Original Article

Indian Journal of Neurotrauma (IJNT)
2007, Vol. 4, No. 1, pp. 25-29

Course of cerebral blood flow and metabolism following severe brain injury. Correlation with neurological function and outcome

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Abstract: This study was carried out investigate the course of cerebral blood flow and metabolism in fifty five head-injured patients and to specifically characterize the changes in oxidative and glucose indices in the acute post-traumatic period with regard to neurological condition and functional outcome. Blood flow volume (BFV) measurements were obtained from the extracranial internal carotid artery using a dual-beam angle-independent digital Doppler ultrasound. Cerebral metabolism was studied using blood sample, blood gas, blood saturation, hemoglobin, hematocrit, pH and glucose plasma concentrations. Arterial jugular differences were then calculated and used to determine global cerebral metabolic rates of oxygen (gCMRO2) and glucose (gCMRGlc). In patients with good outcome, 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. CMRO2 showed a significant and progressive correlation with level of consciousness expressed by means of GCS. Lower CBF values were significantly associated with poorer outcome.

Keywords: cerebral blood flow, cerebral metabolism, head injury.

INTRODUCTION

Impairment of cerebral blood flow (CBF) and metabolism following severe traumatic brain injury (TBI) have been repeatedly reported[1,2,3] and related to unfavorable functional outcome. Reduction in glucose metabolism following TBI has been evidenced as well and shown to correlate with poor recovery[4], although the severity of this reduction has been shown to be less than that of oxidative metabolism, indicating relative hyperglycolysis[5,6].

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.

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The purpose of the present study was to investigate the course of cerebral blood flow and metabolism in head-injured patients and to specifically characterize the changes in oxidative and glucose indices in the acute post-traumatic period with regard to neurological condition and functional outcome.

MATERIAL AND METHODS

Patients

Fifty-five consecutive patients suffering from severe head injury (GCS score less than 8) were prospectively recruited for this study between April 2002 and April 2004. Forty-six were men and 9 were women, ranging in age between 16 and 82 years (mean age 37 ± 17 years). 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 oximetry, 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 to 100 mm Hg with cerebral perfusion pressure maintained above 70 mm Hg and the hematocrit between 30 and 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[7] (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: gCBF = averaged ICA BFV*0.108 + 14[8].

Cerebral metabolism

Retrograde catheterization of the internal jugular vein was performed in all patients. Simultaneous blood samples were then drawn every day from the jugular catheter and an arterial line following CBF measurements. For each blood sample, blood gas, blood saturation, hemoglobin, hematocrit, pH and glucose plasma concentrations were measured. Arterial jugular differences were then calculated and used to determine global cerebral metabolic rates of oxygen (gCMRO2) and glucose (gCMRGlc).

Monitoring protocol

Standard clinical monitoring was performed in all patients, including intracranial pressure, systemic arterial pressure, central venous pressure and cerebral perfusion pressure. Glasgow Coma Scale 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). 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 cerebral blood flow 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 Glasgow Coma Scale scores and various parameters were assessed using a General Linear Model of ANOVA. Chi square was used for non parametric data. Linear regression analysis was used to assess the correlation between lactate metabolism and CBF. A *P* value of less than 0.05 was considered significant.

RESULTS

Post-traumatic course of cerebral blood flow

In all patients, CBF showed a moderate though significant reduction during the first 24 hours in comparison with normal subjects[7] and then increased and peaked at the second day in most patients (Fig. 1). In patients with good outcome, 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 $ml.100g^{-1}.min^{-1}$ respectively, P=0.0488 paired t-test). On admission, 71.4% of patients with poor outcome had CBF levels below 35 $ml.100g^{-1}.min^{-1}$ 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

Depression of oxidative metabolism was present in all patients on admission and further decreased progressively during the first week following the injury (Fig. 1). In patients in good outcome, however, gCMRO2 decreased steadily during the first 3 days then stabilized whereas in the poor outcome group, the slope of the initial gCMRO2 decrease was more pronounced defining a significant difference at days 2 to 4. Eventually, the two outcome groups showed opposite trends at the end of the first week (Fig. 1, Table 1).

Index		Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
GCS P_A<0.0018 P_B=0.0001 P_{AB}>0.05	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
	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
CBF P_A<0.0404 P_B=0.0004 P_{AB}>0.05	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
	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
CMRO2 P_A=0.0109 P_B<0.0001 P_{AB}>0.05	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
	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
CMRGlc P_A>0.05 P_B=0.0272 P_{AB}>0.05	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
	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

Table 1: Dynamics of GCS, CBF and metabolism following TBI in respect with outcome Expectedly, patients with poor outcome had lower GCS scores throughout the post traumatic course. Cerebral blood flow 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.

	GOS 5	GOS 4	GOS 3	GOS 2	GOS 1	*P* value (GOS)	*P* value (4-5 vs 1-3)
Age	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

Table 2: Univariate analysis of correlation between outcome and clinical parameters, cerebral blood flow and metabolism.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 Geleneral Linear Model ANOVA for Glasgow Outcome Scale score. P values are indicated for both comparisons. GCS adm: Glasgow Coma Scale score on admission to the neurosurgical intensive care unit.

Post-traumatic metabolic depression affected glucose metabolism as well and was prevalent in a vast majority of patients although to a lesser extent than that found for oxidative metabolism resulting in relative hyperglycolysis present in a large number of patients. Absolute hyperglycolysis[3,5,6], defined as a gCMRGLc higher than 7 mg.100g^{-1}.min^{-1}, 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).

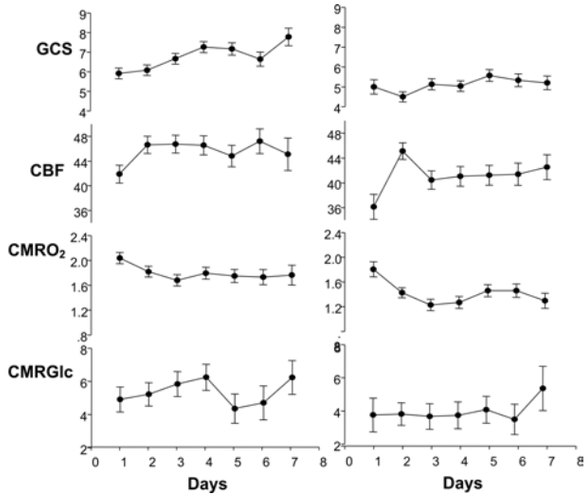

Fig 1: CBF was significantly decreased in all patients on admission though this oligemia was prominent in patients with poor outcome. Oxidative metabolism was more severely affected with a nearly 50% decrease that further deepened in the initial post traumatic period especially in patients with poor 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. For each dot, mean value and its standard error are indicated.

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.

Cerebral blood flow and metabolism and neurological outcome

Lower CBF values were significantly associated with poorer outcome (*P*<0.0001, 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

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, cerebral blood flow and metabolism studies are seldom part of routine evaluation in TBI patients because they are cumbersome, time-consuming, expensive 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. CBF measurements in this series were in accordance with that recently obtained in similar cohorts of patients[3,4]. Interestingly, as observed by Glenn et al., CBF levels were only moderately though significantly reduced in comparison with normal subjects and severe ischemia was seldom noticed[3]. 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 hours, as described by Martin et al[9]. 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.

As expected from earlier studies, oxidative metabolism was markedly decreased following TBI[1,3,10]. This reduction in oxidative metabolism was observed in all patients with a similar pattern although it was more pronounced in patients with unfavorable outcome. Previous studies have provide evidence for uncoupling between brain function and metabolism[2,10,11]. This concept may be challenged by the different course of $CMRO_2$ in patients with favorable and poor outcome but more importantly by the close correlation observed between $CMRO_2$ and GCS scores, as previously reported by Obrist et al[1]. Yet, the significance of such a correlation between GCS and $CMRO_2$ may be ambiguous or even misleading considering the obvious discrepancy between the course of GCS and that of $CMRO_2$. 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 previous observations made in head-injured patients evaluated by [^{18}F]fluorodeoxyglucose positron emission tomography.

In conclusion, this study shows the feasibility and prognostic implications of bedside monitoring of cerebral metabolism. The present results suggest that cerebral metabolism following traumatic brain injury 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.

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