# Quantitative BOLD imaging at 3T: Temporal changes within hepatocellular carcinoma following oxygen challenge

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**Target Audience:** Scientists and Clinicians with an interest in measuring oxygenation changes and vasoreactivity in the liver.

**Purpose:** Hepatocellular carcinoma (HCC) is the fifth most common cancer and the third leading cause of cancer related deaths worldwide. The major risk factor is cirrhosis of the liver, HCC is often secondary to chronic infection, hepatitis and chronic alcoholic liver disease. A number of studies have investigated the utility of Blood Oxygen Level Dependent (BOLD) contrast changes in measuring perturbations in oxygenation. Both oxygen and carbogen gas challenge have been used to investigate if deoxyhemoglobin fraction is a viable endogenous contrast mechanism. These studies have hypothesized that autoregulatory function is compromised in neoplasms as a result of the chaotic vasculature and the abnormal smooth muscle cell development. Studies have predominantly investigated the effect of breathing hyperoxic, hypercarbic mixtures ('carbogen': 95% $O_2$ and 5% $CO_2$), which is thought to increase vasodilation within healthy tissues. Carbogen can therefore alter the deoxyhemoglobin fraction by mitigating the autoregulatory response and induce BOLD response in healthy tissue. The BOLD contrast changes in response to carbogen have been shown to be more consistent than oxygen, however, studies using carbogen have reported a high level of aborted scans as a result of the subject experiencing the sensation of 'air hunger'. Previous BOLD studies in the liver have investigated the ability to detect microvascular invasion within HCC,[1] as well as investigating the ability of native $T_2$* to detect hepatic tumors.[2] The purpose of this study is to investigate the utility of an oxygen challenge and to report the observed temporal changes in $T_2$* in healthy liver tissue and in HCC patients with background liver disease.

**Methods:** Eleven healthy volunteers (9 male, mean age 33.5, range 27-41 years) with no history of hepatobiliary or cardiovascular disease and 10 patients (9 male, mean age 68.7, range 56-87 years) with hepatocellular carcinoma on a background of diffuse liver disease were recruited. All participants were fasted for a minimum of 8 hours prior to the examination. Imaging was performed on a 3T whole body MRI system (Signa HDx, GE Healthcare, Waukesha, WI) using an 8-channel cardiac coil. A multi-echo fast gradient echo sequence was used to acquire 10 separate echoes with the following imaging parameters: TEs: 2.3/6.9/11.5-43.7ms; TR=46ms; FA=15°; matrix size=192×96; ASSET factor=2; FOV=35cm; slice thickness=8mm. The sequence was also modified to allow multi-echo multi-phase operation with respiratory triggering. The BOLD protocol lasted 10 minutes, $O_2$ was administered after 2 minutes of free-breathing at 10L/min. Image registration was performed using an affine transform to mitigate residual motion using in-house software developed using C++ which incorporated the Insight Toolkit libraries (www.itk.org). To optimize the image registration process masks were defined to encompass the extent of the liver. Voxelwise $T_2$* maps were generated from the multi-phase multi-echo images using in-house software developed using Matlab (version 8.3, The Mathworks Inc., Natick, MA). ROIs were subsequently defined on the registered $T_2$* maps to encompassed the background liver (excluding major blood vessels) and the HCC with the assistance of a spatially matched post-contrast $T_1$W image. Mean $T_2$* values pre-$O_2$ were computed by averaging the temporal phases prior to $O_2$ administration. Similarly, the mean $T_2$* post-$O_2$ was computed by averaging the temporal phases post-$O_2$ administration following a 3 minute delay to allow the BOLD effect to equilibrate. Normality assumptions were formally assessed and paired T-tests were subsequently performed to establish if the difference in pre- and post- $O_2$ $T_2$* was statistically significant (using the R programming language, version 3.1.1, The R foundation for statistical computing, Vienna, Austria).

**Results:** The change in $T_2$* following $O_2$ administration in patients with diffuse liver disease was consistently elevated 0.80±0.58ms, range (0.02-1.69ms) and the difference was statistically significant (p=0.002). The magnitude of the BOLD response within the tumors was larger however the response was more variable 1.07±1.46ms (range -0.93-3.26ms), the difference was borderline significant (p=0.046). The BOLD response in the volunteer cohort was not statistically significant (0.59±1.162ms, range -0.81-2.44ms, p=0.121). The native $T_2$* (pre-$O_2$) was elevated within HCC 23.7±7.52ms relative to the diseased background liver (15.2±5.84ms, p=0.01) and with respect to background liver within the volunteer cohort (17.1±3.71, p=0.025).

**Discussion:** The small but consistently elevated BOLD signal intensity response noted following $O_2$ administration in the background liver in patients is consistent with a breakdown in vascular auto-regulatory mechanisms. The study also noted a statistically significant BOLD response within HCC. The later is consistent with previous reports within neoplasms, and it as hypothesized that this is due to the abnormal capillary vessels in tumours. However, our results suggest that factors such as fibrosis also affect auto-regulatory response which is in keeping with Jin et als rat model which measured BOLD response using carbogen[3].

**Conclusion:** Our study results suggest that $O_2$ administration can induce an endogenous contrast response due to the BOLD contrast effect. Further studies with age-matched controls and histopathological validation are required to understand the implications of BOLD response within diffuse liver disease and HCC.

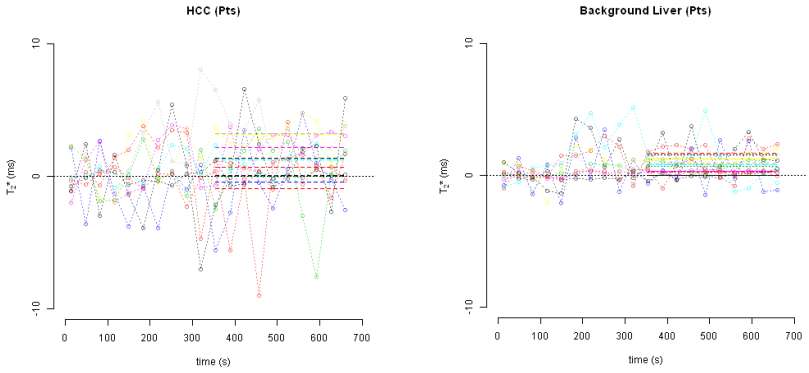


**Figure 1 Change in $T_2$* and best fit lines post-O2 administration within HCC and background liver disease. Temporal changes are normalized to the mean baseline state**

| | | $T_2$* (ms) | | | |
|---|---|---|---|---|---|
| | | Pre $O_2$ | Post $O_2$ | Post-Pre $O_2$ | P-value |
| Pt. | Liver | 15.2±5.84 | 16.0±6.17 | 0.80±0.581 | 0.002 |
| | Tumour | 23.7±7.52 | 24.8±6.87 | 1.07±1.458 | 0.046 |
| Vol. | Liver | 17.1±3.71 | 17.7±4.80 | 0.59±1.162 | 0.121 |

**Table 1 Change in $T_2$* in response to $O_2$**

**References**

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[3] Jin N, Deng J, Chadashvili T, et al. Carbogen gas-challenge BOLD MR imaging in a rat model of diethInitrosamine-induced liver fibrosis. Radiology. 2010. 254(1):129-137