DOCENT- Dynamic Oxygen Challenge Evaluated by NMR T1 and T2* of Tumors

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Introduction: Hypoxia influences tumor response to therapy, in particular limiting efficacy of radiation therapy. Thus, many techniques are being developed to assess hypoxia or quantitative pO_2 (1). Most require insertion of probes or reporter molecules limiting their application in patients. Thus there is a need for non-invasive assays. Blood Oxygenation Level Dependent (BOLD) MRI based on T2* contrast induced by [deoxyhemoglobin] is sensitive to tumor vascular oxygenation and blood flow and has been investigated (2, 3). Recently, studies have suggested a possibility of assessing tissue oxygenation based on the shortening of the tissue water T_1 due to oxygen, so-called TOLD (Tissue Oxygen Level Dependant contrast) (4). This has prompted us to investigate the utility of BOLD and TOLD to evaluate tumor hypoxia and response to interventions. Specifically, we are investigating differences in T_1- and T_2*-weighted signal intensity in response to carbogen breathing between two Dunning prostate R3327 rat tumor sublines (AT1 and HI) noted for their different growth rates, vascular development , levels of hypoxia and known response to hyperoxic gas breathing.

Materials and Methods: Syngeneic Dunning prostate R3327 rat tumor sublines: anaplastic and poorly vascularized AT1 (volume doubling time (VDT) = 5 days) and moderately well differentiated and vascularized HI (VDT = 7 days) were used. Tumors were implanted subcutaneously in the thigh of adult male Copenhagen rats. Tumors were grouped based on size as large (>3.5 cm^3) and small (<2 cm^3). MR measurements were performed on a 4.7 T Varian system. Each rat was maintained under general anesthesia (air and 1.5% isoflurane). A series of interleaved T_1- and T_2^*-weighted proton (water) images were acquired during transition from air to carbogen breathing to assess ability to detect tumor response. Data analysis was carried out on a voxel-by-voxel basis.

Results: Small HI tumors showed large increases in signal intensity in both T_1- and T_2*-weighted signal (mean maximum ΔSI (%) = 20.2 ± 0.8 and 6.5 ± 0.2, respectively). Large HI and small AT1 tumors showed moderate increase in signal intensity in both T_1 and T_2* weighted signal (mean maximum ΔSI (%) = 8.2 ± 0.4 and 4.6 ± 0.1 for big HI and 5.1 ± 0.1 and 3.5 ± 0.1 for small AT1, respectively). On the other hand, there was little response in T_1- or T_2*-weighted images in response to breathing carbogen in large AT1 tumors (mean maximum ΔSI (%) = 0.0 ± 0.1 and 1.17 ± 0.05, respectively. Data for the groups of (n) tumors are shown below.

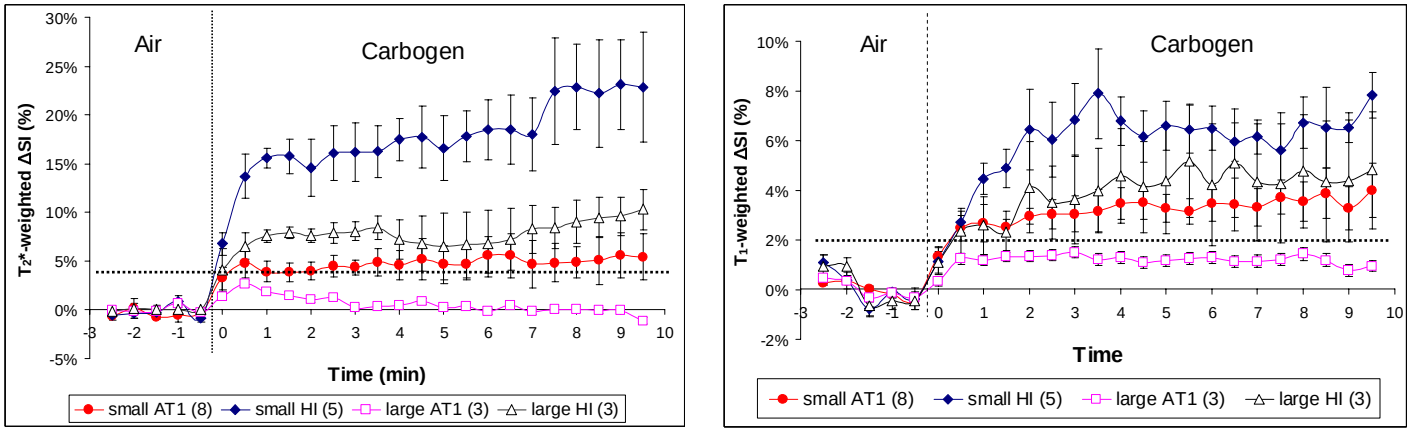

Figure: Changes in SI in response to carbogen breathing in BOLD (left) and TOLD (right) for the four different groups.

Discussion: Changes in T1 and T2* correspond closely with previous reports based on quantitative ^{19}F NMR oximetry (5, 6). Specifically, large AT1 tumors are hypoxic and resist modulation by hyperoxic gas (6). These preliminary data suggest that T_1 and T_2* weighted signal response to carbogen challenge reveals unresponsive hypoxic tumors. Since such measurements are entirely non-invasive they appear worthy of further exploration and correlation with response to therapy. Such measurements have the potential for rapid translation to the clinic and could facilitate identification of patients with hypoxic tumors, which resist interventions.

References:

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