# Sustained Cerebral Hypoxia Increases Cerebral O2 Metabolism

**E. Krizay[1], J. S. Hunt Jr.[1], E. Li[1], B. C. Hsu[1], D. D. Shin[1], Z. Smith[1], R. B. Buxton[1], M. Scadeng[1], and D. J. Dubowitz[1]**
[1]Radiology, University of California San Diego, La Jolla, CA, United States

**Introduction:** Hypoxia decreases arterial oxygenation to the brain and increases resting cerebral blood flow (CBF). Previous studies suggest moderate global hypoxia does not influence resting cerebral oxygen metabolism ($CMRO_2$) [1-3], yet basal metabolic rate has been shown to increase with sustained hypoxia [4]. In this study, we examined the effects of 2 days and 7 days of sustained global hypoxia on $CMRO_2$ and Oxygen Extraction Fraction (OEF) in 8 healthy subjects (4M, mean 29 +/- 7 yrs).

**Theory:** $CMRO_2$ is the product of CBF, OEF and arterial $O_2$ content of blood, $[O_2]a$:

$$\mathbf{CMRO_2 = CBF \,.\, OEF \,.\, [O_2]a}$$

Since $[O_2]a$ is the product of hemoglobin concentration, [Hb], and arterial $O_2$ saturation, Ya, this can be rewritten as:

$$\mathbf{CMRO_2 = CBF \,.\, \{ (1\text{-}Yv)[Hb] - (1\text{-}Ya)[Hb] \}}$$

In this equation, (1-Yv)[Hb] is the concentration of venous deoxyhemoglobin, dHb. In a different study (submitted as a separate abstract), we determined that dHb is related to venous $T_2$ by the equation:

$$\mathbf{dHb = k\,(5.6/T_2 + 0.0273)}.$$

Thus, $CMRO_2$ can be determined from venous $T_2$ , scaling constant k, CBF, arterial $O_2$ saturation (Ya), and Hb concentration.

**Measurements:** Venous $T_2$ was measured using a TRUST ($T_2$ relaxation under spin tagging) MRI technique with single shot spiral readout (TE=2.8ms, TR=8s, TI=1.2s, 4 echoes, 10 mm slice, 80 mm tag, 4 mins). Baseline CBF was measured using a PICORE QUIPSS2 ASL technique (TE=9.1ms, TR=2.5s, $TI_1$=700ms, $TI_2$=1500ms, 6 mm slices, 3.5 mins). $O_2$ saturation was continuously monitored with a Nonin 8600FO MRI-compatible pulse oximeter calibrated against an arterial blood sample. [Hb ]was determined from the arterial blood sample using a IL-682 co-oximeter. Measurements were made during normoxia, and following 2 and 7 days sustained hypoxia at White Mountain Research Station (3,800m altitude, 90 Torr $O_2$, mean Ya of 85.4% at 2 days, 87.88% at 7 days). Subjects remained hypoxic until after the MRI was completed. The order of the 2-day and 7-day exposure was random, with an interval of 2-13 months between measurements to ensure subjects were fully de-acclimatized. CBF measurements were corrected for the effect of $O_2$ desaturation on $T_1$ of blood. Differences in $T_2$ measured with TRUST and conventional spin echo $T_2$ were corrected from a separate phantom calibration measurement. Scaling constant k was adjusted during normoxia such that OEF= 0.4 and $CMRO_2$= 1.6 mmol/g/min. Data were analyzed with repeated measures ANOVA and Fisher PLSD (significant at $p < 0.05$).

**Results:** During normoxia, mean resting CBF was 44.4 ml/100ml/min (+/- 11.1), mean venous $T_2$ in superior sagittal sinus was 43.3 ms (+/- 6.4), mean [Hb] was 9.2 mEq/L (+/- 0.8),and mean $SaO_2$ was 98.5% (+/- 0.5). Proportionality constant k was determined to be 36.5 for $CMRO_2$=1.6 mmol/g/min, and OEF=0.4. Following 2 days sustained hypoxia, CBF increased to 53.7 ml/100ml/min (+/- 18.6, p = ns), mean venous $T_2$ in superior sagittal sinus decreased to 30.9 ms (+/- 2.3, $p < 0.001$), and mean $SaO_2$ was 85.4% (+/- 3.8, $p < 0.01$). $CMRO_2$ increased by 59% to 2.5 mmol/g/min (+/- 0.9, $p < 0.01$) , and OEF by 23% to 0.5 (+/- 0.1, p = ns). Following 7 days sustained hypoxia, CBF was 53.3 ml/100ml.min (+/- 27.4, p=ns), mean venous $T_2$ was 32.5 ms (+/- 5.3, $p< 0.001$), and mean $SaO_2$ 87.9% (+/- 2.4, $p < 0.001$). $CMRO_2$ was increased 36% relative to normoxia to 2.2 mmol/g/min (+/- 0.8, $p < 0.05$), and OEF increased 18% to 0.5 (+/- 0.1, p = ns) relative to normoxia.

**Conclusions:** The combination of arterial $O_2$ saturation and [Hb] with two MRI measurements (venous $T_2$ and baseline CBF) provides a valuable method for determining $CMRO_2$, and extending the utility of TRUST MRI to hypoxic conditions. Our results indicate that there is a 59% increase in $CMRO_2$ after 2 days hypoxia, falling to 36% after 7 days. This trend is similar to increases in basal metabolic rate seen during sustained hypoxia.

**References:** [1] Nioka et al. 1990. J Appl Physiol 68:2527-35. [2] Shimojyo et al. 1968. Neurology 18: 127-33. [3] Moller et al. 2002. J Cereb Blood Flow Metab 22: 118-26. [4] Butterfield et al. 1992. J Appl Physiol 721741-1748. **Support:** NIH R01 NS053934