Is R1 of Lipids related to pO2? Lessons from two tumor models

Florence Colliez[1], Marie-Aline Neveu[1], Julie Magat[1], Thanh Trang Cao Pham[1], Bernard Gallez[1], and Bénédicte F Jordan[1]
[1]*Louvain Drug Research Institute, Biomedical Magnetic Resonance Research Group, University of Louvain, Brussels, Belgium*

Target audience: MR scientists who are interested in oncology and tumor hypoxia mapping

Introduction: Tumor hypoxia is acknowledged as a major factor of resistance of solid tumors to treatment. Improving tumor oxygenation at the time of treatment could lead to an improved response to both chemotherapy and radiotherapy[1]. Variations in T_1 and T_2* are potentially valuable MRI tools to follow changes in tumor oxygenation. T_2* is sensitive to the relative Hb/HbO_2 ratio in vessel[2], while T_1 change is sensitive to dissolved oxygen which acts as a T_1-shortening paramagnetic contrast agent[3]. The aim of the current work is to investigate the quantitative aspect of a new oxygen mapping method: MOBILE (Mapping of Oxygen By Lipids relaxation Enhancement). This non-invasive method is based on the changes in the relaxation properties of the tissue lipids by exploiting the higher solubility property of oxygen in lipids than in water[4]. For this purpose, two tumor models were submitted to (i) hyperoxic challenges induced by carbogen breathing and (ii) hypoxic challenges induced by Combetastatin A-4 Phosphate, a vascular disrupting agent (VDA) known to induce hypoxia within 3 hours[5]. Actual pO_2 was obtained by EPR oximetry. We compared sensitivities of the MOBILE technique with the classical '*oxygen enhanced MRI*'[6] sensitivity that measures global T_1 mainly influenced by water protons.

Methods:
Tumor models: Mammary NT2 and human MDA-MB-231 tumor cells were inoculated at orthotopic site in FVB/Nrj and NMRI nude mice respectively (n=5 for each tumor model).
MR imaging: Experiments were performed with a 11.7T (Bruker, Biospec) using a surface coil cryoprobe. *'Oxygen enhanced MRI':* A segmented IR FISP (Inversion-Recovery Fast Imaging with Steady state Precession) sequence (SSFP FID mode) was used to acquire parametric images of T_1 relaxation time ('oxygen enhanced MRI'). Acquisition parameters were TR/TE/FA/BW/matrix = 4 ms/1.2ms/5°/100kHz/64x64, 4 segments, and a total acquisition time of 1min20s. *'MOBILE'*: The difference in Hertz between water and lipid peaks was evaluated on a single pulse spectrum. These offsets were then used as an imaging frequency offset in the same IR FISP protocol and the water signal was spoiled.
EPR experiments: A 1.1 GHZ in vivo L-band EPR Magnettech system was used 24h after injection of a paramagnetic oxygen reporter probe.
Hyperoxic challenge: A set of 3 images of each type (Global T_1 and Lipids T_1) were acquired at baseline and 10 minutes after a switch to carbogen breathing. The same challenge was repeated 3hours later to achieve actual pO_2 by EPR oximetry.
Hypoxic challenge: A set of 3 images of each type (Global T_1 and Lipids T_1) were acquired at baseline and 3hours after CA4P injection (100mg/kg).

Results: Parametric maps of Lipids R1 were provided for each tumor before and after challenges.

Fig.1

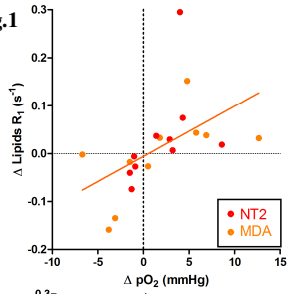
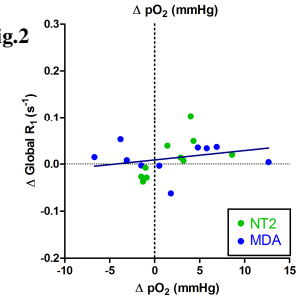


Fig.2



A significant linear regression has been established between variations of Lipids R_1 in regard to variations of pO_2 ($Y = 00.015051 \pm 0.004181\ X + 0.005921 \pm 0.0235$; $p=0.0217$)(Fig. 1). However, no correlation was statistically demonstrated despite a trend between variations of Global R_1 and variations of pO_2 ($Y = 0.001995 \pm 0.001823\ X - 0.008542 \pm 0.008872$; $p=0.2882$)(Fig. 2).

A significant linear regression was demonstrated between actual pO_2 and mean Lipids R_1 calculated for each tumor ($Y= 0.007493 \pm 0.003249\ X + 1.048 \pm 0.03150$; $p=0.0275$)(Fig.3) However, we observed no significant linear regression between actual pO_2 and Global R_1 even if a slightly trend was observed ($Y= 0.002283 \pm 0.001970\ X + 0.8656 \pm 0.01910$; p=0,2548).(Fig.4)

Fig.3

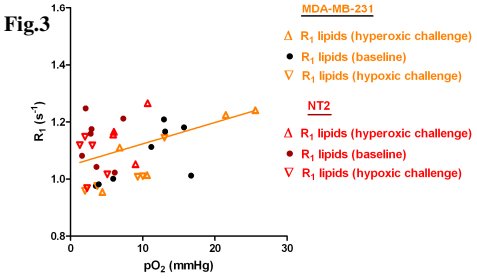
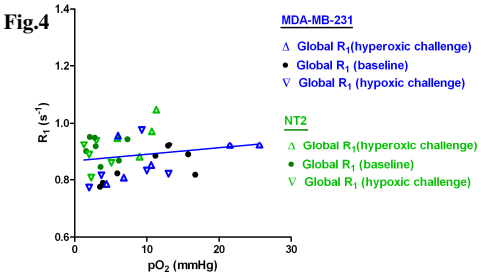


Fig.4



Discussion & Conclusion : The quantitative aspect of MOBILE has been demonstrated. Actual pO_2 was measured in two tumor models (NT2 and MDA-MB-231 tumors) by EPR oximetry and significantly correlated to mean values of Lipids R_1 obtained with MOBILE at baseline and after both hyperoxic and hypoxic challenges, induced respectively by carbogen breathing and CA4P administration.

References: **1.**Kaanders et al, *Lancet Oncol* 2002, 3, 728-737 **2.**Baudelet et al, *Magn Reson Med* 2002, 48, 980-986 **3.** O'Connor et al, *Int J Radiat Oncol Biol Phys* 2009, 75, 1209-1215 **4.** Jordan BF, et al. Magn Reson Med. 2013; 70:732–744 **5.** Iversen AB et al., *Acta Oncol.* 2013 Oct;52(7):1320-6 **6.** O'Connor JP et al., *Int J Radiat Oncol Biol Phys 2009* ;75(4) :1209-15