Elevated CO2 mitigates the rise in CMRO2 during acute hypoxia and improves cerebral tissue oxygenation

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Introduction: The brain has a high-energy demand and a low tolerance for interruptions of oxygen (O_2) availability. We previously reported increased cerebral metabolic rate of O_2 ($CMRO_2$) during sustained hypoxia, despite limited O_2 availability[1]. The biological rationale for this paradoxical response is unclear, and is the motivation for the present study

In general, changes in cerebral tissue oxygenation (PtO_2) depend on the balance of changes in arterial PaO_2, cerebral blood flow (CBF), and the cerebral metabolic rate of O_2 ($CMRO_2$), providing several potential mechanisms for controlling tissue oxygenation (PtO_2). This balance of O_2 supply and demand in the cerebral tissues is further complicated by the influence of arterial carbon dioxide ($PaCO_2$) since CBF and $CMRO_2$ are both independently impacted by PaO_2 and $PaCO_2$.

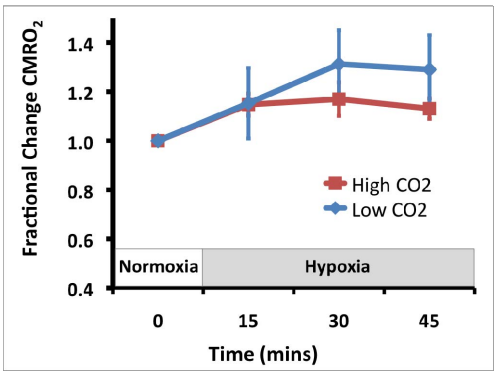
$CMRO_2$ in the human brain can be determined with MRI from measures of oxygen extraction fraction and CBF. Further, PtO_2 in cerebral tissue can be estimated from an O_2 diffusion model we have developed [2]. We applied these methods to investigate the influence of $PaCO_2$ on the paradoxical rise in $CMRO_2$, and on the PtO_2 in hypoxic conditions.

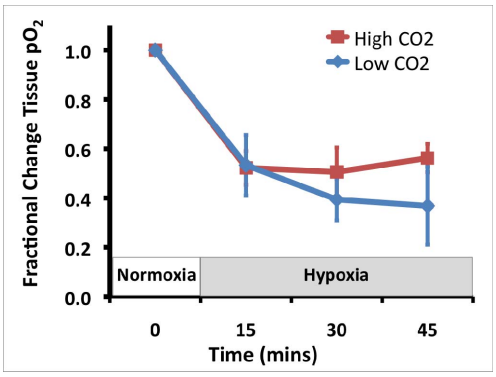
Measurements: 11 healthy subjects (age 27 +/-6 yrs) participated in 2 groups; one group (n=5) freely modulated their end-tidal CO_2 during FIO_2=0.125 hypoxic conditions ("low CO_2 group"), while another group (n=6) experienced the same hypoxic conditions but had their end tidal CO_2 clamped at normoxic levels ("high CO_2 group").

Venous T_2 was measured using a modified TRUST (T_2 relaxation under spin tagging) MRI technique with BIR4 pulses for T_2 preparation [3] and a single shot spiral readout (TE=2.8ms, TR=8s, TI=1.2s, 4 echoes, 10 mm slice, 80 mm tag, 4.5 mins). CBF was measured using phase-optimized pseudocontinuous arterial spin labeling (optPCASL) ASL technique (TE=3.3ms, TR=4.2s, temporal bolus=2s, 5 mm slices, 5 mins). Measurements were made as repeated blocks of CBF and T_2 measure during normoxia and over a period of 45 mins of hypoxia. CBF measurements were corrected for physiological noise and the effect of O_2 desaturation on T_1 of blood. T_2 measured with TRUST were calibrated against a prior control group [1] (previously scaled such that OEF= 0.4 & $CMRO_2$=1.6 mmol/g/min in normoxia).

Results: The mean $CMRO_2$ during normoxia was 1.58 +/-0.18 mmol/min in the group with unrestrained ("low") CO_2 ($ETCO_2$=33.9 +/-2.6 torr), and 1.69 +/-0.27 mmol/min with clamped ("high") CO_2 group ($ETCO_2$=36.4 +/-1.6 torr). Over 45 minutes of hypoxia the mean $CMRO_2$ rose to 2.01 +/-0.45 mmol/min with low CO_2 (29% rise), and 1.92 +/-0.43 mmol/min (10% rise) with high CO_2. Over the same interval estimated PtO_2 fell from 25 mmHg to 9.2 +/-7.9 mmHg during low CO_2 (73% fall), and to 13.0 +/-2.4 mmHg with high CO_2 (44% fall).

Discussion: $PaCO_2$ influences both $CMRO_2$ and PtO_2 during hypoxia. Reduced PaO_2 may cause a fall (or no change) in $CMRO_2$, and an increase in CBF [4,5] (an appropriate response to low O_2 availability). However, reductions in $PaCO_2$ increase neuronal firing and hence increase $CMRO_2$ [6], accounting (in part) for the paradoxical $CMRO_2$ response during acute hypoxia. The low $PaCO_2$ also decreases CBF. This high $CMRO_2$ / low CBF combination likely acts to compound the PtO_2 decline in hypoxic conditions. $PaCO_2$ thus represents an important covariable in the cerebral response to hypoxia.





Figures show fractional changes in $CMRO_2$ (left) and cerebral PtO_2 (right) during 45 min acute hypoxia (O_2=12.5%). Blue curve is unrestrained CO_2 ("low CO_2"). Red curve is CO_2 clamped to normoxia level ("high CO_2"). The paradoxical increase in $CMRO_2$ is partially mitigated when CO_2 remains high. High CO_2 also improves cerebral tissue oxygenation during acute hypoxic conditions.

References: [1] Krizay et al. 2010 *Int Soc Magn Res Med:* 721. [2] Buxton 2010. *Front Neuroenerg:* 1-16. [3] Wong et al. 2010 *Int Soc Magn Res Med:* 2853. [4] Dyer et al. 2008 *Respir Physiol* 128: 263-76. [5] Hochachka et al. 1994 *J Cereb Blood Flow Metab* 14: 671-79. [6] Dulla et al. 2005 *Neuron* 48: 1011-23. **Supported by:** NIH NS 053934 (DJD). NIH NS 36722 (RBB).