Autoregulation and CO₂ responses of cerebral blood flow in patients with acute severe head injury

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Regional cerebral blood flow (rCBF), cerebral intraventricular pressure (IVP), systemic arterial blood pressure, and cerebral ventricular fluid (CSF) lactate and pH were studied repeatedly in 23 patients during the acute phase of severe brain injury lasting from 3 to 21 days after the trauma. Cerebrovascular autoregulation was tested repeatedly by means of angiotensin infusion in 21 of the patients, and CO₂ response in 14 by means of passive hyperventilation. The pressure in the brain ventricles was measured continuously in all patients and kept below 45 mm Hg during the study. If the IVP increased more than 10 mm Hg during the angiotensin infusion (as in one case), the autoregulation test was considered contraindicated and the angiotensin infusion was discontinued.

Dissociation between cerebrovascular autoregulation and CO₂ response was a common phenomenon. Typically, autoregulation appeared preserved in the most severely injured areas of the cerebral cortex when the patient was deeply comatose, but deteriorated concomitantly with recovery; by the time the patient became alert, the autoregulation was always impaired. The CO₂ response was impaired only in patients who were deeply comatose and had attacks of decerebrate rigidity; during recovery the CO₂ response became normal. Thus, preserved autoregulation associated with impaired CO₂ response indicated very severe brain damage, whereas impaired autoregulation associated with preserved CO₂ response suggested moderate or severe brain damage in recovery. These paradoxical observations raise the question whether the preserved autoregulation seen in severely injured brain tissue is a true autoregulation caused by an active vasoconstrictor response to an increase in blood pressure.

Key Words: severe head injury, decerebrate rigidity, regional cerebral blood flow, intraventricular pressure, CSF lactate and pH, false autoregulation, brain tissue acidosis

Knowledge of the pathophysiology of craniocerebral injuries is important in the treatment of patients with severe head injuries. In particular, knowledge of the cerebrovascular response to changes in arterial blood pressure and carbon dioxide tension may serve as a guide for rational therapy. As shown by several authors, maintenance of adequate perfusion pressure is imperative to avoid brain ischemia. On the other hand, an increase in arterial blood pressure can provoke brain edema in injured brain tissue. High carbon dioxide tension (pCO₂) in the brain increases the cerebral blood flow (CBF) in areas with normal vascular reaction, but can provoke...
ischemia in areas with vasoparalysis, the steal phenomenon. Pronounced hyperventilation may decrease CBF to the limit of ischemia in intact (vasoactive) areas, but increases CBF in damaged (vasoparalytic) areas, the inverse steal phenomenon. High intracranial pressure (ICP) caused by brain edema and resulting in low perfusion pressure is an imminent complication in patients with severe head injuries. The treatment of the individual case is, therefore, a precarious balance between the risk of ischemia caused by too low perfusion pressure and the danger of edema caused by an increase in blood pressure. In addition, treatment must find a balance between the beneficial effect of hyperventilation on ICP and oxygen supply and the possible risk of ischemia provoked by too vigorous hyperventilation. Our knowledge of cerebrovascular response in severe head injury is still fragmentary and controversial. It is well known from animal studies and from studies of human beings with exposed brain that autoregulation is very sensitive to brain damage, whereas the CO₂ response is more difficult to impair. It is therefore puzzling that several authors have found a dissociation in the form of preserved autoregulation (unchanged flow in spite of an increase in perfusion pressure) and defective CO₂ response (impaired flow decrease during hyperventilation) in animals as well as in patients suffering from acute severe head injury. These paradoxical observations have given rise to the suspicion that the preserved autoregulation seen in severely injured brain tissue is a false autoregulation which is not caused by the active vasoconstrictor response to an increase in blood pressure found in normal brain tissue.

In a previous publication, we showed that cerebral ischemia did not occur in head injury if the intraventricular pressure (IVP) was kept below 45 mm Hg. On the contrary, hyperemia, mostly in the form of so-called tissue-peak hyperemia, was always present in the most severely injured brain tissue during the acute phase. The hyperemia increased during deterioration, but decreased during recovery, and in patients who became alert in the period of study the hyperemia was replaced by low flow values. In the same study we measured the cerebrovascular autoregulation and CO₂ response, and the results of these measurements are published here.

Like Bruce, et al., and Fieschi, et al., we find that a dissociation between preserved autoregulation and impaired CO₂ response is common in patients with acute severe head injury. In addition, we have gained the impression that poor vascular reactivity to hyperventilation is particularly associated with brain-stem symptoms.

Our clinical material and methods have been described in detail in a previous paper. Here only a summary will be given.

**Clinical Material**

Twenty-three patients whose ages ranged from 14 to 70 years (average 28 years) were studied during the acute phase (for 3 to 21 days) after head trauma. On admission they were all deeply comatose. Emergency management consisted of the usual neurosurgical care, including intubation with controlled ventilation, carotid angiography, and acute craniotomy (17 cases), or performance of exploratory burr holes (four cases). The cortex was carefully inspected and described during large craniotomies for fractures and hematomas. In seven patients repeat craniotomy was performed later in the acute phase because of suspicion of hematoma, but in five of the cases only edema and/or malacia was found. In two patients, the cortex was not inspected. Only patients who, after the initial neurosurgical treatment, remained deeply comatose were included in the series. All patients were artificially ventilated, with a slightly positive end-expiratory pressure. Arterial carbon dioxide tension (PaCO₂) and oxygen tension (PaO₂) were maintained at a constant level in the individual patient. The PaCO₂ level varied from 20 to 40 mm Hg (average 31 mm Hg), and the PaO₂ from 100 to 150 mm Hg.

In all patients the IVP was measured continuously during the entire period of study, and the pressure levels were kept below 45 mm Hg by means of administration of meperidine, chlorpromazine, hyperventilation, mannitol, Nembutal (pentobarbital) Pentothal (thiopental sodium), dexamethasone, ventricular drainage, and, as a last resort in four cases, surgical decompression.

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Based on the clinical picture in the acute phase, the carotid angiograms, and the initial inspection of the cortex through craniotomies or burr holes, the patients were divided into three groups.
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**Group I: Patients with Local Cortical Lesions**

On admission, the six patients with local cortical lesions were all deeply comatose, with defensive flexor movements on painful stimuli. All had focal neurological deficits from the hemisphere studied by cerebral blood flow (CBF) measurement. Five had hemiparesis and one a unilateral Babinski reflex. In the latter patient, hemiparesis developed 8 days after the injury in association with discontinuation of the respirator. In all patients, angiography performed on admission revealed a mass lesion, and craniotomy disclosed severe cortical contusion and laceration with hematomas in the hemisphere in which CBF was measured.

**Group II: Patients with Mainly Brain-Stem Symptoms**

Five patients had symptoms mainly referable to the brain stem. On admission, they were all deeply comatose and had extensor movements on painful stimuli. In addition, all had attacks of decerebrate rigidity and abnormal brain-stem reflexes. The angiograms taken on admission were normal. In three of the patients, the cortex was explored bilaterally through burr holes and found normal. In the remaining two patients, the cortex was not inspected.

**Group III: Patients with Local Cortical Lesions and Brain-Stem Symptoms**

Twelve patients had local cortical lesions and brain-stem symptoms. On admission, nine were deeply comatose with extensor movements on painful stimuli and abnormal brain-stem reflexes. Two patients were comatose with defensive flexor movements on pain and hemiparesis. They had normal brain-stem reflexes initially, but decerebrate rigidity and abnormalities of the brain-stem reflexes developed 4 days after the injury in association with high IVP (pressure levels of about 45 mm Hg with multiple plateau waves of 70 to 90 mm Hg). One patient showed no motor reaction at all from admission until he died 3 days after the injury, but autopsy revealed contusions of both the cortex and the brain stem. In all patients, carotid angiography on admission showed signs of a mass lesion. In seven patients, craniotomy disclosed severe cortical contusion and laceration with hematomas. The remaining five patients had severe contusion, but no hematomas were found.

A follow-up study 2 years after the injury showed that eight patients had died; one was in a vegetative state; seven were demented; and seven coped with their work or school.

**Comment**

The division of the patients in the three groups is, of course, arbitrary, as all patients had severe head injury and thus presumably had some diffuse impairment of the brain. However, the group of patients with localized severe brain lesions (hematoma, laceration, and contusion) had a different regional CBF (rCBF) from patients who did not have signs of local severe cortical damage. We designate the latter group of patients as patients with mainly brain-stem symptoms, because they all had attacks of decerebrate rigidity from the very beginning; we believe these patients most likely also had diffuse disorders in the brain.

The cortical lesions were observed and described by the neurosurgeon during the initial craniotomy, and in seven patients again during a second craniotomy later in the acute phase. Only part of the hemisphere was inspected, therefore, but the craniotomy was placed in the areas of the fractures and the hematomas and was considered to correspond with the most injured areas of the brain. The craniotomies were large and the CBF collimators were placed corresponding to the areas seen by the neurosurgeon. The first CBF determination was done 1 day after the initial craniotomy. If the patients were reoperated on, CBF was measured just before the reoperation. So we feel that we may be allowed to compare the rCBF results with the cortical lesions seen during operation.

**Methods**

Regional cerebral blood flow was measured in all 23 patients by means of the intracarotid \(^{133}Xe\) injection method devised by Lassen and Ingvar.\(^{22}\) In all, 66 separate CBF studies were performed. Sixteen NaJ detectors* were used for the external recording and

* Cerebrograph Model RCBF-161, manufactured by Meditronic A/S, 9560 Hadsund, Denmark, equipped with 16 ½-in. \(\times\) 5-mm NaJ scintillation detectors.

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FIG. 1. Relation between autoregulation response and grade of consciousness. The systemic arterial blood pressure was increased 20% to 35% during the autoregulation tests. It is seen that the autoregulation appears to be preserved in most patients who were comatose with attacks of decerebrate rigidity (left), whereas the autoregulation became impaired when consciousness returned (right).

The rCBF was calculated as the initial slow flow index by automatic linear regression analysis of the first minute of the logarithmically transformed clearance curve. The computer started the calculation when the activity had decreased for 15 seconds and the decrease in activity was less than five standard deviations. Thus, shunt peaks and plateaus were excluded from the calculation. The computer automatically compensated for residual activity.

The rCBF measurements were performed in the most severely injured hemisphere, and the detectors were placed over the most damaged areas of the hemisphere, areas which had been observed and described by the neurosurgeon during the craniotomies. In each patient, the measurements were repeated one to four times during the period of study, depending on the clinical indication for carotid angiography. All CBF determinations were performed under local anesthesia and before angiography. The measurements were done in the resting state, during angiotensin infusion showing a rise in mean arterial blood pressure of 20% to 35% (average 29%), again during resting state, and during hyperventilation resulting in a decrease in PaCO₂ of 5 to 18 mm Hg (average 8.5 mm Hg), depending on the resting PaCO₂. Autoregulation was considered preserved when the rCBF change was less than 20%, and the hyperventilation response was considered normal when the rCBF decrease was more than 2% per mm Hg of PaCO₂ changes.

The IVP was measured continuously in all patients by Lundberg's method. If the IVP increased more than 10 mm Hg during the angiotensin infusion the autoregulation test was abandoned. This happened in only one patient who had a high IVP (about 40 mm Hg). Two patients had a decompression operation, one before, and the other during the period of the CBF studies (Fig. 8). One patient was treated with ventricular drainage on the day of the CBF measurements.

Systemic arterial blood pressure (SAP) was measured continuously through the carotid catheter during the CBF studies and the mean perfusion pressure was calculated as mean SAP (diastolic + 1/3 pulse pressure) minus mean IVP. Arterial blood gases were determined during all CBF measurements.

In 15 patients, samples of cerebrospinal fluid (CSF) were withdrawn repeatedly (two to 10 times, with a total of 92 samples) from the...
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the ventricles of the brain, and CSF lactate, pyruvate, pH, and pCO₂ were determined by enzymatic and radiometric methods, respectively.

Results

Autoregulation

Autoregulation was studied in 21 patients (52 CBF studies). The results are shown in Table 1. In most patients, there seemed to be an inverse correlation between impaired autoregulation and poor clinical condition, as the autoregulation appeared to be preserved when the patients were deeply comatose, but became impaired as the patients recovered (Table 1 and Fig. 1).

In the patients with local cortical lesions, an inverse correlation between autoregulation and the severity of the cortical lesion was found (Table 1). Initially, when the patient was deeply comatose, the response typically was preserved in the most severely injured areas of the cerebral cortex, but in some patients it was also impaired in areas described by the neurosurgeon as only moderately injured (Fig. 2). In a few patients with laceration of the cortex, the rCBF even decreased in the lacerated areas during the test. When the patients recovered, the autoregulation at first appeared normal then became impaired. Thus, in all four patients who became alert during the study (Cases 12, 19, 20, 21) the autoregulation was impaired in the most injured areas (the hematoma areas) at the time they became alert (Fig. 3). Two patients differed from the others. One had impaired autoregulation in the severely injured areas from the beginning (Case 9). He was the only patient who was treated initially with a decompression operation. The other (Case 6) had impaired autoregulation transiently after the removal of a large (250 ml) hematoma (transient decompression).

In all the patients who had local cortical lesions as well as decerebrate rigidity from the beginning, the autoregulation was preserved initially in the most injured cortical areas and remained preserved for weeks. None of these patients became alert during the first month after the trauma. The two patients who died within the first 8 days after the trauma had preserved autoregulation during repeated studies (Cases 4 and 5). In the two patients with cortical lesions who developed attacks of decerebrate rigidity in association with an increase in IVP and development of plateau waves, the autoregulation was preserved in the most damaged areas during the clinical deterioration (Cases 13 and 19) (Fig. 4).

In the patients with brain-stem symptoms, but without local cortical lesions, the autoregulation was found to be impaired initially if they had had attacks of decerebrate rigidity for only a few hours (Cases 10 and 11), whereas the autoregulation appeared to be preserved (Fig. 5) if they had had attacks of decerebrate rigidity for days (Cases 16 and 17). When the clinical condition improved and the decerebrate rigidity disappeared, the autoregulation became impaired. In one patient (Case 8), who had attacks of decerebrate rigidity for 2 weeks, the autoregulation was impaired from the moment continuous ventricular drainage was started 4 days after the trauma (Table 1).

Resting IVP varied at the different CBF determinations, but in only five cases was the
### TABLE 1

**Autoregulation responses in 21 patients with acute severe brain injury**

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Sex, Age</th>
<th>Cortical Lesions</th>
<th>Days after Injury</th>
<th>Consciousness</th>
<th>IVP (mm Hg)</th>
<th>Autoregulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>rt temporal: epidural hematoma (80 ml), severe contusion &amp; edema, laceration of temporal pole</td>
<td>1</td>
<td>comatose + dc</td>
<td>21–19</td>
<td>temporal elsewhere</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>lt frontotemporal: epidural hematoma (35 ml); temporal: severe contusion &amp; edema; base: very severe contusion</td>
<td>1</td>
<td>comatose + dc</td>
<td>25–27</td>
<td>diffuse</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2</td>
<td>comatose + dc</td>
<td>14–18</td>
<td>diffuse</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>lt temporal: subdural hematoma (30 ml), severe contusion</td>
<td>¼</td>
<td>comatose</td>
<td>17–25</td>
<td>temporal elsewhere</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>comatose</td>
<td>13–16</td>
<td>diffuse</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>8</td>
<td>comatose</td>
<td>15–17</td>
<td>diffuse</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3</td>
<td>comatose + dc</td>
<td>14–12</td>
<td>diffuse</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>lt frontotemporal: severe contusion</td>
<td>1</td>
<td>comatose + dc</td>
<td>7–6</td>
<td>diffuse</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2</td>
<td>comatose + dc</td>
<td>19–18</td>
<td>diffuse</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>rt frontal: severe laceration</td>
<td>1</td>
<td>comatose, no motor reaction</td>
<td>43–46</td>
<td>diffuse</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>lt frontotemporal: subdural and intracerebral hematoma (250 ml), temporal laceration; base: severe laceration</td>
<td>1½</td>
<td>comatose</td>
<td>11–11</td>
<td>diffuse</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3½</td>
<td>comatose</td>
<td>10–9</td>
<td>diffuse</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>13½</td>
<td>comatose</td>
<td>25–21</td>
<td>diffuse</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>rt temporal: severe contusion</td>
<td>21</td>
<td>comatose + dc</td>
<td>?</td>
<td>temporal elsewhere</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>lt infratentorial: posterior fossa epidural hematoma; cerebellum: laceration (continuous ventricular drainage from 3rd day)</td>
<td>1</td>
<td>comatose + dc</td>
<td>19–14</td>
<td>diffuse</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4</td>
<td>comatose + dc</td>
<td>19–19</td>
<td>diffuse</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>8</td>
<td>comatose + dc</td>
<td>17–18</td>
<td>diffuse</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>15</td>
<td>comatose + dc</td>
<td>16–15</td>
<td>diffuse</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>lt parieto-occipital: severe laceration; temporal: severe laceration; decompression performed initially</td>
<td>1</td>
<td>comatose</td>
<td>17–18</td>
<td>elsewhere parietal</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3</td>
<td>comatose</td>
<td>14–14</td>
<td>diffuse</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>8</td>
<td>comatose</td>
<td>14–13</td>
<td>diffuse</td>
</tr>
<tr>
<td>10</td>
<td>M</td>
<td>not operated on; normal carotid angiography</td>
<td>1</td>
<td>comatose + dc</td>
<td>11–10</td>
<td>elsewhere scattered diffuse</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2</td>
<td>comatose</td>
<td>9–12</td>
<td>diffuse</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>17</td>
<td>comatose</td>
<td>3–6</td>
<td>normal autoregulation</td>
</tr>
<tr>
<td>11</td>
<td>M</td>
<td>rt frontal, temporal, and parietal cortex normal</td>
<td>½</td>
<td>comatose</td>
<td>10–10</td>
<td>diffuse</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1½</td>
<td>comatose</td>
<td>10–10</td>
<td>diffuse</td>
</tr>
</tbody>
</table>

*The table shows the relation between the initial local cortical lesions in the most injured hemisphere, the clinical condition of the patients (grade of consciousness), the intraventricular pressure (IVP), and the type and location of autoregulation responses. dc = decerebrate rigidity.

**Correlation was found between preserved autoregulation and high CSF lactate and low CSF pH in patients with attacks of decerebrate rigidity, namely, the patients who had increased CSF lactate.**

Thus, in all 10 cases in which the CSF lactate was above 3.5 mmol/liter the autoregulation was preserved.

IVP more than 25 mm Hg, and only in two cases was it above 30 mm Hg. The IVP change (ΔIVP) during the autoregulation tests also varied. The IVP remained unchanged or decreased or increased slightly but indiscriminately, in cases with preserved and impaired autoregulation (Fig. 6).
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TABLE 1 (Continued)*

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Sex, Age</th>
<th>Cortical Lesions</th>
<th>Days after Injury</th>
<th>Consciousness</th>
<th>IVP (mm Hg)</th>
<th>Autoregulation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>False</td>
</tr>
<tr>
<td>12 M</td>
<td>45</td>
<td>It frontal: subdural and intracerebral hematoma (50 ml); temporal and parietal: moderate contusion</td>
<td>1</td>
<td>comatose</td>
<td>18–16</td>
<td>diffuse</td>
</tr>
<tr>
<td>13 M</td>
<td>14</td>
<td>rt frontotemporal: subdural hematoma (30 ml); edema; Day 8: very severe temporal edema; Day 27: temporal laceration</td>
<td>1</td>
<td>comatose</td>
<td>17–20</td>
<td>diffuse</td>
</tr>
<tr>
<td>14 M</td>
<td>24</td>
<td>rt parietal: severe contusion &amp; laceration</td>
<td>2</td>
<td>comatose + dc</td>
<td>24–22</td>
<td>diffuse</td>
</tr>
<tr>
<td>15 M</td>
<td>15</td>
<td>It temporal: severe contusion; parietal: normal; initially abnormal lt brain-stem reflexes</td>
<td>2½</td>
<td>comatose</td>
<td>13–13</td>
<td>diffuse</td>
</tr>
<tr>
<td>16 F</td>
<td>14</td>
<td>temporal &amp; parietal: slight edema; occipital: normal; initial dc for 36 hrs</td>
<td>2</td>
<td>comatose</td>
<td>12–11</td>
<td>diffuse</td>
</tr>
<tr>
<td>17 M</td>
<td>16</td>
<td>not operated on; normal carotid angiography</td>
<td>1½</td>
<td>comatose + dc</td>
<td>26–32</td>
<td>diffuse</td>
</tr>
<tr>
<td>18 F</td>
<td>14 (20 ml)</td>
<td>It diffuse subdural hematoma</td>
<td>1½</td>
<td>comatose</td>
<td>25–20</td>
<td>diffuse</td>
</tr>
<tr>
<td>19 M</td>
<td>23</td>
<td>rt frontal: subdural hematoma, small laceration; parietal: epidural hematoma (20 ml), laceration; temporal: laceration, severe edema; Day 6: severe temporal laceration (malacia)</td>
<td>3</td>
<td>stuporous</td>
<td>20–19</td>
<td>diffuse</td>
</tr>
<tr>
<td>20 F</td>
<td>64</td>
<td>rt frontal: severe contusion; temporal: laceration with intracerebral hematoma (75 ml), severe contusion &amp; edema; base: small laceration</td>
<td>1</td>
<td>comatose</td>
<td>10–12</td>
<td>diffuse</td>
</tr>
<tr>
<td>21 M</td>
<td>23</td>
<td>rt temporal and parietal: epidural hematoma (60 ml), slight contusion</td>
<td>½</td>
<td>alert</td>
<td>21–16</td>
<td>diffuse</td>
</tr>
</tbody>
</table>

*The table shows the relation between the initial local cortical lesions in the most injured hemisphere, the clinical condition of the patients (grade of consciousness), the intraventricular pressure (IVP), and the type and location of autoregulation responses. dc = decerebrate rigidity.

in the most injured areas (Fig. 7), and in the two patients who had the lowest CSF pH (6.66 or 7.12) autoregulation was preserved diffusely during repeated studies. They both died within the first 8 days of the trauma (Cases 4 and 5). On the other hand, all cases with CSF lactate below 2.0 mmol/liter had impaired autoregulation (Fig. 7).

Cerebrovascular CO₂ Response

The cerebrovascular CO₂ response was studied repeatedly in 14 patients (32 CBF studies) by means of passive hyperventilation.
FIG. 3. Case 12. Autoregulation response in a 45-year-old man who on admission had a subdural hematoma (50 ml) localized frontally in the left hemisphere. Parietally and temporally, moderate contusion and edema were seen. The autoregulation response during the first 3 days after injury is shown. One and 2 days after the injury the patient was comatose, and the autoregulation was apparently normal. Initially (upper), rCBF even decreased frontally during the test. Three days after the injury the patient responded verbally to commands. At that time, the autoregulation was impaired (shaded areas) in the most severely injured part of the brain frontally. The CSF lactate was fairly low, but the pH was rather low during the first 2 days. In spite of this, the tissue lactic acid acidosis may have been rather pronounced frontally, where relative hyperemia was seen the first day after the trauma (upper). The severe cortical lesion was very localized in this patient, and a high lactate in a limited area need not influence CSF lactate very much.

Poor response to hyperventilation was correlated to poor clinical condition. All patients who had impaired response were deeply comatose, and all of them were experiencing or had just had a period with attacks of decerebrate rigidity. When the decerebrate rigidity cleared and the level of consciousness improved, the hyperventilation response also improved. Six of 10 patients in whom CBF was studied within the first 3 days of injury had decreased response to hyperventilation focally or diffusely. Three patients showed abolished response after a period with high IVP (pressure levels about 45 mm Hg and numerous plateau waves) and multiple attacks of decerebrate rigidity (Fig. 8, Case 12). One patient (Case 8) showed no response to hyperventilation until 15 days after the injury. In this period, he had a high IVP (requiring continuous ventricular drainage) and numerous attacks of decerebrate rigidity.

Impaired hyperventilation response focally or diffusely was seen in nine CBF studies, combined with preserved autoregulation (Fig.
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Fig. 4. Case 19. Autoregulation response in a 23-year-old man who on admission had a parietal epidural hematoma, a small frontal laceration with a subdural hematoma and, in addition, severe contusion and laceration of the temporal lobe on the right side. At the initial craniotomy, the hematomas were removed. During the first 5 days after injury, IVP was about 20 mm Hg. On the fourth day, the IVP increased to 40 mm Hg and gradually became unresponsive to therapy with hyperventilation and mannitol. On the sixth day, carotid angiography showed a mass lesion on the right side, and the patient was subjected to reoperation. This revealed very severe malacia and edema of the temporal region. It is seen that the autoregulation was impaired (shaded areas) in the severely injured areas 3 days after the injury when the IVP was 20 mm Hg. Six days after the injury, about 1 hour before the operation, when IVP had increased to 40 mm Hg, autoregulation seemed to be preserved in the most severely injured areas temporally. The CSF lactate was low, in agreement with the fact that the patient had a localized cortical lesion and no brain-stem symptoms (cf. Fig. 3).

In five studies, both autoregulation and hyperventilation responses were impaired. Two patients had first a period with impaired hyperventilation and preserved autoregulation response, and then a period in which the autoregulation was also affected. In the remaining 17 studies the hyperventilation response was normal. Thus, dissociation between cerebrovascular autoregulation and CO₂ response was common in our series (Fig. 5).

Discussion

It is well known from animal studies²⁹,³⁴ and from studies in man²⁵ that brain injury is followed by impairment of the cerebral vasomotor regulation. This impairment takes the form of disturbances in autoregulation and CO₂ response and reactive hyperemia. As mentioned before, it is also well known that the autoregulation is very sensitive to brain damage, whereas the CO₂ response is less susceptible to damage.

Concerning the cerebral vasomotor regulation in severe brain injury in man, our study showed:

1. The autoregulation was preserved in the most injured areas of the cerebral cortex during the first few days after the initial neurosurgical operation, which usually involved the removal of a hematoma, if the patient was deeply comatose. At that time the tissue acidosis must be most pronounced.
2. Typically, the autoregulation was preserved in the most severely injured areas, such as the hyperemic areas, areas in which the tissue acidosis must be expected to be most pronounced,⁶,¹⁸,⁴⁰ but at the same time it was impaired in the areas described by the neurosurgeon as normal or slightly contused.
3. The autoregulation became progressively impaired as the patients recovered, but
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FIG. 5. Case 6. Dissociated autoregulation and CO₂ reaction seen in a 66-year-old man, who on admission had an acute subdural hematoma in the left frontal and temporal regions. Lacerations were seen in the frontal and temporal poles. The hematoma was removed at the initial craniotomy. During the first week he was deeply comatose with attacks of decerebrate rigidity. The flow measurement was performed on the third day. It is seen that the autoregulation was preserved, whereas the hyperventilation response was abolished. Actually, an increase in rCBF was seen in the most damaged areas in the temporal pole during hyperventilation (shaded areas). The decrease in IVP during the hyperventilation suggests that some areas of the brain must have responded to the CO₂ decrease, and it may be supposed that the flow increase seen in the most severely damaged areas temporally was due to a counter-steal phenomenon. The CSF lactate was high (3.5 mmol/liter) on the day of the CBF measurement.

became preserved during clinical deterioration. In patients who died within the first week after trauma, the autoregulation appeared to be preserved until death.

4. In a few patients who were treated with decompression (operation or continuous ventricular drainage) the autoregulation became impaired just after the decompression.

5. In patients with very severe contusion and laceration of the cerebral cortex, the rCBF sometimes decreased in the areas of severe contusion and laceration during the autoregulation test, even at the time when the patients were in a very poor clinical condition. Later, the autoregulation appeared to be preserved and finally, when the patients recovered, impaired (Fig. 3).

6. In patients who had had a relatively long period (days) with attacks of decerebrate rigidity, the autoregulation appeared to be preserved, whereas the CO₂ response was abolished. All had increased CSF lactate.

7. The autoregulation appeared to be preserved in all patients who had CSF lactate above 3.5 mmol/liter, but impaired in cases with CSF lactate below 2.0 mmol/liter (Fig. 7).

8. The two patients who had very low CSF pH (6.66 or 7.12) had preserved autoregulation.

9. Impaired CO₂ response was seen only in deeply comatose patients with attacks of decerebrate rigidity.

Thus, our results demonstrate that the autoregulation appeared to be preserved in patients with acute severe brain injury in the most severely damaged areas during the periods in which the patients were in the poorest clinical condition and had the most
pronounced CSF lactic acid acidosis. In addition, the results show that dissociation between preserved autoregulation and impaired CO₂ response is a common phenomenon, as it was found in patients who were comatose with attacks of decerebrate rigidity and high CSF lactate. These paradoxical observations arouse suspicion that the preserved autoregulation seen in the severely injured brain tissue may be a false autoregulation which is not caused by the active vasoconstriction in response to an increase in blood pressure seen in normal brain tissue.

The dissociation between autoregulation and CO₂ response has previously been described in both head injuries, and in other pathological conditions. It has given rise to discussion as to whether the preserved autoregulation seen in severely pathological brain tissue with impaired CO₂ response could be a false autoregulation due to a rise in the ICP occurring simultaneously with the rise in the arterial blood pressure during the hypertension, and thus causing the effective cerebral perfusion pressure to remain unchanged. Like other authors who measured rCBF, ICP, and SAP simultaneously in patients with severe head injury, we rarely saw significant increases in IVP during angiotensin infusion (Fig. 6). Because of this lack of an IVP increase during the autoregulation tests, both Bruce, et al., and Fieschi, et al., concluded that false autoregulation was an uncommon phenomenon in patients with head injury. In view of the results of our studies in which we had the opportunity to follow the autoregulation during the different clinical phases in each patient, and to compare the autoregulation response in each area with the nature of the initial cortical lesion, we are convinced that the autoregulation seen in severely injured and acidotic brain tissue with impaired (or normal) CO₂ response must be false.

In patients with severe local cortical lesions we suggest, like Bruce and Fieschi, that the false autoregulation most likely may be caused by increases in local tissue pressure in the severely damaged areas during the hypertension, leaving the perfusion pressure almost unchanged. The finding that the autoregulation became impaired in patients in a very poor clinical condition when decompression was started supports the theory, as the decompression may neutralize an increase in tissue pressure. The local decrease in rCBF during the autoregulation tests seen in patients with very severe cortical lesions (laceration) may suggest that in these patients the increase in tissue pressure may have been so pronounced that the perfusion pressure decreased during the tests. As we have not been able to measure the local tissue pressure but only the IVP, we cannot prove this theory, but only make this suggestion, and, moreover, refer to the results of animal experiments in which repeated trauma of the head resulted in a state of low flow and apparent autoregulation with abolished CO₂ response.

The cause of the increase in tissue pressure in the contused and acidotic brain tissue during hypertension could be the development of...
FIG. 7. Relation between CSF lactate and autoregulation. It is seen that all cases with CSF lactate above 3.5 mmol/liter have preserved (false) autoregulation, whereas patients with CSF lactate below 2.0 mmol/liter have impaired autoregulation.

congestion and edema focally. Thus, Marshall, et al., observed that marked brain swelling occurred promptly in injured brain tissue of the exposed brain when the SAP was increased. They postulated that the brain swelling was caused by reduced cerebral autoregulation in the injured brain tissue. Unlike us, they always provoked a flow increase during hypertension, whereas we did not see any significant changes in the blood flow in the cases suggested to have "false" autoregulation. This discrepancy could be due to the fact that they studied the exposed brain, whereas we studied the brain in the intact skull, in which the flow increase will be counteracted by an increase in the tissue pressure owing to congestion and development of edema, thus leaving the perfusion pressure almost unchanged. In the few of our patients in whom decompression was performed we also saw flow increase during hypertension. In addition, differences in the degree of cerebral vasoparalysis in their cases and ours could result in different outcomes.

However, if the theory of "false autoregulation" is correct, it is puzzling that focal brain swelling did not increase the IVP significantly. The following explanations might be suggested. As IVP is a sort of mean pressure for the cerebrum, a limited focal pressure change could be too small to influence the IVP appreciably. In our series, the blood pressure was only increased by 20% to 35% during the hypertension, because we wanted to avoid the development of edema, and we stopped the blood pressure increase if the IVP increased more than 10 mm Hg. Thus, in one patient with high IVP (about 40 mm Hg) the autoregulation test had to be abandoned owing to a significant IVP increase. This may have limited the development of edema to involve only the most injured areas. It was thus a characteristic feature that the autoregulation could (apparently) be preserved, for example, in a very contused temporal lobe, and at the same time be impaired in the frontal or parietal region described by the neurosurgeon as only slightly
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![Diagram: Control and Hyperventilation]

**Fig. 8. Case 12. Hyperventilation response in a 14-year-old boy who on admission had an acute subdural hematoma in the right temporal and frontal region and, in addition, diffuse edema. The measurements were performed before (upper) and after (lower) a period with high intraventricular pressure (basic levels about 45 mm Hg and numerous plateau waves unresponsive to hyperventilation) and attacks of decerebrate rigidity. On the eighth day, carotid angiography revealed a mass lesion in the right temporal region. A decompression operation in this region disclosed severe edema of the temporal region, but neither a hematoma, nor malacia was found. It is seen that the hyperventilation was preserved (shaded areas) before the period with attacks of decerebrate rigidity, but 3 days later the hyperventilation was preserved (shaded areas) only in the temporal regions of decompression. The CSF lactate was high just before the period with attacks of decerebrate rigidity, but was not measured during or just after this period.**

damaged. In addition, the IVP changes during the autoregulation tests must be determined by the pressure changes in the unmeasured as well as in the measured areas. In patients with normal autoregulation, for instance, patients with migraine of “low-pressure” hydrocephalus, we have seen a small decrease in the IVP during the autoregulation tests, and we regard this as a sign of preserved autoregulation which decreases the cerebral blood volume. In patients with severe head injury, we observed a change of only a few millimeters of mercury in IVP during the tests, either as an increase or as a decrease in IVP, but no correlation was found between either impaired or “false” autoregulation and an IVP increase (Fig. 6). We suggest that the reason for the latter is that some of the unmeasured areas of the brain had normal autoregulation, and that the decrease in pressure in these areas compensates for the increase in tissue pressure in the severely damaged, measured areas which were supposed to have “false” autoregulation. The IVP thereby remains unchanged, slightly decreased, or increased depending on whether areas with normal autoregulation or areas with impaired or “false” autoregulation dominate. Furthermore, no patients in our series had IVP above 45 mm Hg during the CBF measurements; so they were all situated in the left part of the pressure/volume curve, and an increase in brain volume caused by local brain swelling need not influence the IVP very much. Finally, the progression of the edema could be slow enough to release compensatory mechanisms such as increased CSF outflow preventing an IVP increase during the gradual blood pressure increase in the last 10 to 15 minutes before the CBF measurements.

In patients with brain-stem symptoms, but without severe local cortical lesions, the autoregulation was preserved diffusely if they had had attacks of decerebrate rigidity for a longer period, whereas it was impaired if they had only had attacks of decerebrate rigidity for hours. All patients with preserved auto-
regulation had severe CSF lactic acidosis and impaired CO₂ response, which gives evidence of vasoparalysis owing to tissue acidosis, but they also had low rCBF and low IVP (below 20 mm Hg), and they had no increase in IVP during hypertension. If the diffusely preserved autoregulation in these patients is false, a mechanism other than that suggested for the cortical lesions must exist. We have no idea about this mechanism, but can only point out that in these patients the connection between the brain stem and the cortex was abolished.

The hyperventilation response was abolished in patients who had attacks of decerebrate rigidity, also in those who apparently did not have significant cortical lesions, as they had normal angiography and the cortex appeared to be normal as seen through burr holes on both sides. If the attacks of decerebrate rigidity had been of long duration (days), the autoregulation was preserved. This need not reflect a dual control of the cerebrovascular regulation, as the autoregulation may be false, but it probably indicates that the regulation may be controlled from the brain stem.

The clinical implication of our study is that an increase in blood pressure must be avoided in patients with severe brain injury, because of impairment of the autoregulation which is the basis for the occurrence of brain swelling during hypertension. However, the level of PaCO₂ in patients with attacks of decerebrate rigidity seems to be of minor importance. Obviously, a sufficient oxygen supply still renders moderate hyperventilation necessary, but pronounced hyperventilation may be unnecessary, or may even be contraindicated as it changes cerebral metabolism in the anaerobic direction. This corresponds with the clinical observation we made, namely, that, in patients with multiple attacks of decerebrate rigidity, increases in the IVP became unresponsive to treatment with hyperventilation.

References

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