Feasibility and Reproducibility of R2* Measurement Under Oxygen and Carbogen Challenge in Healthy Subjects and Patients with Hepatocellular Carcinoma at 1.5 T and 3T

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TARGET AUDIENCE: Scientists and radiologists with interest in imaging tumor hypoxia.

PURPOSE: Tumor oxygenation is influenced by several factors including microvessel density, blood flow, blood volume, blood oxygen saturation, tissue pO2 and oxygen consumption rate. BOLD MRI measure R_2* ($1/T_2$*) of tissues, which depends on blood flow, hematocrit, and oxygen saturation of hemoglobin. In hypoxic tissues, the proportion of deoxygenated hemoglobin (Hb) is greater, so R_2* is larger, and is expected to decrease during a hyperoxic respiratory challenge, as deoxyHb becomes more saturated with O_2. The purpose of our initial study is to quantify baseline R_2* and changes after O2 and carbogen respiratory challenges using BOLD MRI in patients with hepatocellular carcinoma (HCC) at 1.5T and 3T. We also assessed measurement reproducibility of R_2* values.

MATERIALS AND METHODS: 8 healthy volunteers (F/M 7/1, mean age 36 y) and 11 preliminary patients with HCC (M/F 10/1, mean age 59 y) underwent BOLD imaging of the liver with hyperoxic and hyperoxic-hypercapnic respiratory challenge at 1.5T (Aera, Siemens) and/or 3T (Skyra, Siemens). 6 subjects had test-retest studies (3 patients/1 volunteer at 1.5T and 2 patients at 3T). Fat-suppressed T_2*-weighted, 2D GRE images of the liver (1.5T/3T: FA 35^0, TR 242/165, 5 in-phase TEs 4.6-23/ 7 in-phase echoes 2.46-17, FOV 225 x 340, 230 x 384, 24 slices, slice thickness 7 mm) were acquired in multiple breath-holds at baseline (room air) and after 10 min. of breathing 100% O2 and/or carbogen (95% O2/5% CO2). Diffusion, T_2-weighted, in and out-of-phase, and (in patients) DCE-MRI were acquired during the same imaging session. R_2* maps were computed using in-house software, by fitting the MGRE signal to a monoexponential fit **(Fig. 1, Fig. 2)**. ROIs were drawn in the right hepatic lobe, paravertebral muscles and in tumors (in patients). Mean R_2* values at baseline, after O2 and carbogen, as well as ΔR_2* (%) $=100*[(R_2*_{baseline} - R_2*_{gas})/ R_2*_{baseline}]$ were calculated for HCCs, liver parenchyma and muscle. A paired t-test was used to compare the R_2* at baseline to the R_2* after gas challenges.

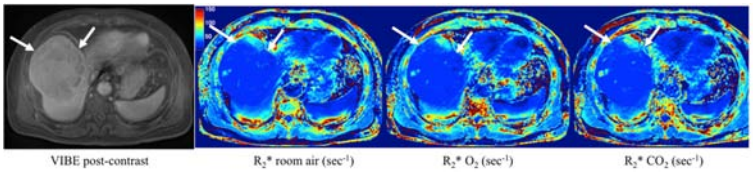

Fig. 1: Patient with HCC evaluated at 1.5T. HCC identified on post-contrast imaging (arrows) shows minimal response to O_2 (R_2* air 23.81 s^{-1}, R_2* O_2 23.65 s^{-1}) and a minimal increase in R_2* with carbogen (R_2* CO_2 25.22 s^{-1}).

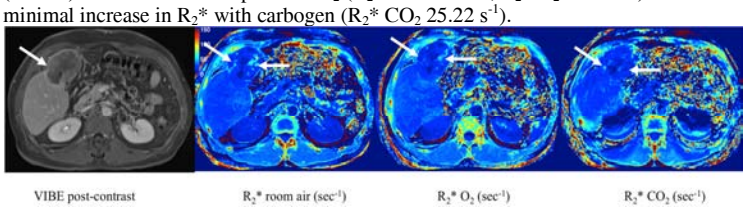

Fig. 2: HCC evaluated at 1.5T, with central necrosis on post-contrast imaging (arrow). Areas of response to hyperoxia are at the periphery (arrows). Overall, HCC shows decrease in R2* with O_2 (R_2* air 23.96 s^{-1}, R_2* O_2 19.87 s^{-1}) and with carbogen (R_2* CO_2 20.06 s^{-1}).

RESULTS: MGRE signal followed monoexponential decay (fit $R^2 > 0.9$) in all tissues. The intrasubject, test-retest mean coefficient of variation (CV) for R_2* measurements at 1.5T for all inhaled gases, liver/muscle and lesions was <15%, while CVs were higher at 3T **(Table)**. There were no statistical differences between liver and muscle R_2* at baseline and after gas challenges, except for muscle with carbogen at 1.5T. 16 HCCs were assessed (8 at 1.5T and 8 at 3T, mean size 5.8 cm, range 1-11 cm). Of the 8 lesions studied with O_2 at 1.5T, 3 showed decrease in R_2* (mean ΔR_2* =10.96 %), 3 showed an increase in R_2* (mean ΔR_2* = -5.47 %), and 2 showed no change. 4/5 lesions studied with carbogen at 1.5T showed an increase in R_2* (mean ΔR_2* = -7.92%). At 3T, 4/8 HCCs showed a decrease in R_2* with O_2 (mean ΔR_2* = 18.04 %), 3 were non-responders and 1 showed an increase (ΔR_2*=-17.5%). Of the 3 lesions studied with carbogen, 2 showed an increase in R_2* (mean ΔR_2* = -25.25 %), with the same behavior reproduced at both field strengths in the same lesion assessed twice (ΔR_2*= -9.96% at 3T and -8.8% at 1.5T).

DISCUSSION: Our findings are in accordance with published work that identified no significant change in R_2* of the liver with O_2 challenge. As previously published (1), we observed statistically significant change in muscle with carbogen at 1.5T, which was not reproduced at 3T. However, unlike O'Connor et al (1), we did not find statistically significant increase in R_2* in the liver with carbogen, findings which could not be reproduced by other investigators (2). For HCC, although studies in animals and humans have previously shown a decrease in R_2* with hyperoxia and hypercapnia (3), the response of lesions can be highly variable due to the flow and oxygen level dependent (FLOOD) effect (4). The increase in R_2* with carbogen administration, observed previously in large rat HCCs (5), can be potentially explained by the vasodilator effect of carbogen, which brings non-oxygen saturated hemoglobin to the tissue, thereby increasing the concentration of deoxyhemoglobin and R_2*. Hypercapnia can also decrease blood pH, which decreases hemoglobin's affinity for oxygen according to the Bohr effect, and thus increases R_2* (4).

		HCC			Liver			Muscle		
		n*	R2*	CV	n	R2*	CV	n	R2*	CV
1.5T	Air	8	27.13 ± 5.43	14.88	13	36.5 ± 9.3	3.85	13	34.3 ± 1.8	11.98
	O2	8	26.69 ± 6.49	12.21	13	35.7 ± 9.5	7.02	13	35 ± 2.5	12.94
	CB	5	30.13 ± 7.18	11.81	9	37.9 ± 11.7	4.66	9	37.7 ± 4.6**	12.57
3T	Air	8	45.69 ± 14.6	8.79	12	65.87 ± 21.74	29.77	12	42.54 ± 4.13	5.92
	O2	8	42.76 ± 16.33	17.49	12	66.08 ± 25.45	30.74	12	41.54 ± 3.98	4.03
	CB	3	62.54 ± 11.43	32.41	9	65.11 ± 21.65	14.64	8	42.45 ± 2.62	-

Table: R_2* (sec-1) in all subjects and mean intrasubject CV(%) in test-retest subjects, at both platforms. CB=carbogen, n* number of lesions studied, n number of healthy tissues studied, **p <0.05; all the rest was non significant.

CONCLUSION: Our preliminary experience with BOLD MRI demonstrates variable response of HCC to O_2 and carbogen challenges, which should be correlated to pathologic findings/tumor biology in this ongoing study.

References:

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