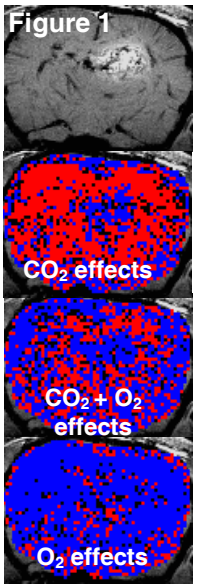
Quantitative Assessment of Vascular Maturation and Function using Contrast Referenced BOLD MRI

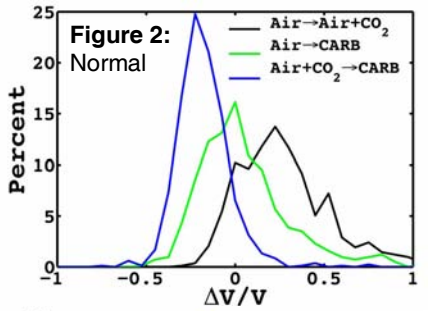
C. C. Quarles[1,2], R. R. Price[1], and J. C. Gore[1,2]

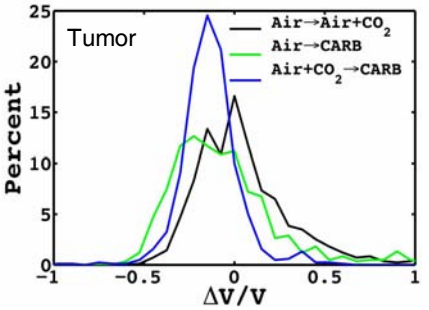
[1]Radiology and Radiological Sciences, Vanderbilt University, Nashville, TN, United States, [2]Institute of Imaging Science, Vanderbilt University, Nashville, TN, United States

Introduction: Despite the success of previous studies demonstrating a reasonable correlation between BOLD MRI signal intensity variations and vascular responsiveness, BOLD remains a qualitative marker of vascular maturation and function because of its sensitivity to both blood oxygen saturation (S_bO_2) and blood volume (BV) (1,2). The purpose of this study is to determine if *contrast referenced* BOLD MRI can separate these confounding effects and provide quantitative markers of vascular maturation and function.

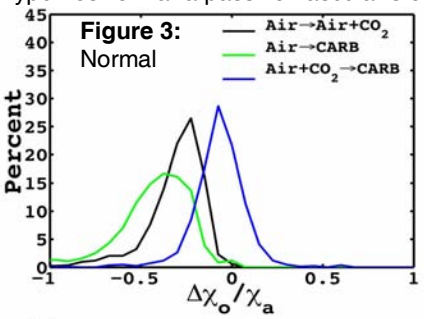
Methods: Contrast referenced BOLD MRI studies were performed using a 7.0T Varian scanner on Wistar rats inoculated with 10^5 C6 glioma cells. Multiple GE images were used to create R_2^* maps while animals inhaled the following: air, air + 5% CO_2 and carbogen. These measurements were then repeated after administration of the intravascular agent Molday-ION (Biophysics Assay Laboratory, Worcestor, MA). From these measurements we calculated maps of relative BV, the change in blood volume ($\Delta V/V$), and the ratio of the change in blood magnetic susceptibility following oxygen perturbation to the absolute susceptibility of the contrast agent ($\Delta\chi_O/\chi_A$) for each oxygen perturbation (3). A negative $\Delta\chi_O/\chi_A$ indicates higher S_bO_2 and decreases R_2^* whereas a positive $\Delta\chi_O/\chi_A$ reflects lower saturation and increases R_2^*. We also collected high-resolution T_1-weighted images after injecting Gd-DTPA to better delineate the tumor tissue. Maps of vascular response were created in which areas of increased BV ($\Delta V/V > 0.05$) following perturbation are displayed in red, decreases in BV ($\Delta V/V < -0.05$) are displayed in blue, and areas of no apparent response are displayed in black ($|\Delta V/V| < 0.05$). An Oxylite system was used to measure the baseline oxygen tension from 35-50 sites within the tumor.

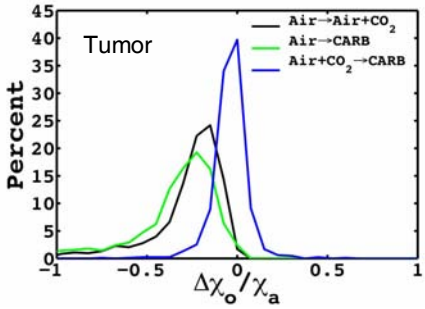






Results: The upper image in Fig. 1 shows a post-contrast T_1 weighted image of a rat brain 16 days after tumor inoculation. The lower 3 images in Fig. 1 show the maps of vascular response for this tumor comparing $\Delta V/V$ between the following conditions: (1) air and air+CO_2 (2) air and carbogen and (3) air+CO_2 and carbogen. The last condition should remove the effects of increased CO_2 and highlight the effects of increased O_2 on the vasculature. Hypercapnia (condition 1) clearly resulted in vasodilation (red) of the contralateral normal appearing brain tissue and reduced BV (blue) in most of the tumor tissue. We hypothesize that a passive vascular steal effect resulting from normal vessel vasodilation is likely the source of the reduced BV in the tumor tissue. This reduced CO_2 responsiveness suggests that the tumor voxels displayed in blue and black in this image are those likely corresponding to immature vessels. As compared to breathing air, carbogen inhalation resulted in a mixture of vasodilation and vasoconstriction in normal tissue and primarily vasoconstriction in tumor tissue (condition 2). By removing the effects of the CO_2 (condition 3) it is apparent that the increased blood oxygen resulted in global vasoconstriction. Frequency histograms (shown as percent of voxels in a ROI) of normal and tumor vascular reactivity, $\Delta V/V$, for these three conditions are illustrated in Fig. 2. Most tumor voxels contained vessels that presented with abnormal responsiveness to CO_2 perturbation as compared to normal tissue's predominantly vasodilatory response (black line). The tumor vessels retained some reactive mechanism to increased levels of blood oxygen saturation (blue line). Figure 3 illustrates the normal and tumor $\Delta\chi_O/\chi_A$ frequency histograms for the 3 conditions. The increase in the tumor S_bO_2 following hypercapnia (black line) and carbogen (green line) was slightly less than that for normal tissue. The Oxylite measurements revealed that half of the tumor had substantially lower than normal baseline pO_2 indicating insufficient oxygen delivery and a lower baseline S_bO_2. Taken together these results suggest that relative to baseline the change in tumor S_bO_2 following perturbation was much lower than in normal tissue where the blood is already highly saturated with oxygen.





Discussion: This preliminary study suggests that contrast referenced BOLD MRI can improve upon current methods to evaluate vascular maturation by providing a quantitative marker of vascular reactivity. Instead of using carbogen inhalation to probe functional vasculature the derived BV maps provide a direct measure of the functional vessels within a tumor. An added feature of this approach is its capacity to measure changes in the S_bO_2. This could be particularly useful for evaluating whether oxygen-enhancing agents, such as carbogen inhalation or RSR13 administration, are increasing the delivery of oxygen to tumor tissue and therefore improving radiotherapeutic response. We are continuing these studies on more animals and following up with histological measures of vascular smooth muscle cell coverage.

References: 1. Neeman, Magn Reson Med 2001. 2. Baudelet, Magn Reson Med 2002. 3. Robinson, NMR Biomed 1999.