MRI-based measurement of tissue O_2

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INTRODUCTION: Diatomic oxygen (O_2), as found dissolved in tissue, is a critical component in aerobic metabolism and a fundamental determinant of physiological functional status. Reliable, non-invasive methods for measuring tissue O_2 content are lacking. Positron emission tomography (PET) and quantitative blood-oxygen level dependent (BOLD) magnetic resonance imaging (MRI) have shown promise as surrogate markers of tissue O_2, however, these methods are indirect and inferential. O_2 is weakly paramagnetic and therefore influences the ^{1}H longitudinal relaxation rate constant (R_1) of tissue water, thus, R_1 can be exploited as a surrogate marker of tissue oxygenation[1-5]. Herein, we quantify the relationship between R_1 and O_2 concentration (relaxivity) and use this relationship to quantify changes in tissue oxygenation in healthy rodent brain, radiation lesions, and tumor lesions to differentiate the two pathologies.

METHODS: *In vivo relaxivity measurements:* R_1 data were collected in healthy mice (n=4) during free breathing of pure oxygen, 12.5% O_2/87.5% N_2, and 95% O_2/5% CO_2 (carbogen) using a fast-spin-echo, inversion recovery imaging sequence at 4.7 T (32 inversion times; non-slice selective inversion pulse to mitigate flow contributions to R_1 measurements). From these data, magnetization recovery was modeled and R_1 was calculated using Bayesian probability theory-based methods (bayesiananalysis.wustl.edu). In a separate experiment, pO_2 was measured in the thalamus of healthy mice (n=4) using an O_2-sensitive optical probe (Oxford Optronix, Abington, OX, UK). Using these data, the relaxivity of tissue O_2 (r_1) was calculated via the relationship: $R_1 = R_{1,0} + (r_1 \times pO_2)$, where pO_2 is oxygen partial pressure and $R_{1,0}$ is the tissue R_1 relaxation rate constant in the absence of O_2 (a constant offset). *Models of pathology:* R_1 data were collected in control-state (n=4), DBT glioma model[6] (n=7), and radiation necrosis model[7] (n=6) mice during free breathing of the 12.5% O_2/87.5% N_2 and carbogen gas mixtures using the sequence described above.

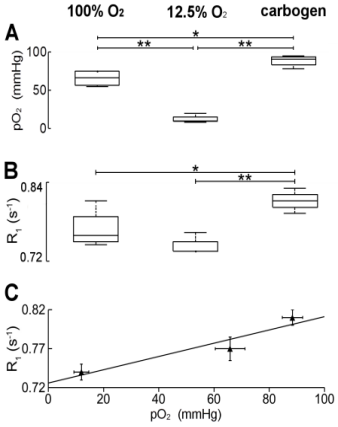

Figure 1 – There is a linear relationship between pO_2 (A) and R_1 (B) measurements made during free breathing of pure O_2, 12.5% O_2/87.5% N_2, and carbogen. The relaxivity of brain tissue O_2 is 8.5×10^{-4} $mmHg^{-1}s^{-1}$ ($R^2 = 0.91$) (C).

RESULTS: *In vivo relaxivity measurements:* Optically measured pO_2 values were 66±11 mmHg, 12±5mmHg, and 88±7 mmHg during free breathing of pure oxygen, 12.5% O_2/87.5% N_2, and carbogen, respectively (Fig. 1A). R_1 values in the thalamus were 0.77±0.03 s^{-1}, 0.74±0.02 s^{-1}, and 0.81±0.02 s^{-1}, respectively (Fig. 1B). The relaxivity of O_2 in the brain was calculated to be 8.5×10^{-4} $mmHg^{-1}s^{-1}$ (R^2=0.91) (Fig. 1C). *Discernment of pathologies:* Tumor and radiation necrosis lesions showed contrast from surrounding tissue in R_1-maps acquired during both breathing-gas conditions (Fig. 2B-C, F-G). Lesion-specific histograms showed a shift in R_1 due to breathing-gas modulation in radiation lesions and cortex from healthy animals, but not in tumor lesions (Fig. 2D,H,L). Lesion-specific changes in R_1 due to breathing-gas modulation distinguished the two pathologies ($p<0.01$): 0.01±0.02 s^{-1} in tumor, 0.05±0.01 s^{-1} in radiation necrosis lesions, and 0.07±0.01 s^{-1} in cortex from healthy control mice. Equivalently, in units of partial pressure (mmHg): 12±24 mmHg in tumor, 59±12 mmHg in radiation necrosis lesions, and 82±12 mmHg in cortex from healthy control mice (Fig. 3).

DISCUSSION AND CONCLUSIONS: Herein, we quantify the relaxivity of brain-tissue O_2 and, subsequently, changes in brain-tissue oxygenation in healthy brain, radiation lesions, and tumor lesions. By quantifying the change in brain tissue oxygenation with MRI, we were able to differentiate tumor lesions from radiation necrosis lesions – two pathologies that have proven extremely difficult to differentiate with common radiological techniques.

Refs: *[1]O'Conner, et al. Magn Reson Med. (2007); [2]Winter, et al. Acad Radiol. (2011), [3]Remmele, et al. Magn Reson Med. (2013), [4]Jordan, et al. Magn Reson Med. (2013), [5]Zhang, et al. Magn Reson Med. (2014), [6]Kumanishi, Jpn J Exp Med. (1967), [7]Jiang, et al. Clin Cancer Res. (2014).*

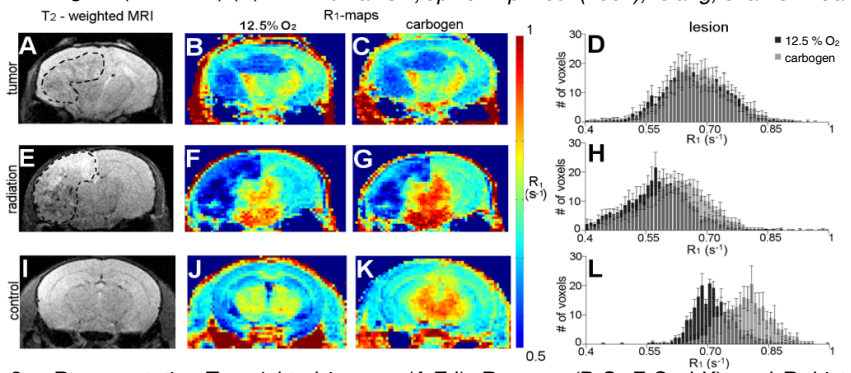

Figure 2 – Representative T_2-weighted images (A,E,I), R_1-maps (B-C, F-G, J-K), and R_1-histograms (D,H,L) from mice with tumors, mice with radiation necrosis, and control mice during free breathing of 12.5% O_2/87.5% N_2 *vs.* carbogen gas. Tumor and radiation necrosis lesions are more conspicuous in R_1-maps (B-C, F-G) than T_2-weighted images. Lesion-specific histograms showed a shift in R_1 due to breathing-gas modulation in radiation lesions and cortex from healthy animals, but not in tumor lesions.

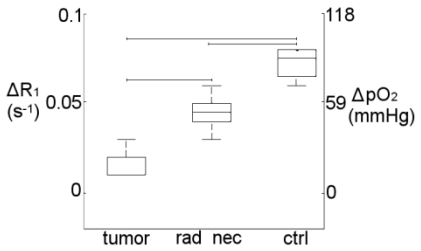

Figure 3 – Tumor lesions, radiation necrosis lesions, and healthy cortex showed small, moderate, and large changes is tissue oxygenation during breathing-gas modulation. Lesion-specific change in R_1 due to breathing-gas modulation distinguished the two pathologies ($p<0.01$).