Analysis of the Changes in the Oxidation of Brain Tissue Cytochrome c Oxidase in Traumatic Brain Injury Patients during Hypercapnoea: a Broadband NIRS Study

Ilias Tachtsidis[1], Martin M. Tisdall[2], Caroline Pritchard[2], Terence S. Leung[1], Arnab Ghosh[2], Clare E. Elwell[1], Martin Smith[1, 2]

[1] Biomedical Optics Research Laboratory, Department of Medical Physics and Bioengineering, University College London, Gower Street, London WC1E 6BT,[2]Neurocritical Care Unit, The National Hospital for Neurology and Neurosurgery, University College London Hospitals, Queen Square, London, UK

Abstract   Using broadband near-infrared spectroscopy (NIRS) and cerebral microdialysis (MD) we investigated cerebral cellular metabolism and mitochondrial redox states, following hypercapnoea in 6 patients with traumatic brain injury (TBI). In all patients hypercapnoea increased intracranial pressure and cerebral blood flow velocity measured with transcranial Doppler. Despite the likely increase in cerebral oxygen delivery, we did not see an increase in the oxidation status of cytochrome-c-oxidase [oxCCO] in every patient. Analysis of the NIRS data demonstrated two patterns of the changes; Group A (n=4) showed an increase in [oxCCO] of $0.34(\pm0.34)\mu M$ and Group B (n=2) a decrease of $0.40(\pm0.41)\mu M$. Although no obvious association was seen between the Δ[oxCCO] and the MD measured changes in lactate and pyruvate concentrations, further work using model informed data interpretation may be helpful in understanding the multimodal signals acquired in this heterogeneous patient group.

1 Introduction

Secondary cerebral damage after traumatic brain injury (TBI) is a multi-factorial process with two components being of key importance - reduction in oxygen delivery below critical thresholds and failing cellular metabolism leading to an inability to utilise delivered oxygen and glucose. Global and regional derangements of cerebral oxygen delivery and utilisation often occur after TBI, rendering the brain susceptible to secondary injury processes. Modern protocolized TBI management strategies use a variety of modality techniques to monitor the injured

brain and guide treatment. In addition within the context of attempting to minimise secondary injury after TBI, it appears vital to ensure adequate O_2 delivery to cerebral mitochondrial [1].

Hypercapnoea causes cerebral vasodilatation and would therefore be expected to increase cerebral oxygen delivery and, in turn, promote cerebral glucose utilization and oxidative metabolism to ensure maintenance of tissue high-energy phosphate reserves [2]. Using broadband near-infrared spectroscopy (BBS), we have recently demonstrated an increase in aerobic metabolism in the healthy human brain following hypercapnoea and hyperoxia [3] and during normobaric hyperoxia (NBH) after TBI [4]. The aim of this study was to investigate whether hypercapnoea also cause changes in cellular and mitochondrial redox state in TBI.

2 Methods

This study was approved by the Joint Research Ethics Committee of the National Hospital for Neurology and Neurosurgery and the Institute of Neurology. As all patients were unconscious at the time of the study, written assent was obtained from their personal representatives. 6 adult patients (5 male and 1 female) with a mean age of 40 years (range 22-51 years) were recruited into the study. The mean time between injury and study was 106 hours (range 38-298 hours).

Multimodality brain monitoring included intracranial pressure (ICP, Microsensor, Codman), brain tissue O_2 tension (PbrO$_2$, Licox PMO, Integra Neurosciences) and cerebral microdialysis. Microdialysate glucose, lactate and pyruvate concentrations were measured at the bedside using a CMA 600 analyser (CMA Microdialysis, Slona, Sweden). The mean blood flow velocity in the basal middle cerebral artery (Vmca) was measured using 2MHz transcranial Doppler ultrasonagraphy (Pioneer TC2020, Nicolet), as a surrogate of cerebral blood flow (CBF) [5]. For the purpose of this study the BBS optodes were placed 3.5cm apart in a black plastic holder and fixed to the upper forehead near to the invasive cerebral monitoring. The BBS system has been described elsewhere [6]; briefly near-infrared spectra between 650 and 980nm were collected at 1Hz with a spectral resolution of 5 nm. Absolute changes in concentrations of oxidised minus reduced cytochrome-c-oxidase ([oxCCO]), and oxygenated and deoxygenated haemoglobin concentrations ([HbO$_2$] and [HHb]) were calculated from changes in light attenuation. Correction factors for the wavelength dependence of the optical pathlength were applied to the chromophore absorption coefficients. The individual optical pathlength was calculated continuously using the second differential analysis of the 740nm water feature of the spectral data [7]. Change in total haemoglobin concentration ([HbT]) was derived from the sum of Δ[HbO$_2$] and Δ[HHb].

All patients received local protocolised intracranial pressure (ICP) and cerebral perfusion pressure (CPP) directed management based on international consensus guidance. During a period of cardiovascular stability, and whilst the patients were

being mechanically ventilated, the minute ventilation was reduced in a stepwise manner to produce an increase in $PaCO_2$ of approximately 1.5kPa. Cerebral microdialysate (MD) specimens were collected and analysed at intervals of 15-20min and arterial blood gases (ABG) for measurements of arterial carbon dioxide tension ($PaCO_2$) and glucose concentrations were measured at intervals of 15-30min. All monitored variables were recorded on a personal computer and synchronised. Summary data were produced for the 2 phases of the study: baseline and hypercapnoea. For the continuous measured variables ([HbT], [oxCCO], ICP and Vmca) a 10 min mean and standard deviation for each phase were calculated, centred on the time of the ABG and MD sampling within that phase. Changes in the continuously measured variables between baseline and hypercapnoea were compared using a Student's paired t-test (significance at $p < 0.05$). Results are presented as mean $\pm$standard deviation.

3 Results

Group analysis demonstrated a significant mean increase in ICP (8.2±4.2mmHg), Vmca (25±18%), Δ[HbT] (4.02±4.91μM) and Δ[oxCCO] (0.1±0.5μM) during hypercapnoea. However not all patients demonstrated an increase Δ[oxCCO]; post-hoc analysis demonstrated two patterns of change in Δ[oxCCO] in response to hypercapnoea. Group A had an increase of 0.34±0.34μM and Group B a decrease of -0.40±0.41μM (Figure 1and Table 1). Figure 2 shows a typical example of the changes recorded from a patient from each group. In Group A $PaCO_2$ was significantly increased from baseline by 1.5±0.8kPa, ICP by 8.9±4.6mmHg, [HbT] by 3.27±5.73μM and Vmca by, 22±11.3%. In Group B $PaCO_2$ was significantly increased from baseline by 2.1±1.1kPa, ICP by 6.8±4.5mmHg, [HbT] by 5.53±3.92μM and Vmca by 31±34.3%.

Table 1 Summary values for measured variables in Group A (4 patients) and Group B (2 patients) during baseline and hypercapnoea. Data presented as mean ±standard deviation.

	Group A (n=4)		Group B (n=2)	
	Baseline	Hypercapnoea	Baseline	Hypercapnoea
$PaCO_2$ (kPa)	4.6(0.2)	6.1(0.7)	3.9(1.1)	6.0(0.0)
ΔVmca (%)	-	22(11.3)*	-	31(34.3)*
ICP (mmHg)	14.5(4.0)	23.4(7.9)*	7.5(5.5)	14.3(0.9)*
LPR	23(10.1)	23(10.1)	20(5.5)	20(7.3)
Lactate (mM)	4.9(2.7)	4.6(2.6)	3.4(1.6)	2.7(1.0)
Pyruvate (μM)	209(27.3)	193(41.2)	166(32.5)	137(0.7)
Δ[oxCCO] (μM)	-	0.34(0.34)*	-	-0.40(0.41)*

LPR is the lactate/pyruvate ratio; *Student's paired t-test significance $p < 0.05$.

There was no association between the Δ[oxCCO] and the MD changes in lactate and pyruvate at any time. However, during hypercapnoea the mean MD lac-

tate and pyruvate concentrations in Group A lay within reported normal levels and in Group B were at the low end and below reported normal levels respectively [8].

4 Discussion

We have previously demonstrated that an increase in cerebral oxygen delivery secondary to hypercapnoea and hyperoxia results in an increase in aerobic metabolism in the healthy human brain [3]. We have also observed that NBH after TBI resulted in an increase in [oxCCO] consistent with an increase in aerobic metabolism secondary to the induced increase in cerebral oxygen delivery [4]. Hypercapnoea would be expected to increase cerebral oxygen delivery via an increase in cerebral blood flow (CBF). However, despite the increase in Vmca and [HbT] in all patients in this study, only four of the six patients showed an increase in the oxidation status of [oxCCO]. Interestingly, and unlike the situation with NBH, changes in MD measured metabolic variables were not associated with the changes in the oxidation status of [oxCCO].

Unlike the effects of hyperoxia, hypercapnoea has multiple effects on cerebral physiology including CBF, pH, nitric oxide (NO) concentration and cerebral oxygen consumption ($CMRO_2$) and these might explain the variability of our results [9]. Also there is wide heterogeneity of pathophysiological changes after TBI, both between and within patients. In the latter, it is also important to note that global and regional changes also evolve with time or in response to treatment [10]. In individual patients, metabolic supply and demand varies substantially; hypermetabolism, therapeutic sedation leading to reduced metabolic requirements or mitochondrial dysfunction may all be present. Due to the large variation between the injury and the time of the study in our patient group the above variations could have affected our results. Further work is required to determine the relationship between changes in the continuous optically measured metabolic variable [oxCCO] (which demonstrated two distinct patterns of change in response to increased cerebral oxygen delivery after hypercapnoea), and the non continuous MD variables lactate and pyruvate. To investigate this we have recently developed a mathematical model to interpret and predict cerebral physiological and biochemical variables [11]. It is possible that, through the use of a combination of multimodal data collection and model informed data interpretation, we will be able to increase our understanding of our measurements, characterize pathophysiological changes after TBI and potentially identify monitor-based, individualized treatment strategies.

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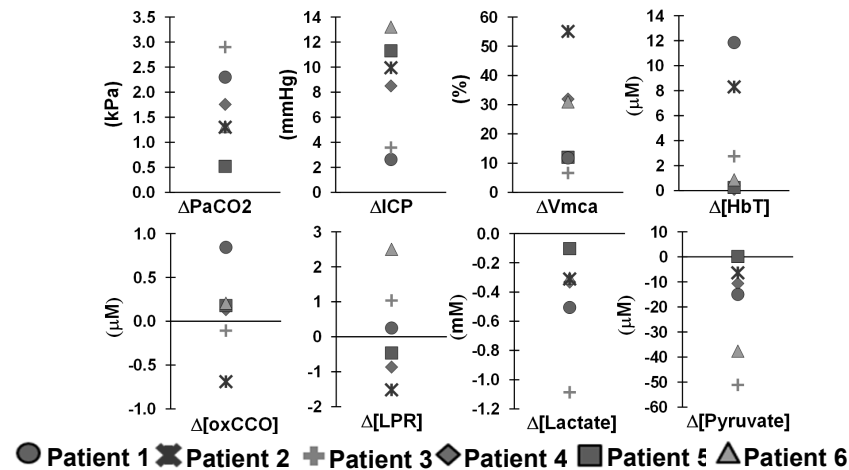
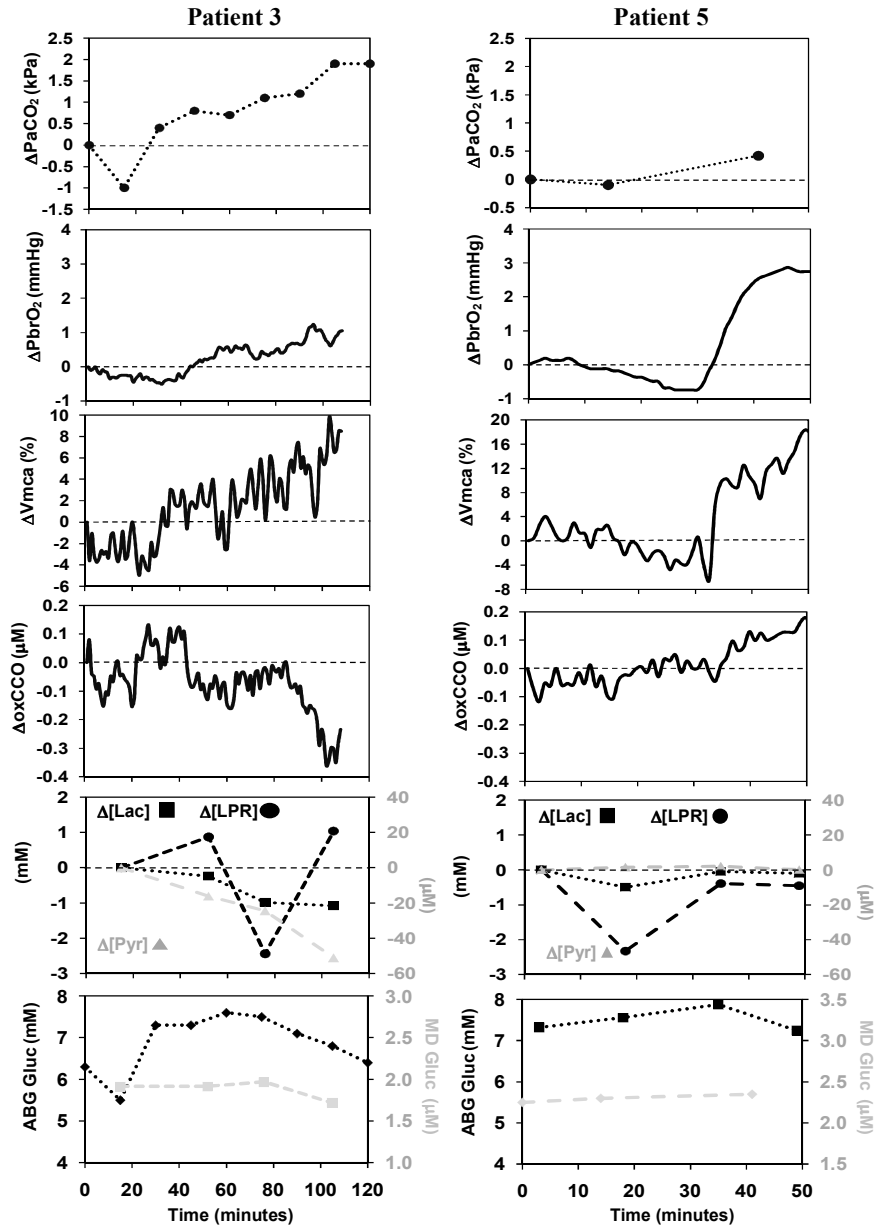**Fig. 1** Mean changes from baseline for each TBI patient.

Fig. 2 In patient 3 intracerebral lactate and pyruvate concentrations dropped and significant reduction in oxCCO was also observed. In patient 5 there were no changes in lactate and pyruvate and a significant oxidation in oxCCO was seen. Even though the intracerebral oxygenation levels increased in both patients as seen by the measured PbrO$_2$ significant differences were observed in the metabolic variables suggesting a possible decrease in aerobic metabolism in patient 3.