Application of MOBILE (Mapping of Oxygen By Imaging Lipids relaxation Enhancement) to monitor changes in tumor oxygenation following administration of the anti-vascular agent CA4.

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Target audience : MR scientists who are interested in oncology, tumor hypoxia and cancer therapies (antivascular and antiangiogenic).

Purpose and objectives: We recently exploited a highly sensitive endogenous contrast to map variations in tumor oxygenation, a technique that we called "MOBILE" (Mapping of Oxygen By Imaging Lipids relaxation Enhancement), based on the changes in the relaxation properties of the tissue lipids[1]. The purpose of the current work was to test the ability of the "MOBILE" technique to monitor adequately a decrease in tumor oxygenation following administration of the anti-vascular agent CA4, in comparison with EPR oximetry. Combretastatin A4 phosphate (CA4P) is the lead compound of class of agents termed vascular disrupting agents that target existing tumor blood vessels[1]. CA4P typically induces rapid tumor necrosis in the center of the tumor and leaves a rim of viable cells in the periphery. Rapid tumor blood flow shutdown has been demonstrated in preclinical models and patients by various techniques such as dynamic contrast enhanced MRI, perfusion computed tomography and PET scans following CA4P infusion[1]. However, the compound usually shows a lack of activity as a single agent because of rapid regeneration from the tumor periphery. Therefore, a beneficial association between radiotherapy and CA4 has been suggested in order to simultaneously tackle the viable ring that is more radiosensitive because of a higher oxygenation level[1]. In this context, it seems particularly relevant to be able to non-invasively map tumor oxygenation before and after treatment with CA4 for the optimization of treatment combination and scheduling.

Material and Methods:

Tumor models & protocol: Human MDA-MB-231 cells mammary tumor models were implanted in the mammary fat pad of NMRI nude mice. Three MOBILE measurements and 5 EPR measurements were acquired before and after administration of CA4 (100 mg/kg) under anesthesia using isoflurane.

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: Fig.1. show typical maps obtained before (a) and 3h after (b) CA4 injection with the MOBILE sequence. Mean basal pO_2 was 7.7±1.0 mmHg and reached 4.5±0.8mmHg three hours after injection as assessed using EPR oximetry. Variations in global R_1 are < 10% and the decrease in pO_2 was linked to a decrease of R_1 for about 50% of the tumors. Using MOBILE measurements, we generally observed a decrease in R_1 of lipids 3 hours after CA4 administration (Fig. 2 and Fig.3).

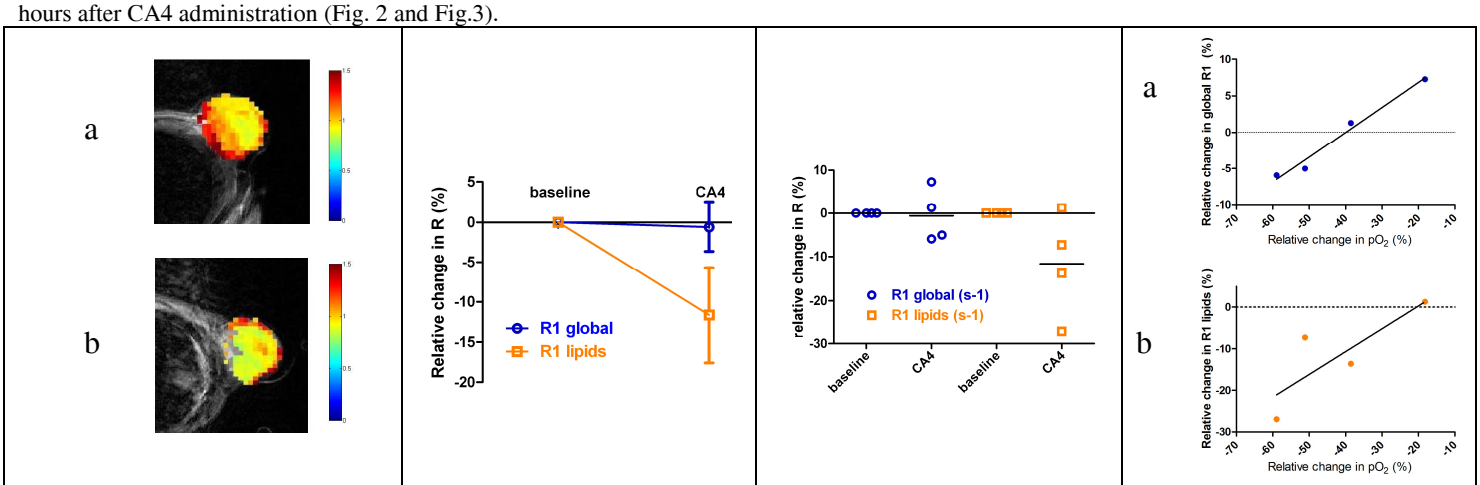

Fig.1.Maps of relaxation time at baseline (a) and 3 hours after CA4 injection (b)

Fig.2. Mean relative changes in relaxation times before and after CA4 injection (n=4)

Fig.3. Relative changes in global R_1 and R_1 lipids induced by CA4 injection (3h later)

Fig.4. Correlation between variations in pO_2 and variations in global R_1 (a) and R_1 lipids (b)

Conclusions: This work established the ability of MOBILE to follow a decrease in oxygenation 3 hours after an antivascular administration (CA4P). A decrease in R_1 lipids was observed in most cases after CA4 injection. This is in accordance with actual pO_2 measurements obtained by EPR oximetry. However, positive variations of global R_1 were sometimes associated with a fall in pO_2. So, MOBILE seems to be more sensitive to variations in oxygenation than global R_1.

References:

(1) Nagaiah G. et al, Future Oncol., 2004, 6, 1219-1228.
(2) Jordan BF & Magat J. et al, Magn Reson Med, 2012 Sep 28. doi: 10.1002/mrm.24511.