CO2 breathing Suppresses Cerebral Metabolic Rate of Oxygen

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INTRODUCTION: CO_2 has been known for its high potency in modulating blood flow. However the effect of CO_2 on neuronal activity and brain energy consumption is not yet known. Characterization of such an effect can provide a new opportunity to non-invasively and conveniently modulate neural activity in humans, which traditionally would have to be done surgically or transcranially. For example, suppressing of neural activity can be used to terminate an epileptic episode (1). Also, the ability of reducing neural activity may provide a potential therapy for insomnia and other sleep disorders. In addition, understanding the effect of CO_2 on neurons is useful in re-assessing CO_2 as a pure vascular challenge as well as in interpreting the data of calibrated fMRI studies. A recent electroneurophysiology study in anesthetized animal provided evidences that mild hypercapnia (HC) reduces neural activity (2). Here we performed an MRI and an EEG study to assess the effect of HC on oxygen consumption and neural activity in humans. In the MRI study, we used a recently developed method (3) to measure cerebral metabolic rate of oxygen ($CMRO_2$) during normocapnia (NC) and HC. In the EEG study, we measured surface electrode potentials during NC and HC.

METHODS: MRI experiments (8 healthy controls, 5 M, 3 F, age 20-35) were performed on a 3T Philips System. Absolute $CMRO_2$ in units of μmol/min was calculated using Fick principle $CMRO_2 = CBF \cdot (Y_a - Y_v) \cdot C_a$, where *CBF* is the blood flow in ml/min, Y_a is the arterial oxygenation (%), Y_v is the venous oxygenation (%), C_a is the amount of oxygen molecules that a unit volume of blood can carry, assumed to be 833.7 μmol O_2/100ml blood based on physiology literature (4). *CBF* was measured with phase contrast (PC) MRI, Y_a was determined by a pulse oximeter; Y_v was estimated with a recently developed technique TRUST MRI (5). In this study, the experiments were performed at the level of sagittal sinus, essentially measuring the oxygen consumption in the brain tissue that is drained by sagittal sinus. Sagittal sinus (SS) was chosen over jugular vein because imaging at SS is more robust and shorter in duration (critical for maintaining constant physiology during the measurement), and the percentage $CMRO_2$ change measured at SS should presumably be the same as that for the whole brain. The sequence parameters were: for TRUST MRI, voxel size 3.44x3.44x10mm^3, TR=8000ms, TI=1200ms, four TEs: 0ms, 40ms, 80ms and 160ms, duration 4.5 min; for PC MRI, voxel size 0.45x0.45x5 mm^3, maximum velocity 80cm/s, duration 30 sec. EEG studies were performed in a separate group of subjects (n=3, age 25-33 y) using a 64-electrode NeuroScan EEG system. Since the open/close of eyes is known to have a significant effect on EEG signal, experiments were performed for both eye open and eye close conditions.

The experiment started with room-air breathing for 5 minutes, during which normocapnic MRI or EEG was performed. Then the breathing air was switched to a Douglas bag containing 5% CO_2, 21% O_2 and balancing N_2. Two minutes were waited for the physiologic state to stabilize at the hypercapnic state. Then MRI or EEG was performed in the next 5 minutes. End-tidal CO_2 was recorded throughout the MRI/EEG experiments.

RESULTS and DISCUSSION: The end-tidal CO_2 were 40.9±3.7mmHg (mean±SD) and 49.6±3.2mmHg for normocapnic and hypercapnic conditions, respectively. Fig. 1a illustrates the TRUST MRI data for the two conditions. The T2 signal decay is much slower during HC, suggesting a longer venous blood T2. Venous oxygenation from TRUST MRI revealed a significant increase (pair t test, p<0.001) from 58.5±8.2% (NC) to 74.5±5.5% (HC). This corresponds to a Y_a-Y_v (also known as oxygen extraction fraction, OEF) reduction from 39.0±8.8% to 24.0±5.8%. Fig. 1b shows the PC MRI results and one can see a clear increase of flow velocity in SS (arrows). Summation of the entire area in SS revealed that CBF increased from 360.65±58.09 ml/min (NC) to 517.43±146.58 ml/min (HC) (p=0.002). Fig. 2 summarizes the percentage change of these parameters. Using the equation described above, the $CMRO_2$ was found to change from 1166.5±322.6 μmol/min in NC to 1004.3±246.1 μmol/min in HC, a 13±5% reduction due to CO_2 breathing (p<0.001). That is, the reduction in OEF dominates over the increase in CBF, and consequently $CMRO_2$ showed a moderate decrease.

The EEG study serves to further elucidate which component of the neuronal energy consumption has changed with HC, as there are three main categories of "energy expenses" in neuron: synaptic potentials, action potentials, and "housekeeping" energy such as protein synthesis. EEG provides an assessment of synaptic potentials, or more precisely the synchrony of synaptic potentials. Fig. 3 illustrates the delta band EEG topography for NC and HC conditions. An increase in EEG power can be seen throughout the brain. Table 1 summarizes the power changes in different frequency bands. The values during NC were set as 100% and the HC condition was in reference to these values. It can be seen that HC increased the power in the delta band (p<0.05) whereas the theta and alpha bands did not show significant changes. It is important to note that increased delta band power during HC is not necessarily in contradictory to the MRI findings of decreased energy consumption. It is well known that delta band power increases when the brain enters a "standby" state such as being drowsy or in sleep. This is also analogous to the widely observed finding that the delta band power is higher when the eyes are closed compared to eye-open state. Thus, it is plausible that a brain state with higher delta band may actually be energetically less active.

In summary, our MRI and EEG studies revealed that HC can cause a reduction in brain oxygen consumption and an enhancement in brain delta wave. A possible mechanism for such an effect is that higher CO_2 concentration in the brain can result in a slight acidosis (lower pH) in brain parenchyma, which may affect pH-sensitive ion channels and switch the brain into a low-arousal state. This is also consistent with the notion that CO_2 has a slight anesthetic effect.

REFERENCES: 1) Ziemann et al. Nat Neurosci, 11:816(2008); 2) Zappe et al. Cereb Cortex, 18:2666(2008); 3) Xu ISMRM Abstract, 678(2008); 4) Guyton et al. Textbook of Medical Physiology (2005) 5) Lu and Ge MRM, 60:357(2008).

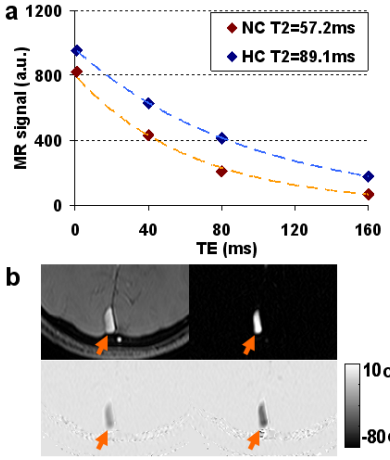

Fig 1 MRI results during NC and HC. (a) TRUST MRI signal as function of TE. The decay time constant is the blood T2, which can be converted to blood oxygenation. The time constant during HC (blue) is longer than that in NC (red). (b) PC MRI in the sagittal sinus. The four images are: raw image, magnitude image, the velocity map during NC, and velocity during HC. Arrows indicate the sagittal sinus. Darker color indicates higher outflow velocity.

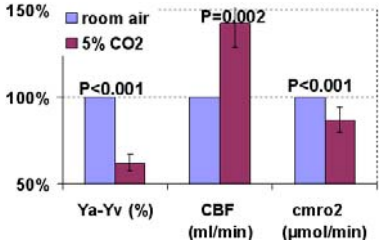

Fig. 2: Percentage changes in OEF, CBF and $CMRO_2$ due to CO_2 breathing. (n=8).

	NC	HC
Delta	100	117.8±19.6*
Theta	100	105.5±12.5
Alpha	100	103.1±12.7

* one tail pair t-test p<0.05

Table 1 EEG power in different frequency bands (mv^2) expressed in percentage of the NC values.

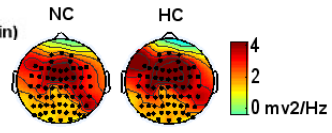

Fig. 3: Topography of 3Hz (in delta band) EEG power for all scalp electrodes during NC and HC conditions.