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

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Introduction

Hypoxia inhibits tumor response to radiation therapy. Thus, many techniques are being developed to assess hypoxia or quantitative pO_2 (1). We have been developing NMR approaches to measuring oxygen tension dynamics (2). Using *FREDOM* (Fluorocarbon Relaxometry using Echo planar imaging for Dynamic Oxygen Mapping) we have demonstrated differential size dependent hypoxia among diverse Dunning prostate tumor lines. Importantly, hypoxic tumors were found to respond less well to irradiation, and indeed, direct correlations were found between the volume doubling time following radiation and pO_2 (3, 4). We are currently evaluating *PISTOL* (Proton Imaging of Silane for Tissue Oxygen Levels) as a potential ^{1}H MRI alternative (5). However, such measurements require introduction of a reporter molecule. Prompted by the report of Matsumoto *et al*. (6) we are exploring the ability to evaluate tumor hypoxia based on the response of tumor T1 and T2* weighted water signals to hyperoxic gas breathing.

Methods

We examined Dunning prostate R3327-AT1 and HI tumors. When tumors reached ~1 cm diameter MR measurements were performed under general anesthesia at 4.7 T. We previously characterized these tumors using *FREDOM* in terms of response to hyperoxic gas challenge (Figures 1-4).

Using quantitative ^{19}F NMR oximetry we are able to categorize tumors according to baseline hypoxia and response to hyperoxic gas breathing into three types: 1) well oxygenated and responsive; 2) hypoxic, but responsive to oxygen challenge, and 3) hypoxic and resistant to modulation (Figures 3 and 4).

Here, series of interleaved T1- and T2*-weighted proton (water) images were acquired during transition from air to carbogen breathing to assess ability to detect tumor response. Measurements were repeated when tumors were >2 cm diameter.

Results

- Tumors known from ^{19}F MRI to be well oxygenated (small HI and AT1) showed a large response in both T1 and T2* signal with respect to breathing carbogen.
- Tumors known to be hypoxic, but responsive to hyperoxic gas challenge (large HI) showed a large response in both T1 and T2* signal with respect to breathing carbogen.
- Tumors known to be hypoxic and not to respond to hyperoxic gas breathing (large AT1) showed very small response in T1 or T2* weighted images in response to breathing carbogen.

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FREDOM (Fluorine Relaxometry using Echo planar imaging for Dynamic Oxygen Mapping)

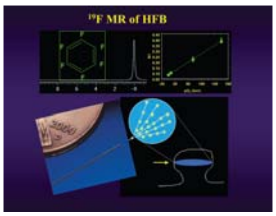

Figure 1 ^{19}F NMR oximetry
Tumor pO_2 may be measured quantitatively using *FREDOM* (Fluorocarbon Relaxometry using Echo planar imaging for Dynamic Oxygen Mapping). This is based on the reporter molecule hexafluorobenzene (HFB), which has a single ^{19}F NMR signal and linear response of the spin lattice relaxation rate (R1) to pO_2. HFB is administered into tissue using a fine needle (32G) and distributed to sample multiple regions (2).

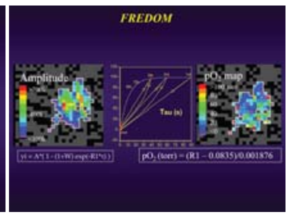

Figure 2 *FREDOM* (Fluorocarbon Relaxometry using Echo planar imaging for Dynamic Oxygen Mapping)
^{19}F MRI provides maps of HFB. Varying a recovery time reveals spin lattice recovery, the rate of which is related to local pO_2. Based on curve fitting and the linear relationship between R1 and pO_2, maps of tumor oxygenation are acquired in 6.5 mins each, with typical resolution 1.25 mm in plane and 1-3 torr precision under relatively hypoxic conditions (2).

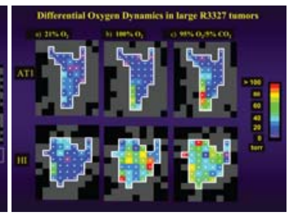

Figure 3 Differential Oxygen Dynamics in large R3327 tumors
Dynamic oxygenation changes observed in Dunning prostate rat tumors in response to breathing oxygen or carbogen. Both AT1 and HI tumors show similar baseline patterns of oxygenation in large tumors, but very different response to hyperoxic gas breathing. In the AT1, only initially well oxygenated regions respond, whereas in the HI tumor essentially all regions become well oxygenated.

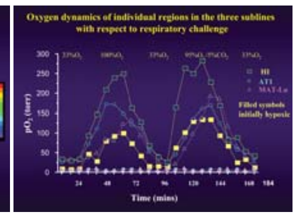

Figure 4 Differential Oxygen Dynamics in individual voxels
In three different Dunning prostate tumor sublines we observe that well oxygenated regions respond to hyperoxic gas breathing. In most lines (here AT1 and MAT-Lu) those regions which are poorly oxygenated respond little, whereas those in the HI tumor show a remarkable increase in pO_2.

The Influence of Hyperoxic Gas Breathing on Reponse to Radiation

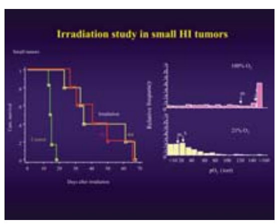

Figure 5 Tumor responses to irradiation
Small HI tumors, which are well oxygenated respond to irradiation. Here, a single dose of 30 Gy (half the TCD_{50}) was applied and the time to double in size was observed. Tumors on rats breathing air or oxygen showed a significant growth delay compared with controls. Baseline hypoxic fraction was small HF_{10}<25% (3).

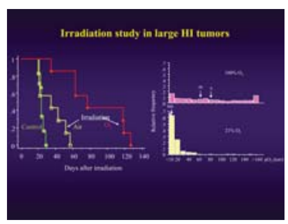

Figure 6 Modulating tumor response to irradiation
Large HI tumors exhibit extensive hypoxia. However, it is essentially eliminated by breathing oxygen resulting in excellent response to irradiation. Here a single dose of 30 Gy was applied and the time to double in size was observed. Tumors on rats breathing air showed little benefit over controls. Baseline hypoxic fraction was high HF_{10}>65%. However, breathing oxygen essentiality eliminated the hypoxic fraction HF_{10}<20% and these tumors showed a significant growth delay compared with controls or irradiated air breathing animals (3).

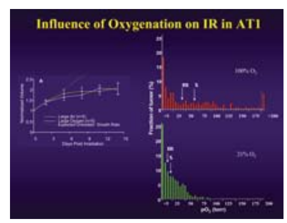

Figure 7 Tumor response to irradiation
Large AT1 tumors exhibit HF_{10} > 40% and this responds little to breathing oxygen. In this case breathing oxygen has negligible effect on response to single dose of radiation (4).

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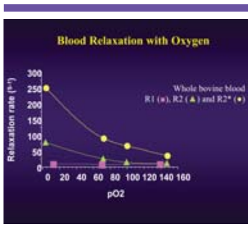

Figure 8 Blood relaxation with oxygen
Relationship between NMR relaxation parameters R1 (■), R2 (▲) and R2* (●) and pO_2 in aliquots of fresh bovine blood observed by MRI at 4.7 T (7)

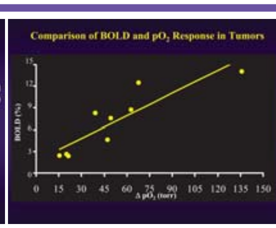

Figure 9 Comparison of BOLD and pO_2 response in tumors
For a group of 13762NF rat breast tumors a strong relationship was found between mean BOLD signal response and change in mean pO_2 in response to breathing oxygen.

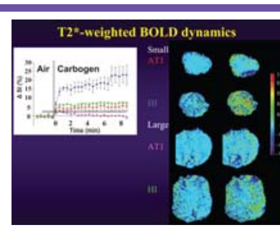

Figure 10 BOLD response to carbogen breathing
BOLD (T2*-weighted) signal response was examined in groups of Dunning prostate AT1 and HI tumors, known to exhibit differential response based on ^{19}F MRI (above). Small HI, AT1 and large HI tumors all showed a substantial signal response (>2%), which was particularly large for the small HI tumors (>10%). Large AT1 tumors showed a significantly smaller response.

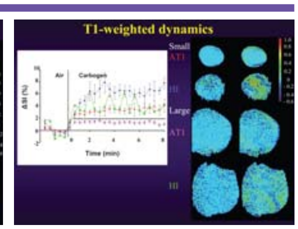

Figure 11 T1 responses to carbogen breathing
Interleaved with the T2* response in Figure 10, T1-weighted signal response was also examined in the groups of Dunning prostate AT1 and HI tumors. As for T2* small HI, AT1 and large HI tumors all showed a large signal response, while large AT1 tumors showed a significantly smaller response.

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Conclusions

These preliminary data suggest that T1 and T2* 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.

Acknowledgements

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