Cerebral Perfusion Pressure in Severe Traumatic Brain Injury and Its Relation to Microdialysis-Assessed Interstitial Brain Glycerol and Lactate-Pyruvate Ratio

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Abstract

Objective The aim of the study was to analyze the relationship of cerebral perfusion pressure (CPP) and its relationship to microdialysis (MD) analysates and their role as predictors of outcome in severe traumatic brain injury (TBI).

Methods A total of 41 patients with severe TBI who underwent decompressive craniectomy were prospectively monitored with intracerebral MD catheters. The relation between cerebral perfusion pressure and MD-measured interstitial brain glycerol and lactate-pyruvate ratio (LPR) concentrations was studied.

Results Twenty-six (63.4%) patients had a good outcome in terms of GOS at 6 months whereas the rest (15 patients) had poor GOS at 6 months. There was significant difference in mean CPP values between the two groups ($p = 0.000$). In the poor outcome group, the mean LPR was 80.16 as compared with a mean of 45.77 in the good outcome group ($p = 0.00$). Taking a cutoff of both LPR < 45 and CPP > 70 mm Hg, a significant difference in outcome was seen ($p = 0.03$).

Conclusion CPP seems essential to maintaining normal metabolism. Low CPP values and high ICP values are associated with a poor outcome. MD variables glycerol and LPR are dependent on CPP and are prognostic factors for the outcome.

Keywords
- microdialysis
- glycerol
- lactate-pyruvate ratio
- cerebral perfusion pressure

Introduction

Traumatic brain injury (TBI) remains a major cause of morbidity and mortality worldwide. Nonmodifiable factors such as initial injury severity, Glasgow coma score (GCS), pupillary response, age, and presence of additional physiologic derangements such as hypoxia or hypotension predominantly affect the outcome in such cases.[1,2]

Secondary insults continue to take place after initial injury and are important in determining outcome.[3] The management of patients with TBI currently focuses on intracranial pressure (ICP) or cerebral perfusion pressure (CPP) therapy.[4–7] Although this approach is an important component, ICP-based monitoring and treatment alone may not be enough to modify TBI prognosis.[8] In a recent meta-analysis, the authors found that the current clinical evidence does not indicate that ICP monitoring overall was superior to no ICP monitoring in terms of the mortality of TBI patients.[9]

Cerebral microdialysis (MD) has been in clinical use for over a decade. However, its utility in neurointensive care has not yet been established. ICP and CPP both have been said to correlate with MD values.[10] Current evidence is mostly based on small scale studies. Dizdarevic et al showed in their recent study that

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the modified Lund concept with bedside MD monitoring showed better results compared with CPP-targeted therapy in the treatment of comatose patients sustaining brain injury after aneurysmal subarachnoid hemorrhage (SAH) and severe TBI.[11]

The study aimed to see the role of glycerol and lactate-pyruvate ratio (LPR) monitoring in the brain parenchyma region and its association with CPP for outcome prediction.

Subjects and Methods

The study was conducted on 41 patients aged > 18 years with severe TBI (Glasgow coma scale [GCS] ≤ 8) who presented to the emergency with a surgically treatable lesion. Patients who were pregnant, had GCS = 3 with fixed dilated pupils, or hemodynamically unstable were not enrolled in this prospective nonrandomized study. As part of routine protocol, the patient underwent a noncontrast computed tomography (NCCT) of the head at admission along with assessment of other systemic injuries. Informed consent and institute ethics review board permission were obtained prior to inclusion in this study. The outcome was assessed using the Glasgow outcome scale (GOS). GOS variable was divided according to favorable and unfavorable outcomes. GOS 4 and GOS 5 were considered as favorable outcome, whereas GOS ≤ 3 as an unfavorable one.

Patient Management

The study included patients of severe TBI with a surgically treatable lesion and/or raised ICP/refractory intracranial hypertension (subdural hematoma [SDH], contusions, diffuse cerebral edema with refractory intracranial hypertension: sustained rise in ICP > 20 mm Hg for over 30 minutes), who were subjected to decompressive craniectomy with augmentation duraplasty. At the time of dural closure, a single MD catheter CMA-70 (20-kDA catheters) was inserted in the brain parenchyma at a depth of 20 mm. These catheters were inserted under direct vision in the cerebral tissue on the predominantly injured side at the time of surgery. They were then connected to the cerebral MD pump that was preloaded with central nervous system (CNS) perfusion fluid. Seven patients had catheters placed bilaterally. These included two patients undergoing bifrontal decompressive craniectomy and five patients had catheters inserted on the contralateral side through burr hole at Kocher's point. All patients also underwent concurrent ICP monitoring using an intraparenchymal ICP catheter–based monitoring. Postoperatively they were managed in the neurointensive care unit. All patients were managed as per standard treatment guidelines as given by the Brain Trauma Foundation[12] (BTF 2007). All patients also had invasive arterial pressure monitoring. Postoperative NCCT of the head was routinely done to confirm the position of the catheter(s) in penumbra/intraparenchymally.

Cerebral Microdialysis

Depending on the availability of an appropriate analytical assay, virtually any soluble molecule in the interstitial space fluid can be measured by MD. The MD probes consist of a tubular dialysis semipermeable membrane through which a solution, usually devoid of the analyte of interest, is passed at a very slow rate. With this perfusion into the extracellular tissue, the analytes diffuse along their concentration gradient and can be recovered. It is important to understand that the measured values for interstitial products using MD vary with perfusion rates. In our study, MD catheter probes (molecular weight cutoff of 20 kDa, 10-mm membrane, CMA-70, CMA Microdialysis, M Dialysis AB, Stockholm, Sweden) were placed in the cerebral tissue on the predominantly injured side at the time of dural closure. The probes were perfused with CNS perfusion fluid at 0.3μL/min (P000151, CMA Microdialysis) and samples collected for intracerebral glycerol and LPR every hour. Concentrations of glucose, lactate, pyruvate, glutamate, and glycerol in the microdialysate were analyzed using the CMA-ISCUS^{flex} MD analyzer (M Dialysis AB, Stockholm, Sweden).

MD catheter was kept in place for a minimum of 3 days and up to a maximum of 5 days. Hourly data points were recorded for each individual. A data point was defined as the MD values acquired each hour in addition to the neurophysiologic parameters from the multimodal brain monitoring including ICP, CPP, mean arterial pressure (MAP), and plasma glucose. Normative data for MD are dependent on several technical factors, including the perfusion rate, MD membrane, and duration of perfusion. Careful assessment of the perfusion rate is required when comparing various studies. With reduction in the perfusion rate to 0.3 μL/min, the in vivo recovery increases. In keeping with the international standards,[13] the standard cerebral MD-based biochemical values for reference are kept as

- Glycerol: 20–50 mM
- LPR: 15–20

All data were tabulated in MS Excel 2011 and analyzed using SPSS v21 (IBM SPSS Statistics for Macintosh, Version 21.0. Armonk, NY: IBM Corp.). To calculate the correlation between CPP and LPR at each data point, the Pearson's correlation coefficient was used with a one-tailed test of significance. The biochemical values obtained during the entire study period (3–5 days) were averaged to calculate the overall mean values of CPP and LPR for each patient. Fischer exact test (two-tailed) was applied to the qualitative variables, and Student's *t*-test was used for between-group comparisons. Mann-Whitney *U* test was used to compare postresuscitation GCS (PRGCS) between the groups. Significance was assumed at $p \leq 0.05$.

Results

Demographic characteristics of the study cohort have been shown in ►**Table 1**. The mean age of the patients enrolled in the study was 33.4 (standard deviation [SD] = 13.6) years (range = 18–85). There were 35 males and 6 females in this group. The mean PRGCS was 6.02 (SD = 1.54) (range = 4–8) (►**Table 1**).

The mean age for the unfavorable outcome group was 36.4 years (SD = 17.5) and for the favorable outcome group was

Table 1 Demographic profile of patients enrolled in the study

	Mean	Median	SD	N
Age	33.42	30	13.55	41
Sex (M/F)				35/6
Postresuscitation GCS	6.02	7	1.54	
Outcome	Good (GOS 4,5)			26 (63.4%)
	Bad (GOS 1–3)			15 (36.6%)
	Expired (GOS 1)			11 (26.82%)

Abbreviations: F, female; GCS, Glasgow coma scale; GOS, Glasgow outcome scale; M, male; SD, standard deviation.

31.5 years (SD = 10.8), the difference being not statistically significant. The median PRGCS of the unfavorable outcome group was 5 (mean = 5.53; SD = 1.64) and for the favorable outcome group it was 7 (mean = 6.3; SD = 1.44). The groups were comparable for age, sex, and PRGCS (►**Table 2**).

A total of 3,697 corresponding CPP and brain MD readings were obtained. In our study, the mean CPP for the whole cohort was 74.3 mm Hg (SD = 14.05). In the poor outcome group, 1,512 values were obtained with a mean CPP of 71.3 (SD = 13.77). In the good outcome group, 2,185 values were obtained with a mean CPP of 76.3 mm Hg (SD = 13.86). There was significant difference in mean CPP values between the two groups ($p = 0.00$). Taking mean CPP of 70 mm Hg as a cutoff, the difference between the two groups was significant in predicting outcome ($p = 0.05$). The mean ICP in the poor outcome group was 17.3 (SD = 6.74) and in the good outcome group it was 14.6 (SD = 8.27). The difference in the ICP between the two groups was significant ($p = 0.00$) (►**Table 3**).

Glycerol

In the poor outcome group, 1,373 values were available for glycerol with a mean of 266.6 (SD = 616.7). In the good outcome group, 2,112 values were obtained with a mean glycerol of 311.7 (SD = 607.2). The difference between the two groups was statistically significant ($p = 0.03$). When compared during the first 2 days of monitoring, the glycerol levels were higher in the unfavorable outcome group (mean 220.9; SD = 25.9) as compared with the favorable outcome group (mean = 191.8; SD = 31.9). However, this difference was not statistically significant.

Lactate-Pyruvate Ratio

In the poor outcome group, 1,354 values were available for LPR with a mean of 80.2 (SD = 320.3). In the good outcome group, 2,047 values were obtained with a mean LP ratio of 45.8 (SD = 169.8). The difference between the two groups was statistically significant ($p = 0.01$). Taking LPR < 45 as a cutoff for mean LPR, the difference between the two groups was not significant in predicting outcome ($p = 0.06$).

However, taking both LPR < 45 and CPP 70 mm Hg as cutoff, there was a statistical significance in predicting outcome ($p = 0.03$).

We also compared the maximum and minimum values of the variables between the two groups. Although the good outcome group showed higher maximum and minimum CPP values, lower maximum and minimum ICP values, and lower maximum and minimum LP ratios. However, none of these differences was statistically significant (►**Table 4**).

Correlations of Cerebral Perfusion Pressure

CPP was seen to have an inverse correlation to LPR for the whole cohort as would be expected with increased perfusion ($p = 0.03$). An inverse correlation was also seen in the unfavorable outcome group ($p = 0.00$). However, it showed a positive correlation to glycerol, which cannot be explained by simply increased perfusion (►**Table 5**).

Discussion

Cerebral blood flow remains constant over a wide range of CPP under physiologic conditions as a result of the cerebral autoregulatory mechanisms. In cases of severe TBIs, these autoregulatory mechanisms may be altered. Depending on the nature of the injury, that is, focal or diffuse, such changes may be more localized or diffuse respectively.[14] With such changes, the cerebral blood flow may reduce even in presence of relatively normal CPP (50–70 mm Hg).[15] However, it must also be pointed out that not all reduction in cerebral blood flow is ischemia. Ischemia occurs following a mismatch between the cerebral blood flow and the metabolic requirements of the affected tissue. Therefore, both ischemia and decreased cerebral blood flow can occur even with CPP ≈ 65 to 75 mm Hg.[16] Therefore, CPP alone is not a reliable indicator to assess adequacy of the CBF in patients.

There remains no consensus for the ideal CPP values in severe TBI. CPP values > 70 mm Hg or even 80 mm Hg may be beneficial in terms of outcome. Some authors have warned about a higher risk of acute respiratory distress syndrome with a CPP > 70 mm Hg with no additional benefit to outcome.[17] A lower CPP goal of 60 mm Hg has been endorsed by the American Association of Neurological Surgeons and recently the Brain Trauma Foundation suggested a general threshold in the realm of 50 to 70 mm Hg.[12] As a result, monitoring with other bedside tools becomes necessary.

Table 2 Baseline characteristics and mean CPP and LPR values for each patient

S. No.	Age	Sex	PRGCS	Mean CPP	Mean LPR	GOS: good = 1, bad = 2	Injury
1	17	M	6	64.03	18.20	2	Parietal contusion
2	30	M	5	84.39	37.20	2	Frontal contusion + SDH
3	85	M	7	80.13	38.52	2	Frontotemporal contusion
4	41	M	7	68.63	85.21	2	Temporal contusion
5	25	M	4	69.48	108.04	2	Frontal contusion + SDH
6	35	M	7	82.92	47.46	2	FTP contusion + SDH
7	24	M	4	66.27	75.18	2	Frontal contusion + SDH
8	27	M	8	68.76	48.61	2	FTP contusion + SDH
9	23	M	4	74.02	147.72	2	FTP contusion
10	50	F	7	76.64	79.92	2	Frontal contusion
11	40	M	8	53.04	50.84	2	FTP contusion + SDH
12	60	M	4	69.43	27.49	2	Frontal contusion + SDH
13	35	F	4	66.58	66.64	2	Frontal contusion + SDH
14	26	M	4	55.39	409.65	2	Temporal contusion
15	28	M	4	87.68	36.89	2	FT contusion + SDH
16	42	M	8	67.27	21.76	1	Frontal contusion
17	18	M	7	67.65	35.21	1	Frontal contusion + SDH
18	35	M	7	87.92	45.53	1	Temporal contusion
19	64	F	8	74.87	32.56	1	FT contusion
20	45	M	4	65.08	131.72	1	Frontal contusion + SDH
21	25	M	4	80.58	38.49	1	FP contusion + SDH
22	35	M	6	74.60	3.89	1	Frontal contusion
23	16	M	5	69.36	69.44	1	FP contusion + SDH
24	25	M	5	81.74	58.18	1	Frontal contusion
25	22	M	7	88.77	113.41	1	FTP contusions + SDH
26	42	M	7	72.82	26.46	1	Frontal contusion + SDH
27	43	M	8	77.19	40.85	1	Frontal contusion + SDH
28	38	M	8	77.67	37.72	1	Frontal contusion + SDH
29	36	M	5	65.01	31.53	1	Frontal contusion + SDH
30	29	M	5	90.54	32.29	1	Frontal contusion + SDH
31	23	F	5	73.16	40.71	1	FTP contusion + SDH
32	38	F	8	56.03	25.13	1	FTP contusion + SDH
33	28	M	7	88.5	49.16	1	FP contusion + SDH
34	18	M	6	73.12	22.09	1	Temporal contusion
35	30	M	8	84.97	66.58	1	Frontal contusion + SDH
36	18	F	7	79.53	34.69	1	Frontal contusion + SDH
37	23	M	7	77.2	26.73	1	Frontal contusion + SDH
38	30	M	4	83.23	28.68	1	Frontal contusion
39	27	M	7	67.79	21.04	1	Parietal contusion + SDH
40	40	M	4	77.9	65.54	1	Frontal contusion
41	30	M	7	76.37	23.80	1	FTP contusion + SDH

Abbreviations: CPP, cerebral perfusion pressure; F, female; FT, frontotemporal; FTP, frontotemporoparietal; GOS, Glasgow outcome score (1–3 = bad GOS, 4, 5 = good GOS); LPR, lactate-pyruvate ratio; M, male; PRGCS, postresuscitation Glasgow coma score; SDH, subdural hematoma.
Note: Groups were similar for age ($p = 0.28$ *t*-test), postresuscitation GCS ($p = 0.13$ Mann-Whitney U test).

Table 3 Levels of MD analysates glycerol and LPR in various groups

Group	Variable	CPP < 70 mm Hg	CPP > 70 mm Hg	*p* Value
Total ($n = 41$)	Glycerol	240.5 (SD = 488.3)	330.2 (SD = 672.9)	0.00
	LPR	52.5 (SD = 68.4)	44.4 (SD = 56.9)	0.01
Good GOS ($n = 26$)	Glycerol	308.1 (SD = 578.8)	322.9 (SD = 623.9)	0.62
	LPR	37.3 (SD = 40.9)	41.5 (SD = 51.7)	0.09
Bad GOS ($n = 15$)	Glycerol	182.7 (SD = 385.9)	345.6 (SD = 765.3)	0.00
	LPR	65.4 (SD = 83.0)	50.4 (SD = 66.0)	0.00

Abbreviations: CP, cerebral perfusion; CPP, cerebral perfusion pressure; GOS, Glasgow outcome score; LPR, lactate-pyruvate ratio; MD, microdialysis; SD, standard deviation.

One such bedside tool is MD. MD assumes importance as a bedside tool to detect ischemia, cell breakdown, and to assess the metabolic state of the injured brain.[18–20] Abnormal LPR has classically been defined as an LPR > 25.[21] LPR >25 is associated with worse outcome after TBI.[22] Some authors have also used an LPR > 40 as marker of cell energy crisis.[21] In routine clinical practice, LPR > 35 to 40 has been used to start therapeutic interventions.

Zauner et al[23] showed in their study that a CPP of 70 mm Hg was associated with an increase in brain tissue oxygenation, brain glucose concentration, and a reduction in brain lactate levels as measured by cerebral MD. Poon et al[24] studied the concentrations of cerebral glucose, lactate, glycerol, glutamate, and pyruvate, and found them to correlate with CPP. They proposed an elevated critical CPP threshold (70 mm Hg) for patients with head injuries to prevent irreversible brain damage. Nordstrom et al[7] showed that significantly higher LPRs existed in pericontusional tissues at CPP < 50 mm Hg as compared with CPP > 50 mm Hg. However, no such difference was seen in the catheter inserted in the normal brain tissue at these CPP cutoff values. Thereby, they suggested that pericontusional brain was more sensitive to changes of CPP. In our study too, a significant difference can be seen in glycerol and LPR values taking a CPP cutoff at 70 mm Hg.

Nelson et al[25] demonstrated that patients with a CPP ≥ 70 mm Hg exhibited better prognosis in TBI. However, they found no significant relation between MD values and outcome. In addition, no correlation between CPP and MD variables was found in their study.

Glycerol is an end product of phospholipid breakdown. Degradation of cell membrane phospholipids leads to an increase in free fatty acids concentration. It can thus be used as a marker of membrane disintegration.[26] It would be expected that patients with TBI/other insults would have higher levels of glycerol indicative of cell breakdown.

Peerdeman et al[27] performed a prospective, observational study, and found that serious secondary adverse events in TBI patients were not associated with increased glycerol levels as measured by cerebral MD. They speculated that monitoring the interstitial brain glycerol was not useful in monitoring cell damage and thereby could not help in preventing further breakdown. In their study, a peak glycerol level > 150 µmol/L was predictive of an unfavorable outcome. However, Peerdeman et al described the insertion of the MD catheters in relatively normal tissue in the brain. This could be one of the reasons of not having got higher glycerol values that would have been the case had they inserted them in the pericontusional tissues. They also speculated that glycerol probably was more indicative of the primary event because

Table 4 Maximum and minimum values

		Maximum	Minimum	*p* Value
CPP (mm hg)	Good GOS	102.1 (SD = 14.6)	49.9 (SD = 17.6)	0.22
	Bad GOS	96.1 (SD = 14.9)	43.3 (SD = 11.6)	0.21
ICP (mm Hg)	Good GOS	22 (SD = 8.3)	7.7 (SD = 5.4)	0.08
	Bad GOS	26.7 (SD = 7.7)	9.4 (SD = 4.7)	0.31
LPR	Good GOS	578 (SD = 1,385)	14.1 (SD = 11.2)	0.45
	Bad GOS	968 (SD = 1,870)	16.7 (SD = 12.7)	0.51
Glycerol	Good GOS	1,817 (SD = 1,205)	1,050 (SD = 1,339)	0.07
	Bad GOS	11.8 (SD = 25.3)	6.7 (SD = 10.7)	0.46

Abbreviations: CPP, cerebral perfusion pressure; GOS, Glasgow outcome score; ICP, intracranial pressure; LPR, lactate-pyruvate ratio; MD, microdialysis; SD, standard deviation.
Note: The maximum and minimum values of each variable were noted for each patient. The means of these values were compared between the two groups. None of the differences were statistically significant.

Table 5 Correlation of various parameters with CPP

Variable	Group	Pearson correlation coefficient	*p* Value
ICP	Total	−0.39	0.00
	Good GOS	−0.35	0.00
	Bad GOS	−0.42	0.00
Glycerol	Total	0.04	0.04
	Good GOS	0.003	0.89
	Bad GOS	0.07	0.02
LPR	Total	−0.04	0.03
	Good GOS	0.06	0.01
	Bad GOS	−0.14	0.00

Abbreviations: CPP, cerebral perfusion pressure; GOS, Glasgow outcome score; ICP, intracranial pressure; LPR, lactate-pyruvate ratio.

values were much higher on day 1 of monitoring in the poor outcome group. Of the 4 patients with favorable outcome (GOS 5 and 4), none had a peak value of glycerol > 150 µmol/L, whereas 6 out of 10 patients (60%) with an unfavorable outcome had. They concluded that glycerol was more dependent on primary trauma rather than being indicative of secondary insults. Clausen at al[28] also observed significantly increased glycerol concentrations when $PbtO_2$ was < 10 mm Hg or when CPP was < 70 mm Hg in TBI patients.

In our study, contrary to expectations glycerol was significantly higher in the good outcome group. During the first 2 days of monitoring, the glycerol levels were higher in the unfavorable outcome group as compared with the favorable outcome group. We believe the higher values of glycerol in the good outcome group are a result of the longer monitoring of these patients. Because some of the bad outcome group patients expired during their course of monitoring, the cell breakdown products did not reach as high values as they would during the course of 5 days.

An elevated LPR can be seen due to ischemia. During episodes of ischemia, elevated lactate is accompanied by low pyruvate and usually accompanied by low levels of cerebral glucose and brain oxygen. LPRs during episodes of ischemia have been reported to be > 40. Also, hyperglycolysis[29] or mitochondrial dysfunction can be another cause of increase in LPR.[30] In these cases, the increase in glycolytic rate causes a massive production of lactate and increase in the LPR although tissue pyruvate remains at a normal level or increases slightly. Therefore, a high LPR is indicative of both mitochondrial dysfunction and ischemia.

Nikaina et al[31] showed that CPP and LPR have significant effects on the long-term outcome prognosis after a spontaneous cerebral hematoma. They took a cutoff CPP of ≥ 75.46 mm Hg and LPR ≤ 36.05. A weak negative correlation was also found between CPP and LPR in their study, much similar to ours. Thereby, the key to finding cutoffs of CPP may be found in keeping a favorable metabolic profile, as indicated by low LPRs.

Parafarou et al[32] in their study of TBI used a CPP cutoff > 75 mm Hg, LPR < 37, and glycerol < 72 as markers of good outcome. Our study shows somewhat similar results (LPR ≤ 45 and CPP ≥ 70 mm Hg).

Keeping all the aforementioned literature in mind, we agree that at present there is no consensus on the absolute or trend values of MD variables. At this point of time, it may be difficult to support a clinical decision making but may act as a useful adjunct in neurointensive care following TBI. Our study adds to growing evidence that LPR cutoff around 40 to 45 are predictive of outcome.

Limitations

This study has several important limitations. First is the lack of contralateral catheters in all patients that would allow us to compare changes in injured and normal brain. The study only includes a subset of TBI patients who underwent decompressive craniectomy. Including conservatively managed patients could give a more comprehensive picture of the pathophysiology in TBI. We did not have access to direct measurements of cerebral blood flow, which would give us a better idea of autoregulatory processes.

Conclusion

CPP monitoring is important for TBI since cerebral blood flow is highly dependent on CPP below the lower limit of cerebral autoregulation (CP p < 50 mm Hg). Our study supports the view that higher CPP by its effect on metabolic parameters, such as LPR, could be associated with a better outcome. MD parameters can thereby be used as a bedside tool to guide CPP targets and any interventions while aiming for the best possible outcome.

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