An and Lin, *JCBFM*, 2000.[3] Longa et al, *Stroke,* 1989.[4] Troprès et al, *Magn Reson Med*, 2001.[5] Jenkinson, *Magn Reson Med*, 2003.[6] Lin et al, Stroke, 2002. [7] Y Chen et al, Phys Med Biol, 2003.