Searching for a truly "iso-metabolic" gas challenge for the use in calibrated fMRI and cerebrovascular reactivity mapping

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TARGET AUDIENCE: Researchers interested in fMRI and physiological MRI of the brain.

PURPOSE: Gas inhalation studies are useful means to investigate vascular and metabolic responses to various physiological challenges. In particular, hypercapnia (e.g. inhalation of CO_2 gas mixture) has been used in calibrated fMRI as well as in mapping of cerebrovascular reactivity in vascular diseases. An important assumption underlying these measurements is that CO_2 is a pure vascular challenge, that is, CO_2 dilates blood vessels but does not alter neural activity or brain metabolism. However, a few recent reports have brought this assumption into question and suggested that CO_2 inhalation may suppress neural activity (1) and brain metabolic rate (2). Therefore, the central goal of our study is to examine whether we can identify a gas challenge that is truly "iso-metabolic" while still producing a clear vascular response. The approach used in this report is to add a hypoxic component to the hypercapnic challenge, as hypoxia has previously been shown to enhance metabolic rate (3). Thus, we hypothesize that the combination of hypercapnia with hypoxia may alleviate the neural suppression effect of hypercapnia alone. A second hypothesis is that, if the cerebral blood flow (CBF) response observed with hypercapnia alone contains both vascular (increasing CBF) and metabolic (decreasing CBF due to metabolic suppression) effects, then CBF response to combined hypercapnia/hypoxia challenge should be greater (in terms of % change per mmHg CO_2 change), since the metabolic effect is removed. In this study, healthy subjects inhaled gas mixture with $5\%CO_2/13\%O_2$ (hypercapnic-hypoxia), while their CBF, venous oxygenation and cerebral metabolic rate of oxygen ($CMRO_2$) were monitored with MRI. For comparison, each subject also inhaled $5\%CO_2/21O_2$ (hypercapnia) and $0\%CO_2/13\%O_2$ (hypoxia) gas.

METHODS: *Study Design:* Twelve healthy subjects (age 29±5 yrd, 7M) were studied on a 3T Philips System. Each subject participated in MRI scans consisting of three different gas challenges. These three gas challenges were conducted in three separate sessions on the same day, with a short break in-between. The order of gas challenges was counterbalanced across subjects. The timing paradigm was similar across sessions. Taking the hypercapnic-hypoxia session, for example, the subjects first inhaled normal room air for 8 min and then the valve was switched to the hypercapnic-hypoxia gas (i.e. $5\%CO_2/13\%O_2$) for 6 min, followed by another 6 min room air breathing scan. The paradigm for the other two gas challenges was the same except that, for hypoxia-only challenge, the hypoxia gas period was 10 min since it takes more time to reach a steady state.

MRI measurement: Arterial oxygenation (Y_a), venous oxygenation (Y_v), CBF, and global $CMRO_2$ was measured using a recently described method (4,5). Briefly, CBF was measured by phase-contrast MRI on the sagittal sinus (Fig. 1a), Y_v was determined by a TRUST MRI technique (Fig. 1b), Y_a was obtained via a pulse oximeter, and $CMRO_2$ (in unit of umol O_2/min) was quantified based on the Fick principle with the following equation: $CMRO_2=CBF\times(Y_a-Y_v)$. These measurements would allow a comprehensive characterization of vascular and metabolic responses to gas challenges. In addition, end tidal CO_2 (Et-CO_2), end tidal O_2 (Et-O_2), and breathing rate were also monitored and recorded continuously on a laptop.

RESULTS: Figure 1 shows representative CBF (a) and Y_v (b) data. Note that, in Fig. 1a, darker color indicates greater flow velocity. In Fig. 1b, slower signal decay indicates a high Y_v.

Figure 2 summarizes the physiological changes during these gas challenges. For *arterial oxygenation (Y_a) (Fig. 2a)*, it changes minimally with hypercapnic gas, but is considerably reduced with hypoxic gas (P<0.01). The extent of the reduction is attenuated in the hypercapnic-hypoxia case, presumably because hypercapnia-induced hyperventilation offsets some of the hypoxia effect. *Venous oxygenation (Y_v) (Fig. 2b)* was elevated by hypercapnia, but reduced by hypoxia. When both gas effects were combined (i.e. in hypercapnic-hypoxia), the CO_2 effect seems to have prevailed, resulting in an Y_v increase (P<0.001). *CBF (Fig. 2c)* was the only parameter that showed a change (P<0.01) in the same direction for all three gas challenges. This is because both hypercapnia and hypoxia tend to increase CBF and their combination, of course, also increases CBF.

These three gas challenges had different effects on *$CMRO_2$ (Fig. 2d)*. Hypercapnia resulted in a suppression of $CMRO_2$ by 7.6% (P<0.01). In contrast, hypoxia increased $CMRO_2$ by 11.1% (P<0.01). Importantly, for hypercapnic-hypoxia, $CMRO_2$ showed no change (-0.4±3.9%, P=0.73), supporting our hypothesis that hypercapnic-hypoxia provides a truly "iso-metabolic" gas challenge.

A corollary of our hypothesis is that cerebrovascular reactivity (CVR) (%CBF change per unit CO_2 change) measured with hypercapnia-alone challenge may be erroneous, because the measured CBF response is likely under-estimated due to a (destructive) summation of vascular effect of CO_2 (which increases CBF) and a metabolic effect (which may decrease CBF via neurovascular coupling). We therefore computed CVR separately using the hypercapnia data and the hypercapnic-hypoxia data. It was found that CVR calculated using hypercapnic-hypoxia data was significantly greater than that using the hypercapnia data (P=0.01, Fig. 3). This finding suggests that either the metabolic differences between the two challenges may have played a role in the measured CBF responses or hypercapnia and hypoxia have additive effect on CBF.

DISCUSSION: In this study, we characterized brain vascular and metabolic responses to the combination of hypercapnia and hypoxia challenge. It has been suggested previously that hypercapnia reduced metabolic activity (2) in the brain while hypoxia increased metabolic activity (3). When combining both challenges, the neural suppression effect of CO_2 appears to be nullified by the metabolic enhancement effect of hypoxia, and results in an unchanged $CMRO_2$.

CONCLUSION: We therefore propose that hypercapnic-hypoxia is an iso-metabolic challenge that may be used for calibrated fMRI studies.

REFERENCES:1. Thesen et al. Hum Brain Mapp 33:715; 2012. 2. Xu et al., JCBFM 31: 58; 2011. 3. Xu et al., JCBFM 32; 1909: 2013. 4. Xu et al., MRM 62: 141; 2009. 5. Liu et al., MRM, 69: 675; 2013.

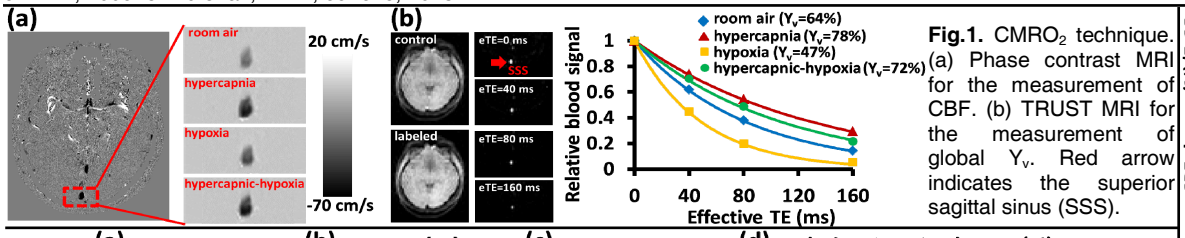

Fig.1. $CMRO_2$ technique. (a) Phase contrast MRI for the measurement of CBF. (b) TRUST MRI for the measurement of global Y_v. Red arrow indicates the superior sagittal sinus (SSS).

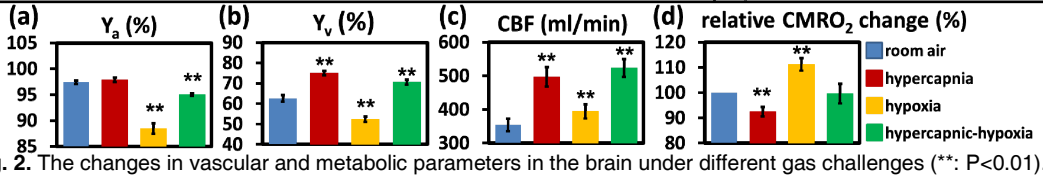

Fig. 2. The changes in vascular and metabolic parameters in the brain under different gas challenges (**: P<0.01).

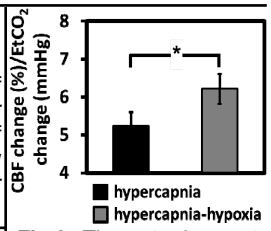

Fig.3. The unit change in CBF per the unit change in the CO_2 concentration (CBF change (%)/Et-CO_2 change (mmHg)) between two gas challenges (*: P<0.05).