Monitoring gas-induced haemodynamic changes in the breast with BOLD contrast

Tess Catherwood[1], Andrew Patterson[1], Martin Graves[1], Reem Bedair[1], Roie Manavaki[1], Mary McLean[2], John Griffiths[2], and Fiona Gilbert[1]
[1]*Radiology, Cambridge University Hospitals NHS Foundation Trust, Cambridge, Cambridgeshire, United Kingdom,* [2]*Cancer Research UK Cambridge Institute, Cambridge, Cambridgeshire, United Kingdom*

Target Audience: Researchers interested in blood oxygenation level-dependent (BOLD) contrast for imaging oxygenation changes

Purpose: Blood oxygenation level-dependent (BOLD) contrast MRI with hyperoxic gas challenge can inform on breast tumour oxygenation[1] and vessel maturity[2], with the potential to predict treatment response[3], and could provide a valuable adjunct to DCE-MRI for characterising breast lesions. Breathing pure oxygen or carbogen (conventionally 95% O_2, 5% CO_2) both increase blood oxygen levels, but have opposing effects on vascular tone, as oxygen is a vasoconstrictor and carbon dioxide is a potent vasodilator. Previous studies measuring BOLD response to interleaved air or oxygen and carbogen in healthy tissue and tumours indicate that BOLD contrast is dominated by changes in vasomotor function. High inter-subject variability in response has also been reported[4], and it has been suggested that measurements may be confounded by the body's normal low frequency haemodynamic fluctuations[5]. The purpose of this study was to measure the strength of BOLD response to two hyperoxic stimulus combinations, compared to each subject's normal physiology. As tolerance to carbogen inhalation can be a problem, this study also tested the efficacy of 'carbogen-light' (2% CO_2) in inducing BOLD contrast in the breast. Previous reports have shown lower CO_2 variants to be equally effective at increasing arterial pO_2, without the respiratory discomfort reported with 5% CO_2 mixtures; however, the effect of these carbogen variants on the magnitude of the CO_2-induced vasodilation effect has not yet been investigated[6].

Methods: MR imaging was performed at 3T (MR750, GE Healthcare, Waukesha, WI, USA) in six healthy volunteers using a multi-phase SSFSE sequence to acquire 240 sequential T_2-weighted sagittal breast images at a single slice location with the following parameters: 8-channel breast coil, TE 58 ms, TR 4 s, bandwidth ±83 kHz, matrix size 128x128, FOV 20 cm, slice thickness 5 mm. 'Carbogen-light' was interleaved with either medical air or oxygen in two minute blocks, for a total of four complete cycles (16 minutes). Gases were delivered to the subject at 14 L/min via an OxyMask™ (Southmedic Inc., Barrie, ON, Canada), with switching controlled by an in-house gas delivery system. A twelve minute medical air breathing period was used to determine background modulation in physiology. The resulting time series images were co-registered to mitigate respiratory and patient motion, using a non-rigid registration algorithm[7]. Images were median-filtered to reduce noise and baseline subtraction of the line of best fit through the data was performed in order to remove linear drift. The first cycle of data was discarded to allow equilibration of the gas inhalation regime. Image analysis was performed using in-house software developed in MATLAB v8.3 (The Mathworks, Natick, MA, USA). The signal intensity response of each voxel was cross-correlated with a sine and cosine wave at the stimulus frequency (0.0042 Hz), which provided robust measures of the correlation and the phase lag between the delivered stimuli and measured BOLD contrast. A nonparametric analysis approach was used to test for a significant activation effect, without making distributional assumptions. Time series were then extracted from the activated ROI and a gas-to-air ratio (GAR) was calculated for each volunteer and stimulus, defined as: $GAR = \frac{\max(Corr_{Gas})}{\max(Corr_{Air})}$.

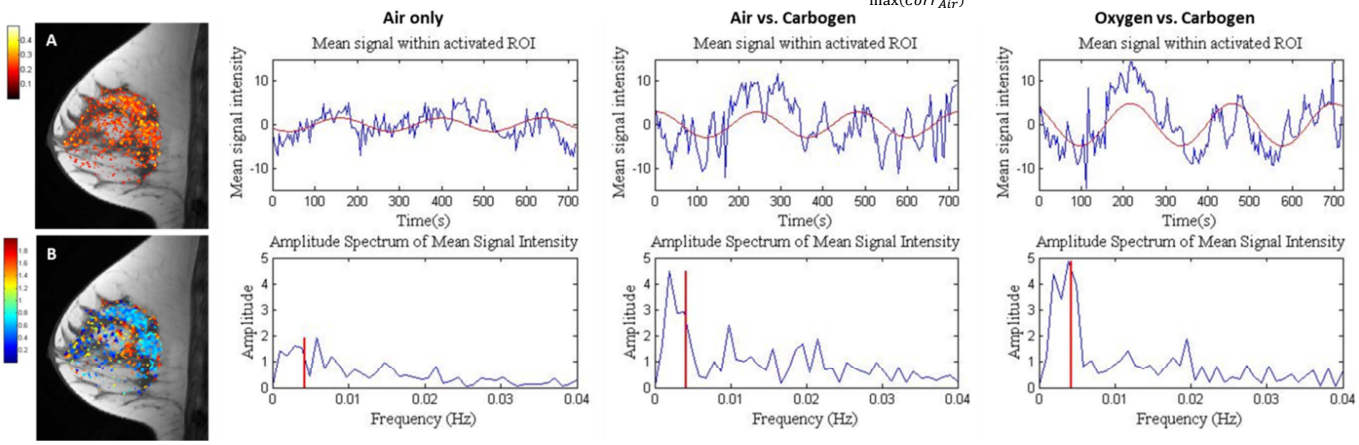

Figure 1. Maps showing (A) correlation and (B) phase lag of response, superimposed on a T_1-weighted anatomy image. Temporal signal modulation extracted from the activated ROI and frequency response during air/carbogen and oxygen/carbogen breathing, compared to an all air control in a single volunteer. Best fit sinusoids at the stimulus frequency (phase shifted to match time lag of response and normalised to the amplitude of response) are overlaid in red.

Results: Maps showing the magnitude and temporal phase of the BOLD response to the gas stimuli are displayed in Figure 1 for a single volunteer. In this volunteer, both stimulus combinations tested had a better correlation to the sinusoidal model compared to the air control, with signal modulation during the gas stimulus exhibiting a much larger peak at the stimulus frequency. However, vascular changes in some other subjects were insignificant compared to physiological noise (i.e. GAR < 1). Box plots of GAR in Figure 2 demonstrate the observed trend that oxygen vs. carbogen-light induced a greater response than air vs. carbogen-light, although the difference was not significant (p = 0.22). A moderate variance in air/air correlations was also observed (coefficient of variation = 16%).

Discussion: Carbogen-light appears to be effective in inducing a BOLD effect and was well tolerated by all subjects. In general, oxygen vs. carbogen-light induced a larger response, which is consistent with previous reports and with the opposing vasomodulatory effects of these two stimuli. The GAR ratio provides a means of characterising changes with respect to normal air variations (biological noise) and should allow for quantitative comparison between healthy and tumour tissue and between subjects. Without this control, natural haemodynamic fluctuations could be mistakenly attributed to the gas stimuli. A larger subject population is currently being studied to verify these results.

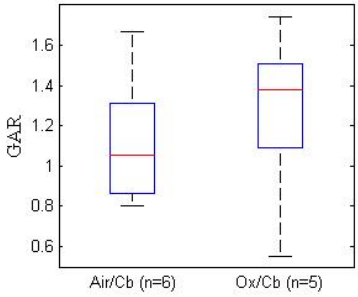

Figure 2. GAR for each gas stimulus in healthy breast parenchyma.

Conclusion: A measurable BOLD effect was observed in healthy breast parenchyma in response to 'carbogen-light' interleaved with oxygen, above the demonstrated level of normal physiological variation seen with air. This technique is clinically feasible and may provide a biomarker of vasomotor function, which could be used to inform on vessel maturity in breast cancer.

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