Cerebral circulation after head injury

Part 3: Does reduced regional cerebral blood flow determine recovery of brain function after blunt head injury?

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A series of comatose young patients with head injuries is presented in whom early regional cerebral blood flow (rCBF) is correlated with neurological outcome, and the critical threshold of rCBF compatible with recovery of responsive communicative interaction with the environment is estimated. Within the 1st week following injury, 63 patients had rCBF studies performed with radioactive xenon by the intracarotid bolus-injection technique and 35-channel external counting. A comparison was made between 2724 rCBF values from this group of patients with 381 from nine controls. Surviving patients were followed for 2 years to determine their eventual neurological outcome.

When histograms of the frequency distribution of rCBF values were examined, it was evident that there was both a wider spread of rCBF and a shift to the left in all outcome groups. In awake controls, no rCBF values were less than 40 ml/100 gm/min, whereas in comatose patients the threshold for recovery of communicative brain function (with or without neurological deficits) was between 17 and 20 ml/100 gm/min. There was a clear difference, however, between patients who recovered communicative brain function (with or without neurological deficit) and those who did not (dying or surviving in a persistent vegetative state). In the latter two outcome groups, 14.5% of rCBF values were less than 20 ml/100 gm/min, with the highest incidence in those examined within the first few hours of injury. The distribution of ischemic rCBF was mainly in the frontal and parietal lobes.

These investigations confirm previous postmortem pathological studies in revealing that cerebral ischemia in the frontoparietal "watershed" areas antemortem is a major factor leading to telencephalic brain death in the early hours after head injury. The pathophysiological mechanisms of this localized ischemia in patients with head injury are not well understood, but probably hemodynamic alterations resulting from increased intracranial pressure are a major factor. The critical threshold for survival of cortical function seems to be similar to that of normal brain, about 17 to 20 ml/100 gm/min.

KEY WORDS · head injury · cerebral blood flow · cerebral ischemia · brain function · neurological outcome

IN the last decade, many studies have shown that during the acute stage following severe head injury a reduction of cerebral blood flow (CBF) is found in most patients, but, in some, hyperemia is encountered. A consistent and reproducible relationship between mean hemispheric CBF and patient outcome has not been established, although recovery of integrative cortical function generally does not occur in patients with mean hemispheric CBF lower than 20 ml/100 gm/min. Less is known about recovery after severe head injury when only a single area or a few regions have flow reduced to this level or below.

In the acute stage, such a relationship cannot be determined, as the patient’s final outcome with regard to brain function must be known. If, however, regional ischemia at the acute stage can be correlated with clearly defined outcome categories, the value of measuring regional CBF (rCBF) in head injury takes on greater significance beyond the mere description of pathophysiological events.

We examined 63 young patients with head injury...
The logarithm of xenon-133 counts for the first 2 minutes of washout from the brain for each of the 35 detectors in the array are displayed on an oscilloscope. The display is then photographed by a Polaroid camera. After carotid angiography, a cutout of the detector array is superimposed on the lateral film to match each detector with its corresponding hemispheric region.

Clinical Material and Methods

Methods

Regional CBF was measured with xenon-133 by the intracarotid bolus-injection technique. The indwelling catheter was positioned in the internal carotid artery, and between tracer injections it was used to monitor arterial blood pressure, expressed as the mean pressure (MABP). The carotid catheter was flushed every 2 minutes by slowly injecting 10 ml of sterile lactated Ringer’s solution at 37°C. Washout of xenon from the hemisphere under study was measured with 35 scintillation detectors, arranged in a fixed array* on the side of the head covering most of the hemispheric cortical areas. Logarithmic displays of the first 2 minutes of washout were photographed on Polaroid film (Fig. 1).

We calculated CBF by two methods: the initial slope method, designated “CBFinit” and the 10-minute height over area method, designated “CBFlo.” Cerebral blood flow was calculated as regional CBFinit (rCBFinit) as described by Olesen, et al.,26 using a manually operated optical slope calculator. The logarithmically displayed slope is linear within the first 1 to 2 minutes in normal brain, indicating a monoeXponential washout of xenon from the normal cerebral cortex. Because many clearance curves were curvilinear in head-injured patients, the clearance curve was divided for analysis into two parts: the initial part of the slope and the later or second part (Fig. 2).

From two to five separate xenon injections were made at each patient study. Only the results of the control or baseline measurement have been used for the assessment. We have generally used the results obtained from the first xenon injection, thereby avoiding the problem of calculating the effect of recirculating xenon.

Following the CBF study, a carotid angiogram was performed and the lateral view of the x-ray film was marked for the superimposing of the 35-detector array (Fig. 1). The position of each detector could thereby be determined in relation to an outline of the hemisphere studied and the calculated CBFinit value for each detector related to the appropriate region of the hemisphere.

Immediately after each xenon injection, arterial blood was withdrawn from the internal carotid artery and analyzed for CO2 and O2 tension as well as O2 saturation with the Radiometer blood gas analyzer.† In 20 patients the internal jugular vein was cannulated via the femoral vein, usually on the right side. X-ray control films confirmed that the tip of the catheter was situated in the bulb of the jugular vein. From this catheter, a venous sample was drawn and

Fig. 2. Dynamic changes in head injury. Two logarithmic 2-minute clearance curves are illustrated: a normal monoeXponential curve (left), and a biexponential curve from a head-injured patient (right). The initial part of the curve represents the fast compartment flow or “tissue peak.”

Fig. 1. The logarithm of xenon-133 counts for the first 2 minutes of washout from the brain for each of the 35 detectors in the array are displayed on an oscilloscope. The display is then photographed by a Polaroid camera. After carotid angiography, a cutout of the detector array is superimposed on the lateral film to match each detector with its corresponding hemispheric region.

* Scintillation detectors manufactured by Memotek a.p.s. Vesteregade 30, DK 8900 Randers, Denmark.
† Blood gas analyzer manufactured by Radiometer, Copenhagen, Denmark.
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analyzed in the same way as the carotid blood sample. The samples were drawn anaerobically and the first 2 ml was discarded. The arteriovenous difference for O$_2$ content was calculated and multiplied with the mean hemispheric CBF, calculated as the CBF$_{10}$. The obtained value for O$_2$ uptake (CMRO$_2$) thus refers to nonregional samples of venous blood. The blood flow value and the analyzed blood samples were from the same run as the rCBF$_{init}$ values used for construction of the histogram distribution.

Intracranial pressure (ICP) was monitored by a Seletz cannula inserted into the lateral ventricle through a burr hole placed just anterior to the coronal suture. The cannula was connected to an Elema-Siemens transducer and amplifier. The ICP was recorded as the mean intraventricular pressure in the cerebral ventricles (MIVP).

In all patients, a free airway was secured by either an endotracheal tube or a tracheostomy, and normal arterial O$_2$ and ventilation were maintained. Rectal temperature was also recorded.

Presentation of rCBF$_{init}$ Values

Each rCBF value was identified by the number of its detector (1 to 35), the side of the study, and the calculated value of the CBF$_{init}$. For data analysis, each rCBF$_{init}$ value was regarded as a single datum point and assigned to one of eight class intervals (cells) as follows: 0 to 19, 20 to 39, 40 to 59, 60 to 79, 80 to 99, 100 to 119, 120 to 139, and over 140 ml/100 gm/min. Histograms were constructed of the distribution of the population of rCBF$_{init}$ values under consideration. A population was the total number of regions (that is, data points) studied in each of the five defined outcome groups.

The occurrence of ischemic flow values (under 20 ml/100 gm/min) was sought at three different times after injury: Day 0 (1 to 24 hours), Days 1 to 4, and Days 4 to 7. A subpopulation of rCBF$_{init}$ values was the total number of regions studied in each outcome group in one of the defined time intervals after injury.

The 79 studies should ideally provide a total of 2765 regional flow values or data points. The actual number for analysis, however, was 2724, as some washout curves were of bad quality. For comparison, 381 rCBF$_{init}$ values from nine persons without demonstrable brain lesion, who had a total of 11 studies, were similarly analyzed.

Patients

The 63 patients were all admitted as emergency cases. A clinical examination was performed immediately on arrival, and a neurological assessment made based on our previously published criteria. They were also assigned a numerical value, by addition of the scores obtained by the Glasgow Responsiveness Scale. All the patients were in coma on admission, and reawakening was evaluated by recording the 1st day of spontaneous eye opening, of obeying commands, and of understandable speech (Table 1). The final neurological outcome of the survivors was determined not earlier than 2 years after the head injury. That late date was chosen so we could confidently place a patient in a final outcome category. The five outcome categories have been defined and published earlier, and are, briefly:

Good Recovery: The patient has resumed all his former activities without limitations and has no mental or neurological deficits

Slight Deficits: The patient has resumed former activities; some limitations, especially in adaptability, are evident especially in children and teenagers, due to mental or neurological abnormalities which can reasonably be ascribed to the injury

Severe Deficits: The patient has clearly reduced capabilities because of neurological or mental sequelae to the injury. The best are capable of self-care, but not working, while the worst require nursing or institutional care

Persistent Vegetative State, also called “apallic syndrome”: This category covers the conditions as defined by Jennett and Plum

Dead.

Patients from the three first outcome groups recovered from coma and regained sufficient brain function to permit responsive communicative interaction with their environment. Those in the last two outcome groups did not.

Management of Patients During the 1st Week

The interval between injury (mostly resulting from road traffic accidents) and admission to the neurosurgical reception area varied from 30 minutes to 68 hours, and was under 6 hours in 51 cases. A total of 41 patients had tracheal intubation before transportation, and respiration was assisted in most cases during the transfer. The average time spent in the reception area with clinical assessment, skull x-ray studies, carotid angiography, CBF study, ventriculography, and operative intervention was 4 hours. Le-
TABLE 1
Clinical data in 63 head-injured and nine control patients*

<table>
<thead>
<tr>
<th>Outcome Group†</th>
<th>No. of Cases</th>
<th>CBF Studies</th>
<th>Age ± SD (yrs)</th>
<th>Classification on Admission‡</th>
<th>Reawakening (mean days ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>Rt:Lt</td>
<td></td>
<td>Score</td>
<td>Open Eyes</td>
</tr>
<tr>
<td>good recovery</td>
<td>13</td>
<td>17</td>
<td>7:10</td>
<td>1 + 1 + 2</td>
<td>10.5 ± 6.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(2-20)</td>
<td>(2-28)</td>
</tr>
<tr>
<td>slight deficits</td>
<td>11</td>
<td>15</td>
<td>8:7</td>
<td>1 + 1 + 3</td>
<td>14.54 ± 9.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(3-30)</td>
<td>(4-38)</td>
</tr>
<tr>
<td>severe deficits</td>
<td>16</td>
<td>16</td>
<td>11:5</td>
<td>1 + 1 + 2</td>
<td>20.81 ± 12.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(3-56)</td>
<td>(17-110)</td>
</tr>
<tr>
<td>persistent vege-</td>
<td>8</td>
<td>11</td>
<td>8:3</td>
<td>1 + 1 + 1</td>
<td>40.8 ± 8.7</td>
</tr>
<tr>
<td>tative state</td>
<td></td>
<td></td>
<td></td>
<td>(35-53)</td>
<td></td>
</tr>
<tr>
<td>died</td>
<td>15</td>
<td>20</td>
<td>12:8</td>
<td>1 + 1 + 2</td>
<td>interval study to death:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(6-410 hrs)</td>
</tr>
<tr>
<td>total</td>
<td>63</td>
<td>79</td>
<td>46:33</td>
<td></td>
<td></td>
</tr>
<tr>
<td>controls</td>
<td>9</td>
<td>11</td>
<td>8:3</td>
<td>37.4 ± 10.9</td>
<td></td>
</tr>
</tbody>
</table>

* CBF = cerebral blood flow; SD = standard deviation. Figures in parentheses indicate range.
† Outcome determined 2 years after injury.
‡ Glasgow Responsiveness Scale scores.

sions requiring surgery were revealed in 27 patients. Two patients had intracerebral hematomas (one parietal, one frontal), six had laceration of brain tissue requiring surgery, six had epidural hematoma, and 13 had an acute subdural hematoma. In 36 patients, a surgical lesion was ruled out. The CBF studies were performed after surgery, in which mass lesions had been removed.

The case histories for each patient were scrutinized for the occurrence of systemic factors that might result in insufficient cerebral circulation. Case notes from the admitting hospitals were searched as well as records made during transfer. No patient was permitted transportation before a telephone consultation had determined that blood pressure was adequate and airways were free. Despite these precautions, a few patients had episodes of hypotensive blood pressure (systolic blood pressure lower than 70 mm Hg) or inadequate respiration including respiratory arrest or obstructed airways. This was recorded in four of the eight patients who survived in a vegetative state and in five of the 15 who died as a consequence of the head injury. Although these complications were corrected immediately after arrival at the neurosurgical department, they may have influenced the level of ICP and the calculated flow values. The interval from injury (traffic accident) to arrival at the neurosurgical department varied from 1 to 8 hours in these two groups of patients. It is also noteworthy that no patient who finally achieved the three best outcome groups had such complications recorded during the first hours or at the neurosurgical department.

In the ward, 45 patients had respirator-assisted ventilation. The PaCO_2 levels were measured twice daily and kept within the range of 30 to 35 torr. Respirator withdrawal was considered appropriate when the patient began to open his eyes; treatment was resumed if PaCO_2 became hypercapnic or pO_2 levels were reduced below 85 torr.

Sedation with barbiturate (phenobarbital) was given primarily to reduce motor disorders, especially motor rigidity and decerebrate posturing, but also to ease spontaneous respiration and to facilitate assisted respiration. Serum levels of barbiturate were determined, usually every 2nd day, and after the 2nd day, levels were usually within the range of 30 to 60 mg/liter (129 to 259 mmol/liter). Only one patient had a short-acting barbiturate just before the CBF study, less than 1 hour after injury. Barbiturate medication was slowly reduced from the moment the patient revealed signs of reawakening. Only a few of the survivors improved to this point within the 1st week after injury.

Barbiturate sedation was variable in the 18 patients

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TABLE 2

Clinical results during the first week

<table>
<thead>
<tr>
<th>Outcome Group</th>
<th>No. of Cases</th>
<th>No. of CBF Studies</th>
<th>First Part of Slope</th>
<th>Second Part of Slope</th>
<th>% Nonlinear Washout Curves (rCBFinit)</th>
<th>mhCBFinit ± SD (ml/100 gm/min)</th>
<th>MABP ± SD (mm Hg)</th>
<th>MIVP ± SD (mm Hg)</th>
<th>CPP ± SD (mm Hg)</th>
<th>PaCO2 ± SD (torr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>good recovery</td>
<td>13</td>
<td>17</td>
<td>63.0</td>
<td>43.5</td>
<td>57</td>
<td>48.9 ± 15.1</td>
<td>102 ± 19</td>
<td>15 ± 4</td>
<td>95 ± 18</td>
<td>37.4 ± 5.9</td>
</tr>
<tr>
<td>slight deficits</td>
<td>11</td>
<td>15</td>
<td>61.9</td>
<td>44.4</td>
<td>52</td>
<td>44.2 ± 9.9</td>
<td>105 ± 20</td>
<td>14 ± 7</td>
<td>91 ± 21</td>
<td>36.5 ± 5.1</td>
</tr>
<tr>
<td>severe deficits</td>
<td>16</td>
<td>16</td>
<td>63.9</td>
<td>43.8</td>
<td>60</td>
<td>47.4 ± 10.8</td>
<td>105 ± 23</td>
<td>15 ± 15</td>
<td>88 ± 22</td>
<td>35.2 ± 6.6</td>
</tr>
<tr>
<td>persistent vegetative state</td>
<td>8</td>
<td>11</td>
<td>50.5</td>
<td>36.2</td>
<td>42</td>
<td>37.3 ± 11.6</td>
<td>108 ± 23</td>
<td>19 ± 8</td>
<td>85 ± 16</td>
<td>34.5 ± 7.0</td>
</tr>
<tr>
<td>died</td>
<td>15</td>
<td>20</td>
<td>43.9</td>
<td>27.6</td>
<td>35</td>
<td>33.4 ± 15.5</td>
<td>104 ± 27</td>
<td>50 ± 29</td>
<td>57 ± 27</td>
<td>33.1 ± 9.5</td>
</tr>
<tr>
<td>controls</td>
<td>9</td>
<td>11</td>
<td>65.2 ± 9.6</td>
<td>65.2 ± 9.6</td>
<td>0</td>
<td>55.2 ± 4.2</td>
<td>39.0 ± 6.3</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* CBF = cerebral blood flow; mhCBF = mean hemispheric CBF; CBFinit = CBF calculated by initial slope method; CBF10 = CBF calculated by the 10-minute height over area method; MABP = mean arterial blood pressure; MIVP = mean intraventricular pressure; CPP = cerebral perfusion pressure.

who were not assisted by a respirator. Dexamethasone was used in only a few patients, and mannitol was given to two patients during surgery, both of whom died.

Results

As illustrated in Table 2, the mean hemispheric CBF, MIVP, cerebral perfusion pressure (CPP), and mean PaCO2 were very similar in the first three outcome groups (good recovery, slight deficits, and severe deficits), and they differed only slightly from our normal values. However, more pathological values were observed in the persistently vegetative survivors and those who died, with reduction of the mean hemispheric CBFinit and mean hemispheric CBF10 in both the latter groups, and elevation of MIVP with consequent reduction of CPP in those who died. Mean hemispheric CBFinit calculated for the second part of the slope was reduced for all outcome groups in relation to the control values.

The distribution of CBFinit values in the histograms (Fig. 3) shows, however, that interregional heterogeneity is a prominent feature after head injury, and that in all outcome groups a considerable proportion of flow values fall outside the normal limits of 40 to 99 ml/100 gm/min. A shift to the left is common to all five outcome groups, but a distinct difference in distribution is evident between the first three groups (recovered, with or without neurological deficit) and the last two (persistent vegetative state and dead). These differences will be discussed in the next section. Flows over 100 ml/100 gm/min were found in all head-injury groups, and had no evident relationship to outcome.

The differences in values obtained between the first and second parts of the slope reflect on the one hand that bi- or multiexponential washout is common in all outcome groups, but on the other hand that the higher values from the first part of the slope represent the highest flows "seen" by each detector (cortical gray matter in normal brain). We shall not at this time discuss the pathophysiology of multiexponential washout curves, since these have been considered in detail in a previous publication. However, in the subsequent discussion of regional ischemic flows, we have used the values obtained from the initial part of the slope, that is, the best perfused tissue in each detector region.

Ischemic Regional Flows

The rCBFinit values of less than 20 ml/100 gm/min were observed in a total of 174 regions in 18 patients. The relationship of regional ischemic flows to neurological outcome and to the time between injury and study has been examined (Table 3). Two observations can be made based on the data in this table. The first is that flows of less than 20 ml/100 gm/min are infrequent in patients in the first three outcome groups (recovered, with or without neurological deficit), with a total of only 18 regions (1.1%) distributed among four patients. One patient with 12 such regions, who eventually made a good recovery, was the only patient in the entire series who was studied shortly after a large intravenous dose of short-acting barbiturate (thiomebumal, 400 mg). If this patient is ignored, it is evident that ischemic flows are rare in these three outcome groups. On further examination, it was also determined that in none of these was the rCBFinit less than 17 ml/100 gm/min.

In the two worst outcome groups, the observations were considerably different. Ischemic flows were ob-
FIG. 3. Histograms of the distribution of the total number of regional flow (rCBF) measurements for each clinical outcome group compared with normal flows. There were 2724 regional flow measurements (probes) in head-injured patients divided into five outcome groups, and 381 in nine control subjects who had no brain pathology. The histogram for each outcome group consists of the total population of the rCBF values for that group. Since logarithmic xenon-133 washout curves from head-injured patients are often curvilinear during the first 2 minutes (see Fig. 2), the rCBF corresponding to both the first and second parts of the slope was calculated and both values are displayed in the histograms.

served in a total of 156 regions (14.5%) in 14 of 23 patients. The difference between the three best and the two worst groups is highly significant (p < 0.0001). The highest incidence was in patients studied within 24 hours of injury who eventually died (29.3%), and the incidence decreased with increasing time after injury. On further examination, it was also found that in 105 of these regions the flow was under 17 ml/100 gm/min.

The second observation arising from this table is that ischemic flows were most frequently observed in the early hours after injury, and bore no relationship to the eventual time of death. In other words, it was evident that ischemic flows were not just antemortem reflections of imminent death. The interval between study and death was in no case shorter than 6 hours; the longest was 410 hours, and the average in the 10 patients who died was 108 hours.

The lobar distribution of regional ischemic flows in the two worst outcome groups was as follows: 46.8% frontal, 35.9% parietal, and 17.3% temporal. This showed a striking frontoparietal predominance, indicating a severe disturbance of the total hemispheric flow pattern in severely injured patients. Figure 4
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TABLE 3

Regional ischemia related to outcome and time from injury*

<table>
<thead>
<tr>
<th>Outcome Group</th>
<th>No. of Cases</th>
<th>No. of Regions</th>
<th>Day 0 (1–24 hrs)</th>
<th>Days 1–4</th>
<th>Days 4–7</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Ischemic/ Total</td>
<td>Ischemic/ Total</td>
<td>Ischemic/ Total</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No. of Cases</td>
<td>No. of Cases</td>
<td>No. of Cases</td>
</tr>
<tr>
<td>good recovery</td>
<td>13</td>
<td>592</td>
<td>12/278 (4.3%)</td>
<td>0/140</td>
<td>0/174</td>
</tr>
<tr>
<td>slight deficits</td>
<td>11</td>
<td>519</td>
<td>2/138 (1.5%)</td>
<td>0/139</td>
<td>0/242</td>
</tr>
<tr>
<td>severe deficits</td>
<td>16</td>
<td>537</td>
<td>2/172 (1.2%)</td>
<td>2/104</td>
<td>0/261</td>
</tr>
<tr>
<td>persistent vegetative state died</td>
<td>8</td>
<td>384</td>
<td>10/69 (14.5%)</td>
<td>13/175</td>
<td>2/140</td>
</tr>
<tr>
<td>died</td>
<td>15</td>
<td>692</td>
<td>81/276 (29.3%)</td>
<td>43/314</td>
<td>9/102</td>
</tr>
<tr>
<td>total</td>
<td>63</td>
<td>2724</td>
<td>107/933 (11.5%)</td>
<td>58/872</td>
<td>9/919</td>
</tr>
</tbody>
</table>

* Ischemic flow values are defined as regional cerebral blood flows of less than 20 ml/100 gm/min, calculated from the first part of the washout slope during the 1st week after injury. For each time interval, the ratio of the number of ischemic flow values to the total subpopulation is illustrated, as well as the number of patients in whom ischemic flow values were found.

![Diagram](image)

**FIG. 4.** Regional flows calculated by the initial curve method (rCBF<sub>ini</sub>) under 20 ml/100 gm/min. See also Table 3. **Left:** A predominantly frontal and parietal location of the low-flow regions is seen in four of the patients who survived in a persistent vegetative state. **Right:** A preponderance of ischemic regions is seen in the frontal and parietal areas in 10 patients who died. Of the total 133 regional ischemic flows, 27% were in the range of 19 to 17 ml/100 gm/min; 32% in the range of 16 to 12 ml/100 gm/min; and 41% in the range of 11 to 1 ml/100 gm/min. These latter measurements are particularly strongly represented in parasagittal zones.

Pathological Correlations of Regional Ischemic Flows

Pathological explanations were sought in the 18 patients with regional ischemic flows. A pharmaco- logically induced diffuse depression of CBF was probable in one patient (the one who made a good recovery). The ischemic regions of the patient who recovered with slight deficits were located in the parietal area over a previously removed intracerebral hematoma. One patient who recovered with severe deficits had a temporal lobe laceration with the two ischemic
regions located in that area. The other patient in this category had two ischemic regions in the temporal lobe over a cerebral contusion.

In the two worst outcome groups, no clear correlation between cortical pathology and regional ischemic flows could be established. Six patients had acute subdural hematomas, two had frontal and one parietal lacerations, and five had cerebral contusions. These lesions did not, however, define the regions of ischemic flow.

A hemodynamic explanation for regional ischemia based on elevated ICP is, therefore, postulated for these two groups. Although the total number of ischemic regions in individual patients did not correlate with the PaCO\textsubscript{2}, MIVP, CPP, or cerebrospinal fluid (CSF) lactate, there was a significant elevation of MIVP and reduction of CPP in patients who eventually died, and a similar but not significant trend in persistently vegetative patients. A hemodynamic explanation best fits the observed frontoparietal distribution of ischemic regions and lack of association with focal traumatic cortical pathology in these patients.

**Oxygen Uptake**

The oxygen uptake (CMRO\textsubscript{2}) was calculated in 20 patients. Results from the 15 patients in the three best outcome groups are shown in Fig. 5. The values for arteriovenous difference for oxygen content are plotted against the mean hemispheric CBF\textsubscript{init} values. A weak inverse correlation may be interpreted as an indication of impaired metabolic regulation of CBF.

There was no relation between arteriovenous difference for oxygen content and flow in the five patients who either survived in a vegetative state or died. The low number of studies precludes a useful conclusion, but it seems warranted to speculate that the coupling between flow and CMRO\textsubscript{2} was abolished in these patients, at least on a global level. The relationship between CMRO\textsubscript{2} and brain injury is discussed in the next paragraph.

**Discussion**

In this study we have tried to correlate early regional cerebral ischemia and patient outcome after head injury. The analysis was based upon 3105 flow values calculated by the rCBF\textsubscript{init} method in 63 patients and nine controls. The clinical observations, the patient outcome category, and the hemodynamic studies were combined after at least 2 years had passed since the last CBF investigation. Only CBF studies performed during the 1st week after severe head injury were included.

For clinical purposes, it seems logical to discuss CBF in severely head-injured patients from the point of view of three different levels of cerebral ischemia: insufficiency of blood supply 1) for functional demands, 2) for metabolic requirements, and 3) for structural integrity of the tissue.\textsuperscript{30} It is clear that in awake healthy persons the term “functional demand” means a broad spectrum of motor and mental activities exerted to meet the challenges of life. As the cortex modulates its activity in accordance with functional demands, the regulation of tissue perfusion...
through redistribution of global flow seems to be the link between function and metabolism. The basic perfusion requirements for functional demands may then be expressed as the lowest measured rCBF under normal resting conditions. Using the rCBF_{init} method, we found no regional value under 40 ml/100 gm/min in our awake control patients. With this definition of minimal rCBF to meet normal functional requirements, the distribution of perfusion in the head-injury patients we have studied is certainly insufficient in many regions to support focal function.

However, in the comatose patient it is difficult to assess potential functional capabilities of the cortex. Information must reach cortical neurons before functional activity can be aroused. It has been shown in baboon experiments by Branston, et al., that evoked cortical electrical responses were undisturbed as long as focal cortical perfusion was kept between 20 and 16 ml/100 gm/min. If local blood flow fell below about 16 ml/100 gm/min, a progressive reduction in the amplitude of the surface-recorded evoked potential occurred, and abolition of the evoked potential followed when flow was below about 12 ml/100 gm/min. The transmission of electrical signals in response to peripheral stimuli implies that information has reached the neurons, but it cannot be equated with a functional response. Thus, the threshold for abolition of these responses is significant in terms of failure of transmission of information but not elicited function.

Flow values of this range are just above those that are followed by an insufficient synthesis of adenosine triphosphate. For example, in biopsy studies of human cortical tissue from patients with tumors, we found that the concentration of energy-rich phosphates was maintained as long as the CBF_{init} of the biopsied region was not lower than 18 ml/100 gm/min. Brain tissue may survive such a low perfusion, but with abolished functional reactivity. However, if the perfusion is lowered further, the structural integrity of the tissue is threatened. This event may be assessed by measuring the extrusion of potassium from the intracellular to the extracellular compartment, which, according to Astrup, et al., occurs when local flow falls to between 11 and 7 ml/100 gm/min. This is the same range of local cortical flow, which, when maintained for 2 to 3 hours, led to microscopic infarction in the experiments by Morawetz, et al.

More recently, the same authors have examined threshold values of local CBF for development of infarction in awake monkeys. A threshold for infarction was a flow of 12 ml/100 gm/min, prolonged for a period of 120 to 180 minutes. This threshold was further lowered for shorter intervals of ischemia. From our viewpoint, it is of interest that they found that the threshold represents an absolute value for CBF rather than a percentage reduction of preocclusion flow. Also, they found no difference in the vulnerability of gray and white matter.

The validity of comparing CBF findings in clinical head injury with the above experimental results obtained in animals with intact brains is uncertain. We have chosen the critical value of rCBF_{init} under 20 ml/100 gm/min as a threshold of regional ischemia because Trojaborg and Boysen, and Sundt, et al., found that 18 to 23 ml/100 gm/min was close to a threshold value for electroencephalographic slowing in carotid artery surgery. We have had the experience that communicative brain function did not recover in patients whose mean hemispheric CBF_{init} was lower than 20 ml/100 gm/min.

For our first three outcome groups it seems to be a condition that no region will have a flow lower than 17 ml/100 gm/min. If the one patient treated with a short-acting barbiturate before the study is excluded, regional flows under 20 ml/100 gm/min were rare in these groups and usually associated with focal surgical lesions. It is apparently not regional flow that determines which of those outcome categories a patient will fall into. The presence or absence of neurological deficit in these patients would seem to be determined by their initial injuries and focal brain pathology, and is not a result of focal cerebral ischemia. However, these cases were only studied after surgical intervention, and we do not know if flow was lower before surgery and therefore if their deficits were partly the result of focal compression. Enevoldsen, et al., studied 23 head-injured patients and concluded that “neither global nor gross regional cerebral ischemia was likely to be present” and that “the low CBF found in many cases seems to be a function of decreased metabolic demands in the brain tissue rather than a primary factor causing the decreased brain function.”

Our findings in patients who survived in a persistent vegetative state or eventually died are at variance with that contention. First, both groups had significantly more regional flows under 20 ml/100 gm/min than the other groups; and second, both had disturbances of global flow distribution best explained on a hemodynamic basis. It should be noted that the ischemic flow distribution in our antemortem studies conforms closely to the postmortem demonstration of cerebral infarction in the frontoparietal “watershed” areas described by Graham, Adams, and Jennett. These authors also found that the “neocortical damage was more often found under the age of 40 than over.” Our patients were all young, and we believe that the present rCBF studies confirm their conclusions that antemortem posttraumatic cerebral ischemia of the
frontoparietal "watershed" areas is a major factor in determining localized neocortical necrosis. The study-to-death interval in our patients clearly suggests that the neuropathological findings of the Glasgow Group represent intravital, not agonal, events.

The four patients with ischemic flows surviving in a persistent vegetative state developed ventricular dilatation within the first 40 days after injury. Three had CSF shunts without any subsequent improvement of their clinical condition. We are, therefore, inclined to conclude that recovery to communicative cerebral function after traumatic coma cannot occur if regional flows are lower than 17 ml/100 gm/min.

Obrist, et al.,29 have published similar studies with a 16-detector equipment for xenon inhalation studies. They found that the CBF "declined to very low levels in all nine patients, who died . . ." We are not fully able to compare their results with ours, because they averaged across all 16 regions of both hemispheres. We would predict that there is a high probability that regional flow values under 17 ml/100 gm/min would have been found in their patients who died, including those seven patients whose bihemispheric fast compartment flow was over 20 ml/100 gm/min, if the detectors had looked at a sufficient number of frontoparietal regions.

The hypothesis of insufficient tissue perfusion needs further proof, of course. Simultaneous measurements of rCBF and regional CMRO2 would provide insight into the relationship between those two parameters. In the normally functioning brain, Raichle and co-workers8 found them "excellently correlated;" however, less so in acute brain damage. The double-tracer technique could possibly 1) confirm or reject the suggested threshold values for metabolic ischemia, and 2) determine when and where flow and metabolism are no longer correlated. Bruce and Langfitt suggested that a CMRO2:CBF10 ratio of less than 30% of 0.07:1 may indicate diffuse neocortical structural damage. We found that, of the 15 patients who recovered communicative brain function, four had a ratio lower than 30%, and, of the five who did not recover, three had a ratio under 30%. These figures are hardly conclusive, but an association between a high CMRO2:CBF ratio and recovery of brain function after traumatic coma would suggest that metabolic regulation of CBF is better preserved in the least injured patients. This agrees with the results by Hass, et al., but not with the figures published by Cold. We are aware that we have insufficient evidence to determine whether the CBFinit values under 20 ml/100 gm/min were caused by regional metabolic depression, a transient cerebral vascular reaction, ischemic damage due to cerebral tissue trauma, or by systemic factors arising at the time of impact. Our incidence of overt early systemic disorders in nine of 23 of the patients surviving in a vegetative state or dying is very close to that reported by Miller, et al.21

Thus, neuropathology and CBF studies both give results that suggest a special risk of traumatic ischemic cortical lesions in areas remote from the brain stem. Animal head-injury studies also have revealed similar spatial and temporal heterogeneity of perfusion. Nilsson found that within seconds after acceleration injury in rats a pronounced cerebral hyperemia was elicited, but it was followed by a long period of flow reduction, and these reactions "were more extensive in the cortex than in brain stem regions." That flow reductions may be more important than hyperemia was stated by Pontén, et al.. . . the brain tissue itself is rather resistant to trauma, but secondary ischemic and hypoxic changes of complex pathophysiology and probably a very inhomogeneous flow are responsible for much of the brain damage, even in the acute phase."

The time scales are very different for observed events in the experimental laboratory and those recorded in patients. The term "secondary" is unfortunate because it leads to management procedures when too late, as in the clinical context this term is understood as the occurrence of an unexpected deterioration. If the term "secondary" is applied to the development of regional ischemia in our head-injured patients, then it is noteworthy that the 10 patients with that finding at Day 0 had no evident clinical neurological deterioration compared with those who did not have ischemic regions. We would therefore discourage the use of the term as applied to this finding, except probably for the patient in whom the low regional flows may be explained by the use of barbiturate.

It may be provocative to suggest that one way to avoid regional ischemia would be the early use of barbiturate sedation. Reducing the metabolic demands of the brain tissue would be in accordance with Nilsson's experimental findings of head injury as an excitatory event, leading to a perfusion deficit because the cerebral vasoconstriction prevents flow meeting the metabolic demands. Another argument is based on Hossmann's demonstration of posts ischemic hypermetabolism which could endanger the tissue if flow, because of posttraumatic vasoconstriction, were unable to cope with demands. The term "secondary ischemia" is meaningful when used on this basis and it indicates that depression of metabolism should be applied as early as possible.

We have no evidence for intact coupling between CBF and metabolism in patients who did not recover

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cerebral function, and we therefore do not consider that \( rCBF_{\text{min}} \) values lower than 20 ml/100 gm/min, and especially under 17 ml/100 gm/min, are the result of metabolic depression. Their location compares with the reported ischemic neuronal destruction after accidents without head injury but involving arterial hypotension as well as systemic hypoxia.\(^2\) Brierley, et al.,\(^7\) have recently reviewed the clinical as well as the experimental evidence for a peculiar vulnerability of these arterial boundary zones, which are located in the parasagittal areas. In their own experiments, which combined hypoxia and common carotid artery occlusion in the spontaneously breathing baboon, they did not measure regional or local blood flow, but they showed that “irreversible neuronal damage along the arterial boundary zones occurs only after an appreciable period of EEG silence.” The time scale for the production of cortical destruction was at least 8 minutes of electrical silence. Taken in combination with the experimental work on focal brain ischemia of Branstion, et al.,\(^5\) Astrup, et al.,\(^3\) and Morawetz, et al.,\(^22\) this gives support to a threshold hypothesis incorporating reduced flow and a time factor.

Our findings confirm that from a hemodynamic point of view the cortical areas most susceptible to damage arising from low-flow states (the frontoparietal arterial boundary zones) are the same in head-injured patients as in patients with various systemic derangements.\(^13\)

The predictive value of measuring \( rCBF \) within the 1st week of severe head injury is thus related to the potential adverse finding of lower than threshold values (17 ml/100 gm/min) of \( rCBF \) in frontoparietal boundary zones. Criteria for recovery of responsive communicative brain function include the absence of such ischemic flow values in these regions during the initial period of traumatic coma.

References


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