Quantitative comparison of MOBILE (Mapping of Oxygen By Imaging Lipids relaxation Enhancement) and EPR oximetry in multiple tumor models.

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

Purpose and objectives: 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 therapy (1). In order to individualize the treatments and select patients who could benefit from tumor reoxygenation, there is a critical need for methods able to monitor dynamically and noninvasively tumor oxygenation. Variations in T_1 and T_2* are potentially valuable MRI tools to changes in tumor oxygenation. T_2* is sensitive to the relative Hb/HbO_2 ratio in vessels (2), while T_1 change is sensitive to dissolved oxygen which acts as a T_1-shortening paramagnetic contrast agent (3). The purpose of the current work was to compare the MOBILE technique, a method developed to map variations in oxygenation 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), with R_1 of H_2O and with EPR oximetry in multiple tumor models. Positive and negative changes in tumor oxygenation were induced by a hyperoxic breathing challenge or administration of an anti-vascular agent in order to determine correlations between the tumor response assessed using each technique in MDA-MB-231 and NT2 mammary tumors.

Material and Methods:
Tumor models & protocol: Mammary tumor models (NT-2 and Human MDA-MB-231 cells) were implanted in the mammary fat pad of FVB/N and NMRI nude mice, respectively. Mice were anesthetized using isoflurane. Three MOBILE measurements were acquired during air breathing and repeated during carbogen breathing. A similar protocol was repeated 4h later with L-band in vivo EPR oximetry. In order to follow the decrease of pO_2 after CA4 administration (100 mg/kg), MOBILE measurements and EPR oximetry were performed at baseline and 3 h after CA4 injection.
MR experiments: MRI Experiments were performed with a 11.7T (Bruker, Biospec), and with a quadrature volume coil (inner diameter of 40 mm). 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. The acquisition parameters were TR/TE/FA/BW/matrix = 4 ms/1.2ms/5°/100kHz/64x64, 4 segments, and a total acquisition time of 1min20s. For the lipids experiment, we first evaluated the difference in Hertz between water and lipid peaks 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. Images were treated using Matlab to determine the T_1 relaxation. EPR experiments were performed on a 1.1 GHZ in vivo L-band EPR Magnettech system 24h after injection of a paramagnetic oxygen reporter probe.

Results:
In NT2 tumors, the basal pO_2 was 8.4±1.1 mm Hg and reached 26.1±6.1 mm Hg during carbogen breathing. The correlation between R_1 H_2O and pO_2 was not significant (p=0.8611, positive linear fit 0.000409±0.002241; r^2=0,005529) (Fig.1), while a positive linear significant correlation was found between R_1 Lipids and pO_2 (0.01744±0.00656; r^2=0.5407, p=0.0376) (Fig.1). In MDA-MB-231 tumors, the basal pO_2 was 7.3±1.2 mm Hg and reached 4.5±0.8mmHg three hours after CA4 injection as assessed using EPR oximetry. Variations in pO_2 induced larger changes in R_1 lipids than in global R_1. A positive fit was found between R_1 lipids and pO_2 (positive linear fit 0.0208±0.224 ; r^2=0.2224) (Fig.2.).
Fig.3 & 4 show typical maps of change in NT2 & MDA-MB-231 tumors, respectively, in response to carbogen breathing, for which pO_2 values were 9.1 mm Hg and 8.4 mm Hg at baseline and reached 31.6 mmHg and 25.6 mmHg during carbogen breathing, as assessed using EPR oximetry.

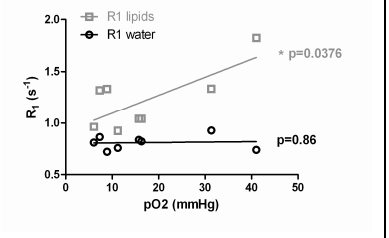

Fig.1. NT2 tumor model: correlation between R_1 values and EPR pO_2 values.

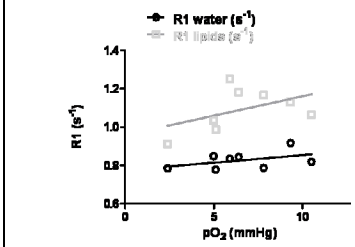

Fig.2. MDA-MB-231 tumor model: correlation between R_1 values and EPR pO_2 values.

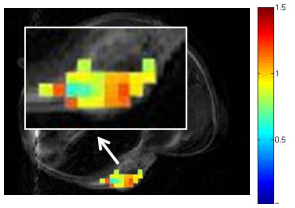

Fig.3. Typical map of change in a NT2 tumor in response to carbogen breathing.

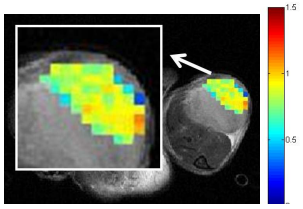

Fig.4. Typical map of change in a MDA-MB-231 tumor in response to carbogen breathing.

Conclusions:
The aim of this work was to show the ability of MOBILE to follow variations in pO_2. Two agents were used as oxygenation modulators : CA4 and carbogen. MOBILE was able to follow both of them in two mammary tumor models (NT2 and MDA-MB-231). Variations in pO_2 were significantly correlated with R_1 lipids whereas the correlation could not be established between pO_2 values and R_1 water measurements in the NT2 model. MOBILE presents a higher sensitivity than global R_1 to monitor changes in tumor oxygenation. In addition, these data stem in favour of a quantitative aspect of MOBILE.

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 & Magat J. et al, Magn Reson Med, 2012, Sep 28. doi: 10.1002/mrm.24511.