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Cerebral extracellular chemistry and outcome following traumatic brain injury: a microdialysis study of 223 patients

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Secondary insults can adversely influence outcome following severe traumatic brain injury. Monitoring of cerebral extracellular chemistry with microdialysis has the potential for early detection of metabolic derangements associated with such events. The objective of this study was to determine the relationship between the fundamental biochemical markers and neurological outcome in a large cohort of patients with traumatic brain injury. Prospectively collected observational neuromonitoring data from 223 patients were analysed. Monitoring modalities included digitally recorded intracranial pressure, cerebral perfusion pressure, cerebrovascular pressure reactivity index and microdialysis markers glucose, lactate, pyruvate, glutamate, glycerol and the lactate/pyruvate ratio. Outcome was assessed using the Glasgow Outcome Scale at 6 months post-injury. Patient-averaged values of parameters were used in statistical analysis, which included univariate non-parametric methods and multivariate logistic regression. Monitoring with microdialysis commenced on median (interquartile range) Day 1 (1–2) from injury and median (interquartile range) duration of monitoring was 4 (2–7) days. Averaged over the total monitoring period levels of glutamate ($P = 0.048$), lactate/pyruvate ratio ($P = 0.044$), intracranial pressure ($P = 0.006$) and cerebrovascular pressure reactivity index ($P = 0.01$) were significantly higher in patients who died. During the initial 72 h of monitoring, median glycerol levels were also higher in the mortality group ($P = 0.014$) and median lactate/pyruvate ratio ($P = 0.026$) and lactate ($P = 0.033$) levels were significantly lower in patients with favourable outcome. In a multivariate logistic regression model ($P < 0.0001$), which employed data averaged over the whole monitoring period, significant independent positive predictors of mortality were glucose ($P = 0.024$), lactate/pyruvate ratio ($P = 0.016$), intracranial pressure ($P = 0.029$), cerebrovascular pressure reactivity index ($P = 0.036$) and age ($P = 0.003$), while pyruvate was a significant independent negative predictor of mortality ($P = 0.004$). The results of this study suggest that extracellular metabolic markers are independently associated with outcome following traumatic brain injury. Whether treatment-related improvement in biochemistry translates into better outcome remains to be established.

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Abbreviations: PRx = cerebrovascular pressure reactivity index; TBI = traumatic brain injury

Introduction

Traumatic brain injury (TBI) remains a major cause of mortality, morbidity and long-term disability, with profound and often long-lasting social and economic consequences. It is recognized that outcome following TBI is related to the initial characteristics of injury, reflecting its severity, such as Glasgow Coma Scale score, pupillary reactivity and radiological appearance, as well as the patient's age and presence or absence of early physiological insults (hypoxia and hypotension). This relationship of early and largely non-modifiable factors to mortality and neurological outcome has been confirmed by the analysis of demographic data from the several recent large randomized controlled trials (Murray *et al.*, 2007; Perel *et al.*, 2008) and has led to development of prognostic scoring systems, which can be used to predict outcome at a group level. Nevertheless, outcomes are also influenced by ongoing pathophysiological processes and secondary insults (Chesnut *et al.*, 1993; McHugh *et al.*, 2007) that continue to take place after initial injury and resuscitation. Detection of these secondary events remains a major target of neuromonitoring and an area of ongoing research. Intracranial pressure and cerebral perfusion pressure are the most widely accepted neuromonitoring parameters and have been shown in many studies to be related to mortality after TBI (Marshall *et al.*, 1979; Saul and Ducker, 1982; Balestreri *et al.*, 2006). More recently cerebral autoregulation (Czosnyka *et al.*, 1997; Reinert *et al.*, 2007) and brain tissue oximetry (van Santbrink *et al.*, 1996; Valadka *et al.*, 1998; Zauner *et al.*, 1998; van den Brink *et al.*, 2000) have been linked to outcome after head injury. Although there is no conclusive proof that optimization of these parameters may influence neurological recovery, indirect evidence of better outcomes in specialized neurocritical care units (Patel *et al.*, 2002, 2005), where tiered therapy is based on neuromonitoring, supports their use and further exploration of their clinical value. Direct monitoring of cerebral extracellular chemistry by microdialysis is a promising technique that has enhanced our understanding of the pathophysiology of brain injury and is maturing as a clinical monitor that can be employed in combination with other monitoring methods (such as cerebral oximetry and intracranial pressure monitoring) to assist in the management of patients on an individual intention-to-treat basis (Bellander *et al.*, 2004; Goodman and Robertson, 2009).

However, the relationship between commonly used microdialysis markers and ratios, and neurological outcome following TBI has not been clearly established. Lack of such information makes it difficult to interpret the significance of both spontaneous and treatment associated changes in tissue chemistry and may limit the clinical utility of cerebral microdialysis. Current evidence is based, with few exceptions, on small-scale studies, often using pooled data with no adjustments for potential confounders. The aim of the current study was to evaluate the relationship between cerebral extracellular biochemistry and neurological outcome in a large group of patients with TBI, who underwent treatment and monitoring with cerebral microdialysis in a single centre.

Materials and methods

The observational neuromonitoring data from 223 patients with acute TBI, prospectively collected during a 10-year period in a single tertiary centre as part of an ongoing research program, were included in the study. All patients required treatment in neurocritical care, including intubation and mechanical ventilation, and were managed according to standardized tiered head injury protocol (Menon, 1999). The intensity of treatment was driven by intracranial pressure and cerebral perfusion pressure targets (<20 mmHg and >60–70 mmHg, respectively) and therapeutic options included head elevation, analgesia, sedation, muscle relaxation, ventriculostomy, moderate hyperventilation, osmotic agents, induced hypothermia and, at the last stage, barbiturate coma and decompressive craniectomy. Six-month functional outcomes were evaluated using Glasgow Outcome Scale questionnaires, either at outpatient follow-up clinical appointments, or by posting the form to the patient. For the purposes of this study, statistical comparisons were undertaken in the following Glasgow Outcome Scale stratifications: (i) mortality versus survival (Glasgow Outcome Scale = 1 versus Glasgow Outcome Scale = 2–5); (ii) dichotomized Glasgow Outcome Scale comparing favourable and unfavourable outcomes, including mortality in the unfavourable category (Glasgow Outcome Scale = 1–3 versus Glasgow Outcome Scale = 4–5); (iii) dichotomized Glasgow Outcome Scale in survivors (Glasgow Outcome Scale = 2–3 versus Glasgow Outcome Scale = 4–5) and (iv) a three-group Glasgow Outcome Scale comparison (Glasgow Outcome Scale = 1 versus Glasgow Outcome Scale = 2–3 versus Glasgow Outcome Scale = 4–5).

Monitoring

All patients included in the study underwent monitoring of intracranial pressure with parenchymal intracranial pressure microsensors (Codman, Raynham, USA) and cerebral extracellular chemistry with microdialysis catheters (CMA70 and CMA 71; CMA Microdialysis AB, Solna, Sweden). The sensors and catheters were inserted via a cranial access device (Technicam, Newton Abbot, UK) almost exclusively into non-dominant frontal white matter. The position of catheters was identified on the post-insertion CT scan and, depending on proximity of the catheter's gold tip to traumatic cerebral lesions, was classified as perilesional or macroscopically normal brain. A standard flow rate of 0.3 μl/min was used in all patients with a routine rate of vial change of 1 h. Samples were analysed at the bedside using CMA microdialysis analysers (CMA600 and ISCUS; CMA Microdialysis AB) for concentrations of glucose, lactate, pyruvate, glutamate and glycerol. Not all patients had a complete set of microdialysis markers. Glucose and lactate were measured in all patients, while pyruvate levels were available in 219, glutamate in 161 and glycerol in 125 patients. Lactate/pyruvate ratio and lactate/glucose ratios were calculated in 219 and 223 patients, respectively. Although intracranial pressure was monitored in all patients, digital recordings of intracranial pressure were available for 143 patients. This recording was performed at the bedside, using ICM+ software (ICM+, University of Cambridge, UK), which in addition to recording physiological variables

(intracranial pressure, cerebral perfusion pressure and mean arterial pressure), allowed on-line calculation of the cerebrovascular pressure reactivity index (PRx). The PRx represents a moving correlation coefficient between 30 mean values (10 s window) of intracranial pressure and mean arterial blood pressure, and reflects the state of cerebral vascular autoregulation. Positive values of PRx imply that increases in mean arterial blood pressure are positively associated with increases in intracranial pressure, suggesting autoregulatory impairment, whereas negative PRx values indicate preserved vascular reactivity, with vasoconstriction and decrease in intracranial pressure in relation to surges in mean arterial blood pressure. The PRx, which has previously been validated against other indices of cerebral autoregulation (Czosnyka *et al.*, 1997), is related to outcome (Czosnyka *et al.*, 2005) and was therefore included in the current study.

Data processing

Following extraction of monitoring data, further processing, statistical analysis and associated graph plotting was performed using Statistical Package for the Social Sciences 15.0 software (SPSS Inc, Chicago, IL, USA). Obvious artefacts, e.g. periods related to disconnection of monitoring devices or flushing of arterial lines as well as data-points outside the analytical range of the microdialysis analysers were manually removed. Data were averaged as follows. The raw data-sampling rate of the pressure-monitoring equipment was 50 Hz, and these data were automatically averaged per minute at the bedside. Microdialysis readings were performed hourly on samples that accumulated over the course of the hour leading up to the point when the collection vial was changed. We therefore averaged the 'per minute' pressure data (intracranial pressure, cerebral perfusion pressure and PRx) over the 1 h periods between microdialysis change times in order to set the pressure data on an equivalent timeframe to the microdialysis. The 72 h averages (see below) and whole-period averages for the pressure data were performed using the hourly-averaged pressure data.

The data analysis was performed using patient-averaged data (i.e. one data-point per patient, which was that patient's average for the period and parameter being evaluated), for calculating medians, interquartile ranges, differences between outcome groups and predictors of outcome (logistic model). We did not pool hourly data from multiple patients. Initial analysis included plotting patient/day averaged daily trends, subdivided by outcome categories. Median values of monitoring parameter averaged by patient, for the whole duration of monitoring, as well as for the first 72 h of monitoring and percentages of times outside 'normal' physiological thresholds were used for evaluating the relationships to outcome. We undertook such comparisons using two time windows. An initial comparison included all of the available data. In addition, we also compared data from the first 72 h period, to minimize possible bias related to the different length of monitoring time between the patients, since not all of them received microdialysis beyond 72 h, e.g. when catheters were removed because patients were woken up from anaesthesia. Also, consideration of the first 72 h minimizes any potential unreliability of long-term monitoring and covers the period of arguably maximum vulnerability of brain tissue. Microdialysis is regarded as being useful as an early warning system for secondary injury following TBI (see consensus by Bellander *et al.*, 2004), and moreover, experience in our own unit has suggested that focusing on the first 72 h of monitoring is a logical approach for the data analysis. Nevertheless, we have also considered the whole period of monitoring for each patient, as well as the first 72 h, since some patients develop brain swelling and abnormal brain chemistry later than 72 h.

The following physiological thresholds were used to calculate the time periods of abnormal values: intracranial pressure >25 mmHg, cerebral perfusion pressure <60 mmHg, PRx >0.2, glucose <1.0 mmol/l, lactate >4 mmol/l, pyruvate <50 μmol/l, glutamate >10 μmol/l and glycerol >150 μmol/l, lactate/pyruvate ratio >25 and >40 and lactate/glucose ratio >10. Statistical methods included simple non-parametric tests (Mann–Whitney U-test), comparing median values across outcome categories, and logistic regression. The latter models included microdialysis parameters (glucose, lactate, pyruvate and lactate/pyruvate ratio), monitoring variables (intracranial pressure, cerebral perfusion pressure and PRx) and established outcome predictors (age, Glasgow Coma Scale, CT Marshall Grade, injury severity score and pupillary reaction) as independent variables and mortality or outcome categories as dependent variables. The forward stepwise method based on likelihood ratio was used. The relationship of monitoring parameters to outcome was initially evaluated separately for each microdialysis catheter location (perilesional or normal brain), but no significant difference in relationship to outcome was found between locations and given the statistical penalty of such an approach, the whole data set was used for final analysis without stratification by catheter location.

Results

Patient demographics

Of 223 patients included in the study, 166 (74%) of patients were male and 57 (26%) were female. The median (interquartile range) age of patients was 35 (22–49) years. Based on the initial post-resuscitation Glasgow Coma Scale, 167 (75%) patients sustained severe (Glasgow Coma Scale = 3–8), 42 (19%) moderate (Glasgow Coma Scale = 9–12) and 14 (6%) mild head injury (Glasgow Coma Scale = 13–15), although all patients eventually required mechanical ventilation and intensive care management. Based on initial CT scan appearance 121 (54%) patients had diffuse injury (Marshall Grade 1–4), 61 (28%) had evacuated (Marshall Grade 5) and 41 (18%) had non-evacuated mass lesion (Marshall Grade 6). The latter group predominantly comprised of patients with cerebral contusions, who were treated non-operatively with intracranial pressure monitoring and conservative management. At 6 months following injury, 102 (46%) patients had favourable (Glasgow Outcome Scale = 4–5), 60 (27%) patients had unfavourable (Glasgow Outcome Scale = 2–3) outcome, 51 (23%) patients had died and 10 (4.5%) of patients were lost to Glasgow Outcome Scale based follow-up, although they were known to be alive.

Monitoring and outcome

Monitoring with microdialysis was commenced on median (interquartile range) Day 1 (1–2) from injury and median (interquartile range) duration of monitoring was 4 (2–7) days. Microdialysis catheters were located in 167 (75%) radiologically 'normal' brains, whereas 56 (25%) were adjacent to traumatic intracranial lesions. Daily trends of monitoring parameters during the first week of monitoring split by outcome groups are presented in Fig. 1. Most consistent trends were seen for lactate and lactate/pyruvate ratio, both of which were lower on a daily basis in patients with favourable outcome as compared with those patients

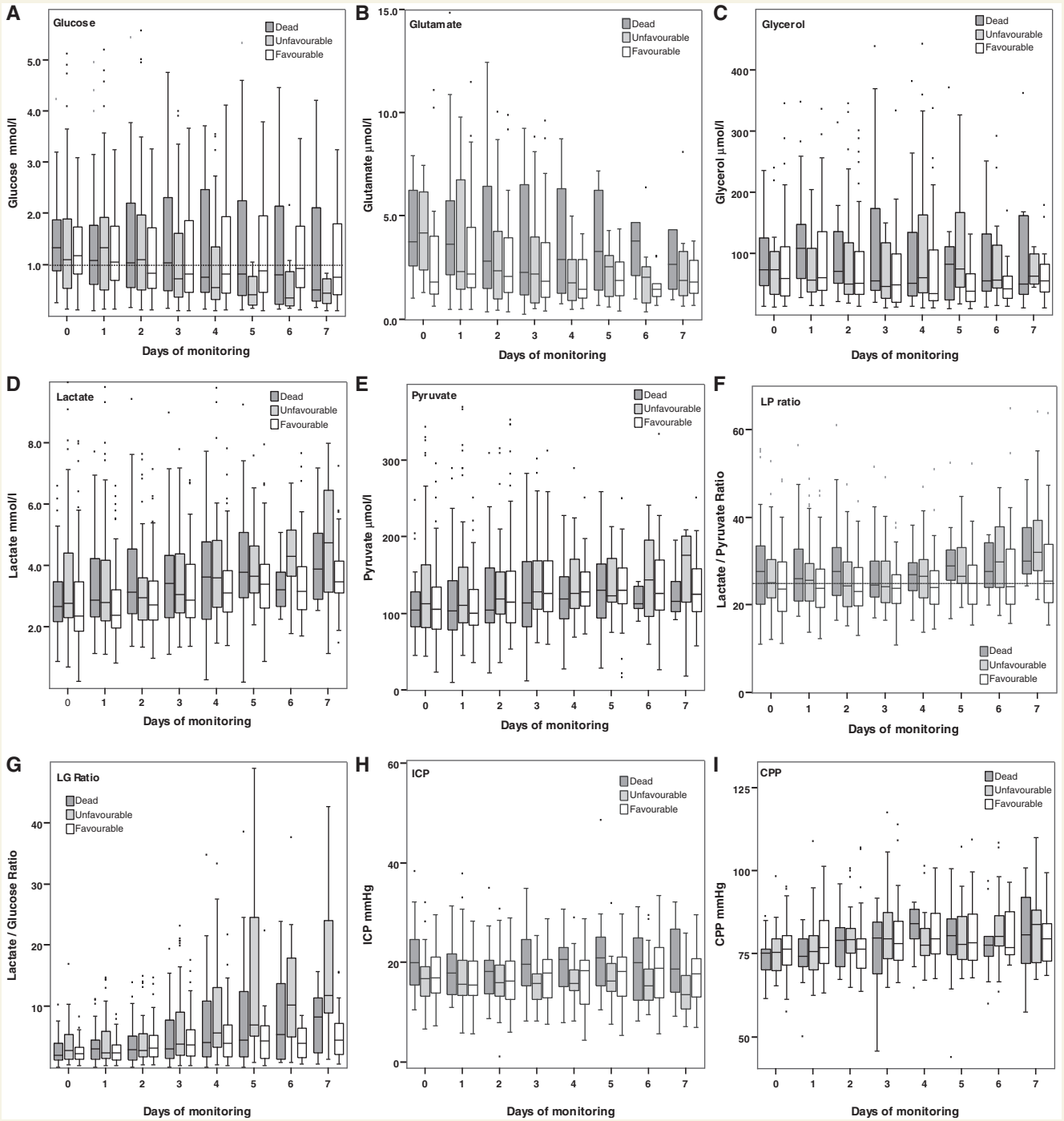

Figure 1 Pooled values of monitoring parameters averaged by day of monitoring and split by outcome categories. Graphs display concentrations (in microdialysates) of glucose (mmol/l) (**A**), glutamate (µmol/l) (**B**), glycerol (µmol/l) (**C**), lactate (mmol/l) (**D**), pyruvate (µmol/l) (**E**), values of microdialysate lactate/pyruvate ratio (**F**), microdialysate lactate/glucose ratio (**G**), intracranial pressure (mmHg) (**H**) and cerebral perfusion pressure (mmHg) (**I**). CPP = cerebral perfusion pressure; ICP = intracranial pressure.

who sustained unfavourable outcome or died. Glutamate, glycerol and intracranial pressure levels also tended to be lower in survivors, whereas other parameters did not demonstrate a consistent daily relationship with outcome. Total stay and 72 h averaged median values of monitoring parameters by outcome group and significance values for between-group comparisons are presented in Tables 1 and 2, respectively. Averaged over the total monitoring period, levels of glutamate, lactate/pyruvate ratio, intracranial pressure and PRx were significantly higher in patients who died (Fig. 2A–D), and median glycerol levels were also higher in the mortality group during the first 72 h (Fig. 3A). During the initial 72 h period, median lactate/pyruvate ratio and lactate levels (Fig. 3B and C) were also significantly lower in patients with favourable outcome, based on dichotomized Glasgow Outcome

Table 1 Median (interquartile range) values of monitoring parameters and percentages beyond pathological thresholds split by outcome groups, with respective statistical significance for intergroup comparisons

Parameter (*n* of data-points)	Outcome groups (Glasgow Outcome Scale)			*P*-value		
	Dead	Unfavourable	Favourable	Dead versus alive	Dead and unfavourable versus favourable	Favourable versus unfavourable
Glucose (*n* = 213) (mmol/l)	1.2 (0.6–1.7)	1.1 (0.5–1.9)	1.0 (0.7–1.8)	0.606	0.968	0.739
Glucose <1.0 mmol/l (%)	35.4 (6.3–85.7)	42.7 (7.2–89.4)	54.5 (10–83.1)	0.791	0.881	0.972
Glutamate (*n* = 155) (μmol/l)	3.2 (1.6–6.2)	2.3 (1.2–5.3)	1.8 (1.3–3.3)	**0.048***	0.154	0.637
Glutamate >10 μmol/l (%)	1.0 (0–12.9)	0 (0–7.8)	0 (0–2.0)	0.065	**0.046***	0.180
Glycerol (*n* = 118) (μmol/l)	72.5 (48.3–131.7)	56.5 (29.3–105.5)	54.9 (33.8–150.3)	0.108	0.615	0.681
Glycerol >150 μmol/l (%)	15.6 (0–36.1)	7.0 (0–37.5)	4.9 (0–49.5)	0.323	0.752	0.797
Lactate (*n* = 213) (mmol/l)	3.0 (2.3–4.2)	3.0 (2.5–4.8)	2.8 (2.2–4.0)	0.885	0.196	0.129
Lactate >4.0 mmol/l (%)	13.3 (1.8–57.1)	14.3 (2.1–78.3)	8.3 (0–50.2)	0.509	0.123	0.139
Pyruvate (*n* = 209) (μmol/l)	107 (82.8–141.9)	121.4 (97.2–170.8)	112.6 (94.5–149.9)	0.057	0.942	0.260
Pyruvate <50 μmol/l (%)	1.7 (0–5.5)	1.0 (0–2.9)	1.2 (0–3.4)	0.170	0.871	0.496
Lactate/pyruvate ratio (*n* = 208)	27.5 (21.6–33.1)	26.0 (20.8–29.5)	23.7 (20.4–28.6)	**0.044***	**0.045***	0.209
Lactate/pyruvate ratio >25 (%)	71.3 (14.2–91.7)	57.8 (21.5–85.7)	34.6 (8.8–77.5)	**0.041***	**0.013***	0.082
Lactate/pyruvate ratio >40 (%)	4.2 (0–25)	2.9 (0–13.5)	1.8 (0–6.7)	0.073	**0.039***	0.177
Lactate/glucose ratio (*n* = 212)	3.0 (1.4–5.6)	3.3 (2.0–8.0)	3.0 (1.5–5.0)	0.682	0.521	0.266
Lactate/glucose ratio >10 (%)	3.6 (0–23.1)	1.5 (0–40)	0.8 (0–11.1)	0.230	0.099	0.232
ICP mmHg (*n* = 137)	19.3 (15.1–22.2)	16.0 (13.8–19.1)	15.1 (12.9–19.3)	**0.006***	0.179	0.958
ICP >25 mmHg (%)	16.9 (2.9–38.6)	2.3 (0–10.9)	3.3 (0–10.8)	<**0.01***	0.088	0.677
CPP (*n* = 137) (mmHg)	76.0 (71.3–81.6)	77.4 (73–80.3)	77.2 (74.3–82.8)	0.342	0.221	0.400
CPP <60 mmHg (%)	2.3 (0–5.9)	0.4 (0–2.2)	0.6 (0–2.5)	**0.018***	0.232	0.934
PRx (*n* = 133)	0.1 (0.01–0.22)	0.02 (−0.06–0.15)	0.01 (−0.07–0.12)	**0.010***	**0.037***	0.362
PRx >0.2 (%)	32 (16.2–52.5)	22.3 (12.9–38.7)	19 (8.9–35.4)	**0.036***	0.059	0.308

Values represent the whole period of monitoring.
*Significant differences ($P < 0.05$) in bold type.
CPP = cerebral perfusion pressure; ICP = intracranial pressure.

Scale. When the data set was split by microdialysis catheter location, the above relationships remained as trends (Fig. 4A), but lost statistical significance for difference between outcome groups, due to reduction in patient numbers in each group. The median lactate/pyruvate ratio values in the unfavourable outcome group were significantly higher in pericontusional tissue compared with 'normal' brain ($n = 60$; $P = 0.004$, Mann–Whitney U-test), with a similar trend in deceased patients ($n = 47$; $P = 0.056$) and no difference between catheter locations in the favourable outcome group ($n = 101$; $P = 0.413$). When similar outcome analysis was performed on a subset of patients with isolated head injury or minor extracranial injury, values of several monitoring variables were also significantly different in the favourable outcome group, as compared with unfavourable outcome with or without mortality (Table 3). In addition to the above data analyses, a preliminary evaluation of outcome versus peak values of parameters for each patient was also conducted but revealed no further insight (data not shown) and so was not pursued.

In a multivariate logistic regression model ($n = 127$) total monitoring period averaged glucose, pyruvate, lactate/pyruvate ratio and PRx, together with age, were significant independent predictors of mortality (Table 4). These were all positive predictors, thus high values of these parameters were associated with elevated mortality, with the exception of pyruvate, which was a negative predictor, meaning that high pyruvate was associated with reduced mortality. Within the same multivariate logistic regression model, Glasgow Coma Scale was also a negative predictor, albeit bordering on significance ($P = 0.055$). In models with dichotomized Glasgow Outcome Scale with or without inclusion of mortality as dependant variable, only 'conventional' parameters— age and Glasgow Coma Scale—were consistent significant independent predictors of outcome.

Discussion

In this observational study, we have demonstrated a relationship between cerebral extracellular biochemical markers measured with microdialysis and neurological outcome following TBI. This, to our knowledge, is the largest cohort of patients with such analysis to date.

Correlation between established monitoring parameters reflecting intracranial physiology (intracranial pressure and cerebral perfusion pressure) and mortality after TBI has been long demonstrated in many observational studies. More recently, other monitoring parameters such as brain tissue oxygenation, indices of cerebral autoregulation and cerebral extracellular pH (Gupta *et al.*, 2004) have also been independently linked to mortality and neurological outcome. Since the introduction of cerebral microdialysis as a monitoring tool for patients with TBI and subarachnoid haemorrhage, several studies have reported a relationship between individual biochemical markers and patients'

Table 2 The initial 72 h of monitoring median (interquartile range) values of monitoring parameters and percentages beyond pathological thresholds split by outcome groups with respective statistical significance for intergroup comparisons

Parameter (*n* of data-points)	Outcome groups (Glasgow Outcome Scale)			*P*-value		
	Dead	Unfavourable	Favourable	Dead versus alive	Dead and unfavourable versus favourable	Favourable versus unfavourable
Glucose (*n* = 185) (mmol/l)	1.3 (0.8–1.8)	1.2 (0.5–1.9)	1.0 (0.7–1.8)	0.401	0.342	0.666
Glucose <1.0 mmol/l (%)	32 (4.3–79.4)	32.3 (4.8–90.1)	52.6 (10.3–81.9)	0.730	0.378	0.492
Glutamate (*n* = 138) (μmol/l)	3.2 (1.7–5.7)	2.3 (1.2–5.7)	2.0 (1.2–5.7)	0.094	0.692	0.589
Glutamate >10 μmol/l (%)	0 (0–11.7)	0 (0–5.1)	0 (0–1.7)	0.214	0.150	0.302
Glycerol (*n* = 106) (μmol/l)	84.5 (58.1–133.5)	54.0 (35.3–110.8)	60.0 (36.6–121.0)	**0.014***	0.223	0.858
Glycerol >150 μmol/l (%)	4.9 (0–39)	0 (0–31.3)	0 (0–31.7)	0.174	0.449	0.959
Lactate (*n* = 185) (mmol/l)	2.9 (2.2–3.9)	2.9 (2.4–4.1)	2.5 (2.0–3.5)	0.224	**0.033***	0.071
Lactate >4.0 mmol/l (%)	8.3 (0–49.2)	6.8 (0–51.0)	2.1 (0–27.7)	0.263	0.112	0.212
Pyruvate (*n* = 181) (μmol/l)	101 (83.2–140.4)	109.6 (94.1–153)	104.5 (87.8–149.3)	0.361	0.609	0.236
Pyruvate <50 μmol/l (%)	1.5 (0–3.9)	0 (0–2.3)	1.3 (0–3.5)	0.427	0.713	0.349
Lactate/pyruvate ratio (*n* = 180)	26.9 (21.2–33.1)	25.4 (21.7–30.7)	23.8 (19.9–28.2)	0.055	**0.026***	0.120
Lactate/pyruvate ratio >25 (%)	72.2 (14.1–97.9)	51 (16.1–86.6)	32.8 (6.4–81.0)	**0.028***	**0.013***	0.094
Lactate/pyruvate ratio >40 (%)	4.2 (0–19.8)	2.3 (0–13.7)	1.5 (0–5.1)	**0.046***	**0.017***	0.099
Lactate/glucose ratio (*n* = 184)	2.7 (1.4–4.2)	2.4 (1.9–6.4)	2.7 (1.6–4.6)	0.867	0.872	0.650
Lactate/glucose ratio >10 (%)	0 (0–10.2)	0 (0–14.2)	0 (0–3.5)	0.295	0.067	0.107
ICP (*n* = 115) (mmHg)	18.1 (15.2–21.5)	16.0 (13.4–19.4)	17.5 (14.2–20)	0.262	0.849	0.373
ICP >25 mmHg (%)	8.9 (0–27.9)	1.5 (0–11.4)	5.4 (0–18.1)	0.127	0.554	0.094
CPP (*n* = 115) (mmHg)	75.4 (71.5–79.2)	75.6 (72.9–80)	76.2 (72.2–78.9)	0.741	0.788	0.929
CPP <60 mmHg (%)	0 (0–3.2)	0 (0–3.3)	0 (0–3.2)	0.958	0.747	0.712
PRx	0.03 (−0.08–0.18)	−0.08 (−0.13–0.03)	−0.13 (−0.16 to −0.05)	**0.045***	0.118	0.516
PRx >0.2 (%)	19.8 (6.6–40.8)	15.6 (3.4–27.6)	11.6 (3.5–24.2)	0.112	0.137	0.712

CPP = cerebral perfusion pressure; ICP = intracranial pressure.
*Significant differences ($P < 0.05$) in bold type.

outcome. In the hitherto largest series of 126 patients with TBI, Goodman *et al.* (1999) found that elevated lactate and lactate/glucose ratio correlated with death. However, only univariate statistical methods were used. Other TBI studies have found relationships with outcome for the concentrations of excitatory amino acids, glucose, lactate/pyruvate ratio and cerebral interleukins (Zauner *et al.*, 1997; Koura *et al.*, 1998; Goodman *et al.*, 1999; Winter *et al.*, 2004; Hutchinson *et al.*, 2007; Marcoux *et al.*, 2008). However, most of these reports were based on small groups of patients, used mortality as an outcome measure and focused on single markers in univariate analysis and/or used pooled data. One of the most important initial steps in assessing clinical utility of novel monitoring technique is evaluating its independent contribution as distinct from that afforded by physiological data. As many neuromonitoring parameters are strongly inter-correlated, it is difficult to confirm whether novel techniques, e.g. microdialysis and brain tissue oximetry, are contributing any additional clinical information without testing them in multivariate models, accounting for the effects of other important monitored variables. Zauner *et al.* (1998) used multiple logistic regression analysis in 60 patients who underwent multimodality monitoring and found that brain oxygen was the strongest independent predictor of outcome. Sarrafzadeh *et al.* (2004) found that both lactate/pyruvate ratio and glutamate were significant independent predictors of outcome along with known strong predictors, such as age and World Federation of Neurosurgical Societies grade in 149 patients with subarachnoid haemorrhage.

The most consistent finding in our analysis, including temporal changes and multivariate analysis, is the significant association of higher lactate/pyruvate ratio with increased mortality and unfavourable outcomes after TBI. The lactate/pyruvate ratio reflects the metabolic state, and the elevation of lactate/pyruvate ratio may reflect the presence of either mitochondrial dysfunction (Verweij *et al.*, 2000) or lack of oxygen supply, due to ischaemia or hypoxia (Hlatky *et al.*, 2004). In the modern setting of protocol-driven neurocritical care true ischaemic states are rare occurrences (Vespa *et al.*, 2005). Nevertheless, the analysis of individual patients' temporal patterns of lactate/pyruvate ratio and other markers often reveals fluctuating values reflecting clinical course and changing energy metabolism. In addition, persistent abnormalities that are refractory to clinical interventions are also common, especially in the vicinity of the injured cerebral tissue (Vespa *et al.*, 2007). Both of these static and dynamic metabolic abnormalities can have an impact on survival and outcome. Our data support such a link, demonstrating persistently higher lactate/pyruvate ratio in non-survivors and in patients with unfavourable outcome. Moreover, the present study's findings support the previously suggested (Reinstrup *et al.*, 2000) physiological threshold of lactate/pyruvate ratio = 25 as a discriminator, with higher threshold of 40 not adding significant value to the model. It is

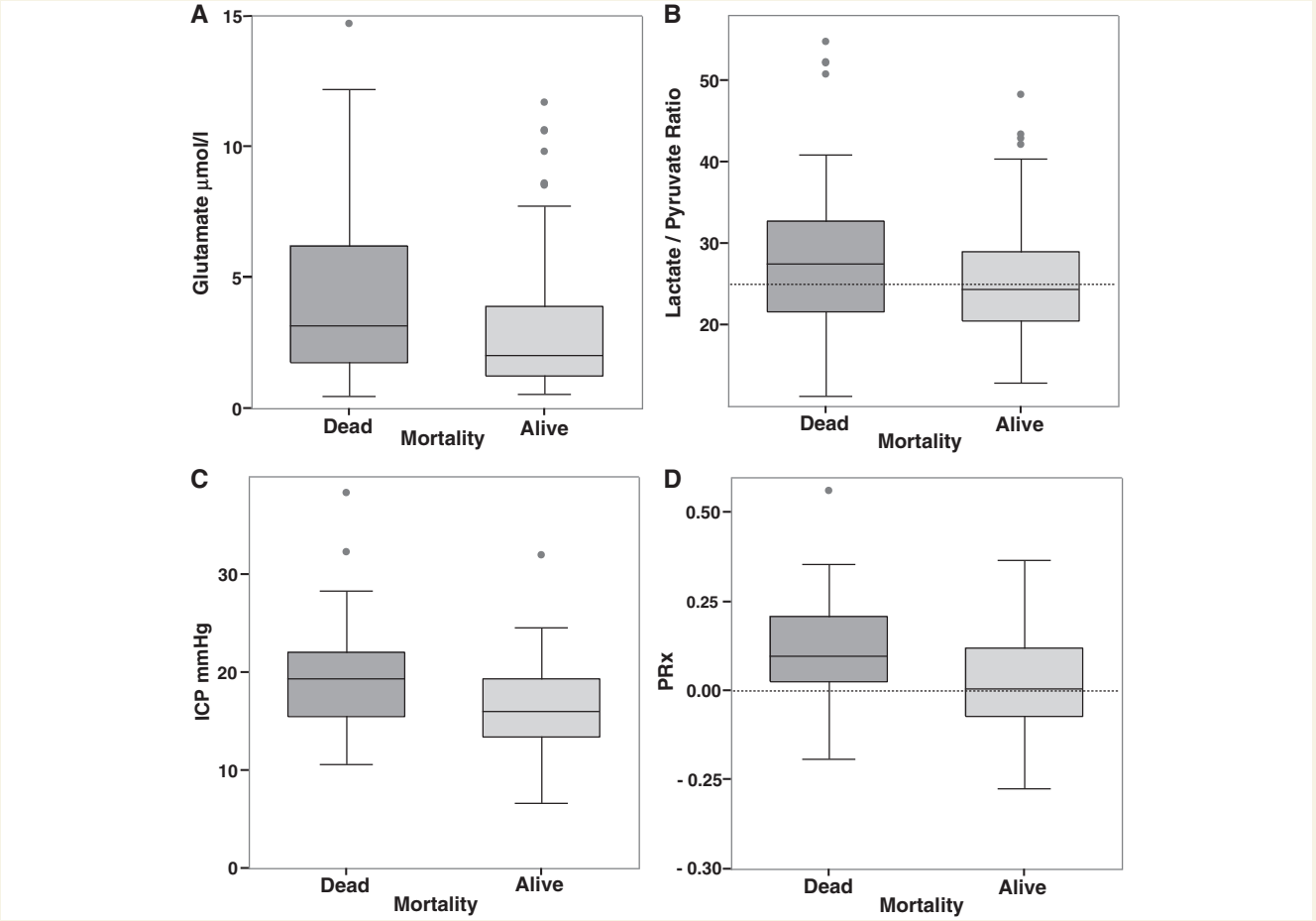

Figure 2 The median values of monitoring parameters split by mortality categories (data represent the whole monitoring period). Graphs display concentrations (in microdialysates) of glutamate (µmol/l) (**A**), values of microdialysate lactate/pyruvate ratio (**B**), intracranial pressure (mmHg) (**C**) and cerebrovascular pressure reactivity index PRx (**D**).

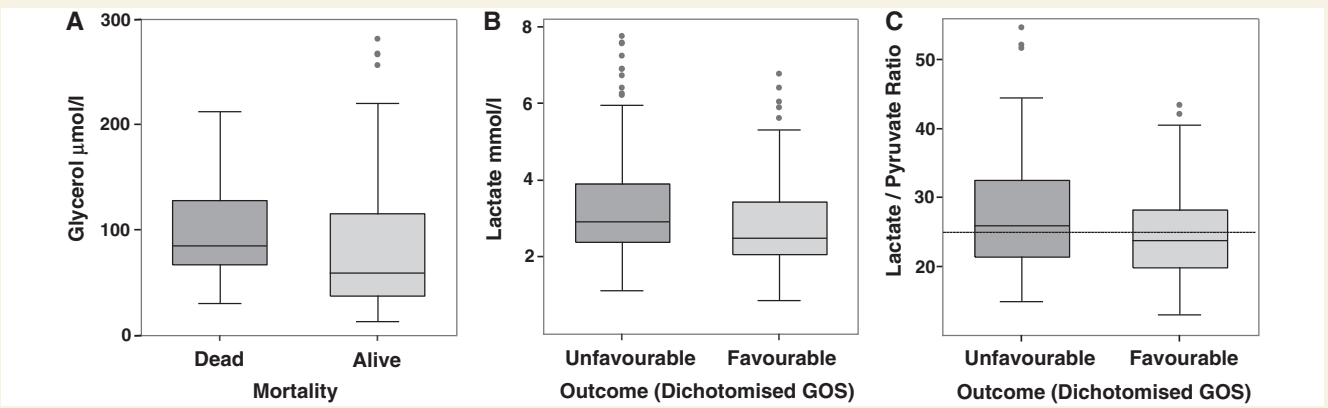

Figure 3 The median values of monitoring parameters split by mortality (**A**) and dichotomized Glasgow Outcome Scale (GOS) (**B and C**) during the initial 72 h of monitoring.

also possible to suggest that early after the injury, at least within the first 72 h, the changes in lactate/pyruvate ratio and other markers have a stronger association with outcome, possibly due to the period of unstable physiology and maximum tissue vulnerability soon after the injury. During these early periods, the lactate/pyruvate ratio can differentiate between survival categories, and moreover can discriminate between favourable and unfavourable outcome groups. A significant difference in

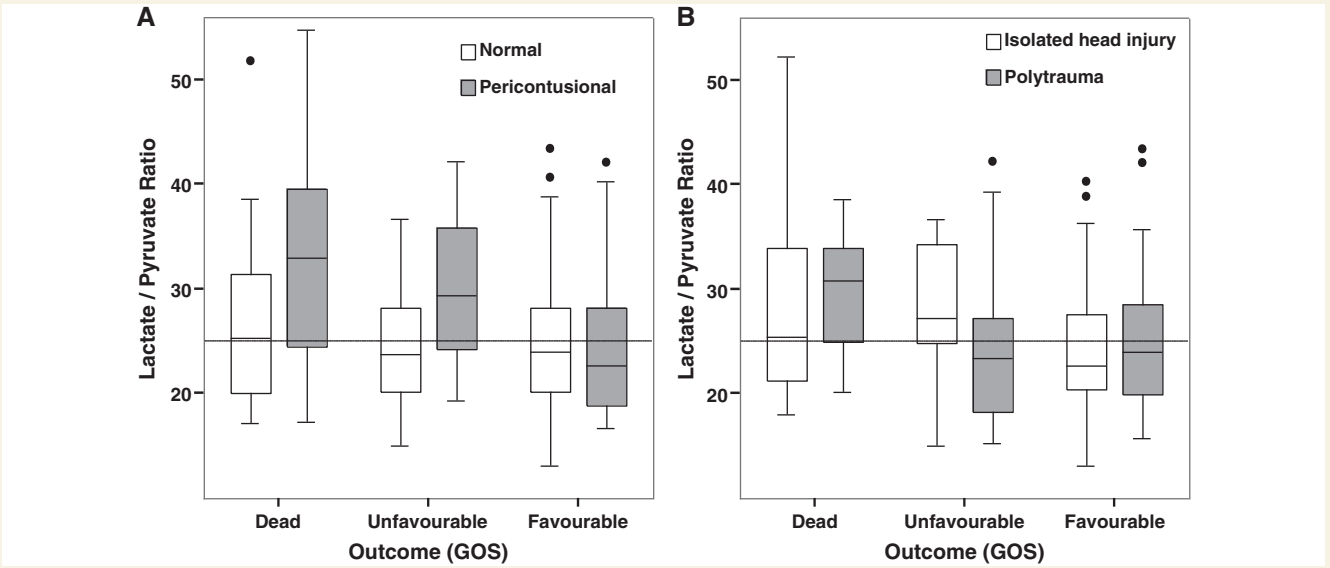

Figure 4 (**A**) Median values of the lactate/pyruvate ratio split by outcome groups and catheter location. (**B**) Relationship between lactate/pyruvate ratio and outcome depending on the presence of significant extra-cranial injury. GOS = Glasgow Outcome Scale.

Table 3 The values of monitoring parameters and percentages beyond pathological thresholds split by outcome groups, with intergroup comparisons for a subgroup of patients with isolated head injury or only minor extra-cranial injury

Parameter (*n* of data-points)	Outcome groups (Glasgow Outcome Scale)			*P*-value		
	Dead	Unfavourable	Favourable	Dead versus alive	Dead and unfavourable versus favourable	Favourable versus unfavourable
The whole duration of monitoring						
Lactate (*n* = 106) (mmol/l)	3.1 (2.6–4.3)	2.8 (2.5–4.3)	2.6 (2.0–3.3)	**0.019***	**0.003***	**0.047***
Glutamate (*n* = 73) (μmol/l)	2.9 (2.0–10.7)	1.5 (1.1–4.0)	1.8 (1.2–2.6)	**0.016***	0.326	0.679
Lactate/pyruvate ratio (*n* = 105)	27.7 (22.9–38.0)	27.4 (24.3–33.2)	23.7 (20.9–29)	0.058	**0.007***	**0.042***
Lactate/pyruvate ratio >25 (%)	74.6 (34–99.1)	72.9 (41.5–90.3)	34.7 (9.3–73.8)	**0.039***	**0.002***	**0.015***
Lactate/pyruvate ratio >40 (%)	5.2 (0.6–35.7)	7.5 (1.2–20.4)	1.5 (0–7.5)	0.188	**0.013***	**0.038***
ICP % > 25 mmHg (*n* = 76)	14.7 (2.5–30.6)	1.3 (0–19.3)	6.4 (0–14.5)	**0.017***	0.282	0.498
CPP % < 60 mmHg	1.4 (0–6.2)	0 (0–2.2)	0 (0–1.7)	**0.044***	0.135	0.831
The initial 72 h of monitoring						
Glutamate μmol/l (*n* = 63)	3.2 (2.3–10.4)	1.5 (0.9–3.7)	1.8 (1.5–3.6)	**0.019***	0.88	0.138
Lactate mmol/l (*n* = 91)	3.2 (2.5–4.6)	2.9 (2.4–3.6)	2.2 (1.9–2.8)	**0.001***	**<0.01***	**0.004***
Lactate > 4 mmol/l (%)	9.8 (1.8–62.1)	4.9 (1.6–29.1)	1.6 (0–9.9)	**0.015***	**0.001***	**0.018***
Pyruvate μmol/l (*n* = 89)	136 (92.8–163.2)	105.3 (95.2–116.3)	95.6 (84–107.5)	**0.012***	**0.003***	**0.047***
Lactate/pyruvate ratio (*n* = 89)	25.5 (21–34.5)	27.2 (24.8–34.6)	22.7 (19.7–27.6)	0.277	**0.008***	**0.01***
Lactate/pyruvate ratio >25 (%)	59.7 (17–98.9)	71.9 (46.7–81.6)	28.1 (5.9–78.3)	0.137	**0.004***	**0.011***
Lactate/pyruvate ratio >40 (%)	2.9 (0–20)	10.2 (1.5–25.8)	0 (0–5.3)	0.395	**0.005***	**0.003***
Lactate/glucose ratio >10 (*n* = 89) (%)	0 (0–3.6)	2.5 (0–30.1)	0 (0–0.9)	0.563	0.087	**0.010***
PRx >0.2 (*n* = 62)	0.04 (−0.01–0.19)	−0.01 (−0.12–0.08)	−0.04 (−0.1–0.12)	**0.040***	0.172	0.980

CPP = cerebral perfusion pressure; ICP = intracranial pressure.
*Significant differences ($P < 0.05$) in bold type.

lactate/pyruvate ratio and other microdialysis markers between the favourable and unfavourable outcome cohorts is also more pronounced in patients with isolated head injury, probably because major extracranial injury is likely to influence functional outcome, diluting the effects of deranged cerebral biochemistry.

The biological significance of the lactate/pyruvate ratio is incompletely understood. Originally, high lactate/pyruvate ratio was interpreted as ischaemia, but more recently it has also come to be regarded as arising from mitochondrial dysfunction, although the precise biological and biochemical details of this dysfunction in

Table 4 Binomial logistic regression with mortality as dependent variable

Model summary				
Predictor	***B* (Standard error)**	***P*-value**	**Exp(*B*)**	**95% CI for Exp(*B*)**
Glucose	0.61 (0.27)	**0.024***	1.84	1.09–3.13
Pyruvate	−0.02 (0.008)	**0.004***	0.98	0.96–0.99
Lactate/pyruvate ratio	0.08 (0.03)	**0.016***	1.09	1.02–1.16
ICP	0.15 (0.07)	**0.029***	1.16	1.02–1.33
PRx (×10)[a]	0.46 (0.22)	**0.036***	1.58	1.03–2.41
Age	0.06 (0.02)	**0.003***	1.07	1.02–1.11
Glasgow Coma Scale	−0.18 (0.09)	**0.055**	0.84	0.7–1.00
Constant	−5.78 (1.88)	**0.002***	0.003	

Model summary: $\chi^2 = 29.69$, $P < 0.0001$; $R^2 = 0.436$ (Nagelkerke).
*Statistically significant ($P < 0.05$). ICP = intracranial pressure.
[a]Original PRx values were multiplied by a factor of 10 (to achieve comparable scale) before entering into the logistic regression model.

patients with TBI remain unclear. Evidence from experimental models of TBI indicates various mitochondrial abnormalities microscopically and biochemically (e.g. Singh *et al.*, 2006; Opii *et al.*, 2007; Gilmer *et al*., 2009). The lactate/pyruvate ratio in patients with TBI can be regarded as a surrogate marker based on statistics, and is clearly not 100% selective for outcome. Even so, the incidence (%) of lactate/pyruvate ratio >25 emerges as a much better discriminator between outcome groups than incidence (%) of lactate/pyruvate ratio >40 (Table 1). The significance of lactate/pyruvate ratio in the present study reinforces earlier findings in smaller studies and supports the consensus of Bellander *et al*. (2004). It may be possible in future to devise better composite markers for adverse cerebral metabolism, based on multimodal monitoring of the present panel of parameters and possibly also novel parameters that may emerge as surrogate markers from further prospective research. We are further investigating the biological significance of abnormal brain chemistry in TBI. It is important to remember that microdialysis is a focal technique and local effects may or may not influence outcome. In a microdialysis study of three amino acids (glutamate, aspartate and threonine) in 80 patients, in which the catheter was placed close to a focal lesion if present, different sub-types of TBI (diffuse injury, contusion, subdural haematoma and epidural haematoma) evoked differences in brain chemistry (Bullock *et al.*, 1998). We consider the role of abnormal chemistry as a putative mechanism of secondary injury by means of which the primary injury eventually evolves into outcome.

Interpretation of changes in other microdialysis markers is confounded by the influence of recovery, which can in turn be affected by many extrinsic and intrinsic factors (Hutchinson *et al.*, 2002). However, in line with previous reports, our data suggest that other common 'bedside' markers, including glucose, lactate, pyruvate, glutamate and glycerol can be associated with mortality and functional outcome, although less consistently compared with the lactate/pyruvate ratio. Interestingly, pyruvate emerged as a negative predictor of mortality (i.e. relatively high pyruvate was associated with reduced mortality) in the logistic regression model. This is consistent with evidence, in rats, for neuroprotection by pyruvate (Lee *et al.*, 2001; Fukushima *et al.*, 2009; Moro and Sutton, 2010), and merits further investigation in humans. Somewhat unexpectedly, multivariate analysis suggested that higher, rather than lower cerebral glucose was associated with increased mortality, contradictory to the previous reports (Goodman *et al.*, 1999; Vespa *et al.*, 2003). This observation is likely to be due to the low incidence of hypoglycaemia and cerebral ischaemia in this data set, minimizing the frequency of episodes and potential impact of reduced cerebral glucose on outcome. On the other hand, higher cerebral glucose is likely to reflect hyperglycaemia, the deleterious effect of which on patients with neurological injury is well known. Alternative explanations include decreased consumption in the injured brain or hypermetabolic states, such as hyperglycolysis, where the transport of glucose via blood brain barrier may be increased, to match the demand. Blood glucose levels appear to influence brain metabolism in patients with TBI, evidenced by arterial-jugular venous difference measurements (Holbein *et al.*, 2009) and cerebral microdialysis (Diaz-Parejo *et al.*, 2003; Meierhans *et al.*, 2010). Blood glucose levels within the range 6–9 mM and brain microdialysate glucose levels of 1–5 mM were associated with minimizing the corresponding microdialysate lactate/pyruvate ratio and glutamate concentration, while microdialysate glucose levels <1 mM and >5 mM were associated with high lactate/pyruvate ratio and high glutamate, respectively, albeit in a small study (Meierhans *et al.*, 2010). Defining the optimal ranges of both cerebral and plasma glucose is beyond the scope of the present study and requires well-designed prospective studies.

Impaired cerebral autoregulation may have impact on tissue oxygenation and chemistry and our analysis supports PRx—the index of cerebrovascular pressure-reactivity—as a strong independent predictor of outcome, in line with our previous reports. Alongside microdialysis, pressure parameters are routinely part of our multimodality monitoring in TBI, and if we had omitted these non-chemical factors from the data analysis we would have risked missing significant findings. The relationship of chemical factors to outcome might be at least partly mediated via pressure reactivity, and we explored this possibility. However, it was not possible to conclude whether the changes in autoregulation lead to biochemical impairment, or vice versa, as temporal monitoring trends from individual patients suggest that both of these scenarios are possible, with no prevalence of any given pattern.

Limitations of the study

The study is based on an observational data set and therefore only the relationship between biochemistry and outcome can be reported, without definitive proof that chemistry directly influences outcome. Although one of the largest to date, the size of the study group is still not large enough to reliably account for all important variables or draw firm conclusions about absence of relationships, which may not be significant due to insufficient statistical power. These data were collected over a long period of time and this could introduce bias due to gradually changing monitoring and clinical practices. Furthermore, the nature of microdialysis as a focal monitoring tool may also limit generalization of the

findings. The issue of catheter location is complicated by the fact that the traumatic penumbra is difficult to define in TBI (in contrast to stroke, etc.). Technical constraints and the heterogeneity of brain injury make selective insertion at the outset into pericontusional or 'normal' brain often difficult to achieve in practical terms, depending on where contusions and 'normal' tissue are situated within the brain. Frontal placement of catheters is the most practicable option for clinical monitoring, with the nature of the tissue judged retrospectively from scans. Notwithstanding, stereotactic placement of catheters is possible, though technically more demanding and time-consuming, and may be used more in future, though might not be an option in all cases for clinical reasons, bearing in mind that these patients are critically injured. For the future, there is scope for more sophisticated mathematical modelling, e.g. to explore relationships between time-variant brain chemistry and outcome. Advances in modelling may lead to improved utility of microdialysis and other multimodality monitoring data to predict outcomes and guide interventions.

Conclusion

The results of this study suggest that extracellular metabolic markers are independently associated with outcome following TBI with the lactate/pyruvate ratio being the most consistent predictor at the threshold of approximately 25. Particularly within the first 72 h from injury and in patients with isolated head injury, lactate/pyruvate ratio can discriminate between favourable and unfavourable outcome in addition to mortality. Whether treatment interventions can influence cerebral biochemistry and whether this translates into better outcome remains to be established.

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Conflict of interest

ICM+ software for brain monitoring (www.neurosurg.cam.ac.uk/icmplus) is licensed by the University of Cambridge, Cambridge Enterprise Ltd. P.S. and M.C. have financial interests in a part of licensing fee. P.J.H., M.C. and J.D.P. are Directors of Technicam.

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