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 CO₂ (PaCO₂) 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 CO₂ (PetCO₂) and O₂ (PetO₂) 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 mm³, labeling slab/gap of 150 mm/5 mm, Ti1/Ti2/TE/TR of 700ms/1400ms/25ms/3s) under randomized (a) HO levels of 150, 250 and 350 mmHg increases in PetO₂ under fixed PetCO₂ and (b) HC levels of 3, 5, 7 and 9 mmHg increases in PetCO₂ under fixed PetO₂ (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 PetCO₂, PetO₂ and respiratory rates we monitored. A 3D T1-weighted data set (1x1x1 mm³) 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 α = 0.38, β = 1.5 and the fractional change in the venous vasculature, [dHb]_v/[dHb]_o, estimated from PaO₂ inferred via PetO₂ measurements (6):

\[
M_{\text{HC}} = \frac{\Delta \text{BOLD}}{\text{CBF}} = \frac{\alpha - \beta}{1 - \beta} \text{(Eq1)}
\]

\[
M_{\text{HO}} = \frac{\Delta \text{BOLD}}{\text{CBF}} = \frac{\text{dHb}_v}{\text{dHb}_o} \text{ (Eq2)}
\]

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 vasconstrictive 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 PaCO₂ (Haldane effect), not present when employing the computerized-gas system. The low levels of HO employed herein also remove a potential T₂* attenuating effect at arterial pressures in excess of 350 mmHg due to appreciable plasma concentration of dissolved O₂ (8).

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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 PaO₂ 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 isometric HC model (10,11), as well a correlation with the onset of breathlessness, detrimental to patients.


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