Towards MRI-based measurement of tissue oxygen content

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INTRODUCTION: A MRI method to quantitatively measure tissue oxygen content would be a significant advance. We, and others[1-2], are pursuing a strategy that takes advantage of the paramagnetic property of molecular oxygen (O_2), as found dissolved in tissue. Herein, we map the tissue-water longitudinal relaxation rate constant ($R_1 = 1/T_1$) in mouse and rat brain while modulating the oxygen and carbon dioxide content of breathing gases. We demonstrate differentiation of tumor and radiation necrosis and contralateral ("normal appearing") brain tissue.

METHODS: Control-state, DBT glioma model, and radiation necrosis model female BALB/c mice and control-state Sprague-Dawley rats were anesthetized with isoflurane. Highly time-resolved inversion-recovery R_1 data were collected during free breathing of either pure oxygen followed by the mildly hypoxic reference gas (12.5% O_2/87.5% N_2) or carbogen (95% O_2/5% CO_2) followed by the reference gas. For mice, a fast spin-echo pulse sequence with a non-slice-selective inversion pulse and 32 inversion times ranging from 0.005 sec to 4.5 sec was used to collect R_1 data at 4.7T. For rats, a fast inversion recovery spin-echo echo-planer imaging sequence (FIR SEPI) at 11.7T with non-slice selective inversion pulse and 64 inversion times ranging from 0.004 to 6.2 sec was employed. Relaxation data were analyzed using the exponential modeling package[3] in the Bayesian toolbox developed in our laboratory http://bayesiananalysis.wustl.edu/.

RESULTS: Modeling of longitudinal relaxation as mono-exponential showed that breathing of either pure O_2 or carbogen increased the R_1 in brain tissue of control mice by 5.7 ± 3.4% and 9.2 ± 1.7%, respectively, compared to breathing of the reference gas. Mice with tumors, mice with radiation necrosis, and control mice responded differently to the breathing gas challenge, with R_1 at the lesion site (or comparable cortex in control animals) increasing by 2 ± 2.4% (negligible, tumor), 7.8 ± 1.7% (radiation necrosis), and 9.2 ± 2.5% (control), respectively, during carbogen breathing compared to the reference gas (Fig. 1). Remarkably, these changes are not limited to the lesion site; whole brain ROIs reveal R_1 changes of 1.5 ± 2.4% (negligible, tumor), 5.9 ± 2.7% (radiation necrosis), and 9.2 ± 1.7% (control). R_1 changes with breathing gas modulation were significantly different between groups of animals with tumors, groups of animals with radiation lesions, and control animals, both in lesion specific ROIs and across the whole brain ($p \leq 0.05$).

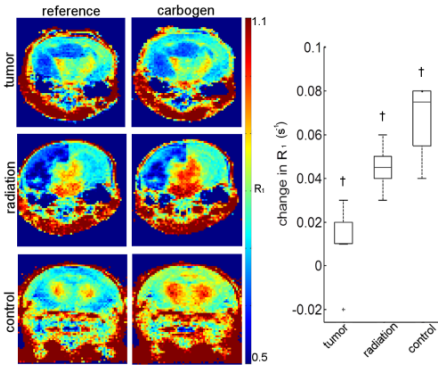

Figure 1 - R_1 maps collected during free breathing of the reference gas and carbogen at 4.7T. Data from one animal from each group (tumor, radiation, and healthy control) are shown. Mice with tumors, mice with radiation induced necrosis, and control mice respond differently to the carbogen breathing gas challenge ($p \leq 0.05$). Interestingly, this effect is not limited to the site of the lesion, but is instead diffuse across both brain hemispheres.

In the higher fidelity (64 inversion times) 11.7T rat relaxation data, a bi-exponential recovery -- slow (R_{1long}) and fast (R_{1short}) -- was chosen by Bayesian model selection as best representing the data. This is consistent with a previously report from this lab in which R_{1long} was identified with the "apparent" bulk water fraction and R_{1short} was identified with the "apparent" magnetization transfer (MT) fraction[4]. Breathing gas modulation affects only R_{1long}, which is 12.3 ± 5% greater during carbogen breathing than during breathing of the reference gas. We note that the R_{1long} changes with breathing gas modulation were maintained in the presence of a small b-value (50 s/mm^2) diffusion-sensitizing gradient to suppress IVIM-type effects[5] (re possible blood flow modulation of relaxation), Fig. 2. The change in R_{1long} (carbogen *vs.* reference gas) was ~20% greater than that measured using R_1 from mono-exponential modeling.

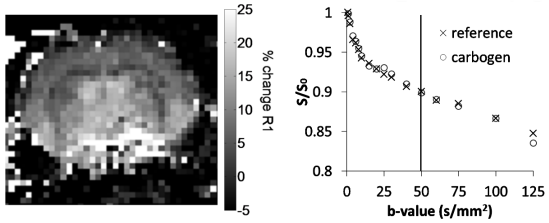

Figure 2 - Carbogen administration yields a 12.3 ± 5% increase in tissue "apparent" bulk water longitudinal relaxation rate constant (R_{1long}) compared to the reference gas (left panel). By quantifying R_{1long}, a 20% greater R_1 change during breathing gas modulation was observed compared to a mono-exponential fit. The data shown here are acquired with a diffusion gradient of b = 50 s/mm^2 to suppress IVIM signal (blood flow). Our data (right panel), and previous publications, suggest that b = 50 s/mm^2 is sufficient to eliminate IVIM effects. These data suggest that R_1 changes induced by breathing gas modulation can be isolated to parenchymal tissue.

DISCUSSION: Consistent with the paramagnetic nature of O_2, R_1 in brain tissue increases as a function of O_2 content in the breathing gas. The addition of CO_2 to a hyperoxic gas mixture further increases R_1. It is reasonable to hypothesize that these changes in R_1 are a function of the amount of O_2 dissolved in the brain parenchyma and that tissue O_2 content can be measured/correlated by quantifying the R_1 of "bulk water" (R_{1long}). Further, data presented herein suggest that this approach can distinguish radiation damage from tumor - a distinction which has been difficult to make using other methods. Experiments to further characterize and validate these findings in rodent models of cancer and radiation necrosis are ongoing, as are complementary electrode-based measurements.

Refs: ***(1)*** *O'Conner, et al. Magn Reson Med. 58:490-496 (2007);* ***(2)*** *Zhang, et al. Magn Reson Med. epub ahead of print (2013);* ***(3)*** *Bretthorst, et al. Concepts Magn Reson. 27A:55-83 (2005);* ***(4)*** *Prantner et al. Magn Reson Med. 60:555-563 (2008);* ***(5)*** *Neil, et al. J Magn Reson. 98:436-442 (1992).*