MR Based Quantification of Global Cerebral Metabolic Rate of Oxygen Consumption during Hypercapnia

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Introduction: Hypercapnia is a common occurrence in pathophysiologic conditions (e.g. cardio-respiratory disease processes) [1]. Carbon dioxide is a potent cerebral vasodilator. Hypercapnia induced hyper-perfusion is often used as a diagnostic tool to measure cerebral vascular reactivity (CVR) to assess the integrity of cerebral circulation which can be altered in pathophysiological states [2]. While the vascular effects of hypercapnia on cerebral blood flow have been well documented, there is no general consensus on its metabolic effects [3]. A recent paper suggested therapeutic effects of hypercapnia in neonates with congenital heart disease (CHD) at risk for hypoxic ischemic injury secondary to hypoperfusion. However, quantification of cerebral metabolic activity during hypercapnia in such a population remains inadequate [4]. Additionally, from a neuroscience research perspective, assumption of constant cerebral metabolic rate of oxygen consumption ($CMRO_2$) during hypercapnia is used for calibrating blood oxygen-level dependent (BOLD) response in functional magnetic resonance imaging (fMRI), yet verification is pending [5]. Here, we present a robust and reliable method for quantifying $CMRO_2$ during hypercapnia by simultaneously measuring total cerebral blood flow (tCBF) and venous oxygen saturation (S_vO_2) in the major cerebral supply and drainage vessels with a temporal resolution of ~30s.

Methods: Moderate hypercapnia was induced in 10 healthy male volunteers (25±5 years) by administering 5% CO_2 gas mixed in room air (20% O_2; 75% N_2) through a 100L Douglas bag to allow resistance-free supply of air via a mouthpiece. End-tidal CO_2 ($EtCO_2$), heart rate and arterial oxygen saturation was monitored throughout the experiment. The experiment consisted of 3 phases: normocapnia (baseline) , hypercapnia and normocapnia (recovery) for a duration of 3, 3 and 5 mins, respectively. An interleaved GRE sequence consisting of four interleaves was used for simultaneous measurement of S_vO_2 in the superior sagittal sinus (SSS) using MR-susceptometry based oximetry and tCBF in the internal carotid and vertebral a. using PC MR [6]. The first and third interleaves were flow compensated, varied in TE and used for quantifying S_vO_2. The second and fourth interleaves were flow encoded to quantify tCBF. The S_vO_2 quantification relies on the measurement of relative magnetic susceptibility,$\Delta\chi$, of intravascular blood and surrounding tissue by modeling the vessel of interest as a long paramagnetic cylinder [7,8]. Oxygen saturation ($\%HbO_2$) is determined as $\%HbO_2 = \left[1 - \frac{2|\Delta\phi|}{\gamma\Delta\chi_{do}B_o(\cos^2\theta - 1/3)Hct}\right]\times 100$ where $\Delta\phi$ is the average phase difference between intravascular blood and surrounding tissue, $\Delta\chi_{do} = 4\pi(0.27$ ppm) [9] is the susceptibility difference in SI units between fully deoxy/oxygenated erythrocytes, hematocrit (*Hct*) is the volume fraction of the packed erythrocytes in whole blood and θ is the tilt angle of the vessel with respect to the main field B_o. All MR experiments were performed on a 3T Siemens Tim Trio system. Scan parameters: FOV = 208 × 208 × 5 mm^3, voxel size = 1 × 1 × 5 mm^3, flip angle = 25°, TR=35ms, VENC = 60cm/s (normocapnia) and 100 cm/s (hypercapnia), total scan time = 28s. Additionally, a T1-weighted 3D magnetization-prepared rapid gradient-image dataset (voxel size = 1 x 1 x 1 mm^3) was used to estimate intracranial volume. $CMRO_2$ was calculated using Fick's equation and a paired t-test was used to compare tCBF, S_vO_2 and $CMRO_2$ measurements during normocapnia and hypercapnia.

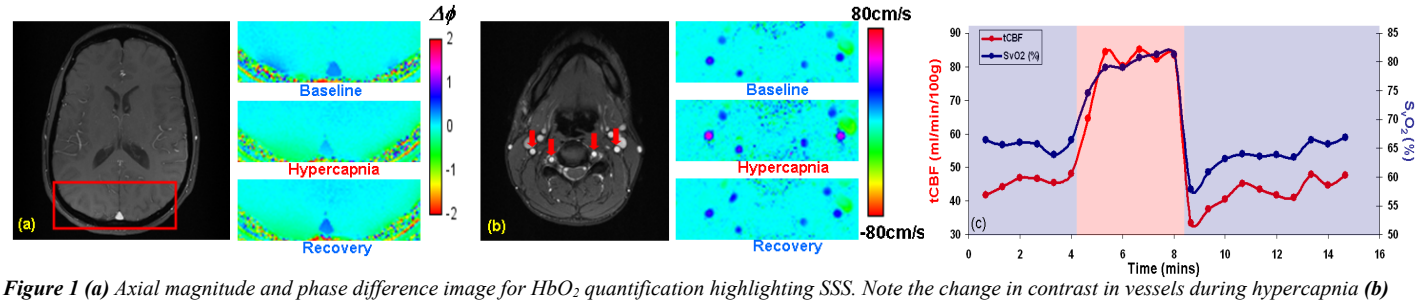

Figure 1 (a) *Axial magnitude and phase difference image for HbO_2 quantification highlighting SSS. Note the change in contrast in vessels during hypercapnia* ***(b)*** *Axial magnitude and velocity images of the neck showing the major cerebral inflow vessels (internal carotid and vertebral arteries)* ***(c)*** *Plot of time resolved measurements of tCBF and S_vO_2 during normocapnia (blue) and hypercapnia (pink).*

	S_vO_2	tCBF	$CMRO_2$
Baseline	65 ± 6	48 ± 7	130 ± 9
Hypercapnia	78 ± 7	81 ± 13	127 ± 12
Recovery	64 ± 5	46 ± 6	129 ± 7

Table 1: *Average S_vO_2 (%), tCBF (mL/100g/min) and $CMRO_2$ (μmol/100g/min).*

Results and Conclusion Average SvO_2 , tCBF and $CMRO_2$ as shown in **Table 1** are in good agreement with literature values [6,10]. Also, a significant correlation was observed between baseline SvO_2 and tCBF (R^2=0.77; p<0.005) as has been reported previously [5,9]. Statistically significant changes (p<0.005) were observed in SvO_2 and tCBF during hypercapnia (**Figure 1**,**Table 1**). However, global $CMRO_2$ remained unchanged (p = 0.97). Additionally, a statistically significant linear correlation was observed between % ΔtCBF and $\Delta EtCO_2$ (R^2=0.72; p<0.005) and CVR (= %ΔtCBF/ $\Delta EtCO_2$) was computed to be 6.1, in excellent agreement with previous results [2,3].

In summary, we introduce a fast, robust and reliable method to accurately determine $CMRO_2$ during hypercapnia with a high temporal resolution (~30s). Our preliminary findings support the assumption of negligible change in $CMRO_2$ in normal healthy adults under conditions widely used to determine CVR and for calibrated fMRI studies. In the future, a similar protocol will be extended to study the effects of hypercapnia on tCBF, oxygen extraction fraction (OEF) and $CMRO_2$ in neonates with CHD in an ongoing clinical MR study at our institution.

References **[1]** Pollock et al., AMJR 2008;30:378-385; **[2]**Noth et al., NMR Biomed 2008;21(5):464-72; **[3]** Chen at al.,JCBFM 2010;1-6; **[4]**Jansen et al., Behav Brain Res. 1996;78(2):189-94; **[5]**Davis et al., PNAS 1998;95:1834–9; **[6]** Jain et al., JCBFM 2010;1598-1607; **[7]** Haacke et al. Human Brain Mapping 1997;5:341-346; **[8]**Fernandez-Seara et al.MRM 2006; 55:967–973; **[9]**Spees et al MRM 2001; 45: 533 – 542; **[10]**Xu et al.,MRM 2010 62:141-8;
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