An analysis of carbogen induced R_2^* changes for determining alterations in tumor blood pO_2

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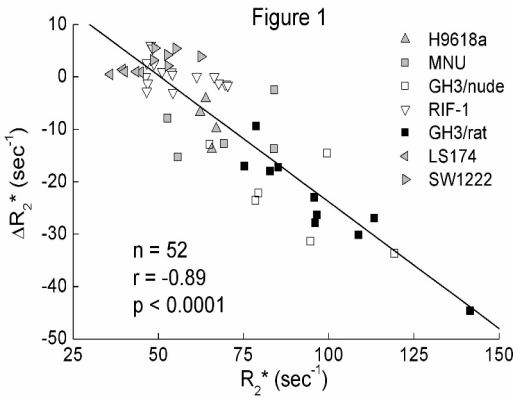
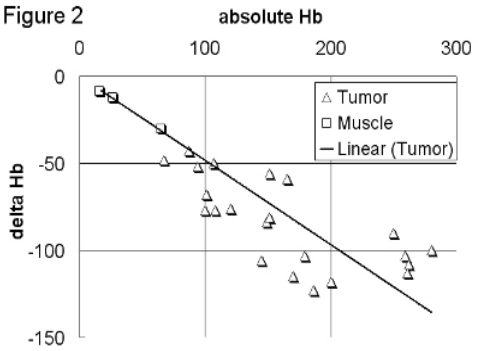
Introduction Tumor vascularity and oxygenation can be interrogated with MRI via R_2* and its change with carbogen breathing because of its dependence on tissue deoxyhemoglobin (Hb) concentration[1]. Hb can also be determined by Near Infrared Spectroscopy (NIRS)[2], hence we have compared data obtained by these complementary techniques. We have also made a theoretical analysis that relates the results to changes in tumor blood pO_2 via the oxygen dissociation curve.



Methods A retrospective analysis was undertaken of gradient echo images of rodent (GH3 prolactinomas, MNU, H9618a) and murine (GH3, RIF-1 LS174 and SW1222) tumors, acquired using a Varian 4.7T horizontal bore MR system. R_2* maps were calculated during air and carbogen breathing and the average R_2* and change in R_2* (ΔR_2*) calculated over the central slice of each tumor. Additionally, absolute Hb and changes in Hb, oxyhemoglobin (HbO) and total Hb (HbT) during carbogen breathing were determined in GH3 prolactinomas and rat thigh muscle by NIRS. The NIR spectrometer was operated in transmission mode with analysis of the 2nd derivative spectrum with the water absorption used as a quantitation reference and differential path length correction[2].

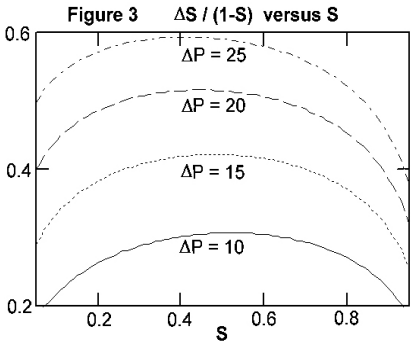
Results GH3, MNU and H9618a tumors all showed significant decreases in R_2* with carbogen breathing with the greatest changes occurring for those with the greatest baseline R_2*. RIF1. LS174 and SW1222 tumors showed very little R_2* change. Taking all the tumor data together, there was a strong correlation between the carbogen induced ΔR_2* and the baseline R_2* with a slope of -0.5 (see Fig. 1). For the NIRS measurements on GH3 prolactinomas and muscle, we also found a correlation between ΔHb and Hb with a slope of -0.5 when assuming a zero intercept (see Fig. 2). HbT did not change significantly with carbogen, indicating there were negligible blood volume changes.

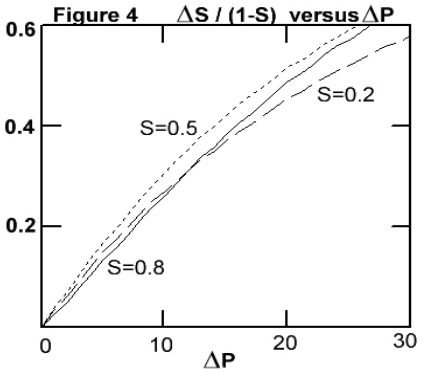


Discussion If the relaxation rate R_2* = R_0* + k.V.Hb, where k is a constant relating to blood vessel geometry, V is blood volume and Hb the blood deoxyhemoglobin concentration, then ΔR_2* / (R_2* - R_0*) = ΔHb / Hb = -ΔS / (1-S), when V is constant, with S an average tumor blood saturation S = P^n / (P_{50}^n + P^n) and P an average blood oxygen partial pressure. Hence, the MRI and NIRS data show similar slopes. Following Hull et al[3] we can write a difference equation that relates ΔS to a change ΔP in blood pO_2, thus

$$\Delta S / (1-S) = \{(P(S) + \Delta P)^n / [P_{50}^n + (P(S) + \Delta P)^n] - S\}/(1-S) \quad (1)$$

where $P(S) = [S/(1-S)]^{1/n} P_{50}$. Figs 3 and 4 show Eq. 1 plotted for n=2.5 and P_{50}=33mmHg (values from Ref 3) as a function of S and ΔP (mmHg) which relates to both NIRS and MRI data. Eq. 1 is more dependent on ΔP than S over the range S=0.2 to 0.8, and the slope ΔS/(1-S) is a monotonic function of ΔP. Using Fig. 4 we determine that on average, blood pO_2 in the GH3, MNU and H9618a tumors (and muscle) changes by 20 mmHg with carbogen breathing, with a range of values from 10 to 40mmHg for individual tumors, and changes less than 10 mmHg for RIF, perhaps because RIF-1 tumors are more hypoxic[1]. The value of R_0* (the R_2* value at ΔR_2*=0) must be known for ΔP to be estimated by MRI. The data in Fig. 1 suggest that R_0* may be fairly constant for studies with similar geometry and tissue type, but further work is needed to assess this. These preliminary results suggest that changes in average tumor blood pO_2 during carbogen breathing could be estimated with the spatial resolution of MRI and so provide a parameter, essentially independent of blood volume, to assess tumor oxygenation status.





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References 1) Robinson SP et al. *J Magn Reson Imag* **17**:445–454; 2003 2). Cooper CE et al. *Pediatric Res* **39**:32; 1996. 3) Hull EL et al. *Brit J Canc*. 79:1709-1716; 1999.