

RELATIONSHIP BETWEEN BRAIN TISSUE HAEMODYNAMICS, OXYGENATION AND METABOLISM IN THE HEALTHY HUMAN ADULT BRAIN DURING HYPEROXIA AND HYPERCAPNEA

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Abstract: This study investigates the relationship between changes in brain tissue haemodynamics, oxygenation and oxidised cytochrome-c-oxidase ([oxCCO]) in the adult brain during hyperoxia and hypercapnea. 10 healthy volunteers were studied. We measured the mean blood flow velocity of the right middle cerebral artery (V_{mca}) with transcranial Doppler (TCD) and changes in concentrations of total haemoglobin ([HbT]=[HbO₂]+[HHb]), haemoglobin difference ([Hbdiff]=[HbO₂]-[HHb]) and [oxCCO] with broadband near-infrared spectroscopy (NIRS). We also measured the absolute tissue oxygenation index (TOI) using NIR spatially resolved spectroscopy. During hyperoxia there was an increase in TOI ($2.33\pm 0.29\%$), [Hbdiff] ($4.57\pm 1.27\mu\text{M}$) and in the oxidation of [oxCCO] ($0.09\pm 0.12\mu\text{M}$); but a reduction in V_{mca} ($5.85\pm 4.85\%$) and HbT ($1.29\pm 0.91\mu\text{M}$). During hyperoxia there was a positive correlation between [oxCCO] and TOI and [Hbdiff] ($r=0.83$ and $r=0.95$) and a negative association between [oxCCO] and V_{mca} and [HbT] ($r=-0.74$ and $r=-0.87$). During hypercapnea there was an increase in TOI ($2.76\pm 2.16\%$), [Hbdiff] (7.36 ± 2.64), [HbT] ($2.61\pm 2.7\mu\text{M}$), V_{mca} ($14.92\pm 17.5\%$) and in the oxidation of [oxCCO] ($0.25\pm 0.17\mu\text{M}$). Correlation analysis shows that there was association between [oxCCO] and TOI, [Hbdiff] and [HbT] ($r=0.83$, $r=0.93$ and $r=0.82$) but not with V_{mca} ($r=0.33$). We conclude that an increase in [oxCCO] was seen during both challenges and it was highly associated with brain tissue oxygenation.

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1. INTRODUCTION

Measurement and monitoring of changes in haemodynamics, oxygenation and metabolism in the brain, reliably, non-invasively and at the bedside is an important aim in diagnosis and management of patients in neurocritical care. This may be achieved with a combination of two techniques, near-infrared spectroscopic (NIRS) and transcranial Doppler (TCD).

NIRS is a non-invasive technique which exploits the fact that biological tissue is relatively transparent to near infrared light allowing interrogation of the cerebral cortex by optodes placed on the scalp. Biological tissue is a highly scattering medium but if the average pathlength of light through tissue is known, the modified Beer-Lambert law,¹ which assumes constant scattering losses, allows calculation of absolute changes in chromophore concentration. NIRS has been used in animals and humans to measure the change in concentration of oxy-haemoglobin ($\Delta[\text{HbO}_2]$), deoxy-haemoglobin ($\Delta[\text{HHb}]$), and oxidized cytochrome oxidase ($\Delta[\text{oxCCO}]$).²⁻⁴ Cytochrome c oxidase (CCO) is the terminal electron acceptor of the mitochondrial electron transfer chain and catalyses over 95% of oxygen metabolism, thereby driving aerobic adenosine triphosphate (ATP) synthesis and playing a central role in the maintenance of mitochondrial function.⁵

Transcranial Doppler (TCD) is a non-invasive ultrasound technique which uses the Doppler shift from moving red blood cells to calculate cerebral blood flow velocity. TCD is not able to provide absolute measurements of cerebral blood flow (CBF), but if the angle of insonation and the diameter of the insonated vessel remain constant then changes in TCD measured cerebral blood flow velocity correlate with changes in CBF.⁶ Several studies have shown minimal changes in the diameter of basal cerebral arteries during various physiological challenges.⁷ Typically the TCD signal is acquired from the middle cerebral artery.

Hyperoxia and hypercapnea are routinely used as a treatment technique and an intracranial compliance test respectively in patients with brain injury. In the human brain the changes in brain blood flow and oxygenation during these challenges are well documented; however the changes in brain metabolism and their relationships are not.

In this study we use the combination of NIRS and TCD to investigate the relationship between changes in brain tissue haemodynamics, oxygenation and metabolism in the healthy human adult brain during hyperoxia and hypercapnea.

2. MATERIAL AND METHODS

This study was approved by the Joint Research Ethics Committee of the National Hospital for Neurology and Neurosurgery and the Institute of Neurology. We studied 10 healthy subjects (7 male, 3 female, median age 32 years, range 30-39).

The optodes from a broadband spectrometer (BBS) previously described by Tisdall et al.⁴ were placed 3.5 cm apart on the right side of the forehead. NIR spectra between 650 and 980 nm were collected at 1Hz with a spectral resolution of ~5nm. Absolute $\Delta[\text{oxCCO}]$, $\Delta[\text{HbO}_2]$, and $\Delta[\text{HHb}]$ were calculated from changes in light attenuation using a multiple regression technique termed the UCLn algorithm.⁸ Individual baseline optical pathlength was calculated using second differential analysis of the 740-nm water feature of the initial 60 seconds of spectral data.⁹ Change in total haemoglobin

concentration $\Delta[\text{HbT}]$ was defined as $\Delta[\text{HbO}_2] + \Delta[\text{HHb}]$ and change in haemoglobin difference concentration $\Delta[\text{Hbdiff}]$ as $\Delta[\text{HbO}_2] - \Delta[\text{HHb}]$.

The optodes from the NIRO 300 (Hamamatsu Photonics KK) were placed below the BBS optodes, with and interoptode spacing of 5cm and were used to measure absolute cerebral tissue oxygenation index (TOI) over the frontal cortex using the SRS technique¹⁰.

Blood flow velocity in the basal right middle cerebral artery was collected at 50 Hz using a 2 MHz transcranial Doppler ultrasonography (Pioneer TC2020, Nicolet, UK) fixed in place over the right temporal region. Mean velocity of the middle cerebral artery (Vmca) was calculated from the velocity envelope using a trapezoidal integration function (MatLab, Mathworks Inc.). A modified pulse oximeter probe (Novamatrix Medical Systems Inc., USA) measured SaO₂, and a Portapres finger cuff (Biomedical Instrumentation, TNO Institute of Applied Physics, Belgium) measured mean blood pressure (MBP). A modified anaesthetic machine was used to alter FiO₂ and EtCO₂ which were measured using an inline gas analyser (Hewlett Packard, UK) and a CO₂SMO optical sensor (Novamatrix Medical Systems Inc.) respectively.

During hyperoxia FiO₂ was increased to 100% for five minutes and then returned to normoxia for five minutes. The cycle was repeated three times and the subjects adjusted their minute ventilation to maintain normocapnea throughout the study. During hypercapnea approximately 6% carbon dioxide (CO₂) was added to the inspired gases and was titrated to induce an increase in EtCO₂ of 1.5kPa. The elevated EtCO₂ was maintained for ten minutes and the inspired carbon dioxide fraction was then returned to zero for a further five minutes. The start and end of each hyperoxia and hypercapnea period was identified from the FiO₂ and EtCO₂ data respectively. To enable description of the group data, each individual hyperoxia and hypercapnea was divided into equal time periods, with each time point representing an eighth of the total time course of the challenge. This produced nine time points with point 1 representing the point just prior to the start of the challenge and point 9 the end point of the challenge. The same technique was applied separately to the recovery period, producing points 9 just prior to start of recovery to 17 at the end of recovery period. At each time point, the mean of the preceding 10 seconds of data was calculated. For the hyperoxia challenge data from the three experimental cycles were averaged to give a single course of hyperoxia and recovery for each subject. Group mean changes from baseline at each time point were produced. Statistical analysis was carried out using the SPSS software (version 13 for windows) and p values ≤ 0.05 were considered significant. Group changes were compared with baseline using a two-tail Student's t-test. Correlations between variables were assessed by applying Spearman rank correlation to data from the 9 time points start to the end of challenge.

3. RESULTS

Group summary data are shown in Figure 1 and correlation analysis shown in Figure 2. During hyperoxia there was a significant increase in TOI ($2.33 \pm 0.29\%$), [Hbdiff] ($4.57 \pm 1.27 \mu\text{M}$) and in the oxidation of [oxCCO] ($0.092 \pm 0.117 \mu\text{M}$); but a reduction in Vmca ($5.85 \pm 4.85\%$) and [HbT] ($1.29 \pm 0.91 \mu\text{M}$). Correlation analysis shows a high positive association between [oxCCO] and TOI and [Hbdiff] ($r=0.83$ and $r=0.95$) and a high negative association between [oxCCO] and Vmca and [HbT] ($r=-0.74$ and $r=-0.87$).

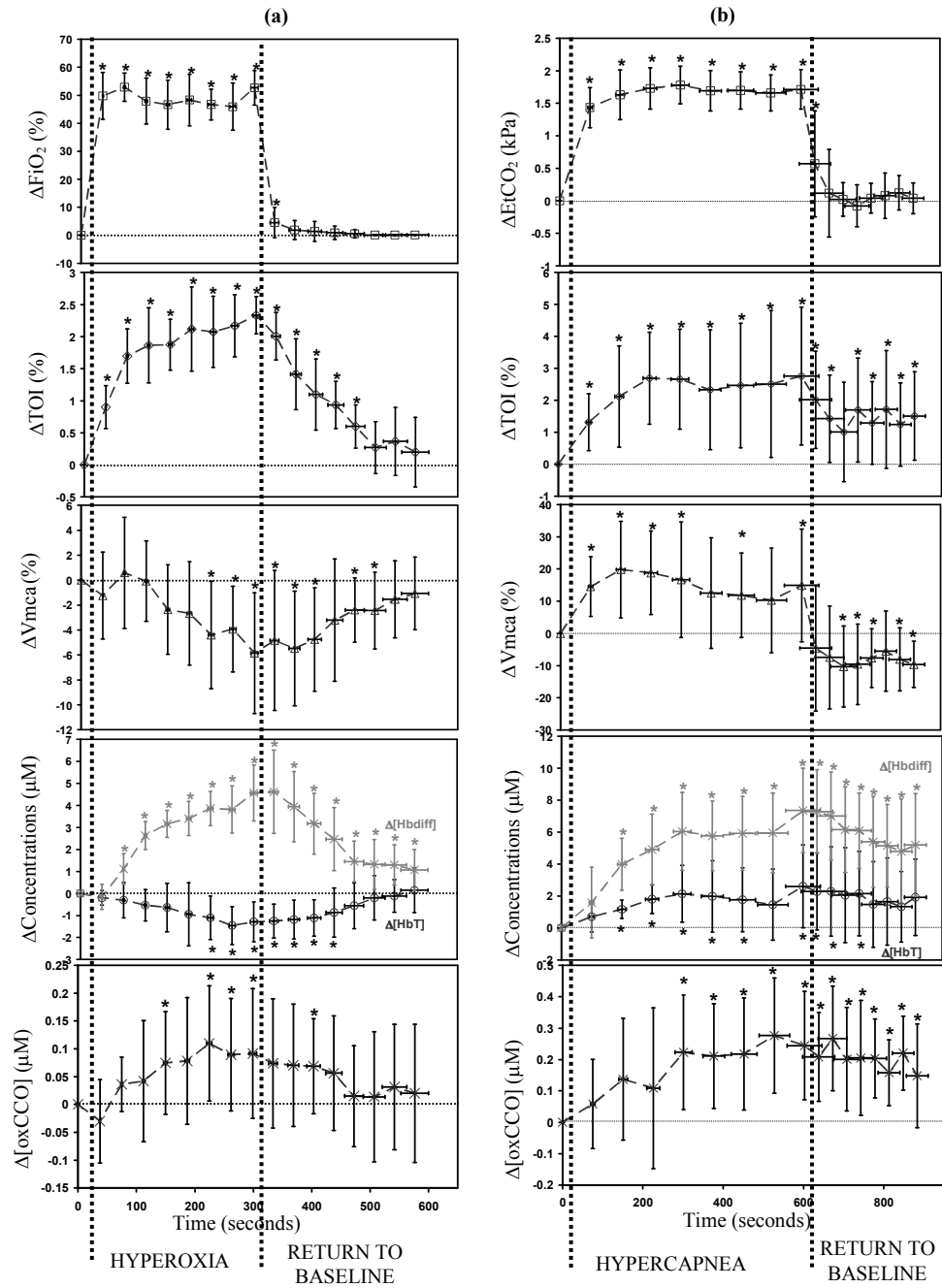


Figure 1. Mean and standard deviation ($n=10$) for monitored variables during (a) hyperoxia and (b) hypercapnea ($*p \leq 0.05$ for changes from baseline).

During hypercapnea there was an increase in TOI ($2.76 \pm 2.16\%$), [Hbdiff] ($7.36 \pm 2.64 \mu\text{M}$), HbT ($2.61 \pm 2.6 \mu\text{M}$), Vmca ($14.91 \pm 17.49\%$) and in the oxidation of [oxCCO] ($0.245 \pm 0.172 \mu\text{M}$). Correlation analysis showed that there was a linear association between [oxCCO] and TOI, [Hbdiff] and HbT ($r=0.83$, $r=0.93$ and $r=0.82$) but not between [oxCCO] and Vmca ($r=0.33$).

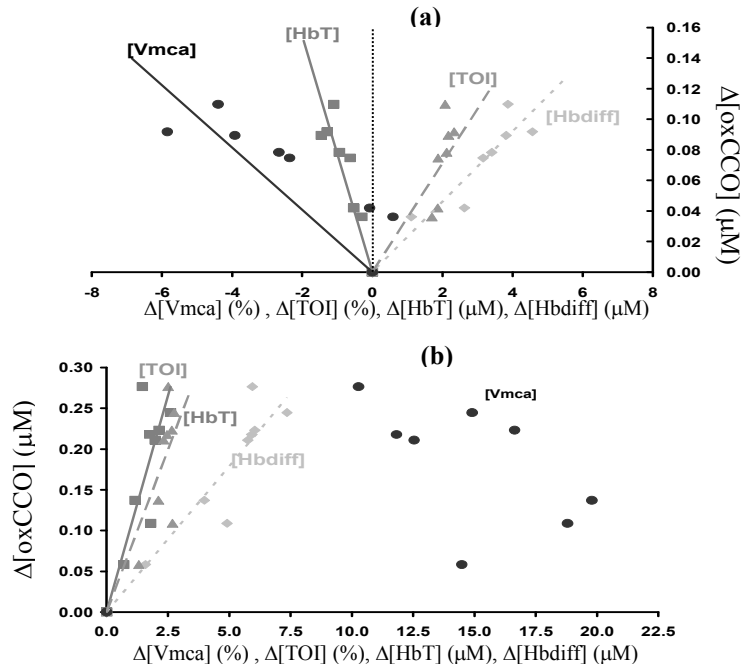


Figure 2. Scatter plot using group mean changes ($n=10$) from baseline to the end of (a) hyperoxia and (b) hypercapnea. Lines show the linear regression estimation between $\Delta[\text{oxCCO}]$ and each variable.

4. DISCUSSION

We investigated two paradigms that increase cerebral oxygen delivery to the healthy adult brain by different methods – increase in arterial oxygen content (hyperoxia) and increase in cerebral blood flow (hypercapnea). A significant decrease in Vmca and [HbT] during hyperoxia confirmed blood flow reduction, presumably related to the known vasoconstrictive effects of 100% oxygen; and an increase in both Vmca and [HbT] during hypercapnea confirmed the known increase in CBF secondary to rises in PaCO_2 . In both cases, however, oxygen delivery seemed to increase as evidenced by the rise in TOI and [Hbdiff] – the rise in arterial oxygen content in hyperoxia more than compensating for the drop in flow. Both scenarios showed an increase in the oxidation of the mitochondrial cytochrome oxidase CuA centre ([oxCCO]). *In-vivo* studies in animals confirm that cerebral CCO can be oxidised by increases in oxygenation induced by hypercapnea or reactive hyperaemia.^{2,11} Our data support the conclusion that, at normoxic normocapnea, cerebral CCO is not fully oxidized in the human adult and that further oxidation is possible.

In order to further investigate the above claim, correlation analysis was done between the haemodynamic, oxygenation and [oxCCO] variables. We found high correlations in the hyperoxia challenge between the changes in flow velocity, oxygenation and [oxCCO]; however during the hypercapnea challenge no association was found between flow velocity and [oxCCO]. CCO oxidation state is affected by factors other than oxygen tension, for example electron flux through the enzyme, pH changes and changes in ADP concentration.^{12,13} In the case of hyperoxia it is difficult to see these other factors being as important as the rise in oxygenation and we may be seeing a direct effect of oxygen on CCO in this case. However, changes in CO₂ will have metabolic effects further to the changes in oxygenation most notably to cause a decrease in pH. It is possible that the oxidation of [oxCCO] during hypercapnea may also be related to secondary metabolic effects, whereas those of hyperoxia are more likely to be direct effects of oxygen tension.

5. ACKNOWLEDGMENTS

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