DEPRESSION OF CORTICAL GRAY MATTER $CMRO_2$ IN AWAKE HUMANS DURING HYPERCAPNIA

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INTRODUCTION:

Hypercapnia induced by carbon dioxide (CO_2) inhalation causes a robust increase in cerebral blood flow (CBF). Far less understood are the effects of CO_2 on neuronal activity and cellular metabolism. Recent studies measuring the cerebral metabolic rate of oxygen ($CMRO_2$) in response to hypercapnic challenge have yielded contradictory findings [1,2]. In this study, a newly developed method called QUantiative Imaging of the eXtraction of Oxygen and TIssue Consumption (QUIXOTIC) [3] was used evaluate the hypercapnic $CMRO_2$ response in cortical gray matter (GM) of awake humans. To our knowledge, this is the first time cortical $CMRO_2$ response to hypercapnia has been assessed.

METHODS:

Four healthy human volunteers were scanned (2 male, 2 female, ages 26 to 31) at 3T (MAGNETOM Trio, a Tim System (Siemens Healthcare, Erlangen, Germany), 32-channel head coil) using QUIXOTIC protocols. A custom gas delivery system supplied either compressed air or CO_2/air mixture to produce steady-state conditions of normocapnia and mild hypercapnia, respectively. End-tidal CO_2 was held constant at a target of ~7 mmHg above subjects' habitual baseline PCO_2 during the hypercapnic condition by dynamically changing gas flow and CO_2 fraction on a breath-by-breath basis.

QUIXOTIC MRI consisted of 1) venular-blood-weighted imaging at four effective echo times (TE_{EFF}): Vcutoff = 2 cm/s, TI= 725 ms, ΔTE_{EFF} = 18.4 ms, 80 measurements per TE_{EFF}, TR = 4s [3], 2) PICORE/Q2tips pulse arterial spin labeling (PASL) [4]: TI_1 = 700 ms, TI_1-stop = 1400 ms, TI_2 = 1600 ms, PASL tag width = 160 mm, TR = 2s, 120 measurements, and 3) Double inversion recovery (DIR): TI_1 = 3700 ms, TI_2 = 4280 ms, one slice, one measurement. Common to these three imaging sequences is a GRE-EPI readout (TE = 12 ms, Phase Partial Fourier 6/8, BW = 2232 Hz/pixel, matrix size = 64x64, single slice, voxel size = 3.9x3.9x10 mm^3) imaging an identical axial slice positioned superior to the corpus callosum.

The imaging protocol was first run during a normocapnic state and exactly repeated during hypercapnia. A 4.5 minute structural scan was inserted between these periods to allow subjects to reach steady-state respiration and end tidal CO_2 ($ETCO_2$). After conclusion of MRI scanning, hematocrit was measured via finger prick blood sample (UltraCrit, Separation Technologies, Altamonte Springs, Florida).

Data from (1) were subtracted and averaged [3] to produce mean venular-blood-weighted images at each TE_{EFF}. Using the DIR image to segment GM, cortical venular-blood signal intensity (SI) versus TE_{EFF} was exponentially fit to measure T_2. Venular-blood T_2 was calibrated to venular oxygen saturation (Y_v) using empirical and theoretical T_2 versus oxygen saturation relationships [5,6,7] incorporating the subject's hematocrit. The following equation calculated OEF: $(Y_a\text{-}Y_v)/Y_a$ [5], where Y_a is the arterial oxygen saturation measured by pulse oximetry. $CMRO_2$ was subsequently calculated via: $CMRO_2 = OEF \cdot CBF \cdot [Hb_{total}]$ [5], where CBF is estimated from PASL scans and $[Hb_{total}]$ calculated form hematocrit.

RESULTS:

Figure 1 displays representative venular-blood-weighted images at four TE_{EFF}s during normocapnia and hypercapnia. Clearly observable is the slower cortical SI decay in the hypercapnic series. Figure 2 graphs cortical SI versus TE_{EFF} on a log-lin plot, with T_2 fits for both normocapnia and hypercapnia. The substantially longer venular-blood T_2 for hypercapnia is indicated by the shallower slope of the fit curve. This longer T_2 calibrates to larger Y_v; aforementioned equations then calculate OEF and $CMRO_2$ (Table 1). A paired t-test for Y_v, CBF, and $CMRO_2$ shows that differences between normocapnia and hypercapnia are significant at p = 0.01, p = 0.0003, and p = 0.036, respectively. In sum, cortical Y_v and CBF show statistically significant increases during hypercapnia, while cortical OEF and $CMRO_2$ show statistically significant decreases during hypercapnia. Figure 3 depicts cortical GM $CMRO_2$ for all four subjects under the two states of capnia.

DISCUSSION:

By equation 2, the overall reduction in $CMRO_2$ arises from a profound OEF decrease compared to a moderate CBF increase during hypercapnia. This finding has important implications to clinical and functional applications of CO_2-challenge. Calibrated BOLD [8], for example, normalizes CBF and BOLD signals to the hypercapnic signal change and extrapolates relative $CMRO_2$. This process assumes that the hypercapnic BOLD signal is independent of $CMRO_2$; an assumption not supported by the results presented here. As a consequence, hypercapnic calibration may result in erroneous estimates of relative $CMRO_2$ and subsequently confound flow-metabolism observations. In stroke, BOLD CO_2 assesses so-called cerebral vascular reserve (CVR), the ratio of ΔCBF:ΔETCO2, and finds that abnormal CVR correlates to negative outcomes [9]. However, because of $CMRO_2$ depression, the hypercapnic BOLD response will be larger than a purely vascular BOLD response. CVR will be overestimated and could lead to incorrect and potentially dangerous conclusions. For example, a patient at increased risk may be overlooked because of an artificially inflated CVR. Further investigation is needed to better understand the implications of $CMRO_2$ depression during hypercapnia in both disease and functional MRI settings.

Table 1	Normocap	Hypercap	% change
T_2 (ms)	80.6	116.9	45.1
CBF (ml/100g-min)	57.9	76.6	32.2
Yv	0.720	0.840	16.7
OEF	0.273	0.152	-44.5
$CMRO_2$ (µmol/100g-min)	142.8	106.7	-25.3

This is the first time cortical GM $CMRO_2$ in awake humans has been evaluated in response to hypercapnia, a capability uniquely enabled by the QUIXOTIC technique. GM has by far the highest density of neural cell bodies in the brain, and as such houses the vast majority of neuronal signaling, energy consumption, and CBF [10]. As a consequence, $\Delta CMRO_2$ from these regions may be more informative than global measures that include WM and may underestimate neuronal and glial cell CO_2 sensitivity.

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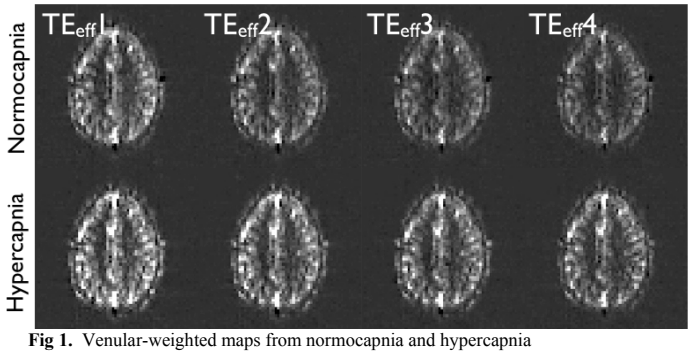

Fig 1. Venular-weighted maps from normocapnia and hypercapnia

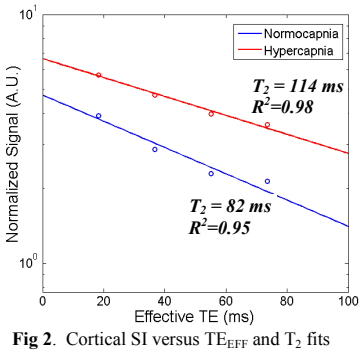

Fig 2. Cortical SI versus TE_{EFF} and T_2 fits

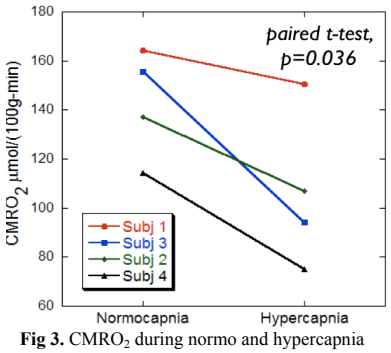

Fig 3. $CMRO_2$ during normo and hypercapnia