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Detecting Blood Oxygen Level Dependent (BOLD) Contrast in the Breast

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Introduction: Detecting and understanding breast tissue oxygenation may help characterize tumors [1], predict susceptibility to treatment [2], and monitor chemotherapeutic response [3]. BOLD contrast MRI has the potential to non-invasively detect breast tumor oxygenation. There are challenges, however, in consistently detecting BOLD contrast in the breast relative to experienced brain approaches, including the need to overcome artifacts from B_0 magnetic susceptibility effects and to determine an optimal stimulus for inducing BOLD contrast in the breast. In this study, we have developed a robust methodology for detecting BOLD contrast in the breast on healthy volunteers and conducted a pilot study on 3 patients.

Methods: Functional data were collected from 15 scans of healthy female volunteers (ages 24 – 29) with a single shot fast spin echo (HASTE) sequence with the following imaging parameters: 3T (GE Healthcare, Waukesha, WI), 8 channel breast coil (GE, Waukesha, WI), TE = 60ms, TR = 4 s, bandwidth = 83 MHz, matrix size = 128 x 128, FOV = 20 cm, slice thickness/spacing = 5mm/5 mm, 240 time frames/slice, 1 coronal slice. Coronal slices were acquired to accommodate a simultaneous study with near infrared optical probes requiring alignment in the coronal plane. A respiratory belt and pulse oximeter were placed on the volunteers to record respiratory motion and cardiac rate. Tidal O_2 and CO_2 were also monitored. We evaluated 4 variations of hyperoxic stimuli (not all volunteers received all stimuli). Each of the 3 paradigms were delivered to the volunteer with 4 block cycles totaling 16 minutes. The block stimuli consisted of: (1)pure oxygen interleaved with carbogen (95% O_2, 5% CO_2) for 4 cycles, (2) room air interleaved with oxygen, and 3) room air interleaved with carbogen.

Retroicor was used to reduce image noise from respiratory motion and cardiac pulsation in time [4]. Next, the BOLD signal time series for each voxel was cross correlated with a sine/cosine model of the periodic stimulus. Thirdly, a sigma filter was applied which averages nearby voxels with less than one standard deviation from the center voxel, thus eliminating noisy single voxels. The first cycle of data was not used in the analysis to avoid inconsistent respiratory gas content prior to the scan. The most consistent stimulus was selected based on the stimulus with minimal variation in phase lag (time lag between task delivery and effective detected BOLD signal) across volunteers, and the task with the maximum correlation coefficient to the detected signal. This vetted stimulus was then tested on 3 patients.

Results: In healthy volunteers, oxygen interleaved with carbogen produced the most consistent results based on phase lag (Table 1). In evaluating the correlation coefficients, oxygen interleaved with carbogen produced the highest correlation coefficient but the value was not significantly different from the two other tasks. In healthy volunteers' glandular tissue, BOLD signal positively correlated to carbogen. In the patient cohort, BOLD signal negatively correlated to carbogen in malignant tissue and positively correlated to carbogen in healthy tissue.

Gas Stimulus	*Mean Phase lag*	*Standard Deviation*	*Number of Studies*
Oxygen vs. Carbogen	0.72 π	0.24 π	13
Air vs. Oxygen	0.17 π	0.68 π	12
Air vs. Carbogen	0.69 π	0.45 π	13

***Table 1**. Mean phase lags between BOLD response and block gas stimulus in healthy volunteers. The lag is delay of the received signal compared to that for the second gas listed in the "Gas Stimulus" column. The circular mean listed is the mean phase lag across the total number of studies conducted with the listed stimulus. F-test results indicated that the standard deviation for the oxygen vs. carbogen stimulus was significantly different than the air vs. oxygen results (p = 0.0009) and the air vs. carbogen results (p = 0.02). The difference between the standard deviations for the air vs. carbogen and air vs. oxygen results was insignificant (p = 0.09).*

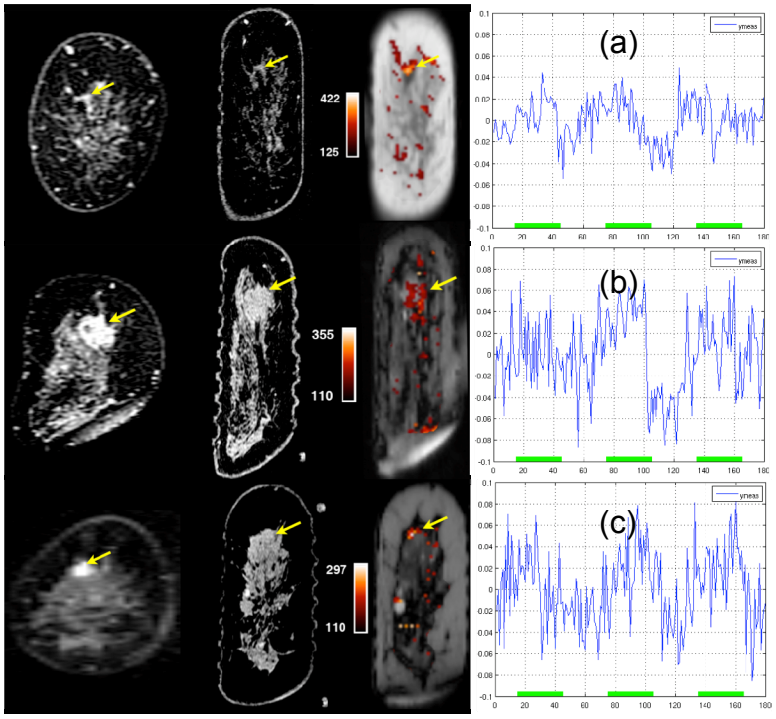

***Figure 1**. BOLD contrast results for the three tumor patients. First column: Reformatted coronal DCE images from previous scan at 1.5T. The yellow arrows identify the tumors. Second column: IDEAL water images allowing anatomic identification of tumor (based on DCE image architecture). Third column: Correlation coefficient maps overlayed on average images. The color bars represent the correlation coefficients multiplied by 1000. Fourth column: Corresponding time series to an ROI encompassing the tumor. The blue signal is the detected BOLD signal and the green bars represent the second listed gas. (a) invasive lobular carcinoma with oxygen vs. carbogen as the stimulus (b) invasive ductal carcinoma with oxygen vs. carbogen as the stimulus (c) invasive ductal carcinoma with air vs. carbogen as the stimulus.*

Discussion: Oxygen interleaved with carbogen acts as a robust stimulus for inducing BOLD contrast in breast tissue. We found that collecting data with an SSFSE pulse sequence eliminated artifacts from B_0 susceptibility effects in comparison to previously collected data with a GRE sequence [5,6]. Our conclusion that BOLD signal in healthy tissue positively correlates to carbogen and signal in malignant tissue negatively correlates to carbogen may be justified by the tumor "steal effect." The "steal effect" accounts for healthy parallel vasculature appropriately dilating in response to a vasodilatory task while diseased tissue does not appropriately respond. The diminished vasodilatory response consequently decreases blood flow to the tumor tissue. In developing a robust method for detecting BOLD contrast in the breast and applying the method to a small patient cohort, we have taken the first steps in non-invasively evaluating breast tumor oxygenation with MRI. The next step will be to apply this technique to a large patient cohort, and correlate tumor oxygenation to therapy response and other detectable breast cancer markers.

REFERENCES: [1] Taylor et al, JMRI, 2001. [2] Gilad et al, Int J Cancer, 2005. [3] Zhou et al, J of Biomedical Optics, 2007. [4] Glover et al, MRM, 2000. [5] Rakow-Penner et al, ISMRM Proceedings #3476, 2006. [6] Rakow-Penner et al, ISMRM Proceedings #586, 2008. Funding provided by NIH P41-RR09784 and the California Breast Cancer Research Program.