Effect of graded O2 challenge on vascular and metabolic parameters

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INTRODUCTION: Calibrated fMRI relies on an iso-$CMRO_2$ challenge to obtain the calibration factor, M (1-3). Typically, the calibration experiment is performed using hypercapnia via inhalation of CO_2 gas mixture. However, recent evidence suggested that CO_2 may cause a suppression of neural activity by 10-15% due to acidosis in the brain parenchyma (4). Thus O_2 challenge became a preferred option for the calibration experiment (3). However, the assumption that O_2 challenge is iso-$CMRO_2$ has not been validated either. The present study will investigate whether physiologic manipulation of O_2 content in the arterial blood will change brain metabolism. We used a recently developed TRUST MRI technique (5-6) to monitor the subject's $CMRO_2$ while altering the O_2 concentration in the inspired air. Our data suggest that O_2 content changes brain metabolism and an inverse relationship was observed between $CMRO_2$ and arterial O_2 content which accounts for both hemoglobin-bound and dissolved O_2 in the blood.

METHODS: Nine young healthy subjects (age 28±5yrd, 3 F 4 M) were studied on a 3T Philips System. Each subject participated in a 50 min session with a graded O_2 challenge in which they breathed four levels of O_2 in the following order: 21%O_2 for 8min, 14%O_2 for 18min, 50%O_2 for 15min, and 98%O_2 for 12min (see color coding in Fig. 1). The duration of each breathing period was determined based on time needed to reach a new steady state after switching the gas (data from tests outside MRI). For example, after switching to 14% O_2 (hypoxia), it takes about 10 min to reach stabilization. The criteria for stabilization used Pulse-Oximeter-derived arterial oxygen saturation fraction (Y_a) for hypoxia and oxygen-sensor-derived oxygen partial pressure (p_aO_2) for hyperoxia, as exhaled O_2 has reached plateau and does not change during hyperoxia. An index for total arterial oxygen content was calculated for each O_2-breathing condition by accounting for both hemoglobin-bound and dissolved O_2: $[O_2]_a=(Y_a x C_h+p_aO_2 x C_d)/C_h$, where C_h (in unit of µmol O_2/100ml blood) and C_d (µmol O_2/100ml blood/mmHg O_2 tension) are associated with hemoglobin oxygen-carrying capacity and plasma's oxygen-dissolving capacity, respectively. The term in the parenthesis was divided by C_h so that the final index is in units of saturation fraction (%). Note that in this study $[O_2]_a$ could reach a value greater than 100% because of the large amount of dissolved oxygen during 50% and 98% O_2 breathing periods.

At each level of O_2 breathing (after stabilizing), four physiologic parameters were determined, including venous oxygen saturation fraction (Y_v), oxygen extraction fraction ($OEF=[O_2]_a-Y_v$), CBF and $CMRO_2$(i.e. OEFxCBF). These measurements would allow a complete characterization of vascular and metabolic responses to O_2 challenge, and the inter-relationship among these parameters are illustrated in Fig. 2. Y_v was estimated using a T2-Relaxation-Under-Spin-Tagging (TRUST) MRI technique via the measurement of pure blood T2 in the major vein sagittal sinus (5). TRUST MRI uses the spin labeling principle to separate flowing blood signals from static tissue, thereby obtaining pure blood signal. T2-weighting was then applied in the sequence with non-slice-selective preparation pulses (inter-pulse interval τ_{CPMG}=10ms). Other imaging parameters were: voxel size 3.44x3.44x5mm^3, TR=8000ms, TI=1200ms, four TEs: 0ms, 40ms, 80ms and 160ms, duration 3.5 min. CBF across the sagittal sinus was measured using a phase-contrast (PC) flow velocity technique with the following parameters: voxel size 0.45x0.45x5 mm^3, maximum velocity 80cm/s, duration 30sec. $CMRO_2$ was calculated using the Fick principle and was based on a previous study (6) except that the dissolved oxygen was also accounted in the present study.

In addition, PC MRI was performed continuously during the transit periods, providing a time course of CBF changes during the entire scan session.

For statistical analysis, correlation coefficients between $[O_2]_a$ and the parameters described above were calculated for each subject, which were then converted to z-scores using a Fisher transform and the group z-scores were compared to 0 using t tests.

RESULTS and DISCUSSION: Fig. 1 shows the time courses of arterial O_2 content ($[O_2]_a$) and CBF in the sagittal sinus (from the continuous PC MRI measurement) during the graded O_2 challenge. Correlation analysis on the steady state data revealed an inverse relationship between CBF and $[O_2]_a$ ($P<0.001$) (Fig. 2). Similarly, Y_v was correlated with $[O_2]_a$ ($P<0.001$) (Fig. 2). The arterial-venous O_2 difference, OEF, was not correlated with $[O_2]_a$ ($P=0.64$), suggesting that tissue extracts identical amount of O_2 from each unit of blood flow regardless the level of arterial O_2 content. Interestingly, $CMRO_2$ was found to be inversely correlated with $[O_2]_a$ ($P<0.001$) (Fig. 2). Fig. 3 shows a scatter plot between $[O_2]_a$ and relative $CMRO_2$ with respect to the room air value for all O_2 conditions and all subjects. Note that different subjects had different $[O_2]_a$ responses to hypoxia (breathing 14% O_2), possibly due to variations in compensatory responses in respiration. This provides a sufficient dynamic range to allow us to compare $[O_2]_a$ and $CMRO_2$ across subjects within the hypoxia condition (blue line in Fig. 3). An inverse correlation ($r=0.81$, $P=0.01$) was again observed. The $[O_2]_a$ variations in hyperoxia across subjects were minimal, thus no further correlation was assessed.

In this study, we characterized brain vascular and metabolic responses to graded O_2 challenge. It appears that O_2 has a suppressive effect on CBF and oxygen metabolism. The reduction in CBF in response to O_2 has been reported previously (7). The suppression on metabolism has not been reported in the literature but appears to be consistent with the notion of a coupling between neural and vascular responses, i.e. reduced $CMRO_2$ may be the underlying reason for a lower CBF. The present study suggests that O_2-based challenge may not be suitable for fMRI calibration experiment as it changes $CMRO_2$. These findings may also be useful in understanding the effect of O_2 therapy in various neurologic diseases.

REFERENCES: 1) Davis et al. Proc Natl Acad Sci 95:1834 (1998); 2) Hoge et al. MRM 42:849 (1999); 3) Chiarelli et al. Neuroimage 37:808 (2007); 4) Zappe et al. Cereb Cortex 18:2666 (2008); 5) Lu and Ge MRM, 60:357 (2008); 6) Xu et al. MRM 62:141 (2009); 7) Sicard et al. Neuroimage 25:850 (2005).

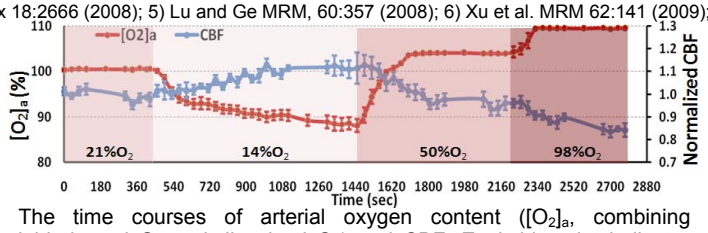

Fig.1 The time courses of arterial oxygen content ($[O_2]_a$, combining the hemoglobin-bound O_2 and dissolved O_2) and CBF. Each blue dot indicates one CBF measurement. The error bars indicate standard errors across subjects (N=9).

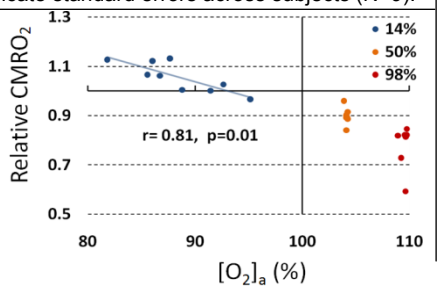

Fig. 3 Scatter plot between $[O_2]_a$ and relative $CMRO_2$ (with respect to the room air value).

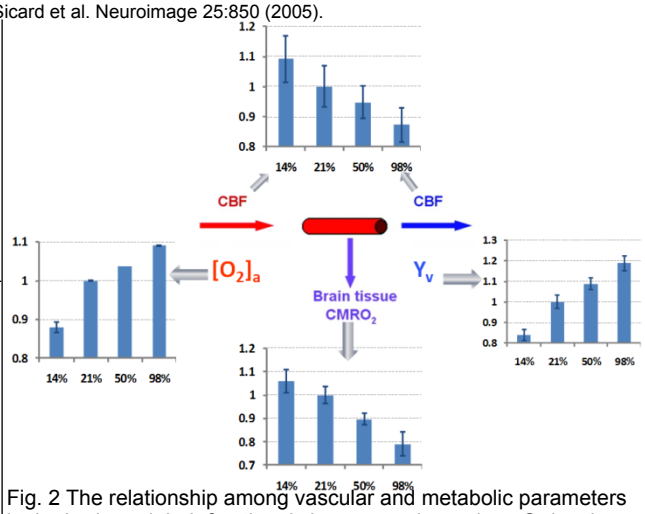

Fig. 2 The relationship among vascular and metabolic parameters in the brain and their fractional changes under various O_2 levels; the error bars indicate standard errors (N=9).