Mapping of Oxygen By Imaging Lipids relaxation Enhancement (MOBILE): Application to Changes in Tumor Oxygenation of Mammary Cancer Models

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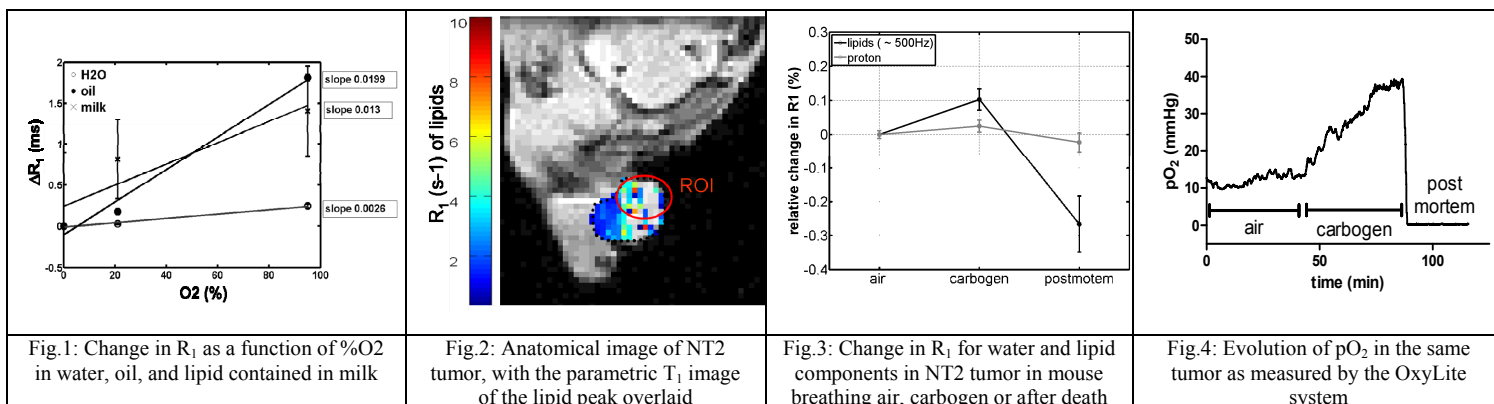
Purpose and objectives: Tumor hypoxia is a major factor of resistance to cytotoxic treatments including radiation therapy. Couteracting tumor hypoxia at the time of treatment could lead to an improved response to therapy (1). In order to individualize the treatments and select patients who can benefit from tumor reoxygenation treatment, there is a critical need for methods able to monitor dynamically and noninvasively the 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/HbO2 ratio in vessels (2), while T_1 change is sensitive to dissolved oxygen which acts as a T_1-shortening paramagnetic contrast agent. Recently, changes in tumor oxygen concentrations have been shown to produce changes in relaxation rate R_1 of water (3). This technique still lacks a good sensitivity. Here, we propose to exploit the higher solubility property of oxygen in lipids than in water (4) to monitor the changes in R_1 of the lipid peak and translate it into pO_2 values. For this purpose, we developed a method to map variations in oxygenation based on the changes in the relaxation properties of the tissue lipids. This technique is called *MOBILE* for Mapping of Oxygen By Imaging Lipids relaxation Enhancement. We first measured in vitro the relaxation properties of water and lipid components in pure aqueous and oil phases, and in mixed systems equilibrated in different oxygen environments. We also monitored the evolution of the R_1 of lipids in vivo in mammary cancer models before and during a carbogen breathing challenge.

Material and methods:

Samples and animals: Calibration curves (R_1 as a function of % oxygen) were established in water, oil, and milk. Mammary cancer models NT-2 were implanted subcutaneously in the leg of NMRI mice (n=5). Mice were anesthetized by isoflurane. An OxyLite MR compatible probe (measuring the pO_2 by fluorescence quenching) was introduced inside the tumor to monitor local changes in pO_2. Three MR measurements were acquired during air breathing. Then, breathing gas was switched to carbogen, and three measurements of R_1 were acquired 10, 25, and 40 minutes after the gas switch. Finally, the animals were killed by switching the gas to nitrogen, and 3 measurements were acquired after the death of the animals. Respiratory triggering was employed to acquire images during the expiration cycle to avoid motion artifact, and the temperature of the animal was kept at 36±1 °C during the experiment.

MR experiments: Experiments were performed with a 11.7T (Bruker, Biospec), and with a quadrature volume coil (inner diameter of 40 mm and length of 100mm). 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 total proton experiment (essentially reflecting the water peak), in order to sample the recovery of the signal, a series of 100 images were acquired between 30 and 11910 ms (TR=120 ms between segments) with a slice thickness of 1mm. For the lipids experiment, we first evaluated with a single pulse sequence the difference in Hertz between water and lipid peaks in the spectrum. These offsets were then used as an imaging frequency offset in the same IR FISP protocol. We added a $\pi/2$ hermite saturation pulse with a bandwidth of 5400Hz.ms to spoil the water signal. A series of 40 images between 30 and 3930ms (TR=100ms between segments) with a slice thickness of 3 mm were acquired. Then, images were treated using a home made program written in Matlab to determine the T_1 relaxation (in ms) in regions of interest.

Results: The evolution of R_1 as a function of the % oxygen in the gas phase in presented in Fig 1. The higher solubility of oxygen led to a higher sensitivity when considering the evolution of R_1 of lipids as a function of oxygenation, compared to the R_1 of water. Typical anatomical image is shown on Fig.2, with the R_1 parametric image overlaid. Overall, the tumor response to the breathing challenge was rather dispersed from one animal to another, and a large heterogeneity of response was also observed within individual tumors. A typical evolution observed in a region of interest of the tumor (imaged in Fig.2) is shown in Fig. 3: R_1 increased during the carbogen challenge, and dramatically decreased after the death of the animal. As shown in Fig.3, the change observed in R_1 measured in lipids was larger than the change in R_1 of water after the carbogen breathing challenge and after death. The evolution of the tumor pO_2 as measured by the OxyLite on the same animal is shown in Fig.4.

| Fig.1: Change in R_1 as a function of %O2 in water, oil, and lipid contained in milk | Fig.2: Anatomical image of NT2 tumor, with the parametric T_1 image of the lipid peak overlaid | Fig.3: Change in R_1 for water and lipid components in NT2 tumor in mouse breathing air, carbogen or after death | Fig.4: Evolution of pO_2 in the same tumor as measured by the OxyLite system |

Conclusions: The measurement of R_1 in lipids offer an increased sensitivity when monitoring the changes in tumor oxygenation compared to previously described techniques that measure the variations of R_1 in the water component.

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) Bennett et al, Invest Radiol 1987, 22, 502-507.