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Original Article

Significance of a Reduced Cerebral Blood Flow During the First 12 Hours After Traumatic Brain Injury

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Background: It is controversial whether a low cerebral blood flow (CBF) simply reflects the severity of injury or whether ischemia contributes to the brain's injury. It is also not clear whether posttraumatic cerebral hypoperfusion results from intracranial hypertension or from pathologic changes of the cerebral vasculature. The answers to these questions have important implications for whether and how to treat a low CBF.

Methods: We performed a retrospective analysis of 77 patients with severe traumatic brain injury who had measurement of CBF within 12 hours of injury. CBF was measured using xenon-enhanced computed tomography (XeCT). Global CBF, physiological parameters at the time of XeCT, and outcome measures were analyzed.

Results: Average global CBF for the 77 patients was 36 ± 16 mL/100 g/minutes. Nine patients had an average global CBF <18 (average 12 ± 5). The remaining 68 patients had a global CBF of 39 ± 15. The initial ICP was >20 mmHg in 90% and >30 mmHg in 80% of patients in the group with CBF <18, compared to 33% and 16%, respectively, in the patients with CBF ≥18. Mortality was 90% at 6 months postinjury in patients with CBF <18. Mortality in the patients with CBF >18 was 19% at 6 months after injury.

Conclusion: In patients with CBF <18 mL/100 g/minutes, intracranial hypertension plays a major causative role in the reduction in CBF. Treatment would most likely be directed at controlling intracranial pressure, but the early, severe intracranial hypertension also probably indicates a severe brain injury. For levels of CBF between 18 and 40 mL/100 g/minutes, the presence of regional hypoperfusion was a more important factor in reducing the average CBF.

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Key Words: Cerebral blood flow; brain injury; xenon-enhanced computed tomography; ischemia; intracranial hypertension.

Introduction

Many factors contribute to the long-term neurological disability in patients after severe traumatic brain injury. The pathology of injury; the patient's neurological status on admission; pupillary response; prehospital events, such as hypotension or hypoxia; the severity of intracranial hypertension; and the age of the patient have been identified as primary determinants of outcome after traumatic brain injury. In some analyses, the level of cerebral blood flow (CBF), especially during the first few hours after injury, has been associated with outcome *(1–7)*.

Even when CBF has been associated with outcome, it remains controversial whether a low CBF simply reflects the severity of injury or whether a low CBF contributes to brain injury. It is also not clear whether posttraumatic cerebral hypoperfusion results from intracranial hypertension or from pathologic changes of the cerebral vasculature causing constriction or obstruction of nutritive blood vessels for the brain. The answers to these questions have important implications for whether a low CBF should be treated, and, if so, what is the optimal treatment.

Recent experimental studies have implicated depletion of nitric oxide in the etiology of the low CBF observed in the controlled cortical impact injury model *(8)*. Postinjury administration of L-arginine in this model restores CBF at the injury site and also reduces the size of the contusion that develops after the trauma *(9)*. A better understanding of the pathophysiology of a low CBF in human traumatic brain injury might benefit the introduction of potential therapeutic interventions, such as L-arginine, into clinical practice.

The purpose of this study was to analyze the factors related to neurological outcome in a group of patients who had measurement of CBF during the first 12 hours after a severe traumatic brain injury. Issues of particular interest were the level of CBF reduction that predicted a poor outcome and the nature of the interaction between intracranial hypertension and ischemia in predicting a poor outcome.

Methods

Patient Selection

Between February 1999 and March 2001, 77 patients who had severe traumatic brain injury (*see* Table 1) and who underwent measurement of CBF using xenon-enhanced computed tomography (XeCT) within 12 hours after injury were included in this study. The XeCT data were prospectively collected as a part of the study design and obtained as soon as practical after injury, resuscitation, and removal of intracranial mass lesions. The XeCT CBF study was a screening test for a pilot randomized clinical trial studying the effects of L-arginine on CBF in posttraumatic patients with cerebral ischemia. Patients who met the inclusion criterion of a critical reduction in CBF either globally or in a lobar distribution were candidates for this L-arginine trial. In addition, the XeCT CBF information was also used clinically to help determine treatment goals for blood pressure and for cerebral perfusion pressure during the early postinjury period.

The research protocol was approved by the Baylor Institutional Review Board for Human Subject Research, and informed consent was obtained from each patient's nearest relative for participation in the study. When relatives were unavailable to give informed consent, the patients were enrolled in the study using an approved emergency consent procedure.

The eligibility criteria for the study included following: (1) traumatic brain injury, (2) age ≥15 years, (3) motor Glasgow Coma Score (GCS) of ≤5 at the time of the CBF measurement, and (4) measurement of CBF by XeCT within 12 hours after injury.

All patients who were admitted to Ben Taub General Hospital with a severe traumatic brain injury were resuscitated per Advanced Trauma Life Support (ATLS) guidelines and evaluated for systemic injuries, as well as for the severity

Table 1
Demographic Characteristics for All Patients, and Subsets Analyzed

Demographics	*Analyzed for 6 month GOS*	*Analyzed for alive at discharge*	*Total group*
Number of patients	54	63	77
Age (years)—mean (SD)	34.7 (12.6)	35.0 (13.4)	34.1 (13.9)
Gender:			
Male	46 (85%)	55 (87%)	67 (87%)
Female	8 (15%)	8 (13%)	10 (13%)
Race/ethnicity:			
White	15 (28%)	17 (27%)	22 (29%)
African-American	10 (19%)	11 (17%)	15 (20%)
Hispanic	28 (52%)	33 (53%)	38 (49%)
Asian	1 (2%)	1 (2%)	1 (1%)
Initial GCS—median (25th, 75th percentiles)	4 (3, 8)	5 (3, 8)	6 (3, 8)
Injury type:			
Mild diffuse (1/2)	16 (30%)	19 (30%)	29 (38%)
Severe diffuse (3/4)	13 (24%)	14 (22%)	14 (18%)
Mass (1/2)	25 (46%)	30 (48%)	34 (44%)
Surgery for intracranial mass lesion:			
At admission	24 (52%)	28 (44%)	32 (42%)
For delayed mass lesion	5 (4%)	6 (9.5%)	6 (8%)

Injury type based on Marshall's computed tomography classification. GCS, Glascow Coma Score. See text for explanation of Marshall's classification.

and nature of the brain injury. Patients with an intracranial mass lesion on the admission computed tomography (CT) scan were taken immediately to the operating room for evacuation of the hematoma. Patients with a diffuse brain injury were taken to the ICU for further stabilization and for placement of invasive monitors.

All patients were managed by a standard protocol that emphasized prompt evacuation of intracranial mass lesions and prevention of secondary insults to the brain. Intracranial pressure (ICP) values >20 mmHg were treated by an algorithm based on the Guidelines for the Management of Severe Traumatic Brain Injury *(10)*. Systemic factors that exacerbate intracranial hypertension, including hypoxia, hypercapnia, fever, and hypotension, were corrected. Treatment goals were defined as mean arterial blood pressure (MABP) of at least 80 mmHg and cerebral perfusion pressure (CPP) of at least 60 mmHg, unless the initial XeCT or other measures of cerebral perfusion indicated that a higher CPP was required.

Arterial blood pressure was monitored in all patients by a radial or femoral artery catheter. ICP was monitored in 69 of 77 patients preferentially using a ventriculostomy catheter (86%) or Codman ICP microsensor placed in the brain parenchyma (14%, Codman Inc.). Jugular venous oxygen saturation ($SjvO_2$) was moni-

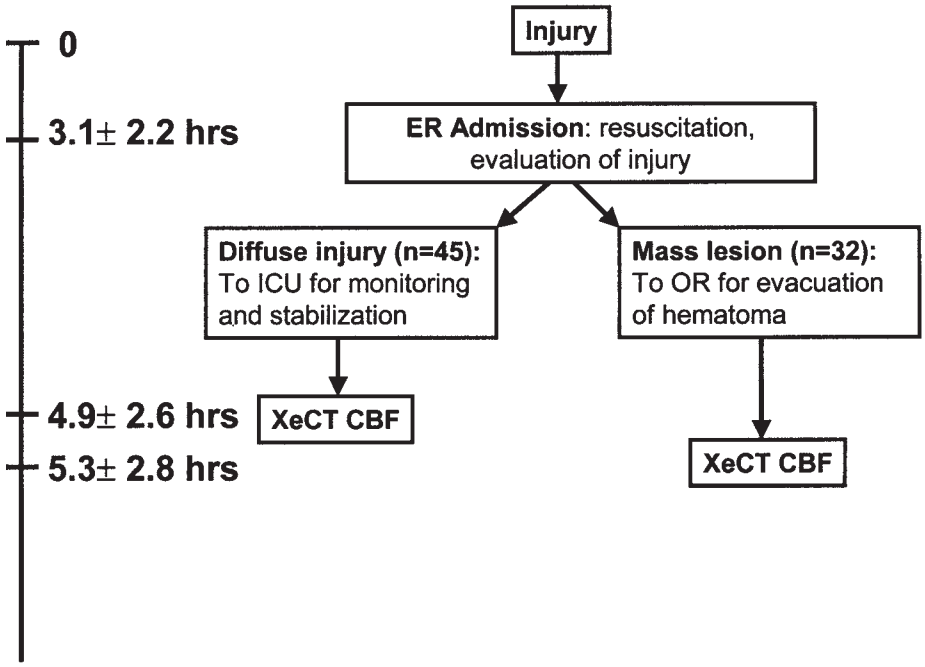

Fig. 1. Diagram of the study design intended to screen patients with severe traumatic brain injury to identify those with a low cerebral blood flow in the first 24 hours after injury. The timing of the xenon-enhanced computed tomography study was not significantly different in the patients initially treated surgically compared to those initially treated medically (p = 0.62, Mann-Whitney rank sum test). ER, emergency room; ICU, intensive care unit; OR, operating room; XeCT, xenon-enhanced computed tomography.

tored in the dominant jugular vein using a fiberoptic catheter (Abbott Laboratories) in 42 of 77 patients. The dominance of jugular bulb was determined by using CT imaging (larger jugular foramen) or by using ultrasonography (larger diameter of internal jugular vein). Partial pressure of oxygen in brain tissue ($PbtO_2$) was continuously measured using a miniaturized Clark electrode–Licox (GMS, Kiel-Mielkendorf, Germany) in 49% of the patients.

Cerebrovascular resistance (CVR) was calculated by the equation CVR = cerebral perfusion pressure (CPP)/CBF. Normal value of CVR is 1.6 ± 0.4 mmHg/mL/100 g/minute.

Measurement of Global CBF

The study protocol is diagrammed in Fig. 1. As soon as feasible after admission, a measurement of CBF using a XeCT technique (Diversified Diagnostics Products, Houston, TX) was obtained. CBF evaluation was performed after the surgical evacuation of a mass lesion in 36 patients and after hemodynamic stabilization in the 41 nonoperative cases. During the CBF measurement, morphine was given if analgesia/sedation was necessary. No other sedative agents were given.

For evaluation of mixed cortical CBF, the CT scans were performed in four axial planes with a thickness of 5 mm, each 20 mm apart. After completion of two baseline scans at each level, a mixture of 32% stable xenon gas and 68% oxygen was administered through the ventilator for 4.5 minutes, during which four additional scans were performed at each level. End-expiratory xenon and CO_2 concentrations, as well as oxygen saturation, electrocardiogram, arterial blood pressure, and ICP, when available, were con-

tinuously monitored. A complete CBF study took 13 to 17 minutes.

Analysis of the XeCT CBF was performed by outlining 20 cortical regions of interest (ROIs) in each of four axial planes. The mixed cortical CBF in all cortical ROIs from all for axial planes was averaged to estimate a global CBF value. This value was used as the global average CBF in subsequent comparisons.

During XeCT measurement, the ventilatory settings of the patients were adjusted to obtain an end-tidal CO_2 ($ETCO_2$) of 33 to 38 mmHg (4.4–5.1 kPa). Where arterial blood sample was available, the ventilatory settings was adjusted to achieve an arterial tension of CO_2 ($PaCO_2$) between 35 and 40 mmHg (4.7 and 5.3 kPa). All available physiological parameters were recorded during CBF measurements, and, where possible, the blood samples from jugular bulb were obtained (*see* Table 2). When available, the brain tissue pO_2 was not recorded during the actual measurement of CBF and the pO_2 values recorded were those obtained in the ICU either just before or just after the CBF measurement.

Table 2
Physiology at the Time of Xenon-Enhanced Computed Tomography Examination in All 77 Patients

Cerebral blood flow	
Average global CBF [mL/100 g/minute]	35.8 ± 16.4
Average CBF	
Level 1	37.7 ± 15.5
Level 2	36.5 ± 16.5
Level 3	35.5 ± 17.1
Level 4	34.3 ± 18.3
Measurement of CBF after injury (hours)	5.1 ± 2.8
Physiology at time of CBF	
ICP (mmHg)	24.1 ± 16.8
MABP (mmHg)	89.9 ± 13.7
CPP (mmHg)	65.1 ± 19.6
SpO_2 (%)	99.2 ± 1.1
$ETCO_2$ (mmHg)	35.6 ± 4.2
$SjvO_2$ (%)	68.5 ± 12.1
$PbtO_2$ (mmHg)	30.9 ± 39.1
Hgb (g/L)	11.6 ± 2.1
PaO_2 (mmHg)	228 ± 107
$PaCO_2$ (mmHg)	37.5 ± 5.8

ICP, intracranial pressure; CPP, cerebral perfusion pressure; SpO_2, pulse oximetry; $ETCO_2$, end-tidal CO_2; $SjvO_2$, jugular oximetry; $PbtO_2$, oxygen tension in brain tissue; Hgb, hemoglobin.

Statistical Analysis

All summary data are expressed as the mean ± standard deviation or median and interquartile range. Mean values were compared by Student's *t*-test. Comparison between groups was performed using one-way repeated measures analysis of variance. For comparisons of differences among the groups, Chi-square test or Fisher Exact test was used. A p value <0.05 was considered a statistically significant result.

Logistic regression analysis was used to examine the factors related to neurological outcome. A favorable outcome was defined as a Glasgow outcome scale (GOS) of good recovery or moderate disability at 6 months after injury; and GOS scores of severe disability, persistent vegetative state, and dead were considered a poor outcome. Age, gender, ICP, MABP, $ETCO_2$, time between injury and XeCT, and average CBF were used as continuous covariates. The gender and presence of two reactive pupils in the emergency room (ER) were used as a binary variable. The six-category Marshall CT classification was recoded to the following three categories: mild diffuse (diffuse injuries 1 and 2), severe diffuse (diffuse injuries 3 and 4), and mass lesion (evacuated and unevacuated). The initial postresuscitation GCS was recoded as follows: 3 and 4 versus 5–13. The analyses were conducted separately for the following two outcomes: alive at discharge and favorable outcome at 6 months. Both analyses proceeded as follows. A full model was fit using logistic regression. The variables in the full model were age, gender, ICP, MABP, $ETCO_2$, initial pupil reactivity, initial CT scan, time between injury and CBF measurement, initial GCS, and global CBF. The significance of a variable was assessed using the log-likelihood difference between the full model and a model,

Table 3
Glasgow Outcome Score at the Time of Discharge from Intensive Care Unit and at 6 Months After Injury

	No. of patients	*Average CBF*
Discharge outcome	77	
Alive	56	40.7 ± 15.1
Dead	21	22.6 ± 12.3
p		< 0.001
6-month GOS	54	
Good recovery/ moderate disability	19	45.0 ± 18.5*
Severely disabled/ vegetative	12	36.8 ± 14.7*
Dead	23	23.2 ± 11.9
p		< 0.001

*, different from dead, $p < 0.5$.

with just that variable removed. The variable having the highest *p* value was removed from the model, and the reduced model was used as the full model for the next analysis. Again, the least significant variable was removed, and the process repeated until only variables that were significant at $p < 0.05$ were retained. This final model was used to generate graphic representations of the effects of the individual variables in the model.

Results

Patient Characteristics

Demographic characteristics of the patients are detailed in Table 1 and are typical of a traumatic brain injury population. Fifty-six (73%) of the 77 patients were alive at the time of discharge from the ICU, and 21 (27%) died during the initial admission. By 6 months after injury, 19 (25%) of the patients recovered to a favorable outcome (good recovery + moderate disability), 12 (16%) remained severely disabled or vegetative, and 23 (30%) were dead. Of the remaining 23 patients, GOS was known at 3 months in 4 patients (3 severely disabled, 1 good recovery), but no long-term follow-up was done in 19 patients (Table 3).

Cerebral Blood Flow Values During the First 12 Hours After Injury

Average global CBF for the 77 patients was 35.8 ± 16.4 mL/100 g/minute, which is slightly below the lower limit of normal for the Xenon CT method (normal = 52 ± 12 mL/100 g/minute) *(11)*, but individual values ranged from extremely low (5.5 mL/100 g/minute) to elevated (88.8 mL/100 g/minute). Nine patients had an average global CBF <18 mL/100 g/minute, 17 patients had a CBF between 18 and 28 mL/100 g/minute, 23 patients had a CBF between 28 and 40 mL/100 g/minute, and 28 patients had a CBF > 40 mL/100 g/minute. Factors that might have contributed to the variability of the CBF during the first 12 hours after traumatic brain injury were examined.

CBF was measured at an average time of 5.1 ± 2.8 hours after injury; all measurements were within 12 hours of injury to be included in the analysis. The timing of the CBF measurement was not significantly longer in the patients who were studied after an initial emergency surgical procedure compared to the nonsurgical patients ($p = 0.62$) (Fig. 1). As shown in Fig. 2, the CBF values were generally lowest when the CBF measurement was done early after injury and increased over time ($r^2 = 0.14$). $ETCO_2$ and $PaCO_2$ during the measurement of CBF were 35.6 ± 4.2 mmHg (4.75 ± 0.56 kPa) and 37.5 ± 5.8 mmHg (4.99 ± 0.77 kPa), respectively. Because the patients were ventilated with normal values for pCO_2 and $ETCO_2$, no significant relationship was found between CBF and CO_2 values. Initial ICP was 24.1 ± 16.8 mmHg and MABP at the time of the CBF measurement was 89.9 ± 13.7 mmHg. Other physiological measures were available in smaller numbers of patients, as listed in Table 2.

Relationship of CBF to Demographic Factors

CBF typically decreases with age in normal subjects *(12)*, and, therefore, age might be expected to be an important influence on the findings of this study. Average global CBF during the first 12 hours after injury decreased after age 40, but this age effect was not significant ($r^2 = 0.09$).

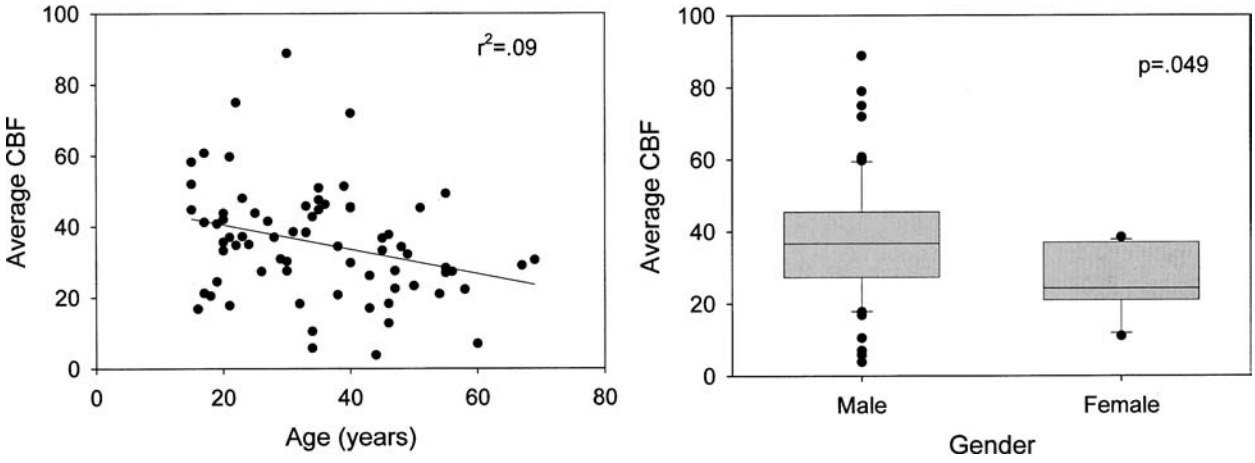

Fig. 2. Relationship between time after injury and cerebral blood flow.

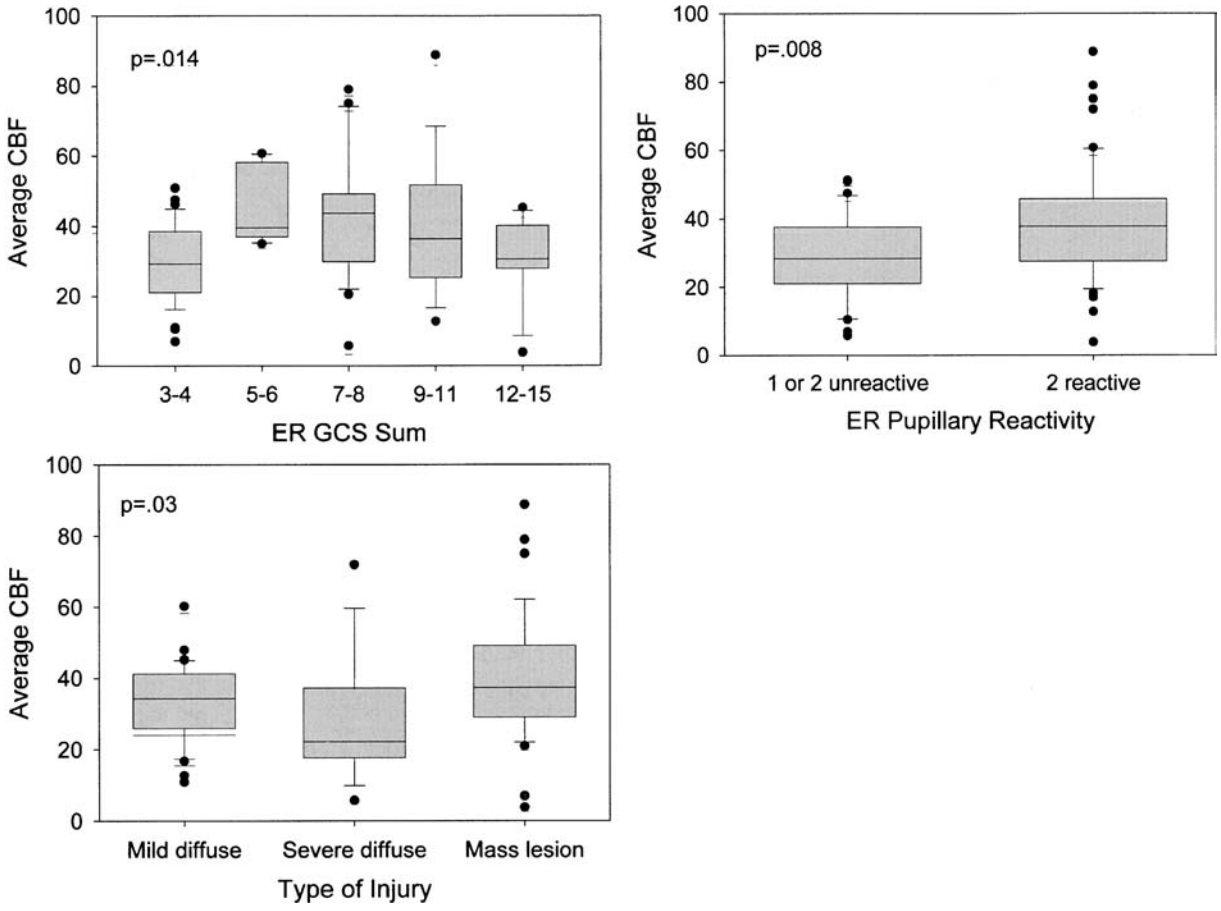

Fig. 3. Relationship between measures of initial injury severity and average cerebral blood flow within 12 hours of injury. ER, emergency room; GCS, Glasgow Coma Scale.

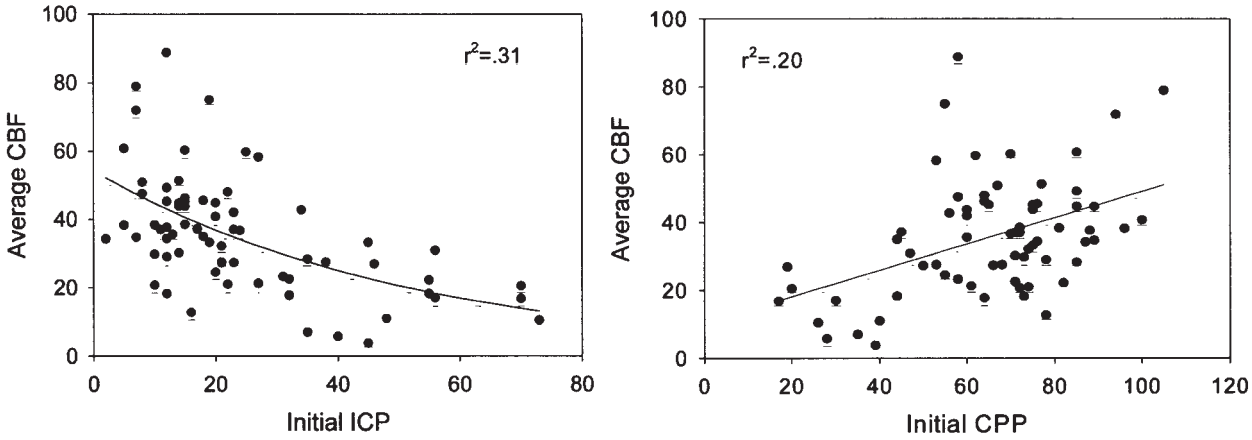

Fig. 4. Relationship between intracranial pressure and global cerebral blood flow (CBF) (left) and between cerebral perfusion pressure and global CBF (right).

Average global CBF during the first 12 hours after injury was slightly lower in women than in men ($p = 0.049$). However, neither of these demographic factors explained the variation in CBF observed in these patients with brain injuries.

Relationship of CBF to Injury Severity and Physiological Variables

CBF is normally closely coupled to cerebral metabolism. In physiological circumstances where cerebral metabolic requirements are reduced, CBF typically decreases. Therefore, it might be expected that the severity of a brain injury would be reflected by the CBF. In addition, CBF depends on an adequate cerebral perfusion pressure, that is, on MABP and ICP, and CBF can be altered by the level of the arterial pCO_2.

Figure 3 shows the relationship between CBF during the first 12 hours after injury and the initial GCS and pupillary reactivity, as well as the type of injury judged by the ER CT scan. For the patients who were admitted with GCS ≤ 8, CBF was related to the initial GCS recorded in the ER. CBF was lowest in the patients with GCS 3–4, averaging 29.7 ± 11.6 mL/100 g/minute. For the patients with an initial GCS > 8, but who deteriorated, usually because of an expanding mass lesion, the CBF was more variable. The average CBF was also lower in the patients who had one or both pupils fixed on the ER examination ($p = 0.008$). The type of injury observed on the initial CT scan was significantly related to CBF, averaging 32.1 ± 11.4 mL/100 g/minute in the patients with mild diffuse injuries (types 1 and 2), compared to 28.9 ± 18.5 in the patients with severe diffuse injuries (types 3 and 4) and 40.8 ± 18.0 mL/100 g/minute in those with mass lesions (types 1 and 2) ($p = 0.03$).

The left side of Fig. 4 illustrates the relationship between CBF during the first 12 hours after injury and ICP. ICP was the only physiological parameter that was significantly related to CBF, and most of the patients with the lowest CBF values had elevated ICP. Because MABP was kept normal even in the patients with low CBF, a significant relationship between CBF and CPP was also observed (*see* Fig. 4, right side). Most of the patients with a low CBF also had a low (CPP < 40 mmHg). MABP and $ETCO_2$ were not consistently related to the CBF values.

To distinguish whether CBF is appropriately reduced because it is coupled to low cerebral metabolic requirements or whether CBF is inadequate, measures of cerebral oxygenation are often used. Arterial-venous oxygen difference ($AVDO_2$) is a global measure of the ratio between CBF and cerebral metabolism *(13)*, and brain tis-

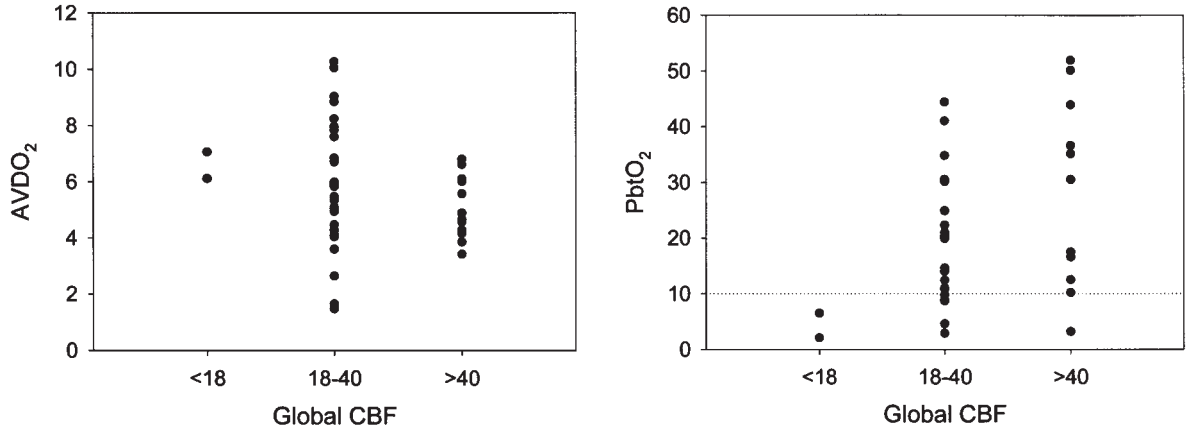

Fig. 5. Relationship between measures of oxygenation and global cerebral blood flow. Left: arteriovenous oxygen difference ($AVDO_2$); right: oxygen tension in brain tissue ($PbtO_2$).

sue pO_2 ($PbtO_2$) is local measure of tissue pO_2 in the brain immediately surrounding the probe. $AVDO_2$ was available at the time of CBF measurement in 42 (55%) of the 77 patients, and $PbtO_2$ (normal value <10 mmHg) was available in 39 patients. As illustrated in Fig. 5, both $AVDO_2$ and $PbtO_2$ were normal in almost all patients with an average CBF > 40 mL/100 g/minute. One patient in this CBF group had a $PbtO_2$ of 4.5 mmHg, but in this patient, the pO_2 probe was located in a small frontal contusion that was not representative of CBF in the rest of the brain. Only two measurements of $PbtO_2$ were available in the patients with a CBF < 18 mL/100 g/minute, but both of these values were low, indicating that the low CBF was not simply a consequence of low metabolic requirements. Despite this low $PbtO_2$, the $AVDO_2$ was not as increased as it was in many of the patients with a higher CBF. In the patients with a CBF between 18 and 40 mL/100 g/minute, these two measures of oxygenation were extremely variable.

Relationship of CBF and Neurological Outcome

GOC at discharge from the ICU and at 6 mo after injury were strongly associated with CBF measured within the first 12 hours after injury. At the time of discharge from the ICU, 1 patient had achieved the outcome category of good recovery, and 19 patients had recovered with moderate disability. In these patients with a favorable recovery at this early time period, the average CBF was 46.1 ± 16.3 mL/100 g/minute. The lowest average CBF (22.4 ± 12.4 mL/100 g/minute) was obtained in the 21 patients who died in during the hospitalization. An intermediate level of CBF was observed in the patients who remained disabled or vegetative at discharge. Table 3 details the average CBF found in outcome groups at ICU discharge and at 6 months after injury.

To further investigate the interactions of these various demographic and physiological factors and outcome, logistic regression analysis was used. From the 77 patients, two subsets of patients were created for further analysis. The difference between the subsets was the outcome variable used. For the mortality analysis, the outcome variable recorded whether the patient was alive or dead at discharge from the hospital, and this outcome measure was available in all 77 patients. Because almost all deaths that occurred in these patients were during the ICU phase, this definition captured the largest number of patients for the analysis. For the analysis of long-term neurological outcome, a dichotomization of the GOS at 6 months postin-

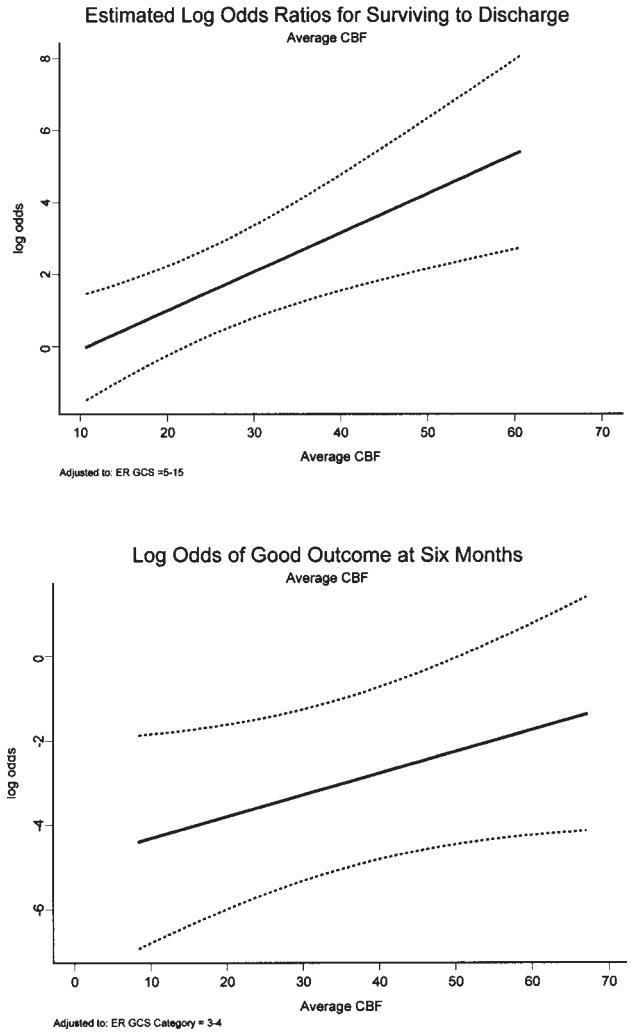

Fig. 6. Graph drawn from the logistic regression models of the relationship between global cerebral blood flow and mortality at intensive care unit discharge (top) and favorable outcome at 6 months after injury (bottom).

jury was used and was available in 67 of the patients. In addition to the outcome measure, both sets of data had to have nonmissing values for age, gender, the initial values for ICP, and MABP and $EtCO_2$ measured at or immediately after the measurement of XeCT CBF. The patients also had to have a recorded CT scan, pupillary reactivity, and postresuscitation GCS measure from the ER. For both subsets, there were eight missing values for age, eight for ICP, and five for $ETCO_2$. The total sample size for the alive at discharge was 63, and the total for the favorable outcome at 6 months was 54.

The initial *p* values for each of the variables included in the logistic regression models and the final *p* values at the time that variables dropped out of the model or in the final best fit model are shown in Table 4 for survival at discharge and in Table 5 for GOS at 6 months. In the survival analysis, only the initial GCS and CBF remained in the final model. The odds ratio for CBF was 2.96, indicating that the probability of survival at discharge was increased threefold for each 10-mL increase in CBF. The analysis of GOS at 6 months after injury was similar with only initial GCS and CBF being represented in the final model, but CBF was less influential on predicting a favorable recovery than on survival. The odds ratio for CBF in the GOS model was 1.68, and the *p* value was 0.08. Graphs demonstrating the relationship of the CBF value during the first 12 hours after injury and outcome adjusted for these factors that were found to be significant are shown in Fig. 6.

Clinical Characteristics of the Patients with Global Cerebral Ischemia

Because the CBF measurements were a screening test to identify patients with critically low CBF, the characteristics of this subgroup of patients were of special interest. Patients were considered to have global ischemia if the average CBF was <18 mL/100 g/minute *(14)*. By this definition, 9 (12%) of the 77 patients had global cerebral ischemia during the first 12 hours after injury. Average CBF in these patients was 11.8 ± 5 mL/100 g/minute, compared to 39 ± 15 mL/100 g/minute in the remaining 67 patients.

The demographic characteristics of this subgroup of patients were not particularly distinguishing. The usual measures of injury severity were not significantly worse in the patients with low CBF. The initial GCS in the ischemic CBF group was 5.5 ± 3.2, compared to 6 ± 2.9 in the nonischemic CBF group ($p = 0.12$). Mass lesions were present in 30% the patients in the low CBF group and in 43% in the nonischemic CBF group ($p = 0.5$).

Table 4
Logistic Regression Model for Alive at Discharge

Variable	*p in initial model*	*p when variable dropped from model*	*p in final model*
Age	0.74158	0.74158	
Gender	0.58997	0.57875	
ICP	0.64137	0.35430	
MAP	0.59664	0.72799	
$ETCO_2$	0.69810	0.67035	
ER pupillary reactivity	0.30825	0.21627	
CT category	0.08961	0.06337	
Time after injury	0.30838	0.25133	
ER GCS	0.14819		0.00492
CBF	0.03566		0.00088
Overall model	0.12367		0.00052

Final Model for Alive at Discharge

Variable	*Odds ratio*	*Lower 95% CL*	*Upper 95% CL*
ER GCS			
GCS 3–4	1.00		
GCS 5–13	9.17	1.96	42.95
CBF (per 10 mL/100 g/min)	2.96	1.56	5.62

ICP, intracranial pressure; $ETCO_2$, end-tidal CO_2; ER, emergency room; CT, computed tomography; GCS, Glasgow Coma Scale.

Table 5
Logistic Regression Model for Glasgow Outcome Score at 6 Months After Head Injury

Variable	*p in initial model*	*p when variable dropped from model*	*p in final model*
Age	0.19922	0.07759	
Gender	0.41139	0.35971	
ICP	0.41681	0.06760	
MAP	0.65352	0.65352	
$ETCO_2$	0.52392	0.39717	
ER pupillary reactivity	0.62617	0.61310	
CT category	0.30770	0.29351	
Time after injury	0.59044	0.56558	
ER GCS	0.01680		0.00150
CBF	0.44950		0.08373
Overall model	0.37328		0.00158

Final Model for Favorable Outcome at 6 Months

Variable	*Odds ratio*	*Lower 95% CL*	*Upper 95% CL*
ER GCS			
GCS 3–4	1.00		
GCS 5–15	36.35	3.96	334.08
CBF (per 10 mL/100 g/min)	1.68	0.93	3.01

ICP, intracranial pressure; $ETCO_2$, end-tidal CO_2; ER, emergency room; CT, computed tomography; GCS, Glasgow Coma Score.

Table 6
Comparison of Patients Based on Different Levels of Cerebral Blood Flow

	Groups of patients based on CBF			
	CBF < 18	*CBF > 18 and > 40*	*CBF > 40*	*p*
No. of patients	9	40	28	
gCBF (mL/100 g/minute)	11 ± 5	30 ± 6	52 ± 13	
Mortality at discharge	8 (89%)	11 (28%)	2 (7%)	< 0.001
GOS at 6 months				
Poor outcome	9 (100%)	23 (64%)	(23%)	< 0.001
Good outcome	0	13 (36%)	17 (77%)	
ICP (mmHg)	46 ± 18	24 ± 16	16 ± 7	< 0.001
MABP (mmHg)	87 ± 11	91 ± 15	89 ± 13	0.500
CVR (mmHg/mL/100 g/minute)	4.3 ± 2.6	2.3 ± 0.7	1.4 ± 0.4	<0.001
$SjvO_2$ (%)	62 ± 2	67 ± 13	68 ± 8	0.763
$PbtO_2$ (mmHg)	4 ± 3	19 ± 12	28 ± 17	0.047

gCBF, global CBF; GOS, Glasgow outcome score; ICP, intracranial pressure; CVR, cerebrovascular resistance; $SjvO_2$, jugular oximetry; $PbtO_2$, oxygen tension in brain tissue.

The physiological findings in this group of patients are summarized in Table 6. The only finding characteristic of the subgroup of patients with ischemic CBF was severe intracranial hypertension, average 44 ± 19 mmHg compared to 21 ± 14 mmHg in the nonischemic patients ($p < 0.001$). The initial ICP was >20 mmHg in 90% of patients and >30 mmHg in 80% of patients in this group, compared to 33% and 16%, respectively, in the patients who were nonischemic. MABP was similar in the two groups, and, consequently, CPP was 43 ± 21 mmHg in the patients with ischemic CBF and 69 ± 16 mmHg in the group that was nonischemic ($p < 0.001$). A value for $SjvO_2$ was available in only three of the patients in the ischemic group and averaged 60 ± 3% at the time of the CBF measurement. None had an $SjvO_2 < 50\%$. Brain tissue pO_2 was measured in two of the patients with ischemic CBF. In contrast to the $SjvO_2$ values, the $PbtO_2$ was <10 mmHg in both of the patients.

Mortality was particularly high in the group with cerebral ischemia; 90% at the time of discharge from the ICU and at 6 months postinjury. The single surviving patient in this group remained severely disabled at 6 months after injury. In contrast, mortality in the patients without global ischemia was only 17.9% at discharge and 19.4% at 6 months after injury. Most of the deaths in the patients with global ischemia occurred within the first 4 days after injury, whereas deaths in the patients who were nonischemic occurred later.

Clinical Characteristics of the Patients with Global Cerebral Hypoperfusion

Another high-risk group was the patients with a global CBF just above the ischemic threshold of 18 mL/100 g/minute, but <28 mL/100 g/minute, which is well below the lower limit of normal CBF (28 mL/100 g/minute = 2 standard deviations below normal mean CBF value of 52 mL/100 g/minute). Seventeen patients had a global CBF in this range between 18 and 28 mL/100 g/minute. The average CBF was 23 ± 3 mL/100 g/minute.

This group of patients had an initial GCS of 5.5 ± 3.1, which was not significantly different from the rest of the patients. Diffuse lesions were the predominant injury type in this group, with only 18% having a mass lesion.

The physiological variables of this group were similar to the group with ischemia, with an elevated initial ICP averaging 35 ± 18 mmHg. ICP was >20 mmHg in 80% of this group and >30 mmHg in 53% of the group. MABP averaged 92 ± 16 mmHg, and CPP was 56 ± 18 mmHg. $ETCO_2$

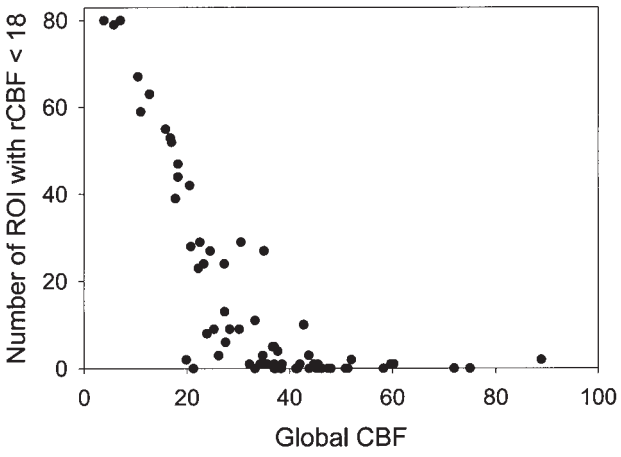

Fig. 7. Relationship between regional ischemia (rCBF <18 mL/100 g/minute) and global cerebral blood flow (CBF) value. In every patient, the regional CBF measurements were performed in 80 standardized cortical regions of interest. rCBF, regional CBF; ROI, region of interest.

and $PaCO_2$ at the time of the CBF measurement were similar to other patients. Measures of cerebral oxygenation suggested hypoperfusion in several of the patients. $SjvO_2$ (11 patients) averaged 61 ± 10% but was <50% in 3 (27%) of the 11 patients at the time of the CBF measurement. $PbtO_2$ (in eight patients) averaged 10 ± 7 mmHg and was <10 mmHg in five (63%) of the patients.

Global CBF could be reduced within this range for two possible reasons. CBF could be homogeneously reduced to a variable degree or the global CBF could represent the mixture of relatively normal CBF in part of the brain with variably sized regions of ischemia. Figure 7 shows a plot of the global CBF against the number of ROIs with average rCBF < 18 mL/100 g/minute. A total of 80 cortical ROIs were measured in each patient. In most of the patients with a global CBF < 40 mL/100 g/minute, the reduction in global CBF was directly related to the number of ischemic ROIs. Only a few patients, especially in the range between 18 and 28 mL/100 g/minute, had a homogeneously reduced CBF.

Although mortality was lower than in the group with global ischemia, the long-term neurological recovery of the patients with global CBF between 18 and 28 mL/100 g/minute was generally poor. At discharge from the ICU, the mortality rate was 30% and almost all patients (94%) had an unfavorable outcome. By 6 months after injury, the mortality rate was 44% and an additional 44% remained severely disabled or vegetative.

Discussion

CBF has been measured after traumatic brain injury using many different techniques, including the original Kety-Schmidt nitrous oxide technique *(3)*, ^{133}Xenon techniques using external radiation detectors *(1,7,15,16)*, CT scan techniques with stable Xenon enhancement (XeCT CBF) *(17,18)*, MRI, and PET techniques. Because the XeCT CBF can be performed at the time of the initial diagnostic CT scan, the technique is practical for assessing CBF in the acute stage of neurological emergencies. Most of the "ultra-early" CBF measurements have been performed with this technique *(4,18)*. In addition, XeCT CBF provides a high-resolution regional picture of CBF, which has elucidated the heterogeneous nature of CBF after traumatic brain injury *(17)*.

Most of the previous studies of CBF after trauma have demonstrated a close relationship between a low CBF and a poor neurological outcome. The present study is no different in this respect. However, instead of finding a threshold for a CBF effect, global CBF was related to outcome throughout the entire spectrum of alues observed in the patients. This was true for both mortality and long-term neurological outcome. The probability of survival at hospital discharge was increased threefold for each 10-mL increase in CBF. For each 10-mL increase in CBF, the probability of a favorable outcome at 6 months was increased by 1.7-fold.

However, the cause of a globally reduced CBF varied throughout the spectrum of values observed in the patients studied. At the lowest end of the CBF spectrum (<18 mL/100 g/minute), intracranial hypertension played an important and probably causative role in global ischemia, because most of the patients had a reduced CPP. The therapeutic implications of this finding are that therapy directed at reduc-

ing ICP might be the most effective way to improve cerebral perfusion. For more intermediate levels of CBF (between 18 and 40 mL/100 g/minute), the presence of regional ischemia was a more important determinant of global CBF. This category of patients might have a situation that is more amenable to treatment directed at either redistributing or increasing CBF.

The CBF threshold of 18 mL/100 g/minute for ischemia has been questioned after traumatic brain injury, and often it has been proposed that low CBF values may be appropriate if the brain is severely damaged and cerebral metabolic requirements are low. A measure of the level of oxygenation in the brain is often helpful in making this distinction between true ischemia and severely reduced metabolic requirements. A value for $SjvO_2$ was available in only three of the patients with global CBF < 18 mL/100 g/minute and averaged 60 ± 3% in this group. None of the patients with a global CBF < 18 mL/100 g/minute had an $SjvO_2$ < 50%. In most circumstances, this information would be interpreted as indicating that the CBF, although low, was adequate for cerebral metabolic requirements at the time. However, interpretation of a normal $SjvO_2$ can be treacherous when the CBF is as low as it was in these patients, becasue extracerebral blood becomes an increasingly larger proportion of the blood drawn from the jugular bulb, contaminating the value *(19)*. Although a low $SjvO_2$ is good evidence for an inadequate CBF, a normal $SjvO_2$ does not provide assurance that CBF is always adequate particularly in this setting. Brain tissue pO_2 was also measured in two of the patients with a global CBF < 18 mL/100 g/minute. In contrast to the $SjvO_2$ values, the $PbtO_2$ was <10 mmHg in both patients, suggesting the presence of ischemia rather than simply a reduction in cerebral metabolic rate.

Most of the previous studies of CBF have demonstrated that the finding of a critically low CBF is most common during the first few hours after injury. It has become a common conception that after 12 hours postinjury, cerebral ischemia is rarely observed. Although serial measurements of CBF do increase with time in many patients, the main reason that critically low CBF values are found only in the initial hours after injury is that the patients with these levels of CBF reduction typically die soon after injury and are not represented in CBF data at later times.

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References

1. Overgaard J, Molsdal C, Tweed TA. Cerebral circulation after head injury. Part 3: does reduced regional cerebral blood flow determine recovery of brain function after blunt head injury? J Neurosurg 1981;55:63–74.
2. Overgaard J, Tweed WA. Cerebral circulation after head injury. Part 4: functional anatomy and boundary-zone flow deprivation in the first week of traumatic coma. J Neurosurg 1983;59:439–446.
3. Robertson CS, Contant CF, Gokaslan ZL, et al. Cerebral blood flow, arteriovenous oxygen difference, and outcome in head injured patients. J Neurol Neurosurg Psych 1992;55:594–603.
4. Bouma GJ, Muizelaar JP, Stringer WA, et al. Ultra-early evaluation of regional cerebral blood flow in severely head-injured patients using xenon-enhanced computerized tomography. J Neurosurg 1992;77:360–368.
5. Muizelaar JP, Marmarou A, DeSalles AA, et al. Cerebral blood flow and metabolism in severely head-injured children. Part 1: relationship with GCS score, outcome, ICP, and PVI. J Neurosurg 1989;71:63–71.
6. Obrist WD, Gennarelli TA, Segawa H, et al. Relation of cerebral blood flow to neurological status on outcome in head-injured patients. J Neurosurg 1979;51:292–300.
7. Kelly DF, Kordestani RK, Martin NA, et al. Cerebral blood flow as a predictor of outcome following traumatic brain injury. J Neurosurg 1997;86:633–641.
8. Cherian L, Goodman JC, Robertson CS. Brain nitric oxide changes after controlled cortical impact injury in rats. J Neurophysiol 2000;83:2171–2178.

9. Cherian L, Chacko G, Goodman JC, et al. Cerebral hemodynamic effects of phenylephrine and L-arginine after cortical impact injury. Crit Care Med 1999;27:2512–2517.
10. Bullock RM, Chesnut R, Clifton GL, et al. Management and prognosis of severe traumatic brain injury. Part 1: guidelines for the management of severe traumatic brain injury. J Neurotrauma 2000;17:449–597.
11. Yonas H, Darby JM, Marks EC, et al. CBF measured by Xe-CT: approach to analysis and normal values. J Cereb Blood Flow Metab 1991; 11:716–725.
12. Leenders KL, Perani D, Lammetsma AA, et al. Cerebral blood flow, blood volume, and oxygen utilization. Normal values and effect of age. Brain 1990;113:27–47.
13. Robertson CS, Narayan RK, Gokaslan Z, et al. Cerebral arteriovenous oxygen difference as an estimate of cerebral blood flow in comatose patients. J Neurosurg 1989;70:222–230.
14. Astrup J, Siesjo BK, Symon L. Thresholds in cerebral ischemia—the ischemic penumbra. Stroke 1981;12:723–725.
15. Cold GE. Cerebral blood flow in acute head injury. The regulation of cerebral blood flow and metabolism during the acute phase of head injury, and its significance for therapy. Acta Neurochir Suppl (Wien) 1990;49:1–64.
16. Obrist WD, Langfitt T, Jaggi J, et al. Cerebral blood flow and metabolism in comatose patients with acute head injury. Relationship to intracranial hypertension. J Neurosurg 1984;61:241–253.
17. Marion DW, Darby J, Yonas H. Acute regional cerebral blood flow changes caused by severe head injuries. J Neurosurg 1991;74:407–414.
18. Bouma GJ, Muizelaar JP, Choi SC, et al. Cerebral blood flow and metabolism after severe traumatic brain injury: the elusive role of ischemia. J Neurosurg 1991;75:685–693.
19. Feldman Z, Robertson CS. Monitoring of cerebral hemodynamics with jugular bulb catheters. In: Diringer M, ed. Critical Care Clinics. Vol 13, number 1. Philadelphia: W.B. Saunders Company, 1997, pp. 51–77.