Cerebral blood flow, vasoreactivity, and oxygen consumption during barbiturate therapy in severe traumatic brain lesions

CARL-HENRIK NORDSTRÖM, M.D., PH.D., KENNETH MESSETER, M.D., PH.D., GÖRAN SUNDBÄRG, M.D., WILHELM SCHALÉN, M.D., MATS WERNER, M.D., AND ERIK RYDING, M.D., PH.D.

Departments of Neurosurgery, Anesthesiology, and Neurophysiology, University Hospital, Lund, Sweden

Mean hemispheric cerebral blood flow (CBF) and intracranial pressure (ICP) were measured in 19 severely head-injured patients treated with barbiturate coma. The CBF was calculated from the clearance of tracer substance monitored by extracranial scintillation detectors after intravenous administration of xenon-133. In 11 of the patients cerebral arteriovenous oxygen differences were measured simultaneously. In all patients the effects of pronounced hyperventilation were recorded prior to initiation of barbiturate treatment. A normal CBF response to hyperventilation (ΔCBF/ΔPaCO₂ > 1) was obtained in eight patients. In these patients induction of barbiturate coma was accompanied by physiological decreases in CBF and in the calculated cerebral metabolic rate of oxygen (CMRO₂); they also exhibited a rapid and lasting decrease in ICP. A decreased or an abolished CO₂ reactivity was recorded (ΔCBF/ΔPaCO₂ < 1) in 11 patients. In 10 of these 11 patients the physiological decreases in CBF and CMRO₂ were not obtained during barbiturate treatment and the decrease in ICP was transitory. This study demonstrates a correlation between cerebral vasoreactivity, physiological effects of barbiturate therapy, and clinical outcome.

KEY WORDS • head injury • cerebral blood flow • autoregulation • cerebral metabolism • barbiturate

Brain ischemia is probably the single most important mechanism in the production of secondary dysfunction and damage after severe head injury. From experimental investigations it is known that, in ischemia, the perturbation of the cellular energy state, the degree of intracellular acidosis, and the ensuing derangements of ionic homeostasis and phospholipid metabolism govern the extent of brain damage. Thus, a logical approach to the intensive care of patients with severe traumatic brain lesions would be to reduce intracranial pressure (ICP), to reduce the cerebral metabolic rate, and to increase intracellular pH. Barbiturate anesthesia brings about all three effects and is consequently of clinical interest in situations with a dangerous increase in ICP. However, although some clinical studies have shown improved outcome in severely head-injured patients treated with high doses of pentobarbital, other investigators have not confirmed these results. These diverging experiences probably illustrate the difficulties in performing ordinary clinical trials in complex situations like traumatic brain injuries.

The intent of the present investigation was twofold: first to explore whether the physiological (potentially beneficial) effects of barbiturate coma are also obtained in patients with very severe traumatic brain lesions, and second to investigate whether it is possible to identify those patients who would benefit from barbiturate therapy by careful recording of the physiological parameters of cerebral blood flow (CBF), cerebral vasoreactivity, and cerebral metabolic rate. The present study is thus an extension of our previously presented preliminary observations in patients with severe head trauma.

Clinical Material and Methods

Patient Population

The Department of Neurosurgery, University Hospital, Lund, is the only neurosurgical clinic in an area with almost 1.5 million inhabitants. Annually, 70 to 80 patients with severe traumatic brain injuries (classification according to Jennett, et al.) are treated in this department. About 90% of these patients are trans-
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**Table 1**

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yrs)</th>
<th>Coma Grade*</th>
<th>Lesion</th>
<th>GOS Score†</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>59</td>
<td>7</td>
<td>4</td>
<td>epidual</td>
</tr>
<tr>
<td>2</td>
<td>21</td>
<td>7</td>
<td>4</td>
<td>subdural</td>
</tr>
<tr>
<td>3</td>
<td>32</td>
<td>7</td>
<td>4</td>
<td>intracerebral</td>
</tr>
<tr>
<td>4</td>
<td>17</td>
<td>6</td>
<td>5</td>
<td>no mass</td>
</tr>
<tr>
<td>5</td>
<td>16</td>
<td>6</td>
<td>5</td>
<td>no mass</td>
</tr>
<tr>
<td>6</td>
<td>18</td>
<td>7</td>
<td>4</td>
<td>no mass</td>
</tr>
<tr>
<td>7</td>
<td>23</td>
<td>6</td>
<td>5</td>
<td>no mass</td>
</tr>
<tr>
<td>8</td>
<td>15</td>
<td>7</td>
<td>4</td>
<td>no mass</td>
</tr>
</tbody>
</table>

CO2 reactivity preserved

| 9        | 30        | 7           | 4      | subdural   | 1          |
| 10       | 43        | 7           | 4      | subdural   | 2          |
| 11       | 54        | 7           | 4      | intracerebral | 2         |
| 12       | 18        | 7           | 4      | intracerebral | 1         |
| 13       | 15        | 7           | 4      | no mass    | 1          |
| 14       | 23        | 6           | 5      | no mass    | 1          |
| 15       | 16        | 7           | 4      | no mass    | 1          |
| 16       | 20        | 7           | 4      | no mass    | 1          |
| 17       | 11        | 7           | 4      | no mass    | 1          |
| 18       | 38        | 6           | 5      | no mass    | 3          |
| 19       | 28        | 6           | 5      | no mass    | 5          |

CO2 reactivity impaired

* Coma level was graded according to the Lund Coma Scale (LCS): Grade 5 = no response to verbal commands, reacts to pain by reflex withdrawal; Grade 6 = reacts to pain by abnormal flexion; Grade 7 = reacts to pain by abnormal extension; Grade 8 = no reaction to pain. Corresponding Glasgow Coma Scale (GCS) scores are given for comparison.

† Glasgow Outcome Scale (GOS) is described by Jennett and Bond: 1 = dead; 2 = persistent vegetative state; 3 = severe disability; 4 = moderate disability; 5 = good recovery.

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Barbiturate coma was induced by intravenous infusion of thiopental (5 to 11 mg · kg⁻¹) followed by a continuous infusion of 4 to 8 mg · kg⁻¹ · hr⁻¹ to achieve and maintain a burst-suppression pattern on the electroencephalogram (EEG). The treatment was continued until the ICP decreased and remained stable at a level below 20 mm Hg for at least 12 hours or until the treatment was considered to be ineffective. In order to secure a cerebral perfusion pressure (CPP) above 60 mm Hg, adequate amounts of crystalloid and colloid fluids were given prior to and during the treatment. In most patients continuous infusion of dopamine (5 µg · kg⁻¹ · min⁻¹) was given to maintain a sufficient CPP. However, only two patients were given dopamine before or during CBF measurements.

Cerebral Blood Flow Measurement

Mean hemispheric CBF was determined after intravenous administration of 0.5 to 0.7 GBq xenon-133 (¹³³Xe) followed by a rapid 20-ml injection of isotonic saline. Clearance of the tracer substance was monitored by two extracranial scintillation detectors covering both hemispheres and from the expired air utilizing mobile equipment.* The validity and reproducibility of the CBF measurements with this equipment has been reported previously. In 11 of the patients simultaneous measurements of regional washout curves were obtained from eight additional scintillation detectors positioned on both sides of the head. Although regional differences were observed in these patients, hyperemia and reduced flow as well as CO₂ reactivity were global in distribution in accordance with the observations by Obrist, et al. This report focuses on the global CBF measurements.

The CBF was calculated as the initial slope index (ISI) from the early segment of the clearance curves by conventional bicompartamental analysis and a delayed-start fit time. Since the ISI is influenced by both the gray and white matter flow, a ¹³³Xe partition coefficient

FIG. 1. Mean hemispheric cerebral blood flow (CBF) in eight patients with preserved (left) and in 11 patients with impaired (right) CO₂ response to hyperventilation. Preserved CO₂ reactivity was defined as \( \Delta \text{CBF}/\Delta \text{PaCO}_2 \geq 1 \). Each pair of circles represents measurements in one patient during moderate and pronounced hyperventilation. Values are mean ± standard error of the mean.

of 1.0 was used for the calculations. In pathological situations such as severe brain lesions, shifts in the relative size of the gray and white matter flow compartments are known to occur.\(^1,3\) This compartment shift may cause erroneous estimations of the gray matter flow. The ISI was used for the present CBF calculations since it has been shown to be less sensitive to shifts between the gray and white matter flow compartments.\(^3\) The calculated CBF values corrected for background and remaining \(^{133}\text{Xe} \) activity were presented on a computer print-out shortly after each measurement.

**Patient Study Protocol**

To reduce stress response and maintain adequate muscle relaxation, all patients were given fentanyl (0.1 mg) and pancuronium (6 to 7 mg) intravenously prior to the CBF measurements. End-tidal CO₂ concentration was continuously monitored in all patients to ensure stability of \( \text{PaCO}_2 \). Repeated arterial samples were analyzed for \( \text{PaCO}_2 \), \( \text{PaO}_2 \), and pH in association with each CBF measurement. The hemoglobin concentration was determined immediately before each sequence of CBF recordings. The results of the blood gas analyses were corrected for deviations in body temperature from 37°C. Ventilation was controlled with a respirator in all patients, and end-tidal CO₂ was monitored continuously by means of a capnograph.\(^1\)

For calculation of CO₂ reactivity, CBF was determined before and after reduction in \( \text{PaCO}_2 \). Inhalation of CO₂ (or reduction in ventilation) was not used in any patient. Tidal volume was increased by about 20% after the first CBF measurement. The second measurement was performed approximately 15 minutes after the increase in hyperventilation was begun. The physiological CBF responses to changes in \( \text{PaCO}_2 \), measured with the same equipment, have been described previously.\(^2,3\) Measurement of CBF was performed following administration of thiopental according to the principles described above. Ventilation was adjusted prior to the measurement in order to obtain a \( \text{PaCO}_2 \) similar to that of the first CBF measurement. Following administration of thiopental, CBF was measured when the patient’s EEG recording had reached the level of “burst suppression.”

In most patients a catheter was inserted into the internal jugular vein, and the placement of the catheter tip at the base of the skull was verified by x-ray examination. Two minutes after the start of the CBF measurement, double samples of arterial and venous blood were collected simultaneously for determination of the total arterial and venous oxygen content and subsequent calculation of the arterial-venous (AV) oxygen difference (AVDO₂). The AVDO₂ was calculated with correction for physically dissolved oxygen, according to the formula:

\[
\text{AVDO}_2 = \frac{1.34 \times \text{Hb} \times \text{O}_2 \text{ sat}(AV) - 0.003 \times \text{pO}_2(AV)}{100}
\]

where Hb = hemoglobin and \( \text{O}_2 \text{ sat} = \) oxygen saturation. The cerebral metabolic rate of oxygen (CMRO₂) was calculated as the product of average global CBF and AVDO₂. Due to technical difficulties, a complete series of simultaneous recordings of CBF and AVDO₂ during moderate hyperventilation, severe hyperventilation, after return to moderate hyperventilation, and following induction of barbiturate treatment was possible in only 11 of the 19 patients.

Arterial blood pressure and ICP were recorded continuously in all patients. Cerebrovascular resistance (CVR) was calculated from mean arterial blood pressure (MABP), mean ICP, and CBF according to the formula: CVR = (MABP - mean ICP)/CBF.

**Statistical Methods**

All values are given as mean ± standard error of the mean (SEM). Student’s t-test for paired data was used for comparison between physiological variables within groups (control data vs. effects of hyperventilation and barbiturate therapy, respectively). Intergroup comparison (preserved CO₂ reactivity group vs. impaired CO₂ reactivity group) was evaluated using the t-test for unpaired data. Inter- or intragroup comparison of data presented as a percentage of controls was carried out on the calculated arithmetic differences. A calculated difference of \( p < 0.05 \) was considered to be statistically significant.

**Results**

In our previous report it was found that the mean CBF response to changes in \( \text{PaCO}_2 \) (\( \Delta \text{CBF}/\Delta \text{PaCO}_2 \)),
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Physiological parameters in patients with preserved and impaired CO₂ reactivity before and after hyperventilation

<table>
<thead>
<tr>
<th>Parameter†</th>
<th>Preserved (8 cases)</th>
<th>Impaired (11 cases)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Hypervent.</td>
</tr>
<tr>
<td>temperature (°C)</td>
<td>37.3 ± 0.2</td>
<td>37.4 ± 0.3</td>
</tr>
<tr>
<td>hemoglobin (gm -1)</td>
<td>116 ± 4</td>
<td>121 ± 6</td>
</tr>
<tr>
<td>PaCO₂ (mm Hg)</td>
<td>32.7 ± 1.1</td>
<td>27.1 ± 1.0</td>
</tr>
<tr>
<td>PaO₂ (mm Hg)</td>
<td>142 ± 13</td>
<td>134 ± 14</td>
</tr>
<tr>
<td>MABP (mm Hg)</td>
<td>97 ± 4</td>
<td>93 ± 4</td>
</tr>
<tr>
<td>ICP (mm Hg)</td>
<td>23 ± 3</td>
<td>15 ± 3</td>
</tr>
<tr>
<td>CVR (mm Hg·ml⁻¹·100 gm⁻min⁻¹)</td>
<td>2.0 ± 0.2</td>
<td>3.4 ± 0.7</td>
</tr>
<tr>
<td>CBF (ml·100 gm⁻¹·100 gm⁻min⁻¹)</td>
<td>40 ± 4</td>
<td>28 ± 4</td>
</tr>
</tbody>
</table>

* Statistical comparisons are as follows (n.s. = not significant):

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Preserved Control vs. Impaired Control</th>
<th>Preserved Control vs. Hyperventilation</th>
<th>Impaired Control vs. Hyperventilation</th>
</tr>
</thead>
<tbody>
<tr>
<td>temperature</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
<tr>
<td>hemoglobin</td>
<td>n.s.</td>
<td>p &lt; 0.0005</td>
<td>p &lt; 0.0005</td>
</tr>
<tr>
<td>PaCO₂</td>
<td>n.s.</td>
<td>p &lt; 0.0005</td>
<td>p &lt; 0.0005</td>
</tr>
<tr>
<td>PaO₂</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
<tr>
<td>MABP</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
<tr>
<td>ICP</td>
<td>n.s.</td>
<td>p &lt; 0.0005</td>
<td>p &lt; 0.01</td>
</tr>
<tr>
<td>CVR</td>
<td>n.s.</td>
<td>p &lt; 0.0005</td>
<td>n.s.</td>
</tr>
<tr>
<td>CBF</td>
<td>n.s.</td>
<td>n.s.</td>
<td>p &lt; 0.005</td>
</tr>
</tbody>
</table>

† Hypervent = hyperventilation; MABP = mean arterial blood pressure; ICP = intracranial pressure; CVR = cerebrovascular resistance; CBF = cerebral blood flow. Values are means ± standard error of the means.

calculated with the same technique, was 2.2 ± 0.6 ISI units in healthy, awake volunteers. In the present study a normal or close to normal CO₂ reactivity (defined as ΔCBF/ΔPaCO₂ ≥ 1) was found in eight patients (Fig. 1 left). In 11 patients ΔCBF/ΔPaCO₂ was less than 1, indicating impairment of cerebral vasoreactivity to hyperventilation (Fig. 1 right). Each patient was assigned to one of these two groups in accordance with our preceding report.

Changes in CBF During Hyperventilation

The physiological variables obtained in the two groups of patients are given in Table 2. There were no significant intergroup differences. The increase in ventilation caused an equivalent significant decrease in PaCO₂ in both groups. In the group with preserved vasoreactivity, the ensuing reduction in CBF as well as the decrease in ICP were highly statistically significant. In the group with impaired CO₂ response, the small increase in CBF was not significant; in spite of this, a significant decrease in ICP occurred, although less pronounced than in the former group. The MABP was not affected by the increase in ventilation in either group. The CVR increased significantly in the group with preserved vasoreactivity and was unchanged in the impaired group.

Changes in CBF During Thiopental Treatment

Physiological parameters before and after induction of thiopental treatment are given for both groups in Table 3. During the hyperventilation test there was already a tendency for the ICP to be higher in patients with impaired vasoreactivity (Table 2). This intergroup difference reached statistical significance (p < 0.05) before initiation of barbiturate treatment. Except for a small clinically irrelevant difference in body temperature, physiological parameters showed no significant intergroup differences. In the group with preserved vasoreactivity, barbiturate coma therapy was accompanied by a highly significant decrease in CBF and a significant decrease in ICP. A fall in MABP also occurred; however, since CVR increased significantly, the measured decrease in CBF was not caused by the fall in MABP. In the group with impaired vasoreactivity, the small increase in measured CBF was not significant and no significant changes occurred in other physiological parameters.

Changes in Cerebral Oxygen Extraction

For technical reasons, a complete series of simultaneous measurements of CBF and AVDO₂ during moderate hyperventilation, severe hyperventilation, after return to moderate hyperventilation, and following induction of thiopental treatment was possible in only
five of the patients with preserved and six of the patients with impaired vasoreactivity. Figure 2 shows the percentage changes in CBF, AVDO₂, and CMRO₂ following hyperventilation in patients with preserved as well as impaired CO₂ reactivity. The control values before hyperventilation for patients with preserved vasoreactivity were (means ± SEM): CBF 38 ± 8 ml · 100 gm⁻¹ · min⁻¹; AVDO₂ 4.6 ± 0.7 vol%; and CMRO₂ 1.9 ± 0.4 ml · 100 gm⁻¹ · min⁻¹. For patients with impaired vasoreactivity, control values were: CBF 36 ± 14 ml · 100 gm⁻¹ · min⁻¹; AVDO₂ 5.5 ± 1.7 vol%; and CMRO₂ 2.2 ± 0.6 ml · 100 gm⁻¹ · min⁻¹. The intergroup differences were not significant.

In the group of five patients with preserved vasoreactivity, CBF decreased by 31% (p < 0.0005) during hyperventilation. The group of six patients with impaired vasoreactivity showed no corresponding change in CBF. In the two groups of patients, AVDO₂ increased by 33% (p ≤ 0.025) and 29% (p ≤ 0.005), respectively. Consequently, the calculated CMRO₂ remained unchanged in patients with preserved vasoreactivity but exhibited an increase of 16% (p ≤ 0.005) in patients with impaired CO₂ reactivity. In the former group CVR increased by 53% (p ≤ 0.0005) and in the latter group CVR remained unchanged.

Figure 3 illustrates the changes in CBF, AVDO₂, and CMRO₂ during thiopental treatment. Control values for patients with preserved vasoreactivity were: CBF 35 ± 7 ml · 100 gm⁻¹ · min⁻¹; AVDO₂ 4.9 ± 0.6 vol%; and CMRO₂ 1.8 ± 0.4 ml · 100 gm⁻¹ · min⁻¹. For patients with impaired response, the corresponding values were: CBF 35 ± 16 ml · 100 gm⁻¹ · min⁻¹; AVDO₂ 5.2 ± 1.3 vol%; and CMRO₂ 1.9 ± 0.7 ml · 100 gm⁻¹ · min⁻¹. The intergroup differences were not significant. During barbiturate treatment, CBF decreased by 29% (p < 0.005) in patients with preserved CO₂ reactivity; CVR increased by 38% (p ≤ 0.025) in these patients. In the group of patients with impaired vasoreactivity, a relatively small decrease in CBF (12%) was recorded; although this decrease was statistically significant (p ≤ 0.025), it was just a reflection of the decrease in CPP since there was no increase in CVR. In patients with preserved CO₂ reactivity, AVDO₂ was unaffected by barbiturate treatment. In the group with impaired reactivity, a statistically nonsignificant increase in AVDO₂...
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was recorded (8%). The calculated CMRO₂ consequently decreased significantly in patients with preserved vasoreactivity (28%; p ≤ 0.025) and remained unchanged in patients with impaired reactivity.

Clinical Outcome

Table 1 illustrates the outcome according to the Glasgow Outcome Scale and its relationship to cerebral vasoreactivity. Of eight patients with preserved CO₂ reactivity, four had a good recovery, two remained moderately disabled, and two died. In 11 patients with impaired or abolished CO₂ reactivity, seven died, two remained in a persistently vegetative state, and only one had a good recovery.

Discussion

Cerebral ischemia is a major factor contributing to secondary damage in severe traumatic brain lesion. In these patients ischemia is caused by direct brain laceration, by an increase in ICP and a decrease in CPP, by cerebral herniations, and by stretching and distortion of the cerebral arteries. Consequently, an increase in ICP is closely correlated to the risk of mortality. In accordance with previous clinical studies, in the present investigation barbiturate therapy was primarily used to reduce ICP and to maintain or improve CPP.

When given in anesthetic concentrations under physiological conditions, all barbiturates studied showed a decrease in CBF, CMRO₂, and cerebral glucose utilization of about 50%. In patients with severe traumatic brain lesions it is known that marked variations in CBF occur, ranging from extremely low values to pronounced hyperemia. It is also known that, in these patients, CMRO₂ is reduced and that this decrease in energy consumption parallels the depth of coma. In the investigation by Obrig, et al., patients in deep coma (Glasgow Coma Scale score < 7) had a reduction in CMRO₂ below 50% of normal (normal value 3.3 ml - 100 gm⁻¹ - min⁻¹ according to Kety and Schmidt). Consequently, it is by no means obvious that barbiturate anesthesia should cause a significant decrease in CBF and CMRO₂ in patients in deep coma.

From experimental investigations it is known that, in cerebral ischemia, besides the perturbation of energy metabolism and the ensuing derangement of ionic homeostasis, the degree of intracellular acidosis significantly contributes to neuronal damage. It is also known that, under physiological conditions, barbiturate anesthesia increases intracellular pH by 0.05 to 0.09 units and that this intracellular alkalosis persists during prolonged anesthesia. The increase in intracellular pH is caused by reduced production of pyruvate and lactate through inhibition of phosphofructokinase. In hypoglycemia and hypercapnia, a similar inhibition of phosphofructokinase occurs leading to oxidation of endogenous carbohydrate and amino acid substrates. In barbiturate anesthesia, however, the oxidation of endogenous substrates is a transient phenomenon. It is thus reasonable to assume that the protective effect of barbiturate anesthesia in ischemia is partly due to the increase in intracellular pH through the decreased production of lactate. Unfortunately, it is presently not possible to measure cerebral intracellular pH during intensive care. However, if barbiturate treatment can be shown to decrease the cerebral metabolic rate in patients with severe brain injuries, it is very probable that the inhibition of phosphofructokinase, the reduced production of lactate, and the increase in intracellular pH also take place.

The objectives of the present investigation were based upon these theoretical considerations. The investigation was thus designed to explore whether barbiturate anesthesia is accompanied by a decrease in CBF and CMRO₂ in patients with severe traumatic brain injuries and whether changes in these physiological parameters are correlated to reduction in ICP and to clinical outcome. In accordance with our previous report, the change in CBF during pronounced hyperventilation was measured in all patients (Table 2). Patients with a calculated ΔCBF/ΔPaCO₂ of less than 1 were assigned to the group with impaired CO₂ reactivity. Since measured regional differences in CBF and CO₂ reactivity appeared to be small, only global values are given. However, it may be that significant regional inhomogeneities in CBF and vasoreactivity exist in areas too small to be detected with the present CBF technique. Regions with low CBF tend to be “overlooked” with the (133)Xe technique. This results in an overestimation of global CBF when the flow is inhomogeneous.

It is well established that under physiological conditions the decrease in CBF during hyperventilation is associated with an unchanged CMRO₂. In the present study the decrease in CBF during hyperventilation in patients with preserved CO₂ reactivity was associated with an equivalent increase in AVDO₂. The calculated CMRO₂ remained constant in these patients (Fig. 2). However, in patients with impaired CO₂ reactivity a significant increase in AVDO₂ was measured, although CBF remained constant. Consequently, the calculated CMRO₂ increased significantly (Fig. 2). This observation must be interpreted as an artifact, presumably due to an overestimation of the CBF. Thus, the increase in AVDO₂ during hyperventilation indicates that the vascular areas with impaired vasoreactivity are intermingled with regions with preserved CO₂ reactivity too small to be detected by the available CBF technique. The problems of measuring CBF and calculating CMRO₂ in these pathological conditions are not easily circumvented. Thus, the original inert gas method, although valid during physiological conditions, may also be subjected to criticism if regions with widely different flow rates exist or if the tissue contains arteriovenous shunts. Presently, we must accept that interpretation of the changes in CBF and CMRO₂ during neurosurgical intensive care is limited by methodological difficulties.
In patients with preserved CO₂ reactivity, thiopental anesthesia was associated with significant decreases in ICP, CBF (Table 3), and CMRO₂ (Fig. 3). Thus, although energy utilization was already reduced in these patients, a further significant reduction in energy consumption was obtained. In accordance with the discussion above, it may be justified to assume that in these patients an increase in intracellular pH also occurred. The rapid and lasting decrease in ICP was in all probability caused by a decrease in intracranial blood volume. In the group of patients with impaired CO₂ reactivity, no significant changes in ICP, CBF (Table 3), or CMRO₂ (Fig. 3) were obtained during thiopental anesthesia. In view of the difficulties in interpreting CBF and CMRO₂ in these patients during hyperventilation, the observations can only be explained tentatively. Thus, it is possible that in these patients no further reduction in CMRO₂ was obtained during barbiturate treatment. However, we cannot exclude the possibility that restricted areas reacting with a decrease in blood flow and energy utilization were mixed with areas lacking physiological response to barbiturate therapy.

Table 3 illustrates that during barbiturate therapy a statistically significant decrease in ICP and increase in CVR was obtained only in the group of patients with preserved vasoreactivity. With one exception (Case 15, Table 1) the decreases in ICP in patients with impaired vasoreactivity were short-lasting. The patient in Case 15 exhibited a pronounced decrease in CBF and CMRO₂ during barbiturate therapy, although the preceding CO₂ response had been impaired. Thus, in the present series a correlation was obtained between the effects of barbiturate therapy on CBF, CMRO₂, ICP, and clinical outcome.

It is concluded that, in patients with severe traumatic brain lesions and a dangerous increase in ICP, measurements of CBF and CO₂ reactivity give information regarding the usefulness of barbiturate therapy and the prognosis for the patient. Thus, in patients with preserved cerebral vasoreactivity, barbiturate coma therapy was accompanied by physiological (probably beneficial) decreases in ICP, CBF, and CMRO₂. In patients with impaired vasoreactivity, the methodological difficulties must be recognized. However, in these patients the physiological decreases in CBF and CMRO₂ were not found, a persisting decrease in ICP was not obtained, and the prognosis was extremely bad.

References
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Address reprint requests to: Carl-Henrik Nordström, M.D., Department of Neurosurgery, University Hospital, S-221 85 Lund, Sweden.

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