Evaluation of breast tumor microcirculation and oxygenation using a combination of BOLD, DCE and 19F MRI

D. Zhao[1], L. Jiang[1], A. Constantinescu[1], E. W. Hahn[1], R. P. Mason[1]

[1]Radiology, UT Southwestern Medical Center, Dallas, TX, United States

Introduction: Tumor microcirculation and oxygenation play important roles in malignant progression and metastasis, as well as response to various therapies (1). Recognizing the intimate interplay of tumor oxygenation and blood flow, we have initiated investigations to compare regional changes in tissue pO_2 with vascularity. We have recently established a novel magnetic resonance approach to measuring regional tumor oxygen tension *FREDOM* (Fluorocarbon Relaxometry using Echo planar imaging for Dynamic Oxygen Mapping) with hexafluorobenzene, as the reporter molecule. This technique allows us to not only simultaneously examine multiple specific locations within a tumor, but also observe dynamic changes at individual locations with respect to intervention. Dynamic Contrast Enhanced (DCE) ^{1}H MRI based on exogenous Gd-DTPA and Blood Oxygen Level Dependent (BOLD) based on endogenous contrast deoxyhemoglobin are each sensitive to vascular characteristics. Here, we apply these MRI approaches to evaluate tumor oxygenation and vascularity and investigate the potential correlations among data set acquired by each technique.

Methods: Syngeneic breast NF13762 carcinomas were implanted in skin pedicles on the foreback of female Fisher rats. When the tumors reached ~ 1 cm diameter (Vol. ~ 0.6 cm^3), MR measurements were performed on a 4.7 T Varian system. Each rat was maintained under general anesthesia (air and 1% isoflurane). Hexafluorobenzene (50 µl) was injected into both central and peripheral regions in a single central plane of the tumor coronal to the rat's body. A tunable (^{1}H/^{19}F) single-turn solenoid coil (2 cm in diameter matched to the tumor size) was placed around the tumor-bearing pedicle. A single 2mm slice parallel to the rat body containing the strongest fluorine signal was chosen for the following ^{1}H DCE and BOLD and ^{19}F pO_2 studies. The transverse relaxation rate $R2^*$ was measured using multigradient echo sequence with 8 echoes (TR=195ms, TE=7ms and spacing =6ms) during air or oxygen breathing. After air equilibration, a series of spin echo planar images (constant recovery time τ = 500 ms (≡ TR) and TE=53 ms) obtained for BOLD response measurements during respiratory challenge. Following BOLD, the coil was retuned to ^{19}F. Tumor oxygenation was assessed on the same 2mm slice using ^{19}F PBSR-EPI of HFB with 6.5 minutes time resolution. A series of pO_2 maps was acquired over a period of 60 min with respiratory challenge, and corresponding regional pO_2 was estimated using the relationship: pO_2 (torr) = (R1-0.0836)/0.001876 (2). Finally, Dynamic Contrast Enhanced (DCE) MRI was performed on the 2mm slice using T1-weighted spin echo sequence (TR= 180ms, TE= 18ms) after a bolus injection of Gd-DTPA-BMA (0.1 mmol/kg, Omniscan) through a tail vein catheter. All data analysis was based on pixel by pixel basis.

Results: Each technique demonstrates intra-tumoral heterogeneity. As shown in Table 1, tumor pO_2 and BOLD SI increased and $R2^*$ decreased in response to respiratory challenge, and tumors with higher initial pO_2 and less hypoxic fraction (HF_{10}) had higher challenged pO_2 values ($r > 0.8$, $p < 0.01$). A significant correlation was found between ΔpO_2 and BOLD response ($r > 0.9$, $p < 0.001$, Fig. 1), while a lack of correlation between baseline pO_2 and the BOLD SI. There was no general correlation among pO_2, $R2^*$ and IAUC.

Table 1. Results of diverse MR approaches

Case	^{19}F pO_2 (torr)			BOLD	R2* (s^{-1})			DCE
no.	Air	HF_{10} (%)	Δ	(%)	Air	Oxygen	Δ	IAUC
1	36.3	0	136	14.1	46.1	42.6	-3.5	0.66
2	16.6	23	64.5	9.3	54.7	52.6	-2.1	1.00
3	12.5	31	49.6	7.5	69.4	63.8	-5.6	0.58
4	12.8	29	67.7	12.3	115.6	101.6	-14.0	0.49
5	11.5	33	21.5	2.9	64.1	66.7	2.6	0.40
6	12.3	21	19.8	2.3	49.9	47.6	-2.0	0.31
7	24.3	25	47.2	4.5	36.2	33.8	-2.4	0.61
8	NA	NA	NA	6.1	90.6	86.6	-4.0	0.87
Mean	18.0	23	58	7.4	65.8	61.9	-3.9	0.62

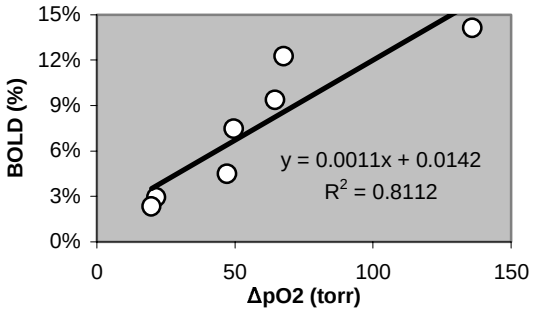

Fig.1. Correlation between ΔpO_2 and BOLD

Discussion: There is increasing evidence that tumor pO_2 has prognostic value in the clinic (1). Using the *FREDOM* approach we are able to detect intra-tumor differences in oxygenation. One might anticipate that non-invasive vascular dynamics could provide surrogate markers for tumor oxygenation. While we have found that BOLD and DCE provide a qualitative indication of tumor vascular dynamics, our results suggest a lack of correlation with tumor pO_2 itself. However, there was a strong correlation between BOLD response and ΔpO_2 accompanying oxygen challenge.

References:

1. Höckel, M., Vaupel, P., *J. Natl. Cancer Inst.*, 93, 266-276, 2001.
2. Hunjan, S., Zhao, D., Constantinescu, A., Hahn, E.W., Antich, P.P., Mason, R.P., *Int. J. Radiat. Oncol. Biol. Phys.*, 49, 1097-1108, 2001.

Acknowledgment: Supported by DOD Breast Cancer DAMD 170310363 and NCI RO1 EB2762 and P20 CA86354.