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Monitoring of Cerebral Blood Flow and Metabolism in Traumatic Brain Injury

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ABSTRACT

The aim of the present study was to investigate the course of cerebral blood flow (CBF) and metabolism in traumatic brain injury (TBI) patients and to specifically characterize the changes in lactate and glucose indices in the acute post-traumatic period with regard to neurological condition and functional outcome. For this purpose, 55 consecutive TBI patients (mean age 37 ± 17 years, mean GCS 6.8 ± 3.2) were prospectively and daily evaluated. Global CBF, cerebral metabolic rates of oxygen (CMRO2), glucose (CMRGlc), and lactate (CMRLct) were calculated using arterial jugular differences. In all patients, CBF was moderately decreased during the first 24 h in comparison with normal subjects although this relative oligemia was more pronounced in patients with poor outcome ($p = 0.0007$). Both CMRO2 and CMRGlc were significantly depressed and correlated to outcome ($p < 0.0001$, $p = 0.0088$). CMRLct analysis revealed positive values (lactate uptake) during the first 48 h, especially in patients with favorable outcome. Both CMRO2 and CMRLct correlated with GCS ($p = 0.0001$, $p = 0.0205$). CMRLct levels showed an opposite correlation with CBF in patients with favorable and poor outcome. In the former group, correlation analysis exhibited a negative slope with evidence for increasing lactate uptake associated with lower CBF values ($r = -0.1940$, $p = 0.0242$). On the contrary, in patients with adverse outcome, CMRLct values demonstrated a weak though opposite correlation with CBF ($r = 0.0942$, $p = 0.2733$). The present data emphasize the clinical significance of monitoring of cerebral blood flow and metabolism in TBI and provide evidence for metabolic coupling between astrocytes and neurons.

Key words: cerebral blood flow; glucose; lactate; oxidative metabolism; traumatic brain injury

INTRODUCTION

IMPAIRMENT of cerebral blood flow (CBF) and metabolism following severe traumatic brain injury (TBI) have been repeatedly reported (Obrist et al., 1984; Jaggi et al., 1990; Robertson et al., 1992; Glenn et al., 2003). Both oligemia due to increased intracranial pressure and reduced cerebral metabolic rate of oxygen (CMRO2) have been shown to be associated with unfavorable functional outcome.

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Reduction in glucose metabolism following TBI has been evidenced as well and shown to correlate with poor recovery (Hattori et al., 2003; Vespa et al., 2003), although the severity of this reduction has been shown to be less than that of oxidative metabolism, indicating relative hyperglycolysis (Bergsneider et al., 1997, 2000). Elevated glycolysis, either globally or regionally (Bergsneider et al., 1997; Ginsberg et al., 1997; Glenn et al., 2003) have been particularly reported during the early post-traumatic period and therefore attributed to increased energy demands mediated by glutamate release.

Since most studies have correlated the magnitude and duration of this post-traumatic metabolic depression with functional recovery, it may be hypothesized that cerebral metabolic rates may reflect at least to some extent the vital and functional status of the injured brain. As such, monitoring of cerebral metabolism may be more sensitive than more commonly used clinical parameters such as intracranial pressure or cerebral perfusion pressure often advocated as an indirect tool for estimation of CBF (Rosner and Daughton, 1990). This assumption, however, has not been confirmed by studies comparing brain metabolic indices with consciousness levels or neurological status. Although Obrist et al. (1984) was able to show some correlation between CMRO2 and Glasgow Coma Scale (GCS) in head-injured patients, subsequent studies failed to establish a definite relationship between GCS score and cerebral metabolism (Bergsneider et al., 1997–-2001). Moreover, positron emission tomography (PET) studies have disclosed cerebral metabolic rates of glucose (CMRGlc) in fully conscious patients as low as that found in severely head-injured comatose patients (Bergsneider et al., 2000). Brain metabolic indices in this respect would basically reflect the severity of the initial injury though would not be reliable for the dynamic assessment of changes in neurological condition of sedated patients or for the evaluation of the impact of various therapeutic regimens.

Yet, important methodological considerations may lead to reconsider the conclusions drawn from CMRGlc data obtained in PET studies. First, these studies did not investigate the possible use of lactate by neurons as an alternative fuel so that significant changes in lactate uptake of the brain in response to dynamic changes in neural activity may have been overlooked (Pellerin, 2003). In a recent *in vitro* study, neurons proved to preferentially use lactate as their main oxidative substrate in a proportion of 79% compared to 21% using glucose, underlying the importance of assessing lactate utilization as an integral part of the investigation of brain metabolism following head injury (Bouzier-Sore et al., 2003). Further, most available PET studies were conducted in a small cohort of TBI patients with most often a single evaluation being done in each patient resulting in low temporal resolution.

In order to address the need for bedside CBF assessment, several authors have investigated the potential value and accuracy of Doppler ultrasound measurement of the internal carotid artery (ICA) blood flow volume (Dorfler et al., 2000; Ho et al., 2002; Scheel et al., 2000; Schoning et al., 2000). Since near 95% of the ICA blood flow is directed to the cerebral hemisphere, ICA blood flow volume should correlate closely with CBF in the ipsilateral hemisphere, provided that no occlusive disease affects the ICA distally or its major branches. Recently, two different studies comparing hemispheric ICA blood flow volume measured by Doppler ultrasound technology with CBF measured by the xenon-133 clearance technique have supported this hypothesis and demonstrated the same close correlation between the two compared parameters (Rothoerl et al., 2003; Soustiel et al., 2003). As such, these findings validate the use of ICA blood flow volume for bedside CBF assessment, offering the opportunity of repeated measures across the clinical course of acute patients. The purpose of the present study was to investigate the course of cerebral blood flow and metabolism in head-injured patients using Doppler ultrasound technology and to specifically characterize the changes in lactate and glucose indices in the acute post-traumatic period with regard to neurological condition and functional outcome.

MATERIALS AND METHODS

Patients

Fifty-five consecutive patients suffering from severe head injury were prospectively recruited for this study between April 2002 and April 2004. Forty-six were men and nine were women, ranging in age between 16 and 82 years (mean age 37 ± 17 years). Inclusion criteria included admission to the Neurosurgical intensive care unit (NICU) and brain injury severe enough to justify mechanical ventilation and intracranial pressure monitoring with a GCS score of 8 or less at the time of admission to the NICU. Exclusion criteria included age less than 16 years old, previous history of cerebral vascular disease, and bilateral fixed dilated pupils on admission. The protocol of the study was reviewed and approved by the Institutional Review Board.

Management Protocol

All patients were admitted to the department after surgery when indicated or after completion of all diagnostic and resuscitation measures. Management protocol included mechanical ventilation, sedation and intracranial

pressure monitoring as needed. Increased intracranial pressure was treated by hyperventilation guided by jugular bulb oxymetry, boluses of 20% mannitol, intravenous drip of propofol, and ventricular drainage according to the clinical situation. In all patients, the fluid regimen aimed at the maintenance of the mean arterial pressure at 95–100 mm Hg, with cerebral perfusion pressure maintained above 70 mm Hg and hematocrit of 30–35%.

Cerebral Blood Flow Measurements

Blood flow volume (BFV) measurements were obtained from the extracranial internal carotid artery using a dual-beam angle-independent digital Doppler ultrasound device (Quantix ND, Cardiosonix-Neoprobe, Dublin, OH) according to a technique previously described (Soustiel et al., 2002). Global CBF values (gCBF) were then calculated using an algorithm derived from linear correlation analysis between averaged BFV in the ICA and gCBF measured by the xenon-133 clearance technique (Soustiel et al., 2003):

$$\text{gCBF} = \text{averaged ICA BFV}*0.108 + 14$$

Cerebral Metabolism

Retrograde catheterization of the internal jugular vein was performed in all patients. A 4-French catheter was placed in the jugular bulb and the position verified by skull x-ray. Simultaneous blood samples were then drawn every day from the jugular catheter and an arterial line following CBF measurements. Samples were collected in 2-cc syringes rinsed with heparin and immediately processed in the nearby laboratory. For each blood sample, blood gas, blood saturation, hemoglobin, hematocrit, pH, glucose and lactate plasma concentrations were measured. Arterial jugular differences were then calculated and used to determine global cerebral metabolic rates of oxygen (gCMRO2), glucose (gCMRGlc) and lactate (gCMRLct). The metabolic ratio (MR = gCMRO2/gCMRGlc) was calculated and added to the remaining metabolic indices.

Monitoring Protocol

Standard clinical monitoring was performed in all patients, including intracranial pressure, systemic arterial pressure, central venous pressure, and cerebral perfusion pressure. GCS score was recorded every day in the absence of sedative drugs. Compiled data was recorded every day for each patient. Monitoring was maintained until recovery or clinical stabilization.

Neurological Outcome

Neurological outcome was assessed at 3 months during follow-up examinations or using information collected from rehabilitation staff or families for severely disabled patients. Outcome was categorized using the Glasgow Outcome Scale (GOS) score (Jennett and Bond, 1975). For statistical purposes, neurological outcome was further divided into favorable (GOS 4–5) and poor outcome (GOS1–3).

Statistical Analysis

A repeated-measures model of ANOVA was used to evaluate variations of CBF and metabolic indices over time and in respect with neurological outcome. For each parameter, both time variations and differences for the two outcome groups were analyzed separately, then the interaction between both factors was investigated. Possible correlations between GSC scores and various parameters were assessed using a General Linear Model of ANOVA. χ^2 was used for non parametric data. Linear regression analysis was used to assess the correlation between lactate metabolism and CBF. A p value of <0.05 was considered significant.

RESULTS

Overview

GCS score on admission ranged from 3 to 14 (mean 6.8 ± 3.2). A total of 321 recordings were performed in all patients. Monitoring was conducted for a mean duration of 4.4 days (range 1–12 days). However, since the number of patients available for monitoring was unacceptably low after the first week and unevenly distributed between the two GOS categories, only data obtained during the first week were considered for analysis.

Post-Traumatic Course of Cerebral Blood Flow

In all patients, CBF was moderately decreased during the first 24 h in comparison with normal subjects (Soustiel et al., 2002), and then increased and peaked at the second day in most patients (Fig. 1). Thereafter, the course of CBF appeared to be different in patients who eventually reached a favorable outcome in comparison with those who died or remained in poor neurological condition (Table 1). In the former group, CBF remained stable within the normal range whereas in patients with poor outcome, the course of CBF was characterized by a triphasic pattern defined by a secondary decrease on the third day (Fig. 1, Table 1). Moreover, CBF was lower in this group on the day of admission in comparison with patients with favorable outcome (36.4 ± 6.9 and 41.8 ± 8.8 mL · 100 $g^{-1} \cdot min^{-1}$, respectively, $p = 0.0488$ paired t-test). Although a CBF level below 35 mL · 100 $g^{-1} \cdot min^{-1}$ cannot be defined as truly ischemic, 71.4%

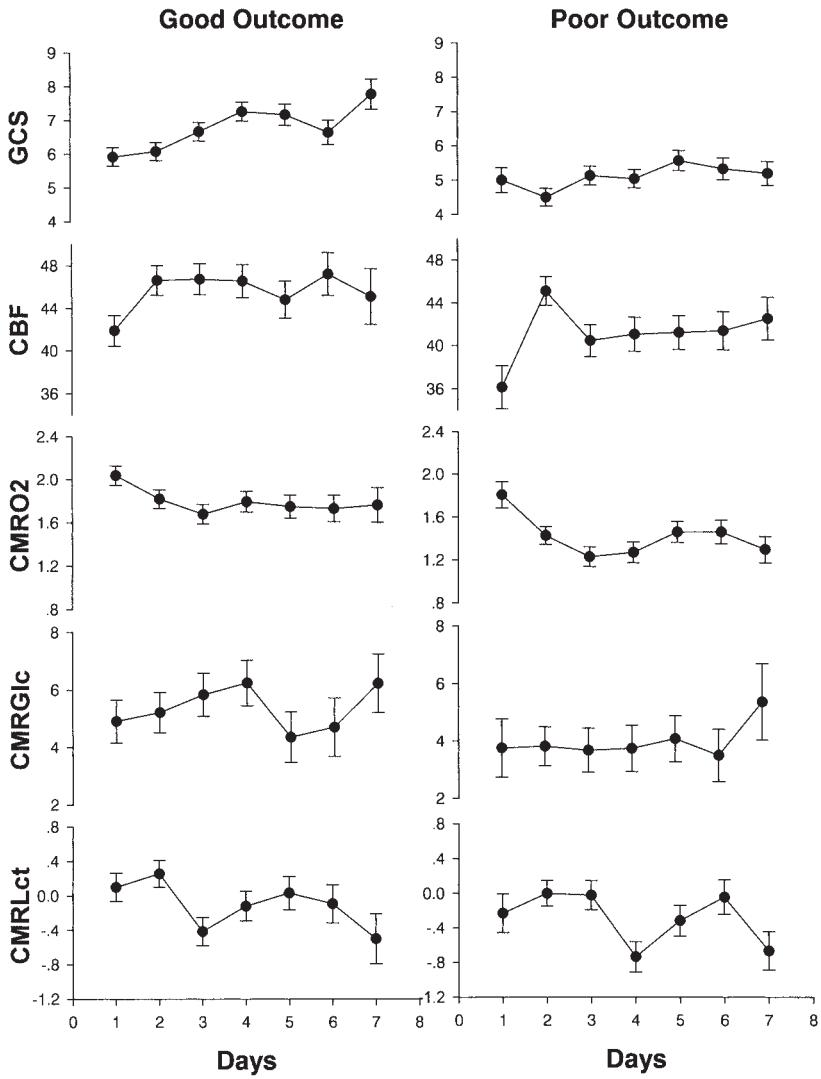

FIG. 1. Cerebral blood flow (CBF) was significantly decreased in all patients on admission, though this oligemia was prominent in patients with poor outcome. Oxidative metabolism was more severely affected with a nearly 50% decrease that further deepened in the initial post-traumatic period especially in patients with poor outcome. In general, the course of CMRO2 showed a significant correlation with that of functional recovery and opposite trends in patients of the two outcome populations. Interestingly, oligemia and depressed oxidative metabolism did not correlate with increased lactate production in the very early post-traumatic period. On the contrary, CMRLct values were positive during the initial 48 h, especially in patients with favorable outcome, as an evidence for lactate uptake by the brain. For each dot, mean value and its standard error are indicated. GCS, Glasgow Coma Scale.

of patients with poor outcome had CBF levels below this value on admission in comparison with patients of favorable outcome in whom only 16.7% had such low CBF values ($p = 0.0007$).

Post-Traumatic Course of Cerebral Metabolism

Oxidative metabolism was globally reduced in all patients on admission and further decreased progressively during the first week following the injury (Fig. 1). As for CBF, the dynamics of oxidative metabolism proved to be different in patients with favorable and poor outcome (Table 1). In the first group, gCMRO2 decreased steadily during the first 3 days then stabilized. In the poor outcome group, however, the slope of the initial gCMRO2 decrease was more pronounced, defining a significant difference at days 2–4. Eventually, the two outcome groups showed opposite trends at the end of the first week (Fig. 1, Table 1).

Post-traumatic metabolic depression affected glucose metabolism as well and was prevalent in a vast majority

Table 1. Dynamics of GCS, Cerebral Blood Flow and Metabolism Following TBI with Respect to Outcome

Index	*Outcome*	*Day 1*	*Day 2*	*Day 3*	*Day 4*	*Day 5*	*Day 6*	*Day 7*
GCS	Favorable	5.9 ± 1.4	6.0 ± 1.2	6.69 ± 1.39	7.3 ± 2.3	7.2 ± 1.5	6.5 ± 1.5	7.8 ± 3
$P_A < 0.0018$								
$P_B = 0.0001$	Poor	5 ± 1	4.6 ± 1.3	5.14 ± 1.49	5 ± 1.3	5.5 ± 1.3	5.4 ± 1.5	5.2 ± 1.5
$P_{AB} > 0.05$								
CBF	Favorable	41.9 ± 8.7	46.9 ± 11	47 ± 9.11	46.8 ± 6.9	45.7 ± 7	47.5 ± 7.8	45 ± 5.8
$P_A < 0.0404$								
$P_B = 0.0004$	Poor	36.4 ± 6.5	45.3 ± 11.7	40.7 ± 9.9	40.7 ± 11.7	41.4 ± 4.9	42.2 ± 5.5	43.7 ± 8.1
$P_{AB} > 0.05$								
CMRO2	Favorable	1.88 ± 0.67	1.79 ± 0.66	1.67 ± 0.7	1.77 ± 0.63	1.78 ± 0.44	1.7 ± 0.59	1.74 ± 0.52
$P_A = 0.0109$								
$P_B < 0.0001$	Poor	2.01 ± 0.58	1.48 ± 0.55	1.31 ± 0.48	1.24 ± 0.39	1.53 ± 0.68	1.5 ± 0.49	1.33 ± 0.4
$P_{AB} > 0.05$								
CMRGlc	Favorable	5.2 ± 3	5.15 ± 2.8	5.7 ± 3.89	6.5 ± 6.2	4.6 ± 3.1	4.93 ± 4.35	6.66 ± 6.7
$P_A > 0.05$								
$P_B = 0.0272$	Poor	3.79 ± 1.82	4 ± 2.8	4.19 ± 3.89	3.76 ± 3.29	3.5 ± 3.3	3.38 ± 2.09	5 ± 3.92
$P_{AB} > 0.05$								
CMRLct	Favorable	0.15 ± 1.14	0.26 ± 0.79	−0.42 ± 1.3	−0.07 ± 0.5	−0.1 ± 0.74	0.009 ± 0.8	−0.38 ± 1.09
$P_A < 0.0018$								
$P_B = 0.0001$	Poor	−0.21 ± 0.5	0.01 ± 0.6	−0.02 ± 0.8	−0.8 ± 1	−0.27 ± 0.7	0.002 ± 05	−0.69 ± 0.7
$P_{AB} > 0.05$								
MR	Favorable	4.2 ± 2.6	3.8 ± 2.3	4.32 ± 4.89	4.36 ± 4	5.8 ± 5.7	2.65 ± 9.3	3.24 ± 2.7
$P_A > 0.05$								
$P_B > 0.05$	Poor	5.9 ± 4.7	6.6 ± 8.6	4.55 ± 4.24	4.91 ± 3.8	7.4 ± 7.9	8.73 ± 13.1	5.45 ± 4.2
$P_{AB} > 0.05$								

Expectedly, patients with poor outcome had lower GCS scores throughout the post-traumatic course. Cerebral blood flow (CBF) and metabolism monitoring disclosed significant differences between patients with favorable and poor outcome characterized by significant decrease in CBF and CMRO2. Variations of CBF and metabolic indices over time, however, were not significantly different in the two outcome groups. Consequently, no post hoc comparisons could be made. The significance of variations over time (P_A), according to outcome (P_B) and of their interaction (P_{AB})is indicated in the table for each parameter. GCS, Glasgow Coma Scale.

of patients although to a lesser extent than that found for oxidative metabolism. This discrepancy in the negative trend characterizing oxidative and glucose metabolism following TBI resulted in a relative decrease of the gCMRO2/gCMRGlc ratio or metabolic ratio (Bergsneider et al., 1997, 2000) indicative of relative hyperglycolysis present in a large number of patients. Absolute hyperglycolysis, defined as a gCMRGLc higher than 7 $mg \cdot 100\ g^{-1} \cdot min^{-1}$ (Bergsneider et al., 1997, 2000; Glenn et al., 2003), could be found in 14% of the patients. The course of gCMRGlc, however, appeared to be different in the two outcome populations (Fig. 1, Table 1). In patients with poor outcome, gCMRGlc was lower than in those with favorable outcome especially during the first 4 days. On the contrary, in patients with favorable outcome gCMRGlc demonstrated noticeable changes during the first week characterized by a marked though transient elevation during days 3 and 4 that was not correlated with any comparable event in the former group. Moreover, the course of CMRGlc in this group showed some similarity with that of GCS. CMRGlc values, however, demonstrated a wide intra- and inter-patient distribution that noticeably reduced the statistical significance of the differences obtained.

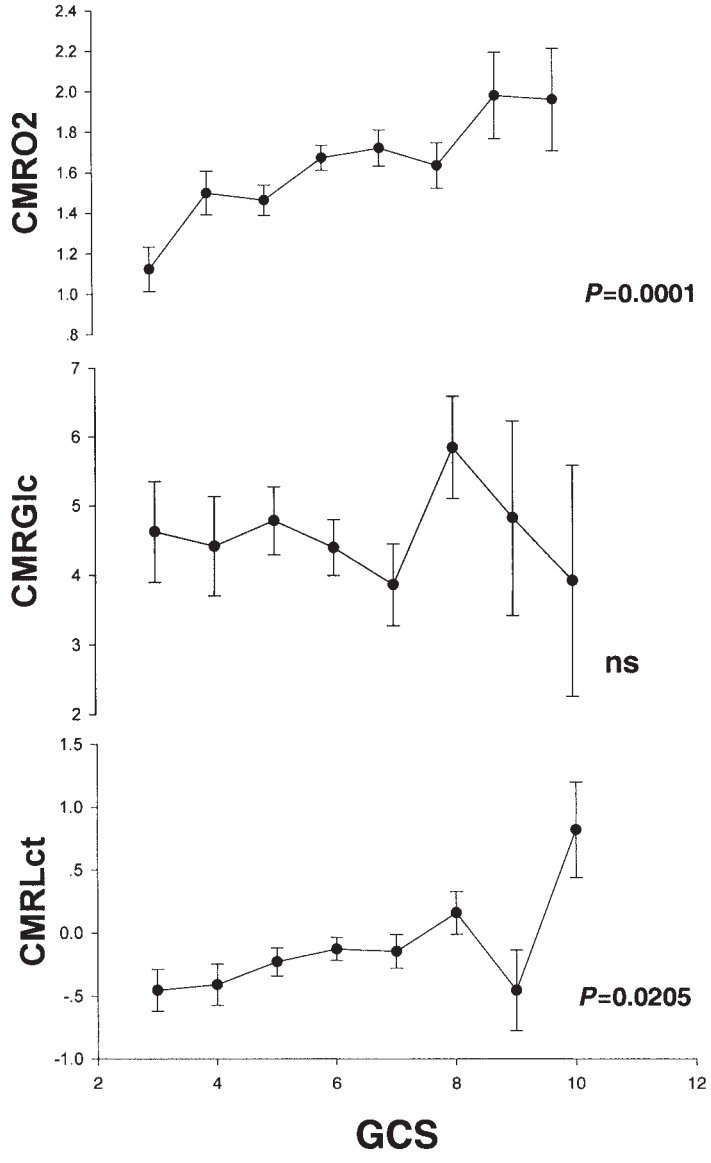

FIG. 2. Correlation between neurological status and cerebral metabolism. For each dot, mean value and its standard error are indicated. GCS, Glasgow Coma Scale; ns, not significant.

Even more than glucose metabolism, lactate metabolism was characterized by a high variability limiting the power of statistical analysis. Most remarkably, gCMRLct showed positive and increasing values for the first two days, indicating lactate uptake by the brain (Fig. 1, Table 1). Evidence for lactate uptake, however, was prominently obtained in patients with favorable outcome even though the gCMRLct difference in the two groups of outcome did not reach statistical significance. In contrast, the prevalence of significant lactate release (CMRLct less than -0.3 mg $\cdot$ 100 g^{-1} $\cdot$ min^{-1}) was higher in patients with poor outcome ($p = 0.0186$). Following this initial phase, a reverse and transient trend of lactate release (negative gCMRLct values) was observed in both outcome populations, although to a lesser extent for the favorable outcome group (Fig. 1, Table 1).

Cerebral Metabolism and Neurological Status

CMRO2 showed a significant and progressive correlation with level of consciousness expressed by means of GCS ($p = 0.0001$, Fig. 2). On the contrary, no correlation could be found between glucose metabolism and GCS ($p = 0.659$, Fig. 2). Paradoxically, some conscious patients harbored CMRGlc levels lower than some other deeply comatose patients. Unlike CMRGLc, CMRLct demonstrated a trend similar to that of CMRO2 (Fig. 2). Most remarkably, CMRLct values showed a significant reversal trend from lactate release to lactate uptake associated with higher levels of consciousness ($p = 0.0205$).

Cerebral Perfusion and Lactate Metabolism

CMRLct levels showed an opposite correlation with CBF in patients with favorable and poor outcome. In the former group, correlation analysis exhibited a negative slope with evidence for increasing lactate uptake associated with lower CBF values ($r = -0.1940$, $p = 0.0242$). On the contrary, in patients with adverse outcome, CMRLct values demonstrated a weak though opposite correlation ($r = 0.0942$, $p = 0.2733$) with CBF values.

Cerebral Blood Flow and Metabolism and Neurological Outcome

Lower CBF values were significantly associated with poorer outcome ($p < 0.0001$; Table 2). This negative impact of impaired cerebral perfusion over neurological outcome was reinforced by a similar statistical trend of CMRLct, suggesting that increased lactate release correlated with poor outcome as well ($p = 0.0507$; Table 2). Metabolic failure also proved to be predictive of adverse neurological outcome as both oxygen and glucose indices were significantly lower in patients with poor functional recovery ($p < 0.0001$ and $p = 0.0088$, respectively; Table 2).

DISCUSSION

The present study emphasizes the feasibility and clinical significance of monitoring CBF and metabolism in severely head-injured patients. Although it is a common practice to manage TBI patients relying on intracranial pressure or cerebral perfusion pressure monitoring, the results of this study confirm the conclusion of previous reports showing that the prognostic relevance of these parameters is limited in comparison with indices of flow and metabolism. Yet, CBF and metabolism studies are seldom part of routine evaluation in TBI patients, because they are cumbersome, time-consuming, and expensive,

Table 2. Univariate Analysis of Correlation between Outcome and Clinical Parameters, Cerebral Blood Flow, and Metabolism

	GOS 5	*GOS 4*	*GOS 3*	*GOS 2*	*GOS 1*	p *value (GOS)*	p *value (4–5 VS. 1–3)*
Age (years)	37.7 (4.7)	32 (5.1)	36 (7.9)	36.4 (6.7)	43.6 (4.7)	0.5738	0.2907
GCS adm	8.7 (0.8)	6.1 (0.9)	6.6 (1.4)	5.9 (1.2)	5.9 (0.8)	0.0932	0.0792
ICP	11.4 (1.3)	12.9 (1.2)	10.9 (1.8)	8.5 (1.6)	16 (1.1)	0.0014	0.5035
CPP	84.6 (1.9)	81.5 (1.8)	79 (2.8)	85.5 (2.4)	78.6 (1.7)	0.0564	0.1841
CBF	44 (1.1)	46.8 (1)	45.8 (1.6)	41.9 (1.3)	39.9 (1)	<0.0001	0.0001
CMRO2	1.7 (0.07)	1.8 (0.07)	1.3 (0.1)	1.5 (0.08)	1.3 (0.07)	<0.0001	<0.0001
CMRGlc	5.3 (0.5)	5 (0.4)	3.3 (0.7)	3.6 (0.6)	4.5 (0.4)	0.0487	0.0088
CMRLct	0.07 (0.1)	−0.18 (0.09)	−0.13 (0.13)	−0.3 (0.13)	−0.32 (0.1)	0.1078	0.0507

For each parameter, correlation with neurological outcome was assessed by paired *t*-test for dual outcome (favorable, GOS 5 and 4; poor, GOS 3, 2, and 1) and by General Linear Model ANOVA for Glasgow Outcome Scale (GOS) score. The *p* are indicated for both comparisons. GCS adm, Glasgow Coma Scale score on admission to the neurosurgical intensive care unit.

and imply for most of them the transfer of critically ill ventilated patients. Repeated exposure to radiation or isotopic tracers further limits a liberal use that would be ideally needed for day-to-day assessment. In the present study, CBF was drawn from BFV in the ICA and combined with arterial jugular differences of oxygen, glucose, and lactate for metabolic studies. Admittedly, this approach would allow only a global assessment of these parameters and therefore lack the spatial resolution provided by more sophisticated techniques such as PET or stable xenon computerized tomography.

Consequently, significant focal impairments of CBF and metabolism, such as those described in pericontusional areas, may be overlooked by a global evaluation. Nevertheless, considering the fact that diffuse axonal injury is the most common type of TBI, especially in severe head-injuries most often related to road traffic accident, and that it is commonly responsible for brain edema and elevated ICP (intracranial pressure), we may hypothesize that significant pathological processes should globally affect CBF in most instances.

This assumption is supported by comparing CBF values in patients with and without elevated ICP. Although CBF showed a weak correlation with ICP, CBF was significantly lower in patients with ICP above 20 mm Hg ($p = 0.0418$). CBF measurements in this series were in accordance with that recently obtained in similar cohorts of patients (Glenn et al., 2003; Hattori et al., 2003). Interestingly, as observed by Glenn et al. (2003), CBF levels were only moderately though significantly reduced in comparison with normal subjects, and severe ischemia was seldom noticed. This observation is likely to be related to the CPP management paradigm adopted for the treatment of patients at the authors' institutions. CBF levels, however, showed significant variations during the post-traumatic course. These changes were mostly characterized by a marked elevation within the first 48 h, as described by Martin et al. (1997). These authors demonstrated a triphasic pattern for the course of CBF following TBI and speculated that the secondary decrease in CBF could be attributed to either brain edema or cerebral vasospasm. In this series, however, the same triphasic pattern could be found in patients with poor neurological outcome, whereas CBF remained at higher and more stable levels at the same time in patients with favorable outcome. This observation may nonetheless be compatible with the hypothesis of Martin et al. (1997) as brain edema obviously accounts for delayed deterioration at least for some patients. Yet, low CBF levels may just as well reflect the severity of the primary brain injury with subsequent decreased metabolism for some other patients. This latter possibility is supported in the present series by the absence of significant difference in ICP and CPP levels between patients with favorable and poor outcome.

As expected from earlier studies, oxidative metabolism was markedly decreased following TBI (Bouma et al., 1991; Diringer et al., 2002; Glenn et al., 2003; Obrist et al., 1984). This reduction in oxidative metabolism was observed in all patients with a similar pattern, although it was more pronounced in patients with unfavorable outcome. Several authors have hypothesized that CMRO2 levels in TBI patients were predetermined by the severity of the primary brain damage and its mitochondrial consequences (Vink et al., 2000; Xiong et al., 1997) and as such, were predictive of outcome, though it did not correlate with dynamic changes (Bouma et al., 1991; Jaggi et al., 1990). If true, there would be little additional clinical value for monitoring the oxidative metabolism in TBI patients. This concept of uncoupling between brain function and metabolism, however, may be challenged by the different course of CMRO2 in patients with favorable and poor outcome but more importantly by the close correlation observed between CMRO2 and GCS scores, as previously reported by Obrist et al. (1984). Yet, the significance of such a correlation between GCS and CMRO2 may be ambiguous or even misleading considering the obvious discrepancy between the course of GCS and that of CMRO2. In this perspective, the correlation observed between CMRO2 and GCS scores may have indirectly expressed the severity of the initial injury responsible for the depth of coma.

Similar observations could be made regarding glucose metabolism, although the high variability of CMRGLc prevented firm conclusions from being drawn. CMRGlc nonetheless showed an apparent match with the course of GCS suggestive of a dynamic link, especially in patients with favorable outcome. This finding supports a previous observation made in head-injured patients evaluated by [^{18}F]fluorodeoxyglucose PET (Bergsneider et al., 2000). In this study, Bergsneider et al. (2000) showed a trend of correlation between CMRGlc and GCS in mildly injured patients. More recently, Hattori et al. (2003) found a significant correlation between consciousness level and glucose metabolism in TBI patients, especially in the thalamus, the brainstem, and the cerebellum but in a lesser extent for the whole brain. Furthermore, patients from the GOS groups 4–5 had higher CMRGlc values than patients with poor outcome, especially during the initial post-traumatic period. Correspondingly, most instances of hyperglycolysis were found during the same acute post-traumatic phase. This finding of early relative or absolute hyperglycolysis is in accordance with previous clinical (Bergsneider et al., 1997; Yamaki et al., 1996) and experimental studies (Thomas et al., 2000). The mechanism underlying hy-

perglycolysis is not clear, though it has been attributed to an increased activity of energy-dependent Na/K pumps compensating the massive ionic influx secondary to the activation of *N*-methyl-D-Aspartate receptors by excitatory amino acids released following post-traumatic depolarization (Sunami et al., 1989; Yoshino et al., 1991). Another advocated mechanism is the energy failure induced by depression of oxidative metabolism secondary to increased mitochondrial calcium concentration (Fiskum et al., 2000; Xiong et al., 1997) and further aggravated by decreased CBF with subsequent impairment of oxygen delivery.

In such conditions, increased anaerobic glycolysis would be necessary in order to increase ATP production and meet energy demands according to the traditional concept of neuronal metabolism (Sokoloff, 1989). Exacerbated glycolysis will, in turn, result in increased lactate production (Yang et al., 1985) with subsequent cellular acidosis, edema, and structural damage. This concept, however, has been recently challenged by several experimental studies, suggesting the existence of a metabolic coupling between astrocytes and neurons (Pellerin, 2003; Pellerin and Magistretti, 1994; Tsacopoulos and Magistretti, 1996). These studies have provided convincing evidence showing that during neuronal activation, lactate produced by glycolysis may be transferred from astrocytes to neurons by monocarboxylate transporters (Debarnadi et al., 2003) to be used preferentially as an energy substrate by neurons (Bouzier-Sore et al., 2003). Our results provide further clinical evidence for the use of lactate by the brain as an alternative fuel and confirm similar observations previously reported by Glenn et al. (2003). In both series, however, a dual behavior of lactate metabolism could be identified, characterizing patients with favorable and poor outcome. In patients with adverse neurological recovery, brain ischemia and energy failure resulted in lactate accumulation and elevated negative CMRLct values. On the contrary, in patients with favorable outcome, lactate was taken up by the brain, presumably to be used as an alternative fuel for improved energy balance. Interestingly, most instances of lactate uptake by the brain were noticed in both series during the early post-traumatic period where energy balance is commonly considered to be at its worst. Yet, arterial jugular differences for lactate probably overlook a significant amount of intercellular lactate transfer and intracellular metabolism or accumulation so that interpretation of CMRLct levels should be carefully considered and take into account that lactate uptake or release as expressed by its concentration in the jugular blood may not be the accurate reflection of its metabolism but rather represents a rough summation of these metabolic events.

CONCLUSION

This study shows the feasibility and prognostic implications of bedside monitoring of cerebral metabolism. The present results suggest that cerebral metabolism following TBI may be dynamically affected by various pathological processes and are not necessarily predetermined. As such, metabolic studies may provide a more accurate insight into the physiological status of the injured brain and its response to various therapeutic regimens. As it is, however, the present study does not allow such a conclusion, and a further dynamic study investigating possible metabolic changes in response to various stimuli or therapeutic measures should be conducted in order to address this issue. The present results further provide evidence for metabolic coupling between glia and neurons, and suggest that the preserved capability of brain tissue to use lactate for improvement of energy balance may be predictive of favorable neurological outcome.

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