Hyperoxic (HO) versus hypercapnic (HC) BOLD calibration under precise control of end-tidal carbon dioxide and oxygen

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Introduction: HC calibration is a vasodilatory approach that depends on intrinsically low signal-to-noise perfusion imaging and individual vascular architecture. Most commonly achieved through manual gas control, it does not provide an ideal modulation of arterial partial pressure in CO_2 ($PaCO_2$) to drive changes in blood flow (1). Hence, the resulting calibration (M)-values are prone to large intra- and inter-subject variations that may bias oxygen metabolism studies (2). As an improvement, rigorous control of end-tidal partial pressures of CO_2 ($PetCO_2$) and O_2 ($PetO_2$) has been shown to achieve controlled, predictable and repeatable HC stimuli (3). Our goal was to apply the same automated feed-forward system [RespirAct™, Thornhill research Inc, Toronto] (4) to investigate HO as a calibration alternative (6) which, rather than causing vasoaction, directly impacts the arterial oxygen saturation, inducing measurable changes in venous oxygen saturation (5). The current study represents the first detailed demonstration of precisely targeted graded HC and HO levels in the same set of subjects in the context of BOLD signal calibration.

Methods: Nine nonsmoking healthy adults (7 females; mean age 27 years) were studied on a 3T TIM Trio system (Siemens, Erlangen, Germany) using a 32-channel head coil and a QUIPSS II echo planar imaging sequence (4x4x6 mm^3, labeling slab/gap of 150 mm/5 mm, $TI_1/TI_2/TE/TR$ of 700ms/1400ms/25ms/3s) under randomized (a) HO levels of 150, 250 and 350 mmHg increases in $PetO_2$ under fixed $PetCO_2$ and (b) HC levels of 3, 5, 7 and 9 mmHg increases in $PetCO_2$ under fixed $PetCO_2$ (relative to baseline levels). Each challenge consisted of one ON/OFF/ON block of 60 s/120 s/120 s preceded by a 60 s initial baseline. Two subjects were excluded from the study due to large stimulus-correlated-head-motion. Changes in $PetCO_2$, $PetO_2$ and respiratory rates we monitored. A 3D T1-weighted data set (1x1x1 mm^3) and functional localizer were collected for anatomical placement of nine oblique axial functional slices through the visual and motor cortices. For each subject, BOLD and CBF images were statistically thresholded separately (cluster-$p < 0.05$, corrected for multiple comparisons) and the signal changes calculated in the region-of-interest (ROI) formed by the overlap of all levels, HC and HO taken separately for spatial coverage comparison. Out of the four HC levels acquired, three were chosen (either at low or high end of the extended range) on a per-subject basis according to individual vascular reactivity. M-values were calculated under HC and HO, based on the deoxyhaemoglobin (dHb) dilution model, with $\alpha = 0.38$, $\beta = 1.5$ and the fractional change in the venous vasculature, $[dHb]_v / [dHb]_{v0}$, estimated from PaO_2 inferred via $PetO_2$ measurements (6):

$$M_{HC} = \frac{\Delta BOLD / BOLD_0}{1 - \left(CBF / CBF_0\right)^{\alpha-\beta}} \quad (Eq1) \qquad \& \qquad M_{HO} = \frac{\Delta BOLD / BOLD_0}{1 - \left([dHb]_{v_0} / [dHb]_v\right)^{-\beta}} \quad (Eq2)$$

Results and discussion: The MR responses measured followed a linear trend with graded levels of either challenge (Fig1). While both challenges induced very similar numbers of BOLD activated voxels in all subjects, HO consistently lacked a CBF response (Fig1&2), thereby validating Eq2 and removing the need to measure and correct for vasoconstrictive effects. The CBF decreases previously reported (6,7) may be explained by the inability of manual gas manipulation to control HO's induced tendency toward hyperventilation and associated decreases in $PaCO_2$ (Haldane effect), not present when employing the computerized-gas system. The low levels of HO employed herein also remove a potential T_2* attenuating effect at arterial pressures in excess of 350 mmHg due to appreciable plasma concentration of dissolved O_2 (8). Precise control of end-tidal gases produced markedly smaller errors in MR responses (Fig1&3), reducing the dispersion of individual and group M-values (Fig3) reported in previous HC studies (9). Moreover, the larger spread of $M_{Subject}$ under HC versus HO, due to low signal-to-noise ratio CBF measurements, suggests inherent individual variability in vascularization that require appropriate characterization using subject-specific calibration in flow-metabolism coupling studies (9). By relying on relatively low-variability end-tidal O_2 measurements, HO is associated with a consistently lower variance on M-values (factor of 2-3 times: $M_{Group,HO} = 6.58 \pm 0.66$ %, $M_{Group,HC} = 5.08 \pm 0.31$ % from fit on entire data set shown in Fig3), as previously reported (6).

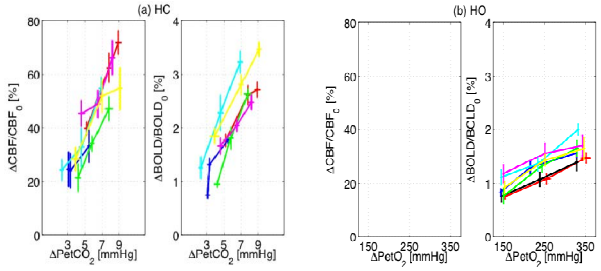

Fig1. CBF and BOLD changes under (a) HC and (b) HO against measured $PetCO_2$ and $PetO_2$ levels, respectively. Error bars for standard deviation over stimulation block. Individual subject (N=7) connected by color lines, 1 subject (black) lacked significant HC response in 2 levels, precluding overlap analysis.

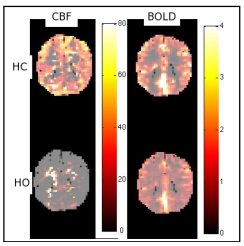

Fig2. Activation maps in single slice and subject for mid levels. Color range is % change, normalized to baseline.

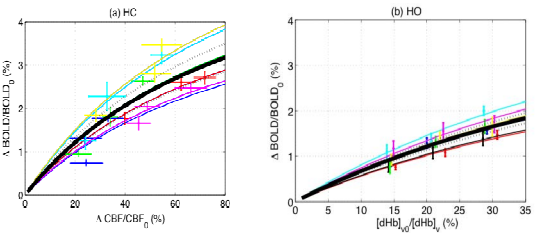

Fig3. BOLD signal change plotted against (a) HC CBF and (b) HO venous deoxygenated response (error bars within marker size). Color code as in Fig1. Lines indicate $M_{subject}$ from fit to Eq1&2. Black lines fit entire data set, dotted lines for 95 % confidence interval.

Conclusion: This study is the first demonstration of robust end-tidal targeting in a direct HC versus HO comparative study in the context of BOLD-calibration. The current findings suggest the viability of precisely controlling HO stimulation to provide M-estimates with lower overall intra and inter-subject variability, based on high SNR PaO_2 measurements, rather than intrinsically noisier perfusion imaging. By eliminating the confound of vascular variation in population observed under HC-calibration, HO not only opens the possibility of obtaining more precise $M_{Subject}$-values, but also eliminates a potential influence of the calibration step on metabolism, currently under debate in the isometabolic HC model (10,11), as well a correlation with the onset of breathlessness, detrimental to patients.

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