Cerebral blood flow and metabolism in severely head-injured children

Part 1: Relationship with GCS score, outcome, ICP, and PVI

The literature suggests that in children with severe head injury, cerebral hyperemia is common and related to high intracranial pressure (ICP). However, there are very few data on cerebral blood flow (CBF) after severe head injury in children. This paper presents 72 measurements of cerebral blood flow ("CBF_{15}"), using the $^{133}$Xe inhalation method, with multiple detectors over both hemispheres in 32 children aged 3 to 18 years (mean 13.6 years) with severe closed head injury (average Glasgow Coma Scale (GCS) score 5.4). In 25 of the children, these were combined with measurements of arteriojugular venous oxygen difference (AVDO$_2$) and of cerebral metabolic rate of oxygen (CMRO$_2$). In 30 patients, the first measurement was taken approximately 12 hours postinjury. In 18 patients, an indication of brain stiffness was obtained by withdrawal and injection of ventricular cerebrospinal fluid and calculation of the pressure-volume index (PVI) of Marmarou. The CBF and CMRO$_2$ data were correlated with the GCS score, outcome, ICP, and PVI.

Early after injury, CBF tended to be lower with lower GCS scores, but this was not statistically significant. This trend was reversed 24 hours postinjury, as significantly more hyperemic values were recorded the lower the GCS score, with the exception of the most severely injured patients (GCS score 3). In contrast, mean CMRO$_2$ correlated positively with the GCS score and outcome throughout the course, but large standard deviations preclude making predictions based on CMRO$_2$ measurements in individual patients. Early after injury, there was mild uncoupling between CBF and CMRO$_2$ (CBF above metabolic demands, low AVDO$_2$) and, after 24 hours, flow and metabolism were completely uncoupled with an extremely low AVDO$_2$. Consistently reduced flow was found in only four patients: 28 patients (88%) showed hyperemia at some point in their course. This very high percentage of patients with hyperemia, combined with the lowest values of AVDO$_2$ found in the literature, indicates that hyperemia or luxury perfusion is more prevalent in this group of patients. The three patients with consistently the highest CBF had consistently the lowest PVI: thus, the patients with the most severe hyperemia also had the stiffest brains. Nevertheless, and in contrast to previous reports, no correlation could be established between the course of ICP or PVI and the occurrence of hyperemia, nor was there a correlation between the levels of CBF and ICP at the time of the measurements. The authors argue that this lack of correlation is due to: 1) a definition of hyperemia that is too generous, and 2) the lack of a systematic relationship between CBF and cerebral blood volume. The implications of these findings for therapeutic modes of controlling ICP in children, such as hyperventilation and the use of mannitol, are discussed.

Key Words: head injury · cerebral blood flow · cerebral metabolism · children

Cerebral blood flow (CBF) and intracranial pressure (ICP) are both important in the pathophysiology of severe head injury. High ICP with severe head injury has received much attention, and there is also a fair amount of literature on CBF after head injury. In one of the earliest papers on CBF after severe head injury, Overgaard and Tweed$^{19}$ found that only one of 12 patients with hyperemia had a favorable outcome. Later, the same authors showed that patients with even small regions of local ischemia generally had...
a poor outcome. Thus, both reduced and increased levels of CBF seem to be related to poor outcome. It has been proposed that the relationship between ICP and CBF after severe head injury is different in children and adults. In children, elevated ICP would be caused mainly by increased cerebral blood volume (CBV). Increased CBV, in turn, is believed to be secondary to hyperemia. Diminished PaCO\textsubscript{2} will lead to diminished CBF by vasoconstriction, so that high ICP in children could be treated almost exclusively with vigorous hyperventilation. This treatment was held responsible for the exceptionally good results reported by Bruce, et al. On the other hand, these authors dismissed the use of mannitol to treat high ICP in children, as this agent had been found to increase CBF in a number of patients with brain injury.

Proof that hyperemia is a common occurrence in children is still lacking; Bruce, et al., actually performed CBF measurements in only six patients. It also has been noted that hyperemia cannot be defined by CBF criteria alone, but that the arteriojugular venous oxygen difference (AVDO\textsubscript{2}) and the cerebral metabolic rate of oxygen (CMRO\textsubscript{2}) in relation to the depth of coma must be taken into account as well. Another problem in relating elevated ICP to hyperemia is that ICP is usually not allowed to run its natural course but is vigorously maintained under a certain present level (usually between 15 and 25 mm Hg). Thus, Obrist, et al., suggested that some measure of brain compliance or stiffness, such as the pressure-volume index (PVI) of Marmarou, et al., be taken into account. This paper presents a series of 32 children in whom measurements of CBF, AVDO\textsubscript{2}, and CMRO\textsubscript{2} could be correlated with the Glasgow Coma Scale (GCS) score, outcome, and measurements of ICP and PVI.

Clinical Material and Methods

Patient Population

The series consists of 32 patients admitted within 12 hours of their head injury, aged from 3 to 18 years (mean ± standard deviation (SD) 13.6 ± 4.8 years). Their distribution in different age groups is shown in Fig. 1. These children represent 21% of 152 patients of all ages in whom CBF was measured in the acute stage following head injury. Except for two patients in whom CBF was first measured on the 3rd day postinjury, the first CBF measurement was performed in all other patients within 18 hours (mean 11 ± 3 hours) postinjury. In all patients the 15-point GCS score was 7 or lower in the 6 hours following injury; the mean GCS score after resuscitation at admission was 5.4 ± 1.2. There were seven (21%) children with bilaterally wide, unresponsive pupils and three (10%) with a unilaterally fixed and dilated pupil, for a total of 31% with pupillary abnormalities. Oculocephalic responses were severely disturbed or absent in 10 (31%) of the children; six children had bilaterally unresponsive pupils and one patient had a unilaterally disturbed pupil. In three children with absent oculocephalic responses no pupillary abnormalities were noted, compatible with a low brain-stem lesion. Thus, this sample represents obviously severely brain-injured children in the acute stage.

Six children were brought acutely to the operating room for removal of epidural (two), subdural (two), or intracerebral (one) hematomas, or a combination thereof (one). Five patients had associated systemic injuries necessitating acute abdominal and/or thoracic surgery. Six of the 32 patients were injured as a result of a fall, and 26 were involved in traffic accidents. For placement of catheters and for all studies, written informed consent was obtained from the next of kin and the protocols were approved by the Committee on the Conduct of Human Research at the Medical College of Virginia.

The outcome in surviving patients was assessed at 6 months or later after injury, using the Glasgow Outcome Scale. In some instances, outcome categories “good” and “moderately disabled” were combined into “favorable,” while “severely disabled,” “vegetative state,” and “dead” were together referred to as “unfavorable.” For statistical testing, analysis of variance (ANOVA), chi-square, and Student’s t-tests were used. A probability of 0.05 was chosen for statistical significance.
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Patient Management

Before or after arrival in the emergency room, all children were intubated and ventilated. After resuscitation as necessary, they all underwent an emergency computerized tomography scan of the brain. The patients were managed with controlled ventilation to a PaCO2 of 24 to 34 mm Hg. The other features of management have been described elsewhere.1

Measurements of ICP, PVI, and Blood Pressure

Intracranial pressure was continuously recorded in all patients, in 28 with an intraventricular catheter and in four with a Richmond subarachnoid bolt.42 Attempts were made to maintain ICP below 20 to 25 mm Hg by head positioning, withdrawal of cerebrospinal fluid (CSF), further hyperventilation, and administration of mannitol. Paralyzing agents were also used for ICP control, but most children were already paralyzed most of the time by repeated intravenous doses of pancuronium bromide (Pavulon). Calculations of PVI were performed with injections or withdrawals of a 0.5- to 1.5-ml bolus of CSF as described earlier.23 Normal PVI in children between 3 and 14 years of age varies between 18 and 30 ml, depending on the head circumference and spinal length of the child.43 In this paper, PVI is considered moderately depressed down to levels of 18 ml and considered markedly depressed below this value, with danger of ICP elevation.

In all patients an intra-arterial catheter was placed for continuous recording of blood pressure. In this report, mean arterial blood pressure (MABP) was calculated as diastolic pressure + 1/3 pulse pressure.

Determinations of Cerebral Blood Flow

Measurement of CBF was performed by the 133Xe inhalation or intravenous injection technique of Obrist, et al.34 Initially, a previously described system was used with 16 probes evenly distributed over the two hemispheres, yielding CBFint.22 Later in the series, a system with 10 probes concentrated more in the central frontotemporoparietal regions was used, yielding CBFint. With the inhalation method, the patients breathed a gas mixture containing 5 to 8 mCi 133Xe/liter for 1 minute. With the intravenous injection method 133Xe dissolved in saline (0.3 mCi/kg body weight) was injected, after which ventilation was halted for 20 seconds to let the xenon reach into the systemic circulation and to prevent a large part being expired during the first pass through the lungs. Both CBFint and CBF were equivalent to CBF calculated by the height over area method and both are insensitive to "slippage."33 The CBFint method includes somewhat more slow compartments and may slightly underestimate flow at higher levels, while CBF int may slightly overestimate flow at lower levels. However, these differences are minor and in this report these flow indices are considered similar; both are referred to as "CBFint."

In most instances, we have calculated CBFint to a normative PaCO2 of 34 mm Hg, assuming a 3% change in CBF per 1 mm Hg change in PaCO2.711.12.24.33.37 The 3% change per mm Hg CO2 was not compounded (for instance, to convert a CBFint value of 50 ml/100 gm/min at a PaCO2 of 29 mm Hg, 5 × 3% × 50 = 7.5 ml/100 gm/min was added to obtain 58 ml/100 gm/min at a PaCO2 of 34 mm Hg). This CBF value is designated CBF(34) and is clearly indicated as such where applicable. Normal CBF(34) in awake young adults is 44.1 ± 5.6 ml/100 gm/min (SD).32 Obrist, et al.,34 have defined a CBF(34) as follows: during coma below normal −2 SD (<32.9 ml/100 gm/min) as "reduced flow;" normal ± 2 SD (between 32.9 and 55.3 ml/100 gm/min) as "relative hyperemia;" and above normal +2 SD (>55.3 ml/100 gm/min) as "absolute hyperemia." The same definitions are used in this paper. All CBF values in this paper are the averages of CBF from all of the detectors and hence can be considered as global hemispheric CBF.

Measurement of AVDO2 and CMRO2

In 21 of the 32 patients, a catheter was placed in the jugular bulb through retrograde cannulation of the right internal jugular vein for obtaining AVDO2. The AVDO2 value was calculated from arterial and jugular venous oxygen content. Oxygen content was evaluated by an IL208 co-oximeter.* During the CBF measurements two arterial and jugular samples were taken for AVDO2 determination. The average of these two measurements was used for calculation of CMRO2 (CMRO2 = CBF × AVDO2/100). Normal AVDO2 at a PaCO2 of 40 mm Hg is 6.3 ± 1.2 vol% and normal CMRO2 is 3.2 ml/100 gm/min.17 Values of AVDO2 were, concomitant with CBF, normalized to a value at PaCO2 of 34 mm Hg. A change of 3%/mm Hg change in PaCO2 was assumed just as with CBF but, of course, in the opposite direction so that CMRO2 remains unaltered. Normal AVDO2 at a PaCO2 of 34 mm Hg would be 6.3 + (6 × 3%) = 7.4 vol%.

Results

Relationship of CBF and CMRO2 to GCS Score and Outcome

Figure 2 shows the relationship of AVDO2 and CBF to the GCS score. During the first 24 hours, average values of CBF are within the normal range. The AVDO2 values at GCS scores of 4 and 5 are below normal, indicating uncoupling of blood flow and metabolism. Average AVDO2 at GCS scores of 6 and 7 is just within the normal range. After 24 hours postinjury, all mean AVDO2's are below normal. Excluding the data obtained from a patient with a GCS score of 3, there was a significant trend of greater hyperemia with lower GSC scores (ANOVA: p < 0.05). It is obvious that at all times CBF and AVDO2 tended to be closer to normal as GCS scores increased.

* Co-oximeter manufactured by Instrumentation Laboratories, Inc., Lexington, Massachusetts.
FIG. 2. Relationship between the levels of cerebral blood flow ("CBF", upper) and arteriovenous oxygen difference (AVDO₂, lower) at a normative PaCO₂ of 34 mm Hg and the Glasgow Coma Scale score. Shown are measurements performed within 24 hours postinjury (A) and measurements taken after that period (B). Hatched areas: normal value (broken line) ± 2 standard deviations (SD) obtained from Obrist, et al. Data are means ± standard deviations for the number of patients shown (n).

In the first 24 hours, CBF(34) in patients with a favorable outcome was 48.8 ± 24.8 ml/100 gm/min, and with an unfavorable outcome it was 34.7 ± 9.9 ml/100 gm/min. This difference was almost statistically significant (Student's t-test: t = 1.93, df = 26, p < 0.07). After 24 hours, CBF(34) for patients with favorable and unfavorable outcome was, respectively, 57.6 ± 24.3 and 51.5 ± 22.9 ml/100 gm/min. Thus, early after injury, lower values for CBF seem to be related to a poor outcome. Later after injury, there is no relation between CBF and outcome.

In contrast, CMRO₂ related to GCS scores does not change over time and, as the data points for measurements within 24 hours and those after 24 hours are similar, Fig. 3 shows only the combined data. There is a trend for CMRO₂ to increase with higher GCS scores, but this difference is statistically significant only between CMRO₂ at a GCS score of 3 and CMRO₂ at GCS scores higher than 3.

Throughout the acute stage, there is a good correlation between CMRO₂ and favorable outcome. The CMRO₂ value in a patient with a favorable outcome was 2.19 ± 0.82 ml/100 gm/min (mean ± SD), whereas in patients with an unfavorable outcome this was 1.52 ± 0.58 ml/100 gm/min (Student's t-test: t = 3.54, df = 53, p < 0.001).

Relationship of CBF to ICP and PVI

Table 1 shows the average ICP (measured at the time of the CBF measurement) in different CBF groups. In each of these groups ICP's were not statistically significantly different from each other, nor was there a significant trend toward a higher ICP with higher blood flow. The percentages of patients with an ICP over 20 mm Hg were also not statistically different in the various groups, and were very similar in the groups with reduced flows and with absolute hyperemia. It should be noted that, in the group with reduced flow, two ICP values (60 and 76 mm Hg) have been omitted from these calculations. It was thought that in those two instances low CBF (16 ml/100 gm/min in both cases) was caused by low cerebral perfusion pressure (approximately 25 mm Hg) with uncontrolled ICP as a terminal event; both patients died within hours of these measurements.

Patients were classified into two groups: in one group the ICP never exceeded 20 mm Hg (nine patients, 28%) during the whole course and in the other ICP exceeded 20 mm Hg at some point during the acute phase (23
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### TABLE 1
ICP and PVI at the time of CBF measurements at various levels*

<table>
<thead>
<tr>
<th>Feature</th>
<th>Reduced Hyperemia</th>
<th>Relative Hyperemia</th>
<th>Absolute Hyperemia</th>
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<tbody>
<tr>
<td></td>
<td>(&lt; 32.9)</td>
<td>32.9-38.3</td>
<td>38.4-49.7</td>
</tr>
<tr>
<td>no. of cases</td>
<td>16</td>
<td>8</td>
<td>16</td>
</tr>
<tr>
<td>average ICP (mm Hg)</td>
<td>15.3 ± 7.5</td>
<td>12.8 ± 7.1</td>
<td>16.2 ± 4.0</td>
</tr>
<tr>
<td>% cases with ICP &gt; 20 mm Hg</td>
<td>29</td>
<td>20</td>
<td>13</td>
</tr>
<tr>
<td>no. of cases with PVI &gt; 18 ml</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>no. of cases with PVI &lt; 18 ml</td>
<td>1</td>
<td>0</td>
<td>2</td>
</tr>
</tbody>
</table>

* ICP = intracranial pressure; PVI = pressure-volume index; CBF = cerebral blood flow (ml/100 gm/min). Average is given ± standard deviation.

### TABLE 2
CBF findings in two groups of head-injured children, classified according to ICP and PVI*

<table>
<thead>
<tr>
<th>Acute CBF Findings</th>
<th>Total Cases</th>
<th>Cases with ICP:</th>
<th>Cases with PVI:</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td>&gt; 20 mm Hg</td>
<td>&lt; 20 mm Hg</td>
</tr>
<tr>
<td>hyperemia</td>
<td>28</td>
<td>19</td>
<td>9</td>
</tr>
<tr>
<td>reduced flow</td>
<td>4</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>total cases</td>
<td>32</td>
<td>23</td>
<td>9</td>
</tr>
</tbody>
</table>

* CBF = cerebral blood flow; ICP = intracranial pressure; PVI = pressure-volume index.

patients, 72%). Elevations of ICP during events such as coughing, suctioning, or spuriously high PaCO2 were not considered true elevations for this purpose. These two ICP groups were correlated with the occurrence of reduced flow or with hyperemia (Table 2). Due to the very small number of patients with reduced flow, there is no value in statistical testing.

Although ICP elevations above 20 mm Hg necessitating drainage of CSF or administration of mannitol were common in this series of patients, the number of patients with elevated ICP may have been limited, as most of the patients were rather vigorously hyperventilated: the average PaCO2 of measurements at 24 to 48 hours was 27.2 ± 4.6 mm Hg, and after 48 hours it was 25.5 ± 5.4 mm Hg. Therefore, PVI measurements were also considered in these children. Determination of PVI was performed in 18 of the 24 children most recently treated in this series. On 16 occasions, PVI was calculated within minutes after the CBF measurement. The relationship between the simultaneous CBF and PVI measurements is shown in Table 2. Although a low PVI occurred somewhat more often in the group with absolute hyperemia, this was not significant due to the small numbers. The PVI remained above 18 ml throughout the first 5 days in seven (36%) of the 18 patients (normal PVI group); during this period it was below this value in one patient in a single measurement and in at least two measurements in the other 11 children (61%, low PVI group). These two PVI groups were divided over the two CBF groups (Table 2), but in only one of the four patients with consistently reduced flows were PVI measurements performed, precluding any statistical testing. Nevertheless, it is noteworthy that in seven patients who were hyperemic at some time in their acute course, PVI remained above 18 ml the entire time. On the other hand, the three children with the lowest PVI values (approximately 6 ml) and most consistently below normal (total 19 below-normal and two normal measurements) also had consistently the highest flows (absolute hyperemia eight times, normal +2 SD once). Interestingly, all three children had a favorable outcome.

### Discussion

#### Methodological Considerations

The present paper describes findings of CBF, AVDO2, CMRO2, ICP, and PVI in severely head-injured children. Puberty is usually finished by 18 years of age, but whether the pathophysiology of severe head injury is largely similar from birth to 18 years of age is unknown. In other papers on pediatric head injuries, the upper age limits were chosen between 16 and 19 years. 

Although CBF measurements were taken from the two hemispheres with 10 or 16 detectors, all CBF values and classifications in this paper are based on the average of all detectors (that is, global blood flow measurements). Others have noted that regional and/or hemispheric differences do exist, but that these are usually minor and may be superimposed on global changes in flow. 

In only one paper where 35 detectors over one hemisphere were used, prognostic significance was attributed to differences in regional perfusion or, more specifically, to the occurrence of "ischemia" detected by one or more probes. In the sampling of jugular blood for AVDO2 measurements also reflects global O2 extraction.

Because under pathological circumstances “slippage” can greatly influence the calculations of fast flow or gray matter flow and even of initial slope-based calculations, only CBF15 was used in this paper. The decision to adjust values of CBF15 to a PaCO2 of 34 mm Hg was based on two considerations. First, an attempt was made to use the initial CBF measurement at a
PaCO₂ of 34 mm Hg (although the actual average PaCO₂ at the first measurement was 32.1 ± 6.0 mm Hg) because all head-injured patients are kept at this PaCO₂ for baseline studies including evoked potentials, PVI, compressed-spectrum electroencephalograms, and CBF. Second, adjustment to PaCO₂ of 34 mm Hg makes it easier to compare these findings with data from the recent large series of Obrist, et al., in that study, the average PaCO₂ was 34 mm Hg and all data (CBF and AVDO₂) were adjusted to that PaCO₂, assuming a 3% change/mm Hg change in PaCO₂. Only small adjustments were necessary for flow measurements early after injury when CO₂ reactivity is known to be somewhat diminished. Arterial pCO₂ was 27.2 ± 4.6 mm Hg between 24 and 48 hours and 25.5 ± 5.3 mm Hg later than 48 hours after injury, necessitating rather large adjustments. However, several authors found CO₂ reactivity approximating 3%/mm Hg change of PaCO₂ over a wide range of PaCO₂ measurements in severe head-injured patients in this period after injury. A final methodological problem was that normal CBF values using the 133Xe inhalation method are not well established in children, especially not in the youngest ones. With the nitrous oxide method used by Kety and Schmidt, Kennedy and Sokoloff found an average of 106 ml/100 gm/min in normal children aged 3 to 11 years, but Settergren, et al., found a value of only 65 ml/100 gm/min in children 3 weeks to 14 years old. With the 133Xe method, Younkin, et al., found a CBF of 70 ml/100 gm/min in a normal unanesthetized 15-year-old child (JS Meyer, personal communication, 1987). In four normal unanesthetized children aged 11 to 16 years (mean 12.8 years) an average CBF of 68 ± 4 ml/100 gm/min was found (JP Muizelaar, unpublished data). Thus, normal values for the younger subjects are probably higher than those for the group of young adults reported by Obrist, et al., which were used in this paper as the norm. This may have caused the occurrence of reduced flow to be underestimated and the incidence of relative or absolute hyperemia to be overstated. The findings will be discussed with all of these methodological considerations in mind.

**CBF, CMRO₂, and GCS Scores**

Despite many efforts in the literature, no correlation has been established between CBF and the GCS score or other measure of depth of coma. In this series, there was a correlation between low AVDO₂ and low GCS score and, after 24 hours, an inverse correlation between GCS score and CBF. Both of these findings are indicative of more severe hyperemia and uncoupling of CBF and metabolism at deeper levels of coma. There is no good explanation for hyperemia after head injury occurring more often in children and more severely with deeper coma. It has been suggested that posttraumatic hyperemia, the “luxury perfusion” described by Lang-fitt and coworkers are all related. Lassen considered the “luxury perfusion” after stroke to be due to lactic acidosis. Although high levels of lactic acid have been found in CSF after head injury in several series of patients, a relationship between lactic acid and level of CBF could not be established in our own patients. Moreover, in many cases, elevated CSF lactic acid levels return to nearly normal within 48 hours so that, at the time that hyperemia is maximal, the lactic acidosis is probably no longer present. The cause of “vasomotor paralysis” after experimental brain injury is uncertain. In a cat model with focal brain injury (small cold lesion), generalized vasodilation (remote from the injury site) and loss of CO₂ reactivity were found. These changes were at least partly caused by oxygen radicals as they could be prevented by local administration of radical scavengers. However, this vasodilation is fairly short-lived and CO₂ reactivity returns within a couple of hours. In clinical series, CO₂ reactivity is intact in most cases at the time of the CBF measurements, and autoregulation was also intact in two-thirds of the patients in the present series. Thus, although there is metabolic uncoupling, the blood vessels in most cases still respond to the normal stimuli of CO₂ or blood pressure changes, which is not in accordance with the concept of vasomotor paralysis.

The relationship between depth of coma and CMRO₂ and between outcome and CMRO₂ has been noted by several authors and could be corroborated in the present study. It should be emphasized, however, that this relationship only applies to average values. Standard deviations are large, which precludes making predictions as to outcome in individual patients based on CMRO₂ measurements. However, in this series, all patients whose CMRO₂ was at some point below 0.99 ml/100 gm/min died. Earlier, we reported that adult patients with a CMRO₂ of less than 0.99 ml/100 gm/min do not recover (they died or were in a vegetative state). In the series of Roquefeuil, et al., the limiting CMRO₂ value consistent with recovery was 1.5 ml/100 gm/min; however, these authors used a different method of calculating CBF which resulted in a higher CMRO₂.

**Hyperemia and ICP**

In a landmark paper in 1984, Obrist and coworkers defined reduced flow as CBF below normal -2 SD, relative hyperemia as CBF within 2 SD of normal, and absolute hyperemia as CBF above normal +2 SD (see also Fig. 2). According to these criteria, 73 measurements revealed reduced flow on 16 occasions (22%), relative hyperemia 36 times (49%), and absolute hyperemia 21 times (29%). Thus, hyperemia in this pediatric group was found in 78% of the measurements. In 28 patients (88%) at least one measurement showed hyperemia, which is higher than the 70% found in the group of patients 15 to 20 years of age reported by Obrist, et al. This is further evidence that, indeed,
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hyperemia occurs more often the younger the patients are. Independent confirmation can be found in the (adjusted) AVDO₂ values: within 24 hours 10 determinations (40%) of 25 were below 4.0 vol%, whereas after this period 25 (71%) of 35 were below this value, indicating considerable luxury perfusion. Obrist, et al., reported 34% of AVDO₂ values below 4.0 vol%: thus, our total figure of 58% of adjusted AVDO₂ below 4.0 vol% is another indication that luxury perfusion and age are inversely correlated after severe head injury. As noted above, the reason for this phenomenon remains completely obscure.

After severe head injuries hyperemia has been noted by a number of investigators. Obrist and coworkers and Obrist, et al., have emphasized the association between high ICP and hyperemia. In the present paper, an attempt was made to correlate ICP and the level of CBF in several ways. By looking at the average ICP at the time of CBF measurement in different CBF groups, and by calculating the percentages of ICP below 20 mm Hg at the time of CBF measurements in the various CBF groups, the temporal relationship between ICP measurement and CBF measurement was maintained. We also treated the findings in the same way as Obrist, et al.: a patient who at any time during the course showed hyperemia was regarded as a hyperemic patient and a patient whose ICP rose above 20 mm Hg at any time during the acute stage was defined as having raised ICP; the two groups were then correlated. Based on these three methods, no correlation was found between hyperemia and high ICP.

Several explanations may be proposed for the discrepancy between the findings of Bruce and coworkers and Obrist, et al., on the one hand and the present data on the other hand. First, 28 of 32 children in this report were hyperemic at some point in their course, making any comparison meaningless between those four patients with reduced flow and the group with hyperemia. Second, many of our patients were quite vigorously hyperterventilated at the time of CBF measurement, necessitating large adjustments to obtain a CBF with a PaCO₂ of 34 mm Hg. In all patients with 73 determinations, the average actual CBF, was only 44 ± 22 ml/100 gm/min, which is considerably lower than the average of 68 ± 4 ml/100 gm/min found in four normal unanesthetized children. Moreover, it is even questionable whether, after prolonged hyperventilation, adjustments of CBF to a normative value of PaCO₂ are valid. Vessel diameter is determined not by PaCO₂ but by the pH value in CSF. Within 24 hours of initiation of hyperventilation, CSF pH and vessel diameter (and thus, CBF) have returned to baseline. This not only makes adjustments for PaCO₂ unnecessary, but also leads to a gross overestimation of CBF if calculated values are used rather than the values actually measured. Another problem is that the relationship between CBF and CBV (and thus, ICP) is a linear one, and, in fact, is extremely complicated (Table 3). The CBF is determined by MABP, ICP, blood viscosity, and the diameter of arteries and arterioles, while CBV is mainly determined by the diameter of venules and arterioles, the latter being the only common denominator for both CBF and CBV. Thus, while increased arteriolar diameter will always lead to increased CBV and possibly increased ICP (if compensatory mechanisms have been exhausted), it can be accompanied by high, normal, or even low CBF.

Mannitol administration reduces blood viscosity. As can be seen from Table 3, reduced blood viscosity may or may not lead to increased CBF, depending on the status of autoregulation. However, it never leads to increased CBV or ICP. We, therefore, do not agree with Bruce and coworkers who advised against the use of mannitol in children for fear of increasing hyperemia and, supposedly, increased CBV and ICP.

It has been suggested that looking at some measure of "tightness" of the brain might give more information than mere ICP values, as most head-injured patients are vigorously treated for ICP control. Measurement of PVI is a well-established means of estimating cerebral compliance or tightness. In earlier papers, a good correlation was found between low PVI and ICP elevations and outcome. Such correlation was also suggested in the present patients. Among 12 patients with low PVI, 11 developed ICP problems necessitating treatment; of the six patients with normal PVI, four did not have any significant ICP elevations. Although it must be kept in mind that the patient numbers are small, this study could not establish a statistically significant relationship between PVI and CBF. Among the patients with absolute hyperemia, seven had a low PVI and two had PVI above 18 ml; of the patients with CBV lower than absolute hyperemia, five had a low PVI and four had a normal PVI. Recently, it has been argued that after head injury ICP is determined more by vas-

<table>
<thead>
<tr>
<th>Table 3</th>
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<tr>
<td>Changes in CBF, CBV, and AVDO₂ with primary reduction of various features and with vasospasm*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Feature with Primary Reduction</th>
<th>CBF</th>
<th>CBV</th>
<th>AVDO₂</th>
<th>Reference No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMRO₂ (barbiturate coma)</td>
<td>↓</td>
<td>↓</td>
<td>=</td>
<td>31</td>
</tr>
<tr>
<td>CMRO₂ (after trauma)</td>
<td>↓</td>
<td>=</td>
<td>↓</td>
<td>this paper</td>
</tr>
<tr>
<td>CPP (autoregulation intact)</td>
<td>=</td>
<td>=</td>
<td>↓</td>
<td>= 15, 25, 28, 29</td>
</tr>
<tr>
<td>CPP (autoregulation defective)</td>
<td>↓</td>
<td>=</td>
<td>=</td>
<td>= 15, 25, 28, 29</td>
</tr>
<tr>
<td>blood viscosity (autoregulation intact)</td>
<td>↓</td>
<td>↓</td>
<td>=</td>
<td>= 25, 29, 30</td>
</tr>
<tr>
<td>blood viscosity (autoregulation defective)</td>
<td>↓</td>
<td>↓</td>
<td>=</td>
<td>= 25, 29, 30</td>
</tr>
<tr>
<td>PaCO₂ (acutely)</td>
<td>↓</td>
<td>↓</td>
<td>=</td>
<td>= 27, 31</td>
</tr>
<tr>
<td>PaCO₂ (chronically)</td>
<td>=</td>
<td>=</td>
<td>=</td>
<td>= 27</td>
</tr>
<tr>
<td>conductance vessel diameter (vasospasm above ischemia threshold)</td>
<td>↓</td>
<td>↓</td>
<td>=</td>
<td>= 14</td>
</tr>
</tbody>
</table>

* CBF = cerebral blood flow; CBV = cerebral blood volume; AVDO₂ = arteriovenous difference in oxygen; CMRO₂ = cerebral metabolic rate of oxygen; CPP = cerebral perfusion pressure. ↓: increase; ↓: decrease; =: stable; %= equivalocal.
cular factors than by factors involving CSF.\textsuperscript{21} The present data do not support this contention because of lack of a significant relationship between hyperemia and ICP or PVI. But the present findings are also not at variance with this concept because of the lack of a clear relationship between CBF and CBV; moreover, the three patients in this series with consistently the highest actual CBF and lowest AVDO\textsubscript{2} values (and presumed increased CBV) had the lowest PVI values. Thus, we believe that increased CBV may very well play an important role in pediatric head injury, even though this is not always reflected in a high CBF.

References

Blood flow metabolism in severe head injuries

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Address reprint requests to: J. Paul Muzelaar, M.D., Ph.D., Division of Neurosurgery, P.O. Box 631, MCV Station, Richmond, Virginia 23298.