A Noninvasive Tumor Oxygenation Imaging Strategy using MR Imaging of Endogenous Blood and Tissue Water

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Introduction:

Tissue oxygenation is an important physiological parameter related to perfusion and metabolism. Oxygen partial pressure (pO_2) is a crucial factor in the response of tumors to irradiation and other cytotoxic. An ideal noninvasive tumor oxygenation imaging strategy would provide precise accurate reproducible measurement with spatial and temporal resolution allowing dynamic measurements. The aim of this study was, to develop a new approach that attempts to non-invasively determine tumor pO_2 using multi-parametric ^{1}H **M**RI-based **OX**ygen **I**maging (MOXI) strategy. The proposed strategy for pO_2 measurements was compared with ^{19}F MRI based on the oxygen reporter molecule hexafluorobenzene (HFB).

Method:

Two well-characterized Dunning R3327 rat prostate tumor lines: AT1 (N=4) and MAT-Lu (N=4) were implanted subcutaneously in the thigh of eight male Copenhagen rats. MRI was performed when tumors reached approximately 0.5-2.5 cm in diameter. All data were acquired on 4.7-T system (Varian, Palo Alto, CA) with a 35 mm home-built single-turn solenoid volume coil, tunable to ^{1}H or ^{19}F. Sequential scans including quantitative T_1, T_2 and blood volume fraction measurements were acquired using the same FOV (40mm × 40 mm), acquisition matrix (128 × 64), and single 2-mm thick slice to all co-localization. An Inversion Recovery (IR) turbo Fast Low-Angle SHot (FLASH) pulse sequence with magnitude reconstruction was performed for quantitative T_1 measurement (TR 2700 ms, TE 5 ms, flip angle= 10°). Imaging time for 3 averages was 2 min 50 sec. A multiple spin-echo CPMG sequence was performed for quantitative T_2 measurement (TR 2000 ms, Tcp = 10 ms, and TE = n× Tcp, n=12. Imaging time was 2 min 11 sec. A fast spin echo based diffusion weighted imaging sequence was performed for blood volume fraction measurement (TR 2000 ms, effective TE 56 ms, diffusion gradients were applied in three orthogonal directions and 10 b-values, at b of 0, 25, 50, 100, 150, 200, 300, 500, 1000 and 1500 s/mm^2, were acquired. Imaging time for all diffusion scans with different b values was 6 min 20 s. A total of 5 sequential scans was acquired during air breathing. Tumor pO_2 was subsequently measured using the ^{19}F FREDOM (Fluorocarbon Relaxometry using Echo planar imaging for Dynamic Oxygen Mapping) method (ref Zhao). The FREDOM protocol used: FOV=40×40 mm, matrix size= 32×32, thickness =10 mm, in-plane voxel size = 1.25×1.25 mm, and acquisition time 6.5 min. The ^{19}F R_1 was estimated using a three-parameter mono-exponential fitting, and pO_2 (mm Hg) was estimated using the relationship: $pO_2 = (R_1 - 0.0835)/0.001876$. Tumor and muscle regions of interest (ROIs) were manually delineated on the anatomic T_2-w images. The mean ROI size across animals was 0.93 cm^3 ± 0.72 (standard deviation). Each ROI was transferred on T_1, T_2, fp, Y and pO_2 maps. The quantitative measurements of site-to-site pO_2 made from ^{1}H MRI and ^{19}F MRI were compared by calculation of the intra-class correlation coefficient, linear regression analysis, and the method of Bland and Altman.

Results:

No significant differences were found between the tumor sublines: AT1 (n=4) and MAT-Lu (n=4)and therefore results are combined for the two tumor types (Table 1). Figure1 shows representative ^{1}H MRI-derived parameter maps obtained in one animal. Compared with host tissue (i.e. muscle), tumors have longer T_1 and T_2 relaxation times. Spatially, it is clear that the tumor exhibits heterogeneous blood volume, Y and pO_2 distributions. The pO_2 measurements obtained using ^{1}H and ^{19}F methods are compared in Figure 2a showing a strong linear relationship. Bland-Altman analysis (Fig. 2b) revealed minimal differences between the mean pO_2 (^{1}H MRI minus ^{19}F MRI). Repeat measurements over a period of 70 minutes indicated fluctuations in whole tumor and muscle parameters for a representative tumor (Fig. 3). Each parameter showed fluctuations with greatest variation in fp and pO_2. Tumor T_1 ranged from 1936 ms to 2094 ms and T_2 ranged from 57.7 ms to 59.6 ms, while tumor fp ranged from 0.10 to 0.16 and pO_2 ranged from 16 mm Hg to 25 mmHg. By comparison, the muscle showed less variation in T_1 (from 1380 ms to 1435 ms), T_2 (from 29.5 ms to 29.8 ms) and pO_2 (from 40 mm Hg to 45 mmHg), even though fp had relative greater changes (from 0.18 to 0.24).

Discussion:

A novel strategy has been developed based on ^{1}H MRI derived multi-parametric maps which enables non-invasive *in vivo* measurement of tumor tissue pO_2. The correlation with ^{19}F MRI oximetry confirmed the accuracy of the proposed approach. The approach shows promise as a tool for the non-invasive measurement of tumor oxygenation status.

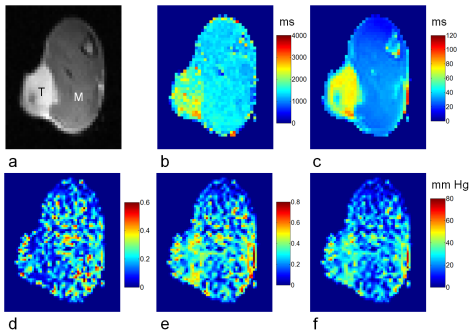

Figure 1: Representative ^{1}H MRI parameter maps, derived Y and pO_2 maps from a MAT-Lu tumor (No. 7). (a) T_2-weighted image; (b) T_1 map; (c) T_2 map; (d) Blood volume fraction (fp) map; (e) Oxygen saturation (Y) map; (f) pO_2 map. Compared to host tissue (*i.e*, muscle (M)), the tumor (T) showed longer T_1 and T_2 relaxation times, heterogeneous blood vessels, Y and pO_2 distributions

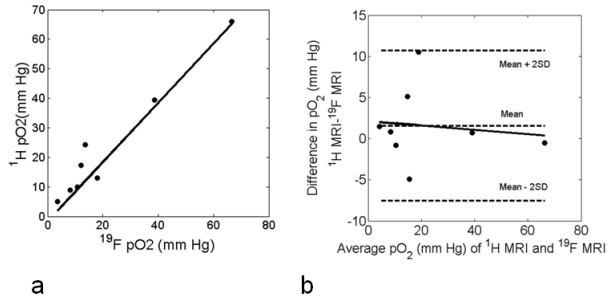

Figure 2: Comparison of pO_2 measurements obtained using with ^{1}H MRI and ^{19}F MRI. **(a)** linear correlation between ^{1}H MRI and ^{19}F MRI: regression line slope = 1.002; intercept = -1.6 (r = 0.953; p < 0.0001). Intraclass correlation coefficient = 0.98 (p < 0.0001). **(b)** Bland-Altman plot shows limits of agreement. For difference (^{1}H MRI minus ^{19}F MRI) in pO_2 measured, 95% CI is –7.6 to 10.7 mm Hg. At statistical power of 0.95, no significant bias is detected. Bias line slope = -0.03; intercept = 2.1; r = 0.01; p = 0.78

Table 1: Quantitative Measurements of T_1, T_2, f_p, Estimated Y and pO_2 in rat muscle and whole tumor by ^{1}H MRI (n=8)

ROI	T_1(ms)	T_2(ms)	fp	Y	pO_2
Muscle	1480±86	29±2	0.22±0.03	0.49±0.06	39±5
Tumor	1980±186	59±9	0.23±0.10	0.53±0.12	36±15

Note: Data are mean ± standard deviation

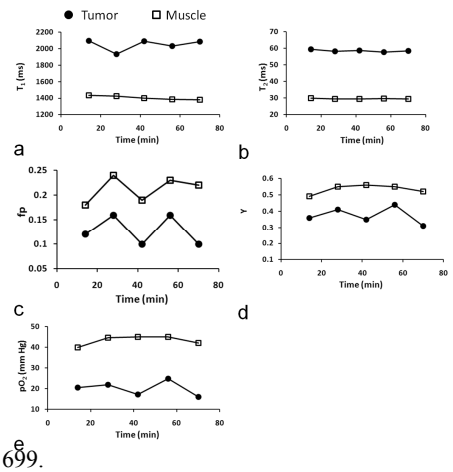

Figure 3: Temporal fluctuations in whole tumor (•) and muscle ( ) parameters over a period of 70 minutes from a MAT-Lu tumor (No.5). **(a-f)** The dynamic changes of T_1, T_2, fp, Y and pO_2 with different time points.

Reference:

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[3] Zhao D, *et al. Methods Enzymol*., 2004.386:378-418