# Hypoxia and hyperoxia alter brain metabolism in awake human

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**INTRODUCTION:** The interaction between neural activity and brain vasculature forms the basis of brain mapping techniques such as functional MRI, PET and optical imaging. Up until now, the interaction has primarily been considered as unidirectional. That is, neural activity can change the vascular parameters (e.g. blood oxygenation), but little attention was received as to whether gas content changes in the blood would reversely alter neural activity. The present study will investigate whether physiologic manipulation of O2 content in the arterial blood will change brain activity and metabolism. We used a recently developed MRI technique (1,2) to monitor the subject's cerebral metabolic rate of oxygen ($CMRO_2$) while increasing or decreasing the O2 content in the inspired air. Our data suggest that hypoxia enhanced oxygen metabolism and hyperoxia suppressed it. Furthermore, the modulation effect appears to be proportional to the O2 content in the arterial blood, rather than to the O2 content in the inhaled air. The characterization of the reverse effect between neural activity and vasculature can provide a new perspective to brain metabolism and its regulation, as well as a potential non-invasive, convenient and cost-effective means to modulate brain activity in certain conditions such as neurodegenerative diseases.

**METHODS:** Twelve healthy subjects were studied on a 3T Philips System, six of which were studied with hypoxia (13.5% $O_2$, 3 F and 3 M, age 19-31) and the other six with hyperoxia (98% $O_2$, 4 F and 2 M, age 23-27). Quantification of $CMRO_2$ was based on a recently reported MRI technique (1, 2). Briefly, this technique uses the Fick principle of arteriovenous difference to estimate the rate of oxygen consumption, $CMRO_2=CBFx[(Y_a-Y_v)xC_a+(P_aO_2-P_vO_2)xC_d]$ , where CBF is cerebral blood flow, $Y_a$ and $Y_v$ are arterial and venous oxygenations (in %) respectively, $C_a$ and $C_d$ are constants associated with hemoglobin's oxygen-carrying capacity and plasma's oxygen-dissolving capacity, respectively. $P_aO_2$ and $P_vO_2$ are O2 tensions in artery and vein, respectively. We should note that usually the oxygen dissolved in plasma is negligible (<2%) compared to the hemoglobin-bound oxygen. However, in the special case of hyperoxia, the dissolved amount is no longer negligible (>10%), which is why we included O2 tension terms in the equation. For this study, the values of $C_a$ and $C_d$ were based on physiology literature. The other parameters were measured on a subject-specific and condition-specific basis as follows: $Y_a$ was measured with Pulse Oximeter, $Y_v$ was measured by TRUST MRI at the sagittal sinus (1), $P_vO_2$ was estimated from $Y_v$ using the oxygen dissociation curve, CBF was measured with the phase-contrast quantitative flow technique at the sagittal sinus, $P_aO_2$ was approximated with alveolar O2 level as measured from the exhaled air with an oxygen sensor. Note that the $CMRO_2$ measured with the above method is a whole-brain measure with no spatial information. However, the O2 effect, if any, is expected to be global since the entire brain will see a change in O2 tension. The sequence parameters were: for TRUST MRI, voxel size 3.44x3.44x5mm$^3$, TR=8000ms, TI=1200ms, four TEs: 0ms, 40ms, 80ms and 160ms, duration 3.5 min; for PC MRI, voxel size 0.45x0.45x5 mm$^3$, maximum velocity 80cm/s, duration 30 sec. Experiments started with room-air, then the breathing air was switched to 13.5% $O_2$ or 98% $O_2$ filled in a Douglas bag. Finally, the air was switched back to room air for another $CMRO_2$ measurement.

**RESULTS and DISCUSSION:** Physiologic parameters during the normoxia, hypoxia and hyperoxia periods are summarized in Table 1. Hypoxia decreased arterial oxygenation as expected. Venous oxygenation level also reduced. Interestingly, the amount of decrease for both parameters appears to be similar, suggesting that the extraction fraction ($Y_a$-$Y_v$) did not change much (p>0.05). CBF increased considerably (by 21±5%, p=0.01) when switching from normoxia to hypoxia, and can be visualized in the phase-contrast velocity map (Figs. 1c and d). Based on these experimental measures, $CMRO_2$ calculated from the equation above showed an increase of 25±6% (n=6, p=0.007). Comparing the two normoxia periods before and after the hypoxia block, the physiologic parameters are not different (p>0.05) and the $CMRO_2$ values were also similar.

For the hyperoxia manipulation (Table 1), the arterial oxygenation level did not change much as virtually all the hemoglobin is already saturated with O2 at normoxia. However, because the oxygen tension (shown as end-tidal O2 in Table 1) increased by approximately five times, the amount of oxygen dissolved in the plasma increased dramatically. Venous oxygenation increased significantly (p<0.001) upon hyperoxia challenge. Earlier we noted that hypoxia did not change the oxygen extraction fraction, thus we also investigated whether the extraction fraction changed with hyperoxia. At the face, it seems that ($Y_a$-$Y_v$) is reduced in this case. However, if we were to also account for the dissolved oxygen in the arterial blood, our calculation showed that the extraction fraction is again unchanged (p>0.05). That is, for each ml of blood passing through the capillary bed, the amount of oxygen that the tissue extracted is approximately the same for normoxia, hypoxia and hyperoxia conditions. CBF is reduced during hyperoxia compared to normoxia (14±2%, also see Figs. 1e and f). The calculation of $CMRO_2$ then showed that the $CMRO_2$ decreased by 10±1% when switching from normoxia to hyperoxia. Comparing the two normoxia periods, the parameters were unchanged.

Figure 2 summarizes the percentage changes in $CMRO_2$ as well as the two multipliers used to calculate it, i.e. CBF and oxygen extraction fraction ($OEF=(Y_a-Y_v)xC_a+(P_aO_2-P_vO_2)xC_d$). We have also tested to see if the $CMRO_2$ modulation has a linear dependence on the oxygen metrics. We found that the $CMRO_2$ change is not linear to the inhaled CO2 fraction (e.g. $P_aO_2$) nor to the arterial oxygenation level (e.g. $Y_a$), but it appears to be linearly correlated with the total O2 content in the arterial blood ($R^2$=0.85; p<0.001), i.e. $Y_axC_a+P_aO_2xC_d$.

Our data suggest that a change in arterial oxygen content can modulate brain metabolism in a dose-dependent manner, with hypoxia increasing metabolic rate of oxygen and hyperoxia decreasing it. Therefore, in addition to the well-known "forward" neurovascular coupling (3) (i.e. neural activity can alter vascular parameters), the "reverse" coupling may also be important in the regulation of brain function.

**REFERENCES:** 1) Lu and Ge MRM, 60:357 (2008); 2) Xu et al. MRM 62:141 (2009); 3) Roy and Sherrington, J Physiol 11:85 (1890).

| Hypoxia study | | | | | Hyperoxia study | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Arterial Oxygenation (%) | Venous Oxygenation (%) | CBF (ml/min) | $CMRO_2$ (μmol/min) | | End tidal O2 (mmHg) | Arterial Oxygenation (%) | Venous Oxygenation (%) | CBF (ml/min) | $CMRO_2$ (μmol/min) |
| Normoxia 1 | 97.7±1.8 | 59.9±8.0 | 341.8±50.8 | 1080.3±192.0 | Normoxia 1 | 114.3±3.5 | 98.7±0.8 | 64.3±8.4 | 386.1±26.2 | 1146.3±270.0 |
| Hypoxia (13.5% O2) | 84.1±2.3 | 44.5±7.5 | 411.0±58.0 | 1356.6±325.5 | Hyperoxia (98% O2) | 686.9±9.8 | 99.0±0.0 | 71.8±9.4 | 333.4±34.9 | 1030.7±256.9 |
| Normoxia 2 | 97.3±2.0 | 61.8±7.1 | 366.3±83.9 | 1082.9±226.2 | Normoxia 2 | 118.2±6.2 | 98.9±0.3 | 61.7±8.9 | 365.4±41.5 | 1163.7±247.9 |

Table.1: Summary of physiologic parameters of hypoxia and hyperoxia studies, (mean±SD).

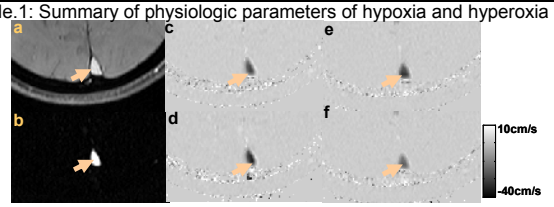


Fig. 1: PC MRI at the sagittal sinus: (a) raw image, (b) magnitude image, and velocity map during (c) normoxia, (d) hypoxia, (e) normoxia, and (f) hyperoxia. (d) appears darker than (c) corresponding to a faster blood flow during hypoxia. Also, (f) appears brighter than (e) corresponding to a slower blood flow during hyperoxia. Arrows indicate the sagittal sinus.

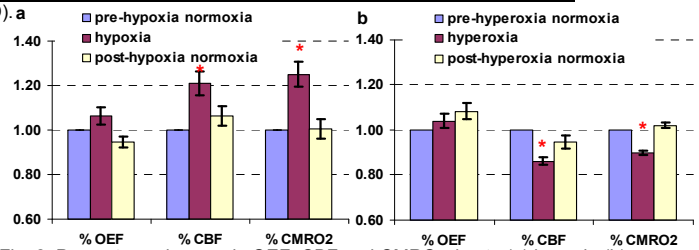


Fig. 2: Percentage changes in OEF, CBF and $CMRO_2$ due to (a) hypoxia (b) hyperoxia (error-bar is standard error, n=6, *paired t-test p<0.01). All values have been normalized to the respective values of the pre-challenge normoxia period. Thus the pre-challenge normoxia values in the plot are all 1 and have no error bars.