Cerebral circulation and metabolism after severe traumatic brain injury: the elusive role of ischemia

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✔ Although experimental and pathological studies suggest an important role for ischemia in the majority of fatal cases of traumatic brain injury, ischemia has been a rare finding in most clinical studies of cerebral blood flow (CBF) in head-injured patients. The hypothesis of the present study was that cerebral ischemia occurs in the first few hours after injury, but that CBF measurements have not been performed early enough. Early measurements of CBF (by the ^{133}Xe intravenous method) and arteriovenous oxygen difference (AVDO$_2$) were obtained in 186 adult head-injured patients with a Glasgow Coma Scale score of 8 or less, and were correlated with neurological status and outcome. During the first 6 hours after injury, CBF was low (22.5 ± 5.2 ml/100 gm/min) but increased significantly during the first 24 hours. The AVDO$_2$ followed the opposite course; the decline of AVDO$_2$ was most profound in patients with low motor scores, suggesting relative hyperemia after 24 hours. A significant correlation between motor score and CBF was found in the first 8 hours after injury (Spearman coefficient = 0.69, p < 0.001), but as early as 12 hours postinjury this correlation was lost. A similar pattern was found for the relationship between CBF and outcome. Cerebral blood flow below the threshold for infarction (CBF ≤ 18 ml/100 gm/min) was found in one-third of the studies obtained within 6 hours, the incidence rapidly decreasing thereafter. A low CBF after 24 hours was not generally associated with a high AVDO$_2$, and was probably a reflection of low oxidative metabolism rather than frank ischemia. In 24 patients, a CBF of 18 ml/100 gm/min or less was found at some point after injury; the mortality rate was significantly higher in this subgroup, and survivors did worse. In some cases, ischemia was successfully treated by reducing hyperventilation or inducing arterial hypertension. These results support the above hypothesis, and suggest that early ischemia after traumatic brain injury may be an important factor determining neurological outcome. Moreover, these data indicate that early hyperventilation or lowering of blood pressure to prevent brain edema may be harmful.

KEY WORDS • head injury • cerebral blood flow • arteriovenous oxygen difference • outcome

D ESPITE the implementation of aggressive strategies of diagnosis and treatment based on the control of intracranial pressure (ICP),[4] the incidence of mortality and morbidity from severe head injury remains frustratingly high. This suggests that raised ICP in many cases reflects the irreversible end result of biochemical and cellular events leading to neuronal death, rather than being itself the cause of such damage. This contention further implies that the efficacy of new therapeutic efforts will depend on successful intervention in the pathophysiological mechanisms that occur early (in the first few hours) after injury. The validity of this concept was recently confirmed for spinal cord injury in a multicenter trial, which showed that treatment with methylprednisolone was effective only when administered within 8 hours after trauma.[5]

The fact that traumatic and ischemic brain injury have been proposed to share a number of common injury mechanisms, such as free radical production[19,28] and excitotoxicity,[12,21] suggests a potential for common clinical treatment strategies. Additionally, the production of common pathological cascades raises the possibility of important interactions between traumatic and ischemic brain injury, which now have been confirmed in the laboratory.[22]

To date, however, no compelling clinical evidence for the occurrence of ischemia after head injury has been presented. Although postmortem studies have indicated that damage resulting from global or focal cerebral ischemia adds to that inflicted by the primary injury in at least 50% of cases,[15,24] the demonstration of ischemia in severely head-injured patients undergoing cerebral blood flow (CBF) measurements has eluded

almost every worker in the field.[11,20,27,32,35,38,39,41] In addition, no correlation between CBF and clinical status or outcome has been found. However, in most studies of head-injured patients, CBF measurements were not obtained until intervals of up to several days after injury, which may have masked flow changes occurring in the first few hours following the impact. Several investigators have suggested that ischemia, if present, occurs only in the very early stages (the first few hours) after injury and has generally subsided by the time the first CBF study is performed.[32,39] Yoshino and co-workers[47] were able to evaluate CBF semi-quantitatively in 29 of 42 patients within 2 hours of impact. In 17 of 25 fatally injured patients, they detected a severely ischemic state. Unfortunately, no CBF measurements were made beyond this acute stage, leaving unanswered the question whether this ischemia was reversed (despite death at a later stage). Moreover, dynamic computerized tomography (CT) scanning as employed by these workers has not consistently been compared with other techniques for determining CBF, which leaves some doubt about the interpretation of these data.

Another factor to be taken into account in determining whether CBF is sufficient to meet the metabolic demands of the injured brain, is that cerebral metabolism is often decreased after severe brain trauma. Consequently, reduced flow does not necessarily mean ischemia in these patients. Therefore, determinations of arteriovenous oxygen difference ($AVDO_2$) are necessary for the proper evaluation of CBF data following head injury, as this parameter reflects the link between flow and metabolism.

The detection of ischemia in humans early after severe head injury would have two important consequences. It would support hypotheses generated from laboratory research on the interaction between common injury mechanisms of trauma and ischemia and extend the applicability of such mechanisms to humans. More important, it might also provide more effective therapeutic strategies for severe head injury by identifying patients who might benefit from early aggressive treatment aimed at the reversal of cerebral ischemia.

At the Medical College of Virginia Hospital, measurements of CBF and $AVDO_2$ have been part of the routine management of severely head-injured patients since 1982. The purpose of the present study was to elucidate the role of ischemia in severe traumatic brain injury through analysis of the accumulated results of these measurements. We hypothesized that early after injury, CBF is reduced and is related to the severity of the injury, and that the presence of initial ischemia is associated with poor outcome. In addition, we speculated that the reversal of ischemia in these patients leads to improved outcome. Because of the possibility that an age-dependent difference in CBF might obscure the analysis,[35] only patients aged 18 years or older were included in this study. Our findings in the younger age group have previously been extensively reported.[35,36]

Clinical Material and Methods

Patient Population and Clinical Management

Between February, 1982, and February, 1990, CBF measurements were performed on 186 patients aged 18 years or older, who sustained severe blunt head injury and were unable to obey simple commands (Glasgow Coma Scale (GCS)[45] score of 8 or less for at least 6 hours). The mean age of this population was 34.9 ± 17.1 years, and 132 of the patients were men. All were admitted to the hospital within 12 hours after injury and were managed according to a standard protocol described earlier.[1,4] All patients were promptly intubated and ventilated mechanically, and were resuscitated as necessary to restore arterial pressure. Diagnostic CT scans were obtained upon admission and at regular intervals thereafter, and patients harboring mass lesions were treated surgically. Intracranial pressure was monitored in all patients, usually through a ventriculostomy connected to a pressure transducer, but in a few patients by a subarachnoid bolt or a fiberoptic device.* Arterial blood pressure (ABP) was monitored from an intra-arterial catheter, and displayed digitally as mean arterial blood pressure (MABP = $\frac{1}{3}$ systolic ABP + $\frac{2}{3}$ diastolic ABP). Neurological examination was performed daily and the GCS score and motor score (ranked 1 to 6, derived from the GCS) were noted every hour. Multimodality evoked potentials (MEP's) were monitored in most patients. The battery of tests included early and long-latency somatosensory evoked potentials (SEP's), monocular and binocular visual evoked potentials elicited by strobe light or light-emitting diode flash stimulation, and auditory brain-stem evoked potentials (BAEP's) in response to monaural click stimuli. These tests were performed and evaluated using a standard protocol described earlier.[16] Outcomes in surviving patients were assessed at 6 months or 1 year after injury by independent observers who had no knowledge of the CBF and $AVDO_2$ data, using the Glasgow Outcome Scale.[23] Written informed consent was obtained from the patients' next of kin for insertion of catheters and measurement of CBF. The protocol was approved by the Committee on the Conduct of Human Research at the Medical College of Virginia.

Measurement of CBF

Measurement of CBF was performed in the neuroscience intensive care unit using the ^{133}Xe inhalation or intravenous technique.[3] All procedures involving ^{133}Xe were performed in accordance with the radiation safety regulations of the Office of Environmental Health and Safety of the Virginia Commonwealth University. In most patients pancuronium was used to induce skeletal muscle paralysis during the CBF studies in order to provide optimal respiratory care, maintain constant $PaCO_2$, and prevent movement artifacts. During the CBF meas-

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* Fiberoptic digital pressure monitor, Model 420, manufactured by Camino Laboratories, San Diego, California.

urements, end-expiratory pCO_2 was monitored† and maintained constant by adjusting the respirator as necessary. Additional arterial pCO_2 measurements were obtained twice during each CBF measurement. With the inhalation method, patients breathed a gas mixture containing 5 to 8 mCi ^{133}Xe/liter for 1 minute; with the intravenous injection method, ^{133}Xe dissolved in saline (0.3 mCi/kg body weight) was injected, after which ventilation was halted for 20 seconds to prevent the xenon from being largely expired during the first passage through the lungs before reaching systemic circulation. The washout of radioactivity from the hemispheres and from expired air was monitored for 15 minutes. Before 1985, a system with 16 probes, concentrically arrayed in a Plexiglas helmet, was used;‡ later studies were performed with a portable system containing 10 probes.§ From the curves obtained, CBF_{15} was calculated: this algorithm is mathematically equivalent to the height-over-area method and is relatively insensitive to the compartmental slippage which is likely to occur with CBF measurements in brain trauma.[40] Because regional and hemispheric differences were usually minor and were always superimposed on global flow changes, as has been found by others,[10,11,35,38] the average value of all detectors has been used in this paper and is considered to represent "global" hemispheric flow. We excluded from the study those measurements performed during administration of any drugs used to influence systemic blood pressure in autoregulation tests (phenylephrine or trimethaphan), cerebral metabolism (barbiturates), or blood viscosity (mannitol), as well as studies obtained with cerebral perfusion pressure (CPP = MABP − ICP) at an insufficient level (CPP ≤ 50 mm Hg). For some of the analyses, CBF data were corrected to a standard $PaCO_2$ of 34 mm Hg by assuming a 3% change in CBF/torr $PaCO_2$.[39] The methodological considerations regarding this have been discussed previously.[35]

The first CBF study in each patient was performed at the earliest possible occasion after injury, as soon as the patient had been admitted to the intensive care unit and cardiopulmonary stabilization had been achieved. Follow-up studies were performed on ensuing days, whenever feasible. In keeping with established thresholds for cerebral perfusion,[2,26] global ischemia was considered to be present if CBF measured 18 ml/100 gm/min or less.

Determination of $AVDO_2$ and $CMRO_2$

In 153 of the 186 patients included in this study, $AVDO_2$ measurements were obtained. This value was calculated by subtracting the oxygen content in simul-

† Capnometer, Model HP 47210 A, manufactured by Hewlett-Packard, Waltham, Massachusetts.

‡ Tasc-5 CBF measurement system manufactured by the Harshaw Chemical Co., Solomon, Ohio.

§ Novo-10a CBF measurement system manufactured by Novo Diagnostics, Hartford, Connecticut.

TABLE 1

Cerebral blood flow and arteriovenous blood oxygen differences in head-injured patients measured at 6-hour intervals postinjury *

Hours Post-injury	CBF (ml/100 gm/min)	CBF_{34} (ml/100 gm/min)	$AVDO_2$ (ml/100 ml)	No. of Cases Studied	No. (%) with Ischemia
4–6	22.5 ± 5.2†	24.8 ± 5.5†	7.1 ± 1.5‡	12	4 (33%)
6–12	29.0 ± 10.0	30.8 ± 9.5	6.3 ± 2.5‡	74	8 (11%)
12–18	33.3 ± 11.0	35.8 ± 11.4	4.7 ± 1.6	50	0 (0%)
18–24	34.8 ± 11.4	37.3 ± 13.8	4.7 ± 1.6	37	2 (5%)
24–30	33.9 ± 10.4	37.2 ± 9.8	4.4 ± 2.4	29	1 (3%)
30–36	33.2 ± 12.0	37.8 ± 16.5	4.6 ± 1.4	23	1 (4%)
36–42	36.9 ± 12.7	38.7 ± 12.6	4.2 ± 1.7	19	1 (5%)
42–48	34.8 ± 14.7	38.2 ± 18.5	3.9 ± 1.1	11	0 (0%)
>48	33.6 ± 12.2	37.0 ± 13.3	4.4 ± 1.6	129	7 (5%)

* CBF = cerebral blood flow; CBF_{34} = cerebral blood flow adjusted to a pCO_2 of 34 mm Hg (see text); $AVDO_2$ = arteriovenous difference of oxygen content. Ischemia is defined as CBF ≤ 18 ml/100 gm/min.

† Significantly lower than values at all later time intervals (Newman-Keuls' test, $p < 0.05$).

‡ $AVDO_2$ values in the first 12 hours postinjury were significantly higher than values of later intervals (Newman-Keuls' test, $p < 0.05$).

taneously obtained arterial and mixed jugular venous blood samples.‖ Mixed jugular venous blood was sampled from a catheter inserted in the jugular bulb through retrograde cannulation of the right internal jugular vein, while arterial blood was drawn from a radial intra-arterial catheter. Determination of $AVDO_2$ was made at 6-hour intervals during the first few days following injury. Additionally, during each CBF measurement, two pairs of blood samples were obtained at a 5-minute interval. The average of these two measurements was used for the calculation of cerebral metabolic rate of oxygen ($CMRO_2$ = CBF × $AVDO_2$/100).

Results

Time Course of CBF and $AVDO_2$ and Relationship to Clinical Status and Outcome

Table 1 shows CBF and $AVDO_2$ values (mean ± standard deviation) at 6-hour intervals following injury. The earliest CBF measurement was performed 4 hours after injury; thus, the first interval in Table 1 reflects the time-span between 4 and 6 hours postinjury. Flow values obtained within this interval were significantly lower than those obtained at any later time (Newman-Keuls' test, $p < 0.05$). During the first 24 hours, CBF increased to values denoting "relative hyperemia" according to the criteria proposed by Obrist, et al.[39] Conversely, $AVDO_2$ values were initially above normal, and decreased rapidly in the first 24 hours, leveling off at about 4.5 ml/100 ml. The highest $AVDO_2$ values early after injury were typically found in patients with

‖ Oxygen content measured with an IL282 co-oximeter manufactured by Instrumention Laboratories, Inc., Lexington, Massachusetts.
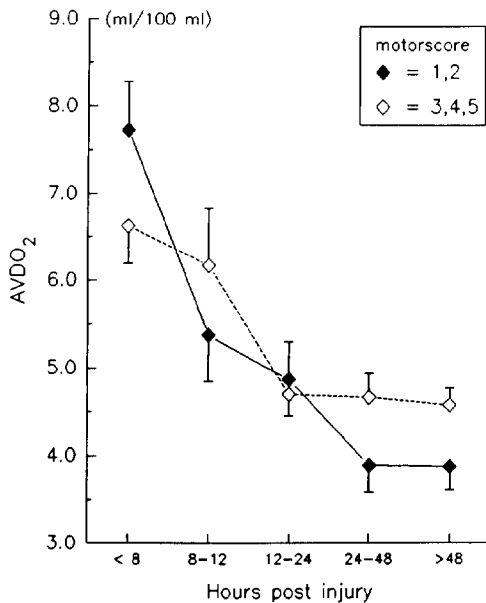
FIG. 1. Time course of mean arteriovenous oxygen difference ($AVDO_2$) in head-injured patients with motor scores of 1 or 2 and those with motor scores of 3 to 5 (motor score is measured as the best response to a painful stimulus: 1 = no response; 2 = extension; 3 = abnormal flexion; 4 = flexion withdrawal; 5 = localizing response). *Error bars* represent the standard error of the mean.

low motor scores, and the steepest fall in $AVDO_2$ during the first 24 hours occurred in these patients (Fig. 1).

The relationship between the level of CBF and the patient's motor score at the time of CBF measurement was examined with regard to the time interval after injury. It should be noted that, unlike the data presented in Table 1, we chose to calculate the first motor score after injury at 8 hours instead of 6 hours, so that each

motor score subgroup would contain a sufficient number of patients. In 32 patients, CBF was measured between 4 and 8 hours after injury (Fig. 2 *left*), and in this group there was an overall difference in mean CBF among the various motor score subgroups that was found to be statistically significant (analysis of variance (ANOVA) $p < 0.001$). Moreover, the correlation between CBF and motor score was also found to be significant (Spearman correlation coefficient $r = 0.69$, $p < 0.001$). In a group of 54 patients studied between 8 and 12 hours postinjury, there was still a trend correlating higher CBF with higher motor scores, although this was less strong ($r = 0.28$, $p = 0.04$) (Fig. 2 *center*). At 12 hours after injury the relationship between CBF and clinical status was completely lost (Fig. 2 *right*). The relationship between the first CBF measurement and patient outcome was analyzed for the subgroup of 32 patients who were studied within 8 hours after injury (Fig. 3). The correlation was positive in these patients; stepwise logistic regression for the effect of CBF, adjusted for motor score and $AVDO_2$, revealed that this relationship was also statistically significant ($p < 0.05$). A similar correlation with outcome did not exist for CBF measured later than 8 hours postinjury, however.

To account for possible artifacts in these analyses caused by differences in arterial pCO_2, all calculations were repeated with the CBF values corrected to a pCO_2 of 34 mm Hg (CBF_{34}), which changed neither the correlations nor the p values.

Ischemia

In 24 (13%) of the 186 patients in the present series, a global CBF of 18 ml/100 gm/min or less was found at some point after injury. These low flow values were found most frequently in the first 6 hours postinjury, the incidence decreasing thereafter (Table 1). The outcome for this ischemic group was compared to the
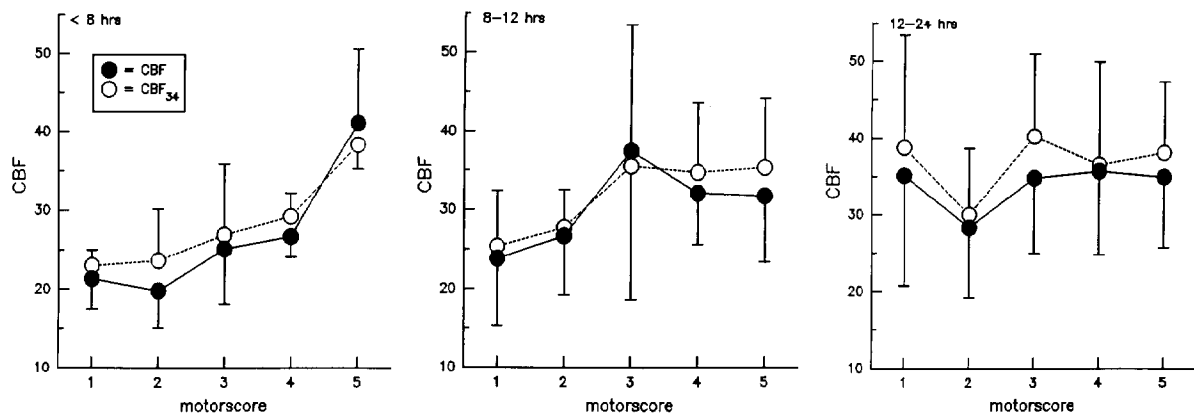

FIG. 2. Relationship between cerebral blood flow (CBF) and motor score, and between CBF corrected for pCO_2 (CBF_{34}) and motor score, in head-injured patients at various measurement intervals postinjury. The CBF is measured in ml/100 gm/min. *Error bars* represent the standard deviation of the measurements. *Left:* Studies obtained within 8 hours after injury in 32 patients showing a significant correlation between CBF and motor score (Spearman coefficient $r = 0.69$, $p < 0.001$). *Center:* Studies obtained between 8 and 12 hours after injury in 54 patients showing diminishing correlation (Spearman coefficient $r = 0.28$, $p = 0.04$). *Right:* Studies obtained between 12 and 24 hours after injury in 87 patients demonstrating no correlation between CBF and motor score.

outcome of the 160 nonischemic patients (Table 2). Two patients whose outcomes were not known were excluded from this analysis. There was a significant trend showing poorer outcome and higher mortality rates in the group of patients in whom a low CBF had been found (chi-square test for trends, p < 0.04). In 14 of these 24 patients, $AVDO_2$ was also determined. These measurements were usually performed after the very early stage. However, as with most of the patients in whom a CBF of 18 ml/100 gm/min or less had been found within 12 hours of injury, a reversed jugular venous catheter had not yet been inserted. In four patients in whom a CBF below 18 ml/100 gm/min was found within 6 hours of injury, we were able to measure $AVDO_2$ as well in only one case, where it was 8.0 ml/100 ml. In eight patients, a CBF below 18 ml/100 gm/min was found between 8 and 12 hours postinjury, and $AVDO_2$ was measured in three of these; a value suggestive of ischemia (> 8 ml/100 ml) was found in two, while the remaining patient had a low $AVDO_2$ of 4.0 ml/100 ml and thus a very low $CMRO_2$ of 0.52 ml/100 gm/min. This last patient died within a few hours after the measurements. However, in the 10 patients in whom low CBF was measured at any time later than 12 hours after injury and in whom $AVDO_2$ was also obtained, $AVDO_2$ was above 8 ml/100 ml in only one case. Thus, in four of these 14 patients, an $AVDO_2$ value above 8 ml/100 ml was found, indicating that CBF did not meet the metabolic demands of the brain. Because these patients were considered to be truly ischemic at the time of their CBF measurement, a more detailed description of these cases is given.

Illustrative Case Reports

Case 1: Low CBF, High AVDO₂, Reversible Low CMRO₂

This 21-year-old woman was involved in a motor-vehicle accident, and was admitted with a GCS score of 6. A CT scan showed scattered punctate white-matter hemorrhages with no midline shift. Evoked potential studies revealed diffuse cortical abnormalities, and BAEP monitoring revealed that wave V was of poor amplitude. During the first 3 days following injury, no ICP problems were encountered and CBF values of

around 30 ml/100 gm/min were measured. However, on Day 4, CBF was 15 ml/100 gm/min at a CPP of 70 mm Hg, while the $AVDO_2$ was determined to be 8.9 ml/100 ml, suggestive of global cerebral ischemia. The patient's blood pressure was raised with phenylephrine to achieve a CPP of 104 mm Hg, causing CBF to increase to 30 ml/100 gm/min. Although the $AVDO_2$ remained at 9.0 ml/100 ml, $CMRO_2$ still increased from 1.32 to 2.70 ml/100 gm/min, concomitant with a slight improvement in cortical evoked potentials. Therefore, it was decided to continue phenylephrine infusion in order to maintain an elevated CPP for several days. Eventually, the patient made a satisfying recovery and was left with moderate disability.

Case 2: Low CBF, High AVDO₂, Nonreversible Low CMRO₂

This 40-year-old man was admitted with a GCS score of 4 after a fall from a silo. The CT scan showed a large right temporal hemorrhagic contusion and a subdural hematoma causing significant midline shift. Right temporal craniectomy was performed with evacuation of the hematoma and temporal lobectomy. At 12 hours postinjury, a CBF of 16 ml/100 gm/min was measured, with an $AVDO_2$ of 8.3 ml/100 ml. Hyperventilation was reduced to raise the arterial pCO_2 from 22 to 27 mm Hg and blood pressure was raised from 89 to 100 mm Hg with phenylephrine. The CBF increased to 34 ml/100 gm/min, but this was accompanied by a fall in $AVDO_2$ to 4.4 ml/100 ml, leaving the $CMRO_2$ almost unchanged. The patient's MEP levels, which initially had been severely abnormal, were also unchanged. The CBF was measured once again on Day 4 and was still borderline at 20 ml/100 gm/min. Intracranial hypertension could not be controlled and the patient was declared brain-dead at Day 5 postinjury.

TABLE 2

Relationship between the presence of ischemia at any time postinjury and outcome in head-injured patients*

Outcome	No. of Cases		Total Cases
	No Ischemia	Ischemia	
good/moderate disability	66	5	71
severe disability	35	4	39
vegetative/dead	59	15	74
total cases	160	24	184

* Ischemia is defined as global cerebral blood flow ≤ 18 ml/100 gm/min, in the absence of low cerebral perfusion pressure (CPP ≥ 50 mm Hg).
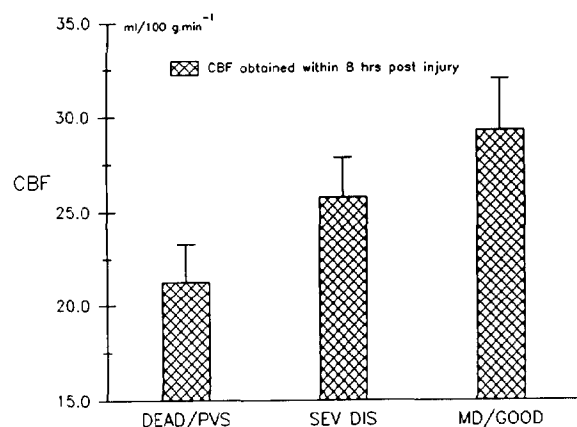

FIG. 3. Mean acute cerebral blood (CBF) in 32 head-injured patients who could be studied within 8 hours postinjury, grouped according to their Glasgow Outcome Scale score. PVS = persistent vegatative state; SEV DIS = severe disability; MD = moderate disability. *Error bars* represent the standard error of the mean. The correlation between CBF and outcome is significant (stepwise logistic regression, p < 0.05).

Case 3: Low CBF, High AVDO₂, Reversible Low CMRO₂

This 19-year-old man was admitted with a GCS score of 4. The CT scan showed bilateral hemorrhagic contusions in the basal ganglia and thalamus, and intraventricular hemorrhage. Eight hours after injury, the CBF was 15 ml/100 gm/min and the $AVDO_2$ was calculated at the very high value of 11.6 ml/100 ml. Subsequently, arterial pCO_2 was raised from 28 to 34 mm Hg by adjusting the respirator, and blood pressure was raised from 110 to 130 mm Hg with phenylephrine administration. These actions caused the CBF to increase to 32 ml/100 gm/min, and even though the $AVDO_2$ had dropped to 7.7 ml/100 ml, the $CMRO_2$ increased from 1.74 to 2.45 ml/100 gm/min. Simultaneously, an improvement of the MEP's was noted, consisting of a decreased central conduction time and an increased amplitude of cortical peaks. In this patient, continuous early MEP monitoring demonstrated that the SEP amplitude was correlated highly with end-tidal pCO_2, such that pCO_2 levels at or below 27 mm Hg were associated with amplitudes as low as 50% of those recorded at an end-tidal pCO_2 near 35 mm Hg. These findings suggested strongly that, in this patient, cerebral ischemia was initially present and contributed to the poor neurological condition. At later measurements, no further evidence of ischemia was found. The patient survived, but with severe disability.

Case 4: Low CBF, High AVDO₂, Nonreversible Low CMRO₂

This 60-year-old man was admitted with a GCS score of 6 after he was injured in a motor-vehicle accident. The CT scan showed a left temporal lobe contusion without significant mass effect. The patient was hypotensive during the first few hours following admission, and his CBF, measured 5 hours postinjury, was 16 ml/100 gm/min at a CPP of 64 mm Hg and an $AVDO_2$ of 8.0 ml/100 ml, consistent with borderline ischemia (the $CMRO_2$ was 1.28 ml/100 gm/min). His blood pressure was raised by fluid replacement and phenylephrine administration from 87 to 115 mm Hg (increasing the CPP to 98 mm Hg); although the CBF increased to 28 ml/100 gm/min, the $AVDO_2$ decreased to 3.9 ml/100 ml, resulting in a slight decrease in $CMRO_2$ to 1.09 ml/100 gm/min. It was concluded that the low CBF was a reflection of the low $CMRO_2$, and that maintaining elevated blood pressure was not useful in this case. This was confirmed by the patient's failure to demonstrate any improvement in SEP amplitude when changes in blood pressure and CBF were effected. Despite intensive treatment for raised ICP, his neurological condition did not improve and he remained in a persistent vegetative state.

Discussion

Occurrence of Ischemia After Head Injury

Cerebral ischemia has long been recognized as a potential cause of secondary injury after brain trauma.

When methods for CBF measurement first became available for clinical use, much effort was put into elucidating the role of ischemia in the pathophysiology and outcome of severe head injury. However, the early studies of CBF in head injury produced conflicting results.[7,13,27,42] Later investigators reported that global cerebral ischemia after head injury was a rare finding and instead emphasized the occurrence of relative or absolute hyperemia in the first days after trauma and its possible relationship with raised ICP.[6,10,20,38,39] However, the time interval after injury at which CBF was measured has not been consistent in these studies and, although some of the authors reported that they studied CBF in the "acute stage" of the injury, most of the measurements were in fact obtained days or even weeks after impact. Although CBF was occasionally measured within 24 hours of injury, data obtained during the first several days postinjury were often pooled, masking possible early changes in flow. Thus, ischemia occurring in the first hours after injury may well have been missed. This is unfortunate, because it is becoming clear from a growing body of experimental and clinical data that the pathophysiological events occurring immediately after the impact are of major importance in determining the clinical course and outcome.[31]

The present study attempts to address this point by detailed analysis of early changes in CBF as measured at consecutive time intervals during the first days postinjury. Within 6 hours of injury, the mean CBF was significantly lower than at any time thereafter, and critically low CBF (below the threshold of infarction: 18 ml/100 gm/min)[2,26] was found in 33% of these cases. However, no measurements were obtained earlier than 4 hours postinjury and from extrapolation of the data in Table 1, one would estimate the incidence of ischemia during this period to be even higher. It should also be emphasized that these early measurements were performed in a somewhat selected group of patients who had suffered no mass lesions and were in a relatively good clinical condition. Since patients with the worst injuries were usually in the operating room early after admission, their first CBF study often had to be delayed for several hours.

An increase of CBF to normal or relatively hyperemic values occurred during the first 24 hours. At 18 hours postinjury, mean CBF values did not significantly differ from those obtained at any time later in the posttraumatic course. Moreover, in the first 8 hours CBF appeared to be related to clinical status and outcome, while as early as 12 hours postinjury this relationship was lost. These findings appear to confirm that ischemia, if present, is usually an early event, and will easily go undetected if CBF measurements are delayed beyond 12 hours after injury.

Although global ischemia was found in only 24 of the 186 patients in this study, it should be noted that in almost half of these cases the low CBF values were found between 4 and 12 hours after injury. Later than 12 hours postinjury, global ischemia was rare and the

mean flow values were in the hyperemic range, which is in agreement with the earlier studies. It is therefore quite possible that, had we been able to study more patients (including those with mass lesions) at 4 hours postinjury or earlier, the number of patients with ischemia would have been much higher.

Ischemia and Outcome

In this study, a relationship was found between early CBF and both clinical status (as reflected by motor score) and outcome. Although these correlations do not prove a causal relationship, they are at least compatible with such a connection. It should be noted that the standard deviations were still fairly high, which precludes relating CBF to clinical status in individual cases. One might also argue that the correlation between early CBF and outcome simply reflects the correlation between motor score and CBF, the relationship between admission GCS score (or motor score) and outcome being well established.[25] However, even after adjustment for motor score in the statistical calculations, the correlation between early CBF and outcome was significant, suggesting that there was some additional deterioration attributable to the low flow. Jenkins, et al.,[22] have demonstrated that an incomplete ischemic insult, in itself not leading to detectable neuronal death, exacerbates the effects of a mild concussive brain trauma, which in isolation would not cause a prolonged functional impairment. The two insults combined resulted in massive neuronal necrosis and significantly impaired recovery of electrophysiological parameters. This increased vulnerability of the traumatized brain to ischemia may persist for at least 24 hours and is in part mediated by biochemical cascades initiated by excitatory receptors.[21] A possible consequence of increased ischemic vulnerability after traumatic brain injury may be that even "borderline" low CBF, above the threshold of infarction in normal brain (18 ml/100 gm/min), may be capable of inflicting ischemic brain damage. This concept is in line with the present finding that early CBF correlated positively with outcome.

The present data suggest that ongoing ischemia later in the posttraumatic course, may well occur occasionally (as in Case 1), but probably plays a minor role in determining overall outcome from head injury, considering its low incidence. Technical limitations inherent in the ^{133}Xe method as used in this study, however, may have led to an underestimation of this incidence (see below).

Treatment of Ischemia

The present results support experimental and pathological studies identifying posttraumatic ischemia as a cause of secondary and possibly preventable injury to the brain.[14,15,22] It has been suggested that successful treatment of head injury should be aimed at the prevention of secondary neuronal injury. Treatment of posttraumatic ischemia may fit into such a strategy, but it may occur too early to be amenable to treatment in

many cases, leaving treatment of the secondary effects of trauma and ischemia as the only viable options.

At this time, one can only speculate about the possible causes of early posttraumatic ischemia in the presence of normal CPP. One possible explanation is vasospasm of the large conducting arteries, which has been shown in angiographic studies to occur in 30% to 40% of cases,[30,37,44] and has also been confirmed by transcranial Doppler ultrasound studies.[46] If vasospasm is indeed the cause, this would also mean that, contrary to common belief, raised ABP in these cases will not increase ICP or enhance cerebral edema. Hence, it may not be beneficial to arbitrarily "stabilize" MABP at a lower level in severely head-injured patients without knowledge of CBF or $AVDO_2$ values. Early hyperventilation to prevent raised ICP may also prove dangerous by provoking ischemia in patients whose CBF is already borderline.

As this study demonstrates, it may be feasible in some cases to treat ischemia in a fashion similar to that in patients suffering from vasospasm following subarachnoid hemorrhage.[33] However, this treatment was not effective in all of the patients in terms of increasing $CMRO_2$ and improving electrophysiological parameters. Comparable observations were made in four other patients who have been described previously,[34] but in whom $AVDO_2$ was not determined. We therefore conclude that treatment of ischemia may be of benefit in some patients, but that the effects of the treatment should be carefully monitored, preferably by measuring $CMRO_2$ and evoked potentials.

Technical Limitations

An important question to be answered with regard to these data is whether the low CBF found in this study indicated inability to meet cerebral metabolic demands, or whether this was merely a reflection of the severity of the brain damage with ensuing low metabolism. One factor that makes it difficult to answer this question is that the metabolic demands of the brain after severe head injury are largely unknown. Although it has been well established that $CMRO_2$ is reduced with coma, it is unclear whether the rate of oxidative metabolism truly reflects brain energy demand. In a cisternal infusion model in cats, $AVDO_2$ and brain energy metabolism as measured by ^{31}P-magnetic resonance spectroscopy apparently correlated well at various levels of ICP,[43] but it should be noted that in such a model no neuronal damage is actually present. One might argue that the low $CMRO_2$ in cases of very severe brain trauma is a result of the inability of damaged neurons to use the oxygen that is supplied due to mitochondrial dysfunction or disturbances of enzymatic activity. This contention is supported by the earlier finding that elevated lactate concentrations in the cerebrospinal fluid after severe head injury were not related to the presence of ischemia, but seemed due to an inability of the central nervous system to metabolize glucose through oxidative pathways.[8] In such a situation, CBF at any

level would be useless to the brain, and could thus be called "luxury perfusion";[29] we suspect that these cases are beyond salvage, irrespective of treatment. Consequently, low AVDO$_2$ may or may not reflect metabolic (mitochondrial) dysfunction, but high AVDO$_2$ always indicates inadequacy of CBF to support brain metabolism. Based on the AVDO$_2$ measurements in 14 of the 24 ischemic patients in this study which showed high values suggestive of ischemia in three of four patients studied in the first 12 hours after injury but in only one of 10 studied at a later stage, we conclude that low CBF early after injury tends to be true ischemia, while the same flow values when found later in the posttraumatic course usually reflect low metabolic needs or brain energy failure.

A few limitations of the ^{133}Xe methodology should be considered when evaluating the role of regional ischemia. First, it is recognized that the ^{133}Xe technique has a relatively poor spatial resolution, and may well have missed focal ischemic areas if they were surrounded by a zone of relatively high flow. This problem, due either to the "look-through phenomenon"[18] or to scattered radiation from adjacent tissue, is most apparent when a relatively small number of extracranial detectors is used, as in the present study. This renders unreliable regional CBF values as measured by individual detectors, which has led us to report and analyze global CBF values only. It is interesting that in the only study where low regional CBF was found in association with poor neurological recovery, CBF was measured with a very high spatial resolution (35 probes per hemisphere) which resulted in the detection of small areas with low flow.[41]

Furthermore, CBF in deeper areas of the brain cannot be adequately assessed by the ^{133}Xe method, therefore the possible role of ongoing ischemia in the brain stem or basal ganglia due to raised ICP and brain shift remains unclarified. It is hoped that future studies using methods such as positron emission tomography or stable xenon-enhanced CT[17] for measurement of CBF will answer these questions.

Lastly, when CBF measurements are performed on an intermittent basis, short-lived episodes of ischemia due to ICP waves, drops in blood pressure, or other causes may go undetected, although these may be sufficiently severe to inflict secondary neuronal damage. The answer may lie in continuous monitoring of CBF using small thermal-diffusion flow probes,[9] and jugular venous oxygen content with fiberoptic devices now available. Conclusive studies employing these methods have not been presented so far. Moreover, a poor correlation between CBF measured with the thermal diffusion method and with the ^{133}Xe method has been reported in head-injured patients (Doberstein, *et al.*, unpublished data), further confounding the interpretation of such studies.

Conclusions

In summary, this study indicates that disturbances

of cerebral circulation and metabolism occurring in the first few hours after a severe brain trauma are the most important correlating factors with regard to clinical status and outcome, but have not yet received sufficient attention in the literature. In this early stage, ischemia is more common than earlier reports have suggested; consequently, its role in the pathophysiology of traumatic brain injury may be more critical than has been believed. How best to obviate this secondary insult, however, remains to be established.

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