Neurosurgical Focus

Cerebral blood flow as a predictor of outcome following traumatic brain injury

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As part of a prospective study of the cerebrovascular effects of head injury, 54 moderate and severely injured patients underwent 184 133Xe-cerebral blood flow (CBF) studies to determine the relationship between the period of maximum blood flow and outcome. The lowest blood flows were observed on the day of injury (Day 0) and the highest CBFs were documented on postinjury Days 1 to 5. Patients were divided into three groups based on CBF values obtained during this period of maximum flow: Group 1 (seven patients), CBF less than 33 ml/100 g/minute on all determinations; Group 2 (13 patients), CBF both less than and greater than or equal to 33 ml/100 g/minute; and Group 3 (34 patients), CBF greater than or equal to 33 ml/100 g/minute on all measurements. For Groups 1, 2, and 3, mean CBF during Days 1 to 5 postinjury was 25.7 ± 4, 36.5 ± 4.2, and 49.4 ± 9.3 ml/100 g/minute, respectively, and $PaCO_2$ at the time of the CBF study was 31.4 ± 6, 32.7 ± 2.9, and 33.4 ± 4.7 mm Hg, respectively.

There were significant differences across Groups 1, 2, and 3 regarding mean age, percentage of individuals younger than 35 years of age (42.9%, 23.1%, and 76.5%, respectively), incidence of patients requiring evacuation of intradural hematomas (57.1%, 38.5%, and 17.6%, respectively) and incidence of abnormal pupils (57.1%, 61.5%, and 32.4%, respectively). Favorable neurological outcome at 6 months postinjury in Groups 1, 2, and 3 was 0%, 46.2%, and 58.8%, respectively ($p < 0.05$). Further analysis of patients in Group 3 revealed that of 14 with poor outcomes, six had one or more episodes of hyperemia-associated intracranial hypertension (simultaneous CBF > 55 ml/100 g/minute and ICP > 20 mm Hg). These six patients were unique in having the highest CBFs for postinjury Days 1 to 5 (mean 59.8 ml/100 g/minute) and the most severe degree of intracranial hypertension and reduced cerebral perfusion pressure ($p < 0.0001$).

These results indicate that a phasic elevation in CBF acutely after head injury is a necessary condition for achieving functional recovery. It is postulated that for the majority of patients, this rise in blood flow results from an increase in metabolic demands in the setting of intact vasoreactivity. In a minority of individuals, however, the constellation of supranormal CBF, severe intracranial hypertension, and poor outcome indicates a state of grossly impaired vasoreactivity with uncoupling between blood flow and metabolism.

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Key Words * traumatic brain injury * cerebral blood flow * cerebral metabolism * cerebral vasoreactivity * hyperemia * intracranial hypertension

Over the last two decades, a number of investigations have addressed the significance of dynamic cerebral blood flow (CBF) changes observed in the acute period after severe traumatic brain injury.[5,6,11,22,25,34-37,40,42] These studies have revealed a relatively consistent temporal profile of CBF, essentially characterized by three phases. During the first phase that occurs in the initial hours after injury, blood flows are lowest, falling on average to approximately 50% of normal.[6,22,36] By as early as 12 hours postinjury the second phase begins, marked by a rise in CBF that approaches or exceeds normal values in some patients and typically persists for the next 4 to 5 days. This phase is followed in turn by a third period of low CBF that lasts for up to 2 weeks postinjury.[5,25,36,37]

Although this triphasic blood flow pattern appears to describe accurately the severely head injured population as a whole, there is considerable heterogeneity among individuals. In some patients, blood flow remains depressed throughout the acute postinjury period, with marked blunting of the second phase, whereas in others a rise in CBF to nearly normal levels occurs early after injury and may remain elevated during both the second and third phases.[37,40,42] The magnitude and temporal profile of these CBF changes correlate with long-term recovery of function in some instances. For example, blood flows in the first phase postinjury are strongly predictive of outcome.[5,6,22] Not surprisingly, ischemia (CBF ¾ 18 ml/100 g/minute) also correlates with poor outcome, regardless of when documented, although it has been observed most often within 24 hours of injury.[5,22,37]

The significance of subsequent CBF changes in the second and third phases, in which classic ischemia is rarely observed, is less certain. Whereas investigations by Overgaard, et al.,[37] and Robertson, et al.,[40] have shown that higher blood flows during the 1st week to 10 days postinjury are associated with improved outcome, the majority of studies have found no such correlation when measurements were obtained more than 12 hours after insult.[5,22,31] In a report by Jaggi, et al.,[11] CBF correlated with outcome only when patients with hyperemia (CBF > 33 ml/100 g/minute) were excluded from analysis. The degree of reduction in the cerebral metabolic rate of oxygen ($CMRO_2$) was also predictive of recovery. Despite the variability in $CMRO_2$, the study by Jaggi, et al., and those of others have consistently shown a marked reduction in $CMRO_2$ to approximately 50% of normal for at least 10 days after severe head injury; this has led to the assumption that global metabolic depression is present during this period.[5,11,35,36]

Recent experimental studies, however, indicate that metabolic demands may increase dramatically after head injury, as evidenced by a transient period of hyperglycolysis.[2,10,14,15,17,48] In new work from our institution, a relative or absolute increase in glucose utilization has been observed following severe head injury in humans, as measured by fluorodeoxyglucose positron emission tomography (PET).[3,4] Interestingly, the temporal profile of hyperglycolysis in humans appears to parallel the period of increased CBF typically seen postinjury. These findings raise the question of whether the rise in blood flow seen in many patients is coupled to a rise in metabolic demands, whereas in others, low but not necessarily ischemic CBF may be inadequate, resulting ultimately in cell death and poor outcome.

Given the unclear relationship between acute CBF changes and outcome, this investigation was undertaken specifically to address the period of maximum blood flow postinjury. It was hypothesized that a significant rise from the initial period of hypoperfusion that typically occurs on the day of injury,

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(Day 0), is a necessary condition for achieving favorable outcome. The major goals of this study included: 1) determining if a lack of increase in global CBF on Days 1 to 5 postinjury was associated with poor outcome, despite being significantly above the traditionally defined threshold for ischemia; 2) identifying the clinical determinants for patients with consistently low CBF, those with both reduced and normal CBF, and those with consistently normal CBF during this postinjury period; and 3) defining the characteristics of patients with normal CBF but with poor outcome.

CLINICAL MATERIAL AND METHODS

Patient Enrollment

From July 1992 to January 1995, 184 acutely head injured patients were prospectively enrolled in the University of California at Los Angeles (UCLA) Brain Injury Research Center Program and treated at either the UCLA Center for Health Sciences or the Harbor-UCLA Medical Center. Informed consent was obtained from family members of all participants in the study. Of the original cohort, 67 patients sustained a moderate or severe head injury, defined as a postresuscitation Glasgow Coma Scale (GCS) score of 13 or less, and underwent serial CBF measurements and intracranial pressure (ICP) monitoring during their stay in the intensive care unit. Within this group, at least one CBF study was performed in each of 54 patients during Days 1 to 5 postinjury, and they are the focus of this report. This cohort differs by 15 patients from that reported in our recent paper concerning hyperemia after head injury.[16] It does not include 10 patients from the previous report because CBF was not recorded on Days 1 to 5 postinjury, and it does include five patients who were excluded from the earlier paper because simultaneous ICP and CBF recordings were not available. Therefore, the two studies include 49 of the same patients.

Determination of CBF

The CBF was measured by the 133Xe intravenous technique of Obrist, et al.,[35] using a bedside instrument with five external collimators placed over each hemisphere (Ceretronix Cerebrograph Cortexplorer model 10; Laco, Inc., Chesterfield, OH). At the time of CBF measurement, patients' ICP, cerebral perfusion pressure (CPP), and $PaCO_2$ were recorded. Concurrently administered vasoactive drugs (dopamine, phenylephrine, or norepinephrine) and metabolic suppressive agents (high-dose pentobarbital or propofol) were also documented. Blood flow studies performed in the setting of high-dose pentobarbital were included for analysis only if therapy clearly failed, as evidenced by persistently high CBF (> 55 ml/100 g/minute) without a decrease from earlier CBF studies before the patient received metabolic suppressive therapy, and intracranial hypertension persisted (ICP >= 25 mm Hg) without a significant reduction from pretreatment values. Previous investigations assessing the efficacy of high-dose pentobarbital for treatment of intractable intracranial hypertension in head-injured patients have shown a significant and concomitant decrease in both CBF and ICP in patients who respond favorably to such metabolic suppressive measures.[28,33] Four studies in four patients were included for analysis on this basis, whereas eight studies in four patients were excluded from analysis because therapy was effective or the effects were equivocal. Two CBF studies performed in patients receiving high-dose propofol were also excluded given that relatively little is known about the effects of this agent on CBF in the setting of severe head injury.[43]

As previously described, the CBF15 was determined for each cerebral hemisphere, and global CBF was defined as the average of the two hemispheric rates expressed in milliliters/100 g/minute.[26] Individual

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CBF studies were not adjusted to a normative $PaCO_2$ given the marked variability in both global and regional $PaCO_2$ reactivity after head injury, which makes the use of this adjustment of questionable validity, and because mild hyperventilation was routinely used.[21,31] Instead, mean $PaCO_2$ values at the time of CBF determination were compared between groups.[16] For each patient in whom more than one CBF measurement was taken for a given CBF phase, a mean value was determined. Subsequent group analyses used the average of the mean CBFs for each patient.

Patient Classification

Patients were divided into three groups based on CBF measurements obtained on Days 1 through 5 postinjury. Group 1 included patients whose CBF was less than 33 ml/100 g/minute on all studies; Group 2 included individuals with CBF both less than and greater than 33 ml/100 g/minute; and Group 3 included patients whose CBF was greater than or equal to 33 ml/100 g/minute on all determinations. A blood flow of 33 ml/100 g/minute was chosen as the threshold point given that this value is 2 standard deviations (SDs) below normal adult CBF (44.1 ± 5.6 ml/100 g/minute) when adjusted for a $PaCO_2$ of 34 mm Hg, as measured by the 133Xe method.[35] Additionally, this value is at the upper limit of blood flows observed on the day of injury and is significantly above the traditionally defined threshold for infarction of 18 ml/100 g/minute.[5,36] By dividing the cohort into three groups based on this reference CBF, the effect of reduced but nonischemic blood flow during this postinjury period could be addressed.

Transcranial Doppler Studies

Serial transcranial Doppler studies were performed using a 2-MHz ultrasound probe (Medisonics Neurogard TCD Unit; Neurogard, Inc., Fremont, CA) via the temporal cranial window, as previously described.[26] Vasospasm was defined as a mean middle cerebral artery (MCA) velocity of greater than 120 cm/second with an MCA velocity/cervical internal carotid artery velocity ratio of greater than 3. Patients were classified as having spasm if these criteria were met at least once unilaterally or bilaterally during Days 1 to 5 postinjury.

Recording of ICP and CPP

The ICP was measured by ventricular catheter in 44 patients or by parenchymal transducer (Camino Corp.; San Diego, CA) in 10 patients. Intracranial hypertension was defined as an ICP greater than 20 mm Hg sustained for more than 5 minutes. The ICP and CPP measurements were recorded on an hourly (end-hour) basis, as performed in the Traumatic Coma Data Bank cohort.[24] Cumulative data were obtained for each patient and consisted of average hourly ICP and CPP and the number of hours that ICP was greater than 20 mm Hg and CPP less than 70 mm Hg.

Other Predictors of Outcome

Additional factors known to be important prognostic indicators after head injury were documented. Systemic hypotension (systolic blood pressure < 90 mm Hg) or an abnormal pupillary response (poorly reactive or an asymmetry of 2 mm or greater) noted in the prehospital setting or during the first 24 hours of hospitalization were recorded. The first two computerized tomography (CT) scans obtained in each patient were also analyzed for perimesencephalic cistern effacement (compressed or absent), diffuse swelling, diffuse swelling with midline shift of more than 4 mm, diffuse injury with punctate hemorrhages, subarachnoid hemorrhage, evacuated mass lesions, multiple contusions, and gunshot wounds.[7,8,45] An Injury Severity Score was also calculated for each patient.[1] Neurological outcome

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was determined at 6 months postinjury using the Glasgow Outcome Scale (GOS), with favorable outcome defined as good recovery or moderate disability, and poor outcome as severe disability, persistent vegetative state, or death.[12]

Patient Management

All patients were admitted to the intensive care unit after initial stabilization in the emergency room or after craniotomy for evacuation of intracranial hematoma. Subsequent therapeutic goals included maintenance of ICP at less than 20 mm Hg and CPP at greater than 70 mm Hg. The ICP therapy was implemented in a stepwise fashion and entailed head elevation to 30š and mild hyperventilation ($PaCO_2$ 30-35 mm Hg) followed by ventricular cerebrospinal fluid drainage, narcotic sedation, neuromuscular blockade, and bolus mannitol therapy as needed. High-dose pentobarbital or propofol were used in select cases for intractable intracranial hypertension refractory to conventional methods. The CPP was maintained at 70 mm Hg or above with the use of intravascular volume expansion and vasopressor therapy.

Statistical Analysis

Between-groups analysis of continuous variables was performed using Student's t-test for comparison of two groups or by analysis of variance (ANOVA) for comparison of more than two groups. Multiple comparisons were not adjusted for an inflated alpha because the level of significance for individual comparisons was so high (typically $p < 0.001$). For those comparisons using ANOVA, simple main effects were compared using appropriate post hoc contrasts. Percentage comparisons were performed using a Bernoulli process. The Mann-Whitney U-test was used to assess differences in the median GCS score and the median number of CT diagnoses. All variances were expressed as a SD.

RESULTS

Patient Characteristics

The 54 patients ranged in age from 17 to 77 years with a mean age (± SD) of 34.5 ± 16 years; 45 (83.3%) were male. Postresuscitation GCS scores ranged from 3 to 13, with a median of 6; 49 patients (90.7%) had an initial GCS score of 8 or less. Closed head injuries occurred in 51 patients (94.4%) and gunshot wounds in three (5.5%). Eleven patients (20.4%) sustained a hypotensive insult and 23 (42.6%) had documentation of an abnormal pupillary response within 24 hours of admission. The median number of CT diagnoses obtained in each patient was three, with a range of zero to eight. Twenty-three patients (42.6%) underwent craniotomy for evacuation of an epidural (eight), subdural (11), or intracerebral hematoma (five), including one patient who underwent evacuation of a subdural and an intracerebral hematoma. Seven patients (13%) were treated with high-dose pentobarbital (six patients) or propofol (one patient) for intractable intracranial hypertension. The Injury Severity Score was 31.9 ± 11 (mean ± SD).

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TABLE 1
PHASIC CHANGES IN CBF AFTER HEAD INJURY IN 54 PATIENTS*

No. of Patients Tested	Post-injury Day	CBF (ml/100 g/min)†	PaCO2 (mm Hg)‡	ICP (mm Hg)	CPP (mm Hg)
14	0	32.7 ± 7.1	30.5 ± 3.7	16 ± 6	77 ± 11
54	1–5	43.1 ± 11.5	33.0 ± 4.5	15 ± 9	83 ± 15
22	6–14	35.8 ± 10.0	35.6 ± 5.4	16 ± 9	81 ± 14

* The CBF is measured by postinjury period and compared with simultaneously recorded PaCO2, ICP, and CPP. Values are expressed as the mean ± SD.
† Significantly different by ANOVA ($p < 0.001$).
‡ Significantly different by ANOVA ($p < 0.01$).

Temporal Profile of CBF Measurements

From Days 0 to 14 postinjury, 184 133Xe-CBF studies were performed with a median of three studies per patient (range one-10). Fourteen studies were performed in 14 patients on Day 0, 127 studies were performed in 54 patients from Days 1 to 5, and 43 were performed in 22 patients from Days 6 to 14. The average CBF on Day 0 was 32.7 ± 7.1 ml/100 g/minute, during Days 1 to 5 it was 43.1 ± 11.5 ml/100 g/minute, and from Days 6 to 14 it was 35.8 ± 10 ml/100 g/minute ($p < 0.001$). The mean $PaCO_2$ at the time of CBF determination was 30.5 ± 3.7 mm Hg for Day 0, 33 ± 4.5 mm Hg for Day 1 to 5, and 35.6 ± 5.4 mm Hg for Days 6 to 14 ($p < 0.01$, Table 1). The $PaCO_2$ values were not available for 17 studies (9.2%). There were no significant differences in ICP or CPP between the three CBF phases at the time of CBF determination.

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TABLE 2
CLINICAL PREDICTORS OF OUTCOME, ICP, AND CPP BY PATIENT GROUP*

Predictors of Outcome	Group 1 (7 patients)	Group 2 (13 patients)	Group 3 (34 patients)
clinical			
mean age (yrs)†	42.4 ± 19.4	45.7 ± 16.6	33.2 ± 15.3
age < 35 yrs (%)	3 (42.9)‡	3 (23.1)§	26 (76.5)§
median GCS score	4 (range 3–11)	6 (range 3–13)	6 (range 3–9)
abnormal pupils (%)	4 (57.1)	8 (61.5)‖	11 (32.4)‖
hypotension (%)	1 (14.3)	3 (23.1)	7 (20.1)
computerized tomography			
no. of median CT diagnoses	3 (range 1–4)	3 (range 0–8)	3 (range 1–6)
effaced cisterns (%)	2 (28.6)	8 (61.5)	15 (44.1)**
diffuse swelling (%)	3 (42.8)	9 (69.2)	20 (58.8)
evacuated SDH / ICH (%)	4 (57.1)††	5 (38.5)‡‡	6 (17.6)‡‡
vasospasm (%)	2 (28.6)	6 (42.6)	16 (47.1)
Injury Severity Score	28 ± 3	26 ± 8	32 ± 12
physiological parameters			
mean ICP (mm Hg)	14 ± 3	13 ± 6	13 ± 6
max ICP (mm Hg)	33 ± 14	32 ± 18	33 ± 19
ICP > 20 mm Hg	19 ± 27 hrs	59 ± 104 hrs	47 ± 80 hrs
mean CPP (mm Hg)	79 ± 7	84 ± 7	80 ± 14
min CPP (mm Hg)	54 ± 9	55 ± 13	52 ± 17
CPP < 70 mm Hg	21 ± 16 hrs	29 ± 43 hrs	32 ± 46 hrs

* All values are expressed as the mean ± SD. Group 1 = CBF always less than 33 ml/100 g/minute; Group 2 = CBF both less than and greater than or equal to 33 ml/100 g/minute; Group 3 = CBF always greater than or equal to 33 ml/100 g/minute. Abbreviations: ICH = intracerebral hematoma; SDH = subdural hematoma.
† Age effect was significant across groups by ANOVA ($p < 0.002$).
‡ Less than 35 years significantly different compared with Groups 1 and 2 ($p < 0.05$). Number of patients/of age.
§ Less than 35 years significantly different between Groups 2 and 3 ($p < 0.001$). Number of patients/of age.
‖ Percentage of patients with abnormal pupils was significantly different between Groups 2 and 3 ($p < 0.02$).
** Percentage of patients with effaced cisterns was significantly different compared with Group 2 ($p < 0.02$).
†† Percentage of patients with evacuated SDH or ICH was significantly different between Groups 2 and 3 ($p < 0.05$).
‡‡ Percentage of patients with evacuated SDH or ICH was significantly different compared to Groups 1 and 2 ($p < 0.02$).

Clinical Determinants of Injury Severity and Outcome by Patient Group

Predictors of outcome, CT data, and physiological data on ICP and CPP are summarized by group in Table 2. The CBF and outcome results are displayed in Table 3. A brief clinical synopsis is provided for each patient group.

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TABLE 3
OUTCOME IN RELATION TO CBF AS MEASURED ON POSTINJURY DAYS 1 TO 5

Group	Flow Values (mean ± SD)		Favorable Outcome (%)	Death (%)
	CBF (ml/100 g/min)	PaCO2 (mm Hg)		
1 (7 patients)	25.7 ± 4.0	31.4 ± 6.0	0 (0)*	4 (57.1)†
2 (13 patients)	36.5 ± 4.2	32.7 ± 2.9	6 (46.2)	5 (38.5)
3 (34 patients)	49.4 ± 9.3	33.4 ± 4.7	20 (58.8)‡	6 (17.6)§

* Significantly different compared to Groups 2 ($p < 0.02$) and 3 ($p < 0.002$).
† Significantly different compared to Group 3 ($p < 0.02$).
‡ Significantly different compared to Group 2 ($p < 0.05$).
§ Significantly different compared to Group 2 ($p < 0.01$).

Group 1 (CBF < 33 ml/100 g/minute). The mean age of these seven patients was 42.4 ± 19.4 years, and the median initial GCS score was 4, with a range of 3 to 11. Four patients (57.1%) had mass lesions requiring evacuation, including three subdural and one intracerebral hematoma; in two individuals effaced cisterns were seen on CT scanning. The ICP was greater than 20 mm Hg for an average of 19 ± 27 hours, and the average CBF was 25.7 ± 4 ml/100 g/minute during Days 1 to 5 postinjury. There were no favorable outcomes and four patients (57.1%) died.

Group 2 (CBF < and >= 33 ml/100 g/minute). The mean age of these 13 patients was 45.7 ± 16.6 years, and the median GCS score was 6, with a range of 3 to 13. Six patients (46.2%) had hematomas that required evacuation (one epidural, four subdural, and one intracerebral), and eight had effaced cisterns detected on CT scanning. The ICP was greater than 20 mm Hg for an average of 59 ± 104 hours, and the average CBF was 36.5 ± 4.2 ml/100 g/minute during Days 1 to 5 postinjury. Favorable outcomes were seen in six patients (46.2%) and five (38.5%) died.

Group 3 (CBF >= 33 ml/100 g/minute). The mean age of these 34 patients was 33.2 ± 15.3 years, and the median GCS score was 6, with a range of 3 to 9. Thirteen patients (38.2%) had hematomas that required evacuation (seven epidural, three subdural, and three intracerebral); 15 had effaced cisterns on CT scanning. The ICP was greater than 20 mm Hg for an average of 47 ± 80 hours, and the average CBF was 49.4 ± 9.3 ml/100 g/minute during Days 1 to 5 postinjury. Twenty patients (58.8%) had a favorable outcome and six (17.6%) died.

Intergroup Comparisons

Groups 1, 2, and 3 did not differ significantly in terms of initial GCS score, incidence of hypotension, number of major CT diagnoses, or mean Injury Severity Score. The incidence of MCA vasospasm was also similar across groups; however, four patients (two each in Groups 1 and 2) did have CBF values of less than 33 ml/100 g/minute in association with vasospasm. There were no significant differences between groups in cumulative ICP and CPP values. Significant differences were found, however, in several injury parameters. There was a significant effect of age across groups, with Group 3 being the youngest on average and having the highest percentage of patients younger than 35 years of age. There were significant differences across groups in the incidence of evacuated subdural or intracerebral hematomas, with Group 1 having the highest incidence (57.1%) and Group 3 the lowest (17.6%). Additionally, Group 3 had a significantly lower incidence of patients with effaced cisterns and abnormal pupils compared to Group 2. As expected, mean blood flow was also significantly different across groups, with the lowest values documented in Group 1 and the highest seen in Group 3 ($p < 0.001$).

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These differences were not related to differences in $PaCO_2$. The rate of favorable outcome at 6 months postinjury was also significantly different between Groups 1, 2, and 3, at 0%, 42.6%, and 58.8%, respectively, whereas the highest and lowest mortality rates occurred in Groups 1 and 3, respectively.

Intragroup Analysis of Patients in Group 3

In contrast to the 20 patients with good outcomes in Group 3, the 14 individuals with poor outcome had a significantly higher number of CT diagnoses and a higher incidence of pupillary abnormalities and hypotension ($p < 0.05$). There were no differences between the two subgroups in terms of age, initial GCS score, Injury Severity Score, mean CBF on postinjury Days 1 to 5, or cumulative ICP and CPP data. However, mean ICP ($p < 0.07$), number of hours that CPP was less than 70 mm Hg ($p < 0.06$), and minimum CPP ($p < 0.07$) showed worsening trends in the poor outcome group. Of the 14 patients with a poor outcome in this group, six had documented hyperemia-associated intracranial hypertension, defined as simultaneous CBF greater than 55 ml/100 g/minute and ICP greater than 20 mm Hg on at least one CBF study.[16] Because our previous analyses indicated that these individuals comprise a relatively unique subset of severely injured patients, an intragroup comparison was performed among the 20 patients with good outcomes, the six patients with poor outcomes who had hyperemia-associated intracranial hypertension, and the eight patients with poor outcomes who did not have hyperemia-associated intracranial hypertension (Table 4).

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TABLE 4
CLINICAL PREDICTORS OF OUTCOME IN GROUP 3: GOOD VERSUS POOR OUTCOMES

Predictors of Outcome	Outcome		
	Good (20 patients)	Poor W/O Hypertension (8 patients)	Poor W/ Hypertension (6 patients)
clinical			
mean age (yrs)*	27.6 ± 7.6	37.6 ± 20.7	21.3 ± 4.6
age <35 years (%)†	16 (80)	4 (50)	6 (100)
median GCS score	6 (range 4–9)	5 (range 3–8)	4.5 (range 3–6)‡
abnormal pupils (%)	4 (20)§	3 (37.5)	4 (66.7)§
hypotension (%)	2 (10)§	2 (25)	3 (50)§
computerized tomography			
median no. of CT diagnoses	1.5 (range 0–5)‖	4.5 (range 0–6)‖	3 (range 2–5)
effaced cisterns (%)**	4 (20)	5 (62.5)	6 (100)
diffuse swelling (%)	9 (45)††	6 (75)	5 (83.3)††
evacuated hematoma (%)	6 (30)‡‡	5 (62.5)‡‡	2 (33.3)
physiological parameters§§			
mean CBF (ml/100 g/min)	47.1 ± 7.1	46.4 ± 7.9	59.8 ± 10.6
PaCO2 (mm Hg)	34.3 ± 4.8	32.7 ± 4.7	31.2 ± 4.3
mean ICP (mm Hg)	11 ± 5	10 ± 4	23 ± 6
maximum ICP (mm Hg)	30 ± 19	28 ± 12	59 ± 26
hours ICP >20 mm Hg	23 ± 42 hrs	6 ± 11 hrs	156 ± 98 hrs
mean CPP (mm Hg)	83 ± 9	82 ± 9	73 ± 5
minimum CPP (mm Hg)	57 ± 16	58 ± 10	28 ± 15
hours CPP <70 mm Hg	18 ± 23 hrs	16 ± 17 hrs	111 ± 73 hrs
metabolic suppressive therapy for uncontrollable ICP (%)‖‖	1 (5)	0 (0)	5 (83.3)

* Age effect was significant across groups by ANOVA ($p < 0.05$).
† Number of patients younger than 35 years of age was significantly different: poor outcomes with compared to poor outcome without hyperemia associated intracranial hypertension and poor outcome without hypertension compared to good outcome ($p < 0.05$).
‡ The GCS score was significantly different between poor outcome with hypertension and good outcome ($p < 0.02$).
§ Percentages of patients with abnormal pupils and hypotension were significantly different in the poor outcome with hypertension compared to the good outcome subgroup ($p < 0.5$).
‖ Number of CT diagnoses was significantly different between the poor outcome without hypertension and the good outcome subgroup ($p < 0.05$).
** Percentages of effaced cisterns were significantly different: poor outcomes with and without hypertension compared to good outcome ($p < 0.0001$ and $p < 0.01$, respectively).
†† Percentage with diffuse swelling was significantly less in the poor outcome with hypertension compared to the good outcome subgroup ($p < 0.01$).
‡‡ Percentage with evacuated hematoma was significantly greater in the poor outcome without hypertension compared to the good outcome subgroup ($p < 0.05$).
§§ All physiological parameters except $PaCO_2$ and mean CPP were significantly different across groups by ANOVA ($p < 0.0001$).
‖‖ Percentage with metabolic suppressive therapy was significantly different: poor outcomes with compared to without hypertension and poor outcome with hypertension compared to good outcome ($p < 0.0001$).

Patients with poor outcomes who did not have simultaneous hyperemia and elevated ICP were older on average and had the highest number of CT diagnoses. Six of eight patients had multiple contusions and five had an evacuated intracranial hematoma. However, these patients had minimal intracranial hypertension and reduced CPP. In contrast, the six patients with poor outcomes who had hyperemia-associated intracranial hypertension showed the most severe degree and duration of elevated ICP and reduced CPP and the highest CBF during Days 1 to 5 postinjury ($p < 0.0001$). Thus, the trend toward significant differences in ICP and CPP between patients in Group 3 with good and poor outcomes was derived almost exclusively from the subset of individuals with hyperemia-associated intracranial

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hypertension. These patients also had the highest incidence of pupillary abnormalities and hypotension, all six had effaced cisterns, and five showed diffuse swelling on CT scanning. Additionally, five of six were treated with metabolic suppressive therapy (four with pentobarbital and one with propofol) for intractable intracranial hypertension, and therapy failed in all of them. If these six patients are excluded from the outcome comparison between Groups 1, 2, and 3, the rate of favorable outcome is 0%, 46.2%, and 71.4%, respectively ($p < 0.01$).

Cerebral Blood Flow as a Continuous Variable

As a further means of determining the relationship between CBF and outcome, the mean blood flow for each patient during postinjury Days 1 to 5 was compared to the GOS as a continuous variable against other predictors of outcome, including age, GCS score, number of CT diagnoses, and ICP and CPP measurements. A significant effect was seen across the GOS for the factors of age ($p < 0.001$), hours of ICP greater than 20 mm Hg ($p < 0.029$), and hours of CPP less than 70 mm Hg ($p < 0.04$), whereas the factors of mean ICP ($p < 0.062$) and CBF ($p < 0.085$) approached statistical significance. When the same analysis was conducted on the cohort after exclusion of the six patients with poor outcomes who had hyperemia-associated intracranial hypertension, a significant effect was seen across the GOS for the factors of age ($p < 0.005$) and CBF ($p < 0.013$) only, whereas the mean ICP ($p < 0.12$), hours of CPP less than 70 mm Hg ($p < 0.12$), and hours of ICP greater than 20 mm Hg ($p < 0.13$) approached statistical significance (Fig. 1).

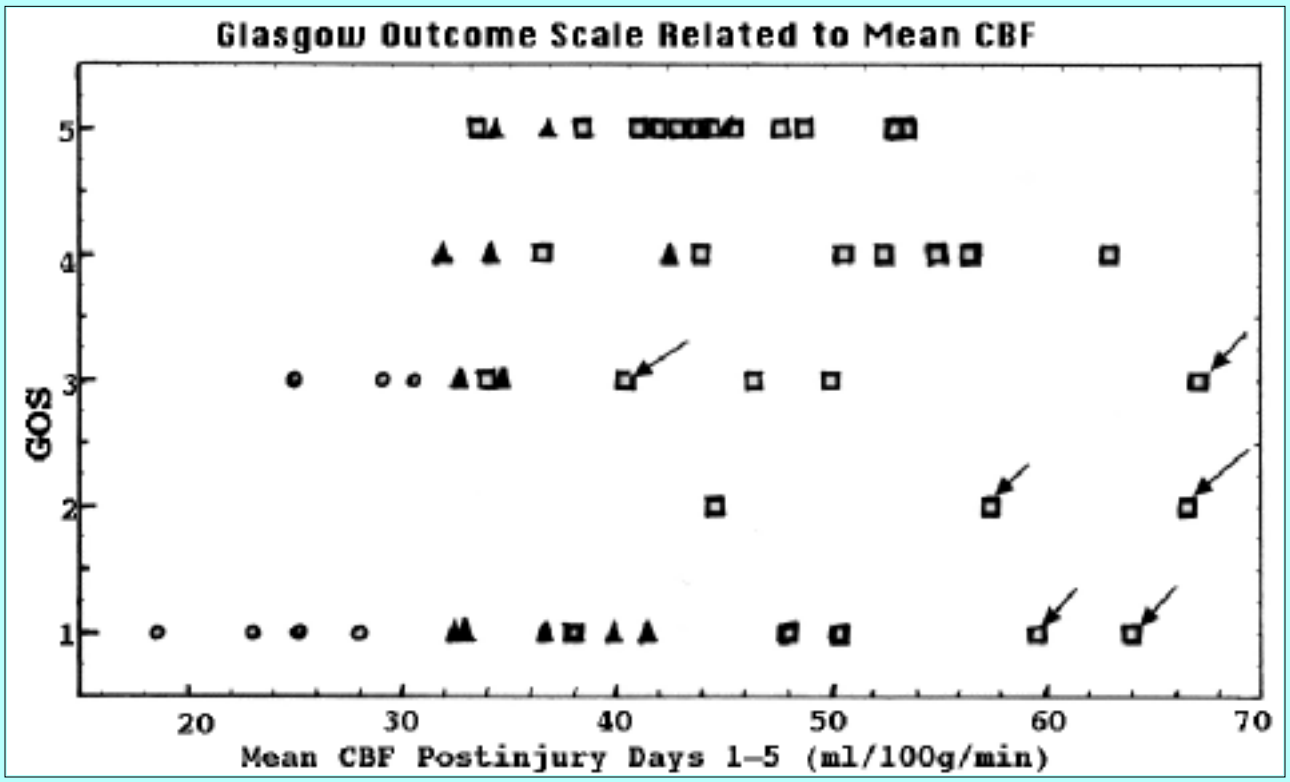

Fig. 1. Graph showing GOS as a function of mean CBF on postinjury Days 1 to 5. When all 54 patients are included, the effect of CBF across the GOS approaches statistical significance ($F = 2.18$, $p < 0.085$). By excluding the six patients with poor outcome who had hyperemia-associated intracranial hypertension (arrows), the effect of CBF across the GOS becomes highly significant ($F = 4.032$, $p < 0.013$). A GOS of 1 = death, 2 = vegetative state, 3 = severe disability, 4 = moderate disability, 5 = good recovery. Patients are also identified by group: Group 1 = circles, Group 2 = triangles, and Group 3 = squares.

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DISCUSSION

Methodological Considerations

This investigation differs from previous studies addressing the relationship between acute CBF changes and outcome after head injury in that a relatively focused period in which to assess blood flow was chosen, namely the phase of maximum CBF.[5,11,22,31,37,40] Several reports using the 133Xe method have shown that peak flows generally occur within 48 to 72 hours of injury, followed by a decline over the next 2 to 3 days.[25,36,37] In the present study this temporal profile was confirmed, with elevated CBF persisting from Day 1 until Day 5 postinjury; mean CBFs were 41.8 ml/100 g/minute and 44.4 ml/100g/minute, respectively. By Day 6, the average CBF had fallen to 33.4 ml/100 g/minute and remained low through the 2nd week postinjury.

The subsequent classification of patients into three groups based on CBF measurements of less than or greater than or equal to 33 ml/100 g/minute during this period of maximum flow provided a way to determine how the duration of reduced blood flow might affect outcome. Using this categorization scheme admittedly introduces a potential sampling error, because CBF measurements were not obtained every day in each patient during the study period. In 12 patients, only one measurement was obtained during Days 1 to 5 postinjury and, therefore, these individuals could not be included in Group 2, which was defined by at least two CBF measurements. Additionally, Day 0 CBF studies, which demonstrated the lowest CBFs for the cohort overall, were performed in only 14 patients, and approximately half of these studies were performed 12 to 24 hours postinjury, after the nadir in CBF had likely already occurred.[6,22,36] A final methodological concern is the use of the 133Xe method, which provides a cortical and subcortical hemispheric blood flow measurement, predominantly of the MCA territory.[34] Consequently, regional areas of critically low blood flow that might have affected long-term outcome may have gone undetected.

Cerebral Blood Flow as a Predictor of Outcome

Despite these limitations, this report demonstrates that CBF measured on Days 1 through 5 postinjury correlates positively with long-term neurological outcome. Older age and more severe injury (as defined by pupillary abnormalities and incidence of evacuated subdural and intracerebral hematomas) are the most important clinical factors associated with low CBF during this period. These findings indicate that the longer the duration of reduced flow, as determined by the number of observations in which CBF was less than 33 ml/100 g/minute, the worse the outcome will be. The importance of adequate CBF during this critical period is also supported by ANOVA when mean CBF is treated as a continuous variable, particularly when individuals with hyperemia-associated intracranial hypertension are excluded from analysis. These results raise several important questions: 1) what is the etiology of reduced CBF during the second phase of blood flow; 2) what are the possible mechanisms by which low but nonischemic CBF results in poor outcome; and 3) why does poor outcome occur in many individuals despite relatively normal blood flow?

Etiology of Hypoperfusion

Blood flow of less than 33 ml/100 g/minute was observed on at least one occasion during postinjury Days 1 to 5 in 20 (37%) of 54 patients. The association between advanced age and low CBF in this cohort is not surprising given the decline in blood flow that normally occurs with aging, presumably as a result of reduced cerebral metabolic demands.[27,32] The strong correlation between age and outcome

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seen in this and other studies, although likely to be multifactorial, may be related to a global reduction in cerebral metabolism.[46] Regarding the increased incidence of evacuated subdural or intracerebral hematomas in Groups 1 and 2, a similar correlation between evacuated intradural hematomas and low blood flow has been reported by Bouma, et al.[6] Salvant and Muizelaar[42] also reported that patients with evacuated subdural hematomas had lower CBFs on Days 1 and 2 postinjury compared with those without mass lesions.

Vasospasm is an additional factor that has been associated with reduced CBF after head injury and likely accounts for some instances of low blood flow in this cohort during Days 1 to 5 postinjury.[26] In four patients with vasospasm, CBFs were less than 33 ml/100 g/minute when spasm was documented. However, the incidence of vasospasm was similar among all three groups during this period, and individuals with vasospasm had similar CBFs at the time spasm was detected compared to those without spasm within the same group. Other factors including duration and severity of intracranial hypertension, reduced CPP, and hypocarbia were also similar across groups. Therefore, it is unlikely that these were important contributors to low CBF in this cohort. It is uncertain whether an excess of vasoconstrictor agents such as neuropeptide Y or a depletion of nitric oxide are factors in CBF reductions at the arteriolar level during this period in human head injury.[38,47]

Why Hypoperfusion Correlates With Poor Outcome

Given that ischemic blood flows were documented in only three of 54 patients during postinjury Days 1 to 5, other factors must be considered in explaining the association of hypoperfusion and poor outcome. Possible causes include: 1) uncoupling between metabolism and blood flow; 2) hypoperfusion-induced depression of protein synthesis; 3) global depression of cerebral metabolism resulting from severe primary injury or secondary insults; and 4) global ischemia that is undocumented because of sporadic CBF measurements.

Metabolic/Blood Flow Uncoupling. An early increase in glycolysis after head injury has been demonstrated in several animal models and recently by means of fluorodeoxyglucose PET following severe human head injury.[2-4,10,14,15,17,18,48] Experimentally, the injury-induced hyperglycolysis occurs during the first few minutes postinjury. In contrast, after severe head injury in humans, regional or global hyperglycolysis appears to have a more prolonged duration, occurring for up to several days postinjury.[3,4] In all six patients from this institution who underwent 133Xe-CBF measurement within 24 hours of PET, global blood flows were in the "relative" or "absolute" hyperemia range as defined by Obrist, et al.[35] Although preliminary, these data indicate that in many acutely head injured patients, elevated blood flow may be due to an increase in demand for glucose metabolism, and therefore does not represent classic hyperemia. Additionally, an increase in glycolysis may be in part a compensatory response to a compromised oxidative energy pathway, as evidenced by persistent depression of $CMRO_2$ postinjury.[5,35,36,39,40] Thus, cerebral energy production may become relatively dependent on glycolysis, not only for reestablishing ionic homeostasis but also for other basic cellular functions. Furthermore because glycolysis is a relatively inefficient energy pathway compared to oxidative metabolism, substantial rises in blood flow well above the ischemic threshold may be needed to meet metabolic demands. This imbalance between metabolism and blood flow in which hyperglycolysis occurs in the setting of low but nonischemic CBF may account for the poor outcome seen in many patients. Uncoupling between glycolysis and CBF during the acute period of hyperglycolysis has been documented very early postinjury in several animal models; however, it remains to be observed after head injury in humans.[2,10,18]

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Depression of Protein Synthesis. Cerebral protein synthesis is an additional factor that may be critically dependent on adequate CBF after head injury and intimately linked to metabolism.[29] Although the duration of cerebral ischemia is known to be a critical determinant of tissue survival and degree of functional recovery, recent data indicate that absolute ischemia is not necessary to induce cell death.[13] In a rat model of MCA occlusion, the CBF threshold for protein synthesis inhibition was significantly higher than that for the loss of adenosine triphosphate.[29] It was concluded that with increasing duration of low CBF, parenchymal survival was determined predominantly by the CBF threshold for inhibition of protein synthesis, rather than the much lower threshold for acute energy failure. This effect of hypoperfusion on cerebral protein synthesis may be highly relevant in head-injured patients in whom persistent global and regional reductions in blood flow commonly occur, yet ischemia, as traditionally defined, is never reached. If subnormal but nonischemic blood flows are of sufficient duration, large-scale cell death may result from this prolonged inhibition of protein synthesis.[9,29,44]

Global Depression of Cerebral Metabolism and Undocumented Ischemia. An additional explanation for the association between persistently low CBF and poor outcome after head injury may be related to global metabolic depression. Marked reduction in both oxidative and glycolytic energy pathways appears most likely to occur in patients sustaining severe primary parenchymal injuries, particularly when associated with hypotension or hypoxia. In this study, hypotension was documented in four of 20 patients with CBF less than 33 ml/100 g/minute, and ischemic blood flows were observed in three patients. Given that ultra-early CBF studies were obtained in only a minority of patients, it is possible that global or regional ischemia went undetected in significantly more patients than was detected. Consequently, ischemia cannot be eliminated as a major contributor to poor outcome in this cohort, particularly because it has been documented in up to one-third of severely head injured patients assessed within 8 hours of injury, and because it correlates so strongly with poor outcome.[5,22,37]

Etiology of Poor Clinical Outcome Despite Relatively Normal CBF

Although relatively normal CBF on postinjury Days 1 to 5 appears to be necessary for achieving favorable outcome, this factor alone does not ensure functional recovery. Despite CBF being consistently documented at greater than or equal to 33 ml/100 g/minute in Group 3 patients, 41% of these individuals still had poor outcomes. Subgroup analysis of these patients illustrates the heterogeneous nature of the pathophysiology of the head injury and the fact that there are multiple factors that affect long-term outcome.[30] In the eight patients with poor outcome with no hyperemia-associated intracranial hypertension, older age and a high number of CT-defined abnormalities appear to be the critical factors that precluded functional recovery. Most notably, poor outcome occurred despite the fact that ICP, CPP, and CBF were maintained at relatively normal levels.

In contrast, the six individuals with at least one episode of hyperemia-associated intracranial hypertension were distinctive in being the youngest, with the lowest GCS scores, the highest CBFs on Days 1 to 5, and the most severe degree of elevated ICP and reduced CPP. In five of six patients metabolic suppressive therapy for intractable intracranial hypertension failed, and three patients sustained a hypotensive episode, indicating that an early ischemic insult had occurred. This injury profile is most consistent with that of severely impaired metabolic vasoreactivity and pressure autoregulation and a state of true hyperemia in which CBF exceeded metabolic demands. A similar clinical profile of patients with severe head injury in whom barbiturate therapy failed has been observed by Nordström and colleagues.[28,33] Experimental work by Lewelt, et al.,[19,20] also indicates that increased injury severity is associated with more profound impairment of vasoreactivity. The study by Jaggi, et al.,[11]

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which showed no correlation between CBF and outcome, may have failed to do so because of a substantial number of patients with true hyperemia. When patients with hyperemia-associated intracranial hypertension were excluded from analysis in the present study, the association between CBF and outcome was even stronger.

CONCLUSIONS

A phasic elevation in CBF on postinjury Days 1 to 5 appears to be strongly related to a functional recovery after moderate or severe traumatic brain injury. Younger patient age and relatively less severe injury were the most important clinical determinants associated with this favorable blood flow pattern. These findings indicate that the ischemic threshold after head injury is dynamic, rising substantially above the threshold for infarction for the first 5 days postinjury. For the majority of patients, it is postulated that this rise in blood flow results from a relative increase in cerebral metabolic demands in the setting of intact vasoreactivity. However, maintenance of relatively normal blood flow postinjury does not ensure functional recovery. Furthermore, in a minority of patients the presence of markedly elevated CBF, severe intracranial hypertension, and poor outcome suggests a state of uncoupling between blood flow and metabolism resulting from grossly impaired vasoreactivity. Finally, although we acknowledge that a lower CBF threshold of 33 ml/100 g/minute is somewhat arbitrary, this value may have clinical utility in the treatment of head-injured patients, similar to the use of ICP and CPP thresholds of 20 and 70 mm Hg, respectively.[23,41]

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