Influence of CO_2 on Cerebral O_2 metabolism during sustained hypoxia

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Introduction: Previously we have found that $CMRO_2$ increases during acute and sustained hypoxia [1, 2]. This $CMRO_2$ increase is partially mitigated if $PaCO_2$ is maintained at normoxic levels and not allowed to decrease [2], possibly involving an adenosine-mediated modulation in neural excitability [3]. Using acetazolamide (AZ), a carbonic anhydrase inhibitor, we investigated if the level of CO_2 (via acetazolamide) also influences the elevated $CMRO_2$ seen during prolonged hypoxia.

Methods: Healthy human subjects participated during normoxia (n=23, 13F, 10M age 29 ±9 yrs), and following exposure to 2-days sustained hypobaric hypoxia at 3,800m under 2 conditions: Once with no acetazolamide treatment (n= 22, 9 F, 13 M mean age 28±8.2), and once while receiving 500mg daily acetazolamide (n= 12, 2F, 10M mean age 30±9.6).

CBF was measured at 3T using a PICORE QUIPSS2 ASL technique (TE=9.1ms, TR=2.5s, TI_1=700ms, TI_2=1500ms, 6 mm slices, 3.5 mins). CBF measurements were corrected for physiological noise and the effect of O_2 desaturation on T_1 of blood. Venous T_2 was measured using a TRUST (T_2 relaxation under spin tagging) MRI technique with a single shot spiral readout (TE=2.8ms, TR=8s, TI=1.2s, 4 echoes, 10 mm slice, 80 mm tag, 4.5 mins). T_2 measured with TRUST were calibrated against a prior control group [1] (previously scaled such that OEF= 0.4 & $CMRO_2$=1.6 mmol/g/min in normoxia). O_2 saturation was continuously monitored with a Nonin 8600FO MRI-compatible pulse oximeter calibrated against arterial blood samples. SvO_2 from venous T2, [Hb] from the blood sample, and pulseox measured SaO_2 allowed for calculation of whole brain $CMRO_2$. Subjects remained hypoxic until after the MRI measurements were completed.

Results: Two days of sustained hypoxia was accompanied by an increase in $CMRO_2$ from 1.65±0.38 to 2.23±0.57 mmol/g/min ($p<0.01$). CBF also increased from 50.1±11.5 to 63.3±14.4 ($p<0.001$). Mean saturation following 2-days hypoxia 84±5 %, and mean $ETCO_2$ 32.3±2.7 torr.

Treatment with acetazolamide resulted in a reduced rise in $CMRO_2$ (1.98±0.45 mmol/g/min) and in CBF (57.9±9. 7 ml/100ml/min). Mean SaO_2 following 2-days hypoxia with acetazolamide was slightly elevated 87±5% (P=NS), and mean $ETCO_2$ was significantly decreased 28.1±2.1 torr ($p<0.001$).

Discussion: Previous studies have demonstrated decreased CO_2 clearance from cerebral tissues with acetazolamide inhibition of carbonic anhydrase [4], with increased extracellular fluid CO_2, and reduced $ETCO_2$ in the lungs. 500 mg is adequate to block erythrocyte and cerebral carbonic anhydrase, thus we expect that in this study too the significantly reduced alveolar CO_2 during acetazolamide treatment is indicative of impaired CO_2 excretion and increased cerebral tissue CO_2 levels. CO_2 thus appears to be a modulator of $CMRO_2$ during sustained hypoxia. Of note, acetazolamide increased ventilatory drive via alteration of the pH in the central chemoreceptors, and a secondary effect of this is the small increase in the mean arterial O_2 saturation from 84% to 87%, which may also be contributing to the final $CMRO_2$.

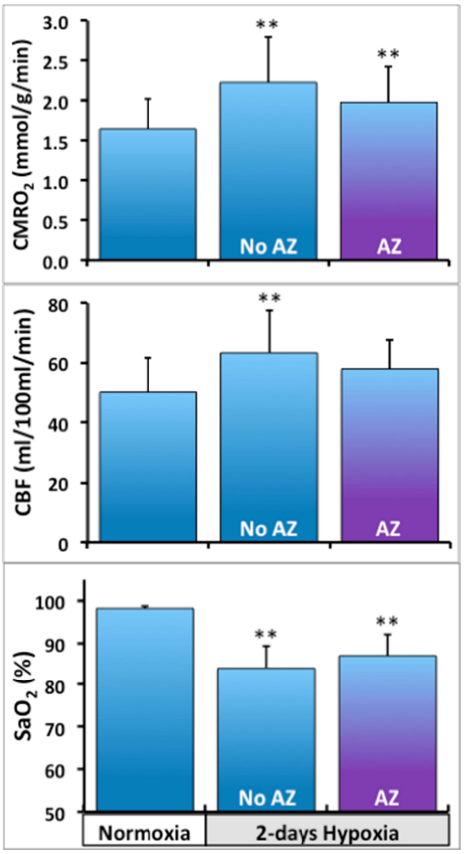

Figure 1: $CMRO_2$, CBF, and SaO_2 from normoxia and 2-days hypoxia with or without acetazolamide (AZ) (error bar = 1 SD, ** $P<0.05$ relative to normoxia).

References: [1] Krizay et al. 2010 *ISMRM:* 721. [2] Smith et al. 2011 *ISMRM:* 4456. [3] Dulla et al. 2005 *Neuron:* 48:1011-1023. [4] Bickler et al. 1988 *J Appl Phys:* 65:422-427. **Supported by:** NIH NS 053934 (DJD).