Blood oxygenation, CBF, OEF, and CMRO2 changes during hypercapnia and hyperoxia using pCASL and TRUST MRI

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Introduction: BOLD and ASL MRI in combination with hypercapnic stimuli are becoming increasingly popular for measuring cerebrovascular reactivity (CVR) in health and disease [1-2]. Hypercapnic stimuli are also frequently used in calibrated fMRI for quantifying neuronally-evoked BOLD responses or for $CMRO_2$ estimation. A common assumption when interpreting these results is that hypercapnic stimuli are iso-metabolic. Additionally, hypercapnic stimuli may be coupled with hyperoxia, for which the effect on metabolism is less clear [2]. Here we evaluate the assumption that two common hypercapnic stimuli (5%CO2: 5%CO2 + balanced room air; and carbogen: 5%CO2 and 95%O2) are iso-metabolic using MRI-based measures of changes in venous blood oxygenation (Yv). Additionally, hypercapnic-hyperoxic stimuli will increase arterial and particulary venous pO2. The degree to which the dissolved oxygen in venous blood plasma binds to dHb depends on the pO2 in the veins; BOLD data have suggested that this effect increases carbogen-induced BOLD responses by two to three-fold relative to hypercapnic normoxic BOLD responses [2]. A secondary aim was therefore to quantify Yv and oxygen extraction fraction (OEF) during hypercapnic-normoxia, normocapnia-hyperoxia, and hypercapnic-hyperoxia. We investigated these aims separately with a non-rebreathing face mask and also a computer-controlled rebreathing device.

Materials and Methods: Healthy volunteers (n=10;age=31+/-3yrs) were scanned at 3T (Philips). Yv measurements were performed on the sagittal sinus using TRUST MRI (TR=3s, TI=1.2s, voxel size=3.4×3.4×5mm^3, 4 T2 weightings (effective TEs: 0, 40, 80, and 160ms), with a tCPMG=10ms; repeats=2 [3-4]. CBF measurements were performed using pCASL MRI. Acquisition parameters and CBF quantification method follow those in [5]. Post label delay=1.7s, label duration=1.5s, TR=3.9s, measurements=13, spatial resolution=3x3x7mm^3, slices=17. For the carbogen condition a blood water T1 reduction from 1.66 to 1.55s was used, which was calculated in separate work by assuming identical gray matter ΔCBF for the 5%CO2 and carbogen conditions. TRUST and pCASL data were sequentially acquired using a non-rebreathing facemask in the following paradigm: 3min room air (RA1) - 3min 5%CO2 - 3min room air (RA2) - 3min carbogen. The order of 5%CO2 and carbogen was randomized between subjects and time was allowed for EtCO2 and Yv to equilibrate. In additional subjects (N=3), sequential pCASL, TRUST, and phase-contrast (PC) MRI [4], were acquired using a rebreathing device (RespirAct™) which allows targeting of PaCO2 and PaO2; hypercapnic-normoxic (+10mmHg PaCO2), normocapnic-hyperoxic (375mmHg PaO2), hypercapnic-hyperoxic (+10mmHg PaCO2, 375mmHg PaO2) in blocks of 5 min interleaved with periods of room air breathing. To account for the dissolved O2 for the hyperoxic conditions, we computed the total arterial O2 content ($[O2]_a$), venous O2 content ($[O2]_v$), and pvO2 using physiological models of O2 hemoglobin saturation and plasma-dissolved O2 [6]. This also takes into account the Bohr-effect, effect, for which O2 binding to Hb is inversely related to the presence of CO2, by using the measured EtCO2. Hct values of 0.42 for males, and 0.4 for females were assumed. OEF was computed as $([O2]_a–[O2]_v)/[O2]_a$, and $CMRO_2=CBF*([O2]_a–[O2]_v)$.

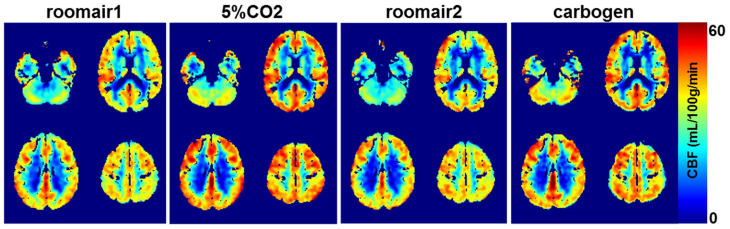

Figure 1. Mean CBF maps (N=10, MNI space) for the room air, 5%CO2 and carbogen (5%CO2/95%O2) conditions. Significant increases in whole-brain (minus ventricles) CBF were observed for the 5%CO2 and carbogen conditions.

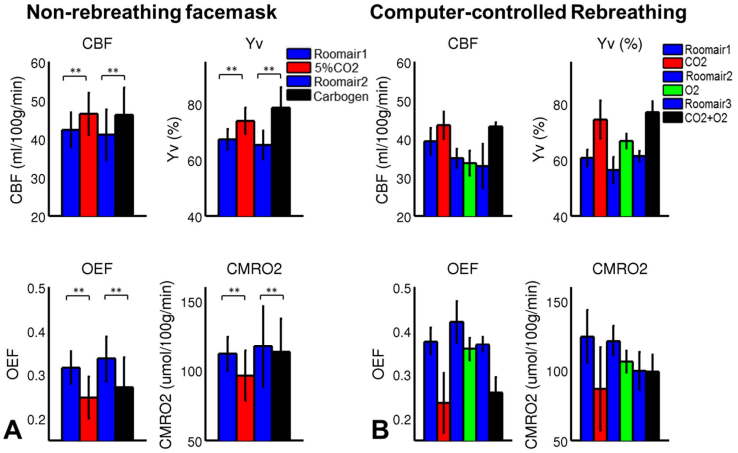

Figure 2. A) Changes in CBF (pCASL), Yv, OEF, and CMRO2 for hypercapnic (5%CO2) and hypercapnic-hyperoxic (carbogen, i.e. 5%CO2+95%O2) stimuli using a non-rebreathing facemask. **denotes significant difference, p<0.05 ANOVA. B) Changes in CBF (pCASL), Yv, OEF, and CMRO2 for hypercapnic (CO2), hyperoxic (O2) and hypercapnic-hyperoxic (CO2+O2) stimuli using a computer-controlled rebreathing mask (RespirAct™). Only significant CMRO2 changes were observed for the hypercapnic stimuli.

Results & Discussion: Fig1 shows the mean CBF maps for the room air, 5%CO2, and carbogen conditions. Fig2A shows significant changes in wholebrain CBF, Yv and OEF for 5%CO2 and carbogen. After correcting for the plasma-dissolved arterial and venous O2, no significant differences in OEF were found between 5%CO2 and carbogen (also observed in the RespirAct data). Data suggests a slight increase in OEF for the carbogen, which could be due to the presence of O2 (Fig2B shows increased OEF also for the hyperoxic condition compared to CO2). Future work is needed to investigate this further. Significant CMRO2 decreases from room air were observed only for the hypercapnic-normoxic conditions (5%CO2 in Fig2A and CO2 in Fig2B) in line with literature findings [7]. Further, we observed a slight decrease in CMRO2 for the hyperoxic condition (Fig2B, RespirAct data). The carbogen and hypercapnic-hyperoxic (CO2+O2) data (facemask and RespirAct data, respectively) revealed no significant decrease in CMRO2. This could indicate that carbogen is potentially a more iso-metabolic stimulus. Possible confounds of the carbogen data analysis are the potentially vasoconstrictive properties of O2 and the changes in blood water T1. However the PC-MRI results using the RespirAct (data not shown) showed no significant decreases in wholebrain CBF for the hyperoxic stimulus. This indicates vasoconstriction might not be a significant confound for these stimuli as has been reported in the PET literature [8]. We believe these findings will be of importance for interpreting calibrated fMRI and BOLD CVR measurements using hypercapnic or hypercapnic-hyperoxic (carbogen) stimuli.

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[6] Dash et al. Ann. Biom. Engin. 2010, [7] Xu et al. JCBFM 2011, [8] Ashkanian M et al. Brian Res 2009