

MEASUREMENT OF CEREBRAL TISSUE OXYGENATION IN YOUNG HEALTHY VOLUNTEERS DURING ACETAZOLAMIDE PROVOCATION: A TRANSCRANIAL DOPPLER AND NEAR-INFRARED SPECTROSCOPY INVESTIGATION

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Abstract: Recent advances in near-infrared spectroscopy (NIRS) allow measurements of absolute tissue oxygen saturation (TOI) using spatially resolved spectroscopy (SRS), while enabling better depth sensitivity. However concerns remain regarding the relative contribution of the extracranial circulation to the cerebral NIRS TOI signal. In this study we investigated this during a period of selective rise in cerebral blood flow (CBF) produced by the administration of acetazolamide (ACZ) in 10 healthy volunteers. A two channel spectrometer (NIRO 300, Hamamatsu Photonics KK) was used to measure absolute cerebral TOI over the frontal cortex using the SRS technique using an optode spacing of 5cm and 1.5cm for channel 1 and 2 respectively. After ACZ administration we were able to observe a significant increase in the velocity of middle cerebral artery (V_{mca} , measured with the transcranial Doppler (TCD)) which was accompanied by an increase in TOI as monitored by the NIRO 300 with an optode spacing of 5cm but not with an optode spacing of 1.5cm. Furthermore a direct relationship was seen between the V_{mca} and the TOI measured at 5cm optode spacing. This work suggests that using this commercial NIRS instrument with an optode spacing of 5cm one is able to detect the intracranial changes.

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1. INTRODUCTION

Near-infrared spectroscopy (NIRS) has been widely used to evaluate changes in cerebral oxygenation and blood volume non-invasively. The technique involves near-infrared emitting and detecting optical probes placed on the scalp, transmitting light through cerebral as well as extracerebral tissues, such as skin, cranial bone, and cerebrospinal fluid (CSF). It is obvious that the position and volume of the interrogated tissue will depend on the position and spacing of the source and the detection fibres and results from mathematical modelling of light transport in tissue suggest that the average penetration depth of the detected near-infrared (NIR) light in the tissue increases with probe separation.¹⁻³ As a result, it is believed that oxygenation changes in deeper tissues of the brain can be detected with large optode spacing.^{4,5}

Recent advances in NIRS technology allow measurements of absolute tissue oxygen saturation (TOI) using spatially resolved spectroscopy (SRS),⁶ while enabling better depth sensitivity.⁷ However concerns remain regarding the relative contribution of the extracranial circulation to the cerebral NIRS TOI signal. The aim of this study was to investigate whether cerebral tissue oxygenation monitored using spatially resolved NIRS reflects changes in intracranial haemodynamics. This was done by monitoring the NIR derived cerebral tissue oxygenation signal using two different inter-optode spacings during a period of selective rise in cerebral blood flow produced by the administration of acetazolamide (ACZ).

2. METHOD

2.1 Subjects

After local ethics committee approval and written informed consent, 10 healthy volunteers (7 men and 3 women; age 27 to 33 years; mean 29.6 years) took part in this study.

2.2 Instrumentation

Figure 1 shows a schematic of the experimental set up. Middle cerebral artery flow velocity (V_{mca}) was measured in the basal right middle cerebral artery using a transcranial Doppler ultrasonography instrument (Pioneer Nicolet Biomedical Inc). After artery identification a permanently fixed 2-MHz probe was used. The envelope velocity was collected at 50Hz sampling rate and the mean V_{mca} was calculated every second using a trapezoidal integration function (MatLab Mathworks Inc).

A two channel continuous wave near-infrared spectrometer (NIRS), with a sampling rate of 6Hz (NIRO 300, Hamamatsu Photonics KK) was used to measure absolute cerebral TOI over the frontal cortex using the SRS technique. The optodes were placed on the forehead (taking care to avoid the midline sinuses) and were secured in position by using an elastic bandage. The optodes for Channel 1 were placed over the right frontal lobe with an optode spacing of 5cm; this measurement of TOI was termed 'Head TOI'. The optodes for Channel 2 were placed over the left frontal lobe with an optode spacing of 1.5cm. This measurement of TOI was termed 'Superficial TOI'. Optical attenuators were used where necessary to optimise the signal to noise ratio.

Skin blood perfusion in the forehead was measured with a laser Doppler system (Moor Instruments). The laser Doppler probe was placed on the left forehead at the height of the eyebrows. The laser Doppler flux signal (the product of skin blood concentration and erythrocyte velocity) was collected continuously with a sampling rate of 50Hz.

End tidal CO₂ (EtCO₂) was measured continuously (1Hz sampling rate) with nasal prongs (HP Merlin). Mean blood pressure (MBP) was monitored using the Portapres® system, which uses small finger cuffs to continuously and non-invasively measure the blood pressure waveform.

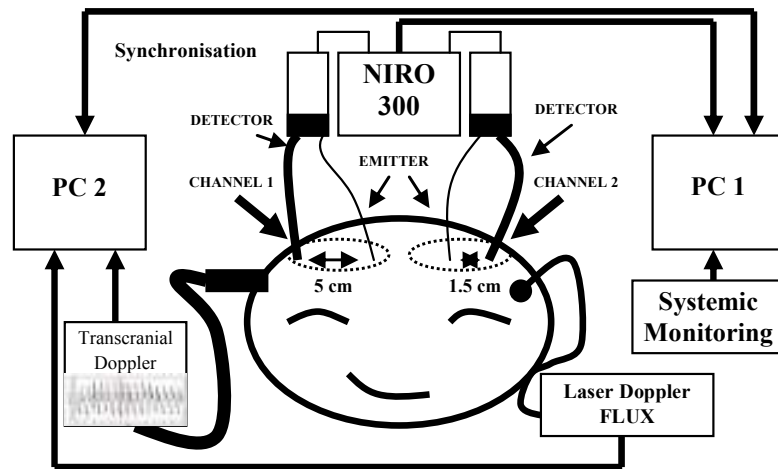


Figure 1. Schematic representation of the experimental set up showing also the placement of the probes on the forehead.

2.3 Procedure

Five minutes resting baseline data were recorded. All volunteers were then given 1 g of ACZ. ACZ was injected intravenously over a 2 minute period with the subject resting in a semi-recumbent position. Monitoring continued for 20 minutes post ACZ administration.

2.4 Analysis

The data from all instruments was collected and resampled to 1 point per minute (0.016Hz) using a cubic interpolation function (MatLab Mathworks Inc.). This optimised data handling without losing the temporal resolution of the ACZ response. Data was then normalised to the start of the ACZ injection. Figure 2 shows typical data from one volunteer during the 25 minute study.

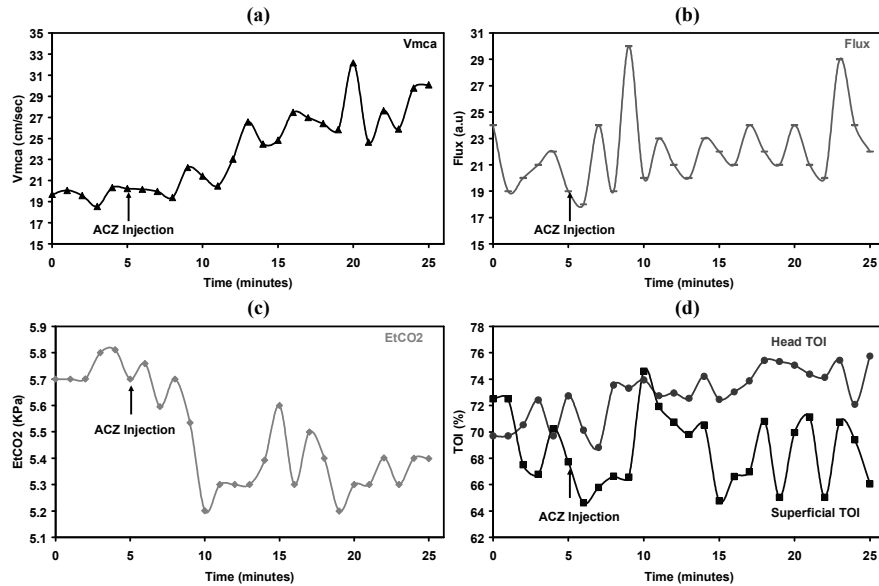


Figure 2. Typical data from one volunteer. (a) EtCO₂ (b) Skin blood perfusion (c) Middle cerebral artery flow velocity (d) NIRS Tissue oxygenation index.

Group data is presented as mean \pm standard deviations. All p values were calculated for two-tailed tests of significance, and differences were considered statistically significant from baseline at $p < 0.05$. Correlations between variables were analysed using the Pearson coefficient.

3. RESULTS

Group summary data is shown in Figure 3. Mean V_{mca} before the ACZ injection was 48.6 ± 28.1 cm/s; the maximum increase in velocity was 21.8 ± 10.3 cm/s which was equal to a mean increase of 51 ± 17 % ($p < 0.01$ from baseline). The mean V_{mca} at the end of the study was 63.3 ± 30.6 cm/s. The mean Head TOI before the ACZ injection was 70.1 ± 3.5 %; the maximum increase was 1.8 ± 2.4 % ($p < 0.05$ from baseline). The EtCO₂ at baseline was 5.1 ± 0.6 kPa; the maximum decrease was 0.8 ± 0.5 kPa ($p < 0.01$ from baseline) which was reached 20 minutes after the injection.

No statistical differences were seen in the laser Doppler perfusion signal, the mean blood pressure and the mean Superficial TOI.

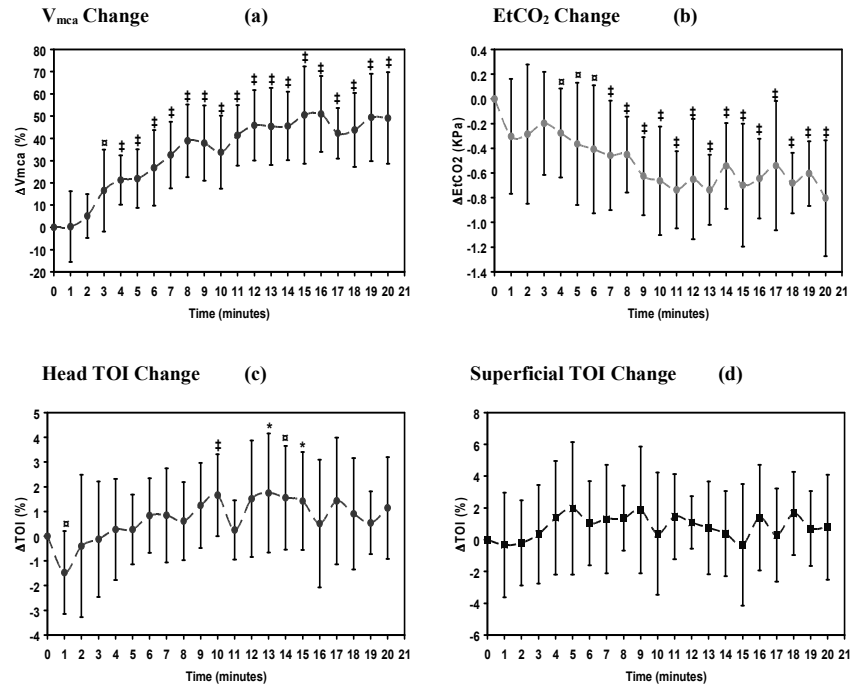


Figure 3. Group summary data (a) Percentage changes in V_{mca} (b) Changes in $EtCO_2$ (c) Changes in Head TOI (d) Changes in the Superficial TOI. (t-test from baseline; * $p < 0.05$ † $p < 0.03$ ‡ $p < 0.01$)

The relationship between the group mean percentage changes in V_{mca} and the mean cerebral Head TOI changes show a significant association ($r=0.77$, $p < 0.01$), no correlation was seen with the Superficial TOI. These results are shown in Figure 4.

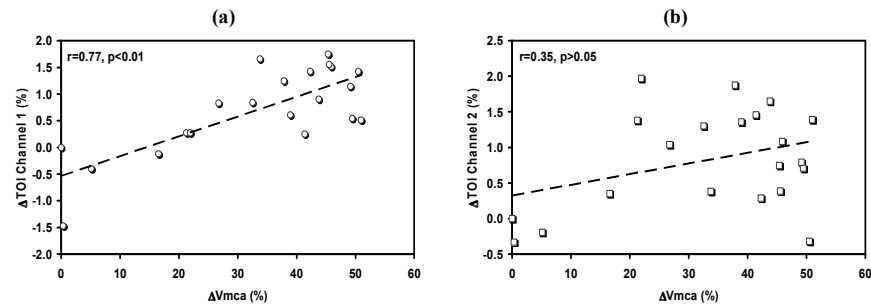


Figure 4. Correlation analysis of the group summary data (a) Changes in Head TOI with percentage changes in V_{mca} (b) Changes in Superficial TOI with percentage changes in V_{mca} .

4. DISCUSSION

In this study a significant rise in the V_{mca} and Head TOI were observed after ACZ injection (see Table 1). These results are similar with a previous study from Kaminogo et al.⁸ who found a mean increase in V_{mca} of 44 % and in regional cerebral oxygenation of 5.4 % using the INVOS-3100 spectrometer (Somanetics Corp).

Skin blood flow and the Superficial TOI did not show any significant rise after the ACZ injection. These results agree with the study of Kohri et al.⁹ who observed a significant increase in the head tissue oxygenation (optode distance 4cm) of 2.4% but no increase in the superficial tissue oxygenation (optode distance 2cm) using a combination of a spatially- and time-resolved NIRS system.

Maximum Changes (Mean \pm SD)	
ΔV_{mca} (%)	51 \pm 17.1
$\Delta EtCO_2$ (KPa)	-0.8 \pm 0.5
Head Δ TOI (%)	1.8 \pm 2.4

Table 1. Maximum mean changes for all the volunteers.

The changes in the Head TOI were not as large as the changes seen in the V_{mca} signal. This may be because the NIRS TOI signal represents a combination of arterial, capillary and venous oxygen saturation and volume data (Eq. 1). Cranial NIRS interrogates a multi-compartmental system of arteries, arterioles, capillaries, venules and veins; the NIRS TOI, is the average ratio of oxygenated to total tissue haemoglobin concentrations in all these compartments. In order to investigate the origins of the Head TOI signal it is useful to simplify the above multi-compartmental system and it is usual to consider just two compartments, one arterial and one venous, with a typical arterial:venous volume ratio $V_a:V_v$ of 25% to 75% in a healthy adult brain.¹⁰ By considering the definitions of arterial oxygen saturation ($SaO_2 = [HbO_2]_{art}/[HbT]_{art}$) and venous oxygen saturation ($SvO_2 = [HbO_2]_{ven}/[HbT]_{ven}$), where $[HbO_2]$ is oxygenated haemoglobin and $[HbT]$ is the total haemoglobin, we have:

$$TOI = SaO_2 \cdot \frac{V_a}{V_a + V_v} + SvO_2 \cdot \frac{V_v}{V_a + V_v} \quad (\text{Eq. 1})$$

One now can replace SvO_2 in Eq. 1 by considering the definition of the Fick equation¹¹ shown below:

$$SvO_2 = SaO_2 - \frac{CMRO_2}{k \cdot CBF \cdot [Hb \cdot 10^{-2}]} \quad (\text{Eq. 2})$$

where $CMRO_2$ is the oxygen consumption (in ml of Oxygen/min), k is the oxygen combining power of Hb (~ 1.306 ml of Oxygen/g of Hb) and CBF is cerebral blood flow (in ml/min) and Hb is the haemoglobin (in g of Hb/dL of blood). Therefore:

$$\text{TOI} = \text{SaO}_2 - \left(\frac{V_v}{V_a + V_v} \right) \cdot \left(\frac{\text{CMRO}_2}{k \cdot \text{CBF} \cdot [\text{Hb} \cdot 10^{-2}]} \right) \times 100\% \quad (\text{Eq. 3})$$

Equation 3 demonstrates the direct relationship of the NIRO 300 TOI signal with the arterial/venous volume ratio, oxygen consumption and the indirect relationship with CBF.

ACZ is a selective inhibitor of carbonic anhydrase, which reversibly catalyses the conversion of $\text{CO}_2 + \text{H}_2\text{O} \leftrightarrow \text{H}_2\text{CO}_3$. It therefore causes an increase in the H^+ , HCO_3^- and CO_2 concentrations in the extracellular fluid of the brain, which are assumed to be the stimuli for the increase in CBF.¹² Bearing in mind Eq. 3 and with the knowledge that ACZ markedly increases CBF without any changes in oxygen consumption¹³ or arterial oxygen saturation, it is possible that an increase in the venous volume ratio will attenuate the increase in TOI resulting from the rise in CBF. Furthermore each of the cerebral haemodynamics compartments has different saturations and volumes which may respond differently to ACZ causing a possible change in the $V_a:V_v$.

5. CONCLUSIONS

After ACZ administration we were able to observe a significant increase in CBF (measured with the transcranial Doppler) which was accompanied by a small increase in absolute tissue oxygenation as monitored by the NIRO 300 with an optode spacing of 5 cm but not with an optode spacing of 1.5 cm. Furthermore a direct relationship was seen between the changes in V_{mca} and the Head TOI. This work suggests that using this commercial NIRS instrument with an optode spacing of 5cm one is able to detect the intracranial changes. Further experimental work is needed to determine the relationship between TOI, CBF, CBV and CMRO_2 .

6. ACKNOWLEDGMENTS

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7. REFERENCES

1. G.H. Weiss, R. Nossal, R.F. Bonner, "Statistics of penetration depth of photons re-emitted from irradiate tissue" *J. Mod. Opt.* **36**, 349-359 (1989).
2. C. Cui, C. Kumar, B. Chance, "Experimental study of migration depth for the photons measured at sample surface" *Proc SPIE* **1431**, 180-191 (1991).
3. E. Okada, M. Firbank, D.T. Delpy, "The effect of overlying tissue on the spatial sensitivity profile of near-infrared spectroscopy" *Phys. Med. Biol.* **40**, 2093-2108 (1995).
4. D.N.F. Harris, F.M. Cowans, D.A. Wertheim, S. Hamid, "NIRS in adults – effects of increasing optode separation" *Adv. Exp. Med. Biol.* **345**, 837-840 (1994).
5. E. Okada, D.T. Delpy, "Near-infrared light propagation in an adult head model. I. Modelling of low-level scattering in the cerebrospinal fluid layer" *Applied Optics* **42**(16), 2906-2914 (2003).
6. S. Suzuki, S. Takasaki, T. Ozaki, and Y. Kobayashi, "A tissue oxygenation monitor using NIR spatially resolved spectroscopy," *Proc. SPIE* **3597**, 582-592 (1999).

7. P.G. Al Rawi, P. Smielewski, P.J. Kirkpatrick, "Evaluation of a near-infrared spectrometer (NIRO 300) for the detection of intracranial oxygenation changes in the adult head," *Stroke* **32**, 2492-2500 (2001).
8. M. Kaminogo, A. Ichikura, S. Shibata, T. Toba, and M. Yonekura, "Effect of acetazolamide on regional cerebral oxygen saturation and regional cerebral blood flow," *Stroke* **26**, 2358-2360 (1995).
9. S. Kohri, Y. Hoshi, M. Tamura, C. Kato, Y. Kuge, N. Tamaki, "Quantitative evaluation of the relative contribution ratio of cerebral tissue to near-infrared signals in the adult human head: a preliminary study" *Physiol. Meas.* **23**, 301-312 (2002).
10. H. An, and W. Lin, "Cerebral venous and arterial blood volumes can be estimated separately in humans using magnetic resonance imaging," *Magn. Reson. Med.* **48**, 583-588 (2002).
11. G.A. Dienel, "Energy generation in the central nervous system," *Cerebral blood flow and metabolism*, Edvinsson L. and Krause D.N., eds., (Lippincott Williams & Wilkins, Philadelphia, 2001), 140-161.
12. N.A. Lassen, "Is central chemoreceptor sensitive to intracellular rather than extracellular Ph?" *Clin. Physiol.* **10**(4), 311-319 (1990).
13. S. Vorstrup, L. Henriksen, O.B. Paulson, "Effect of acetazolamide on cerebral blood flow and cerebral metabolic rate of oxygen" *J. Clin. Invest.* **74**, 1634-1639 (1984).