Experimental head injury in the rat

Part 3: Cerebral blood flow and oxygen consumption after concussive impact acceleration

BENGT NILSSON, M.D., AND CARL-HENRIK NORDSTRÖM, M.D.

Brain Research Laboratory, and Department of Neurology and Neurosurgery, University Hospital, Lund, Sweden

Cerebral blood flow (CBF) and oxygen consumption (CMRO2) were determined during the immediate posttraumatic period in rats subjected to concussive impact acceleration. According to previous studies an impact of 9 m/sec velocity elicited typical and marked symptoms of experimental concussion and often a prolonged comatose state, accompanied by cerebral metabolic signs of energy failure. During the immediate concussive response there was an increase of the CBF, followed within the next few minutes by a decrease to about one-third of normal flow, and then by a tendency toward normalization of flow 20 to 40 minutes posttrauma. Simultaneous measurements of cerebral oxygen extraction indicated an increase of the CMRO2 during the first minute. During the ischemic phase oxygen extraction increased, but the lowest CBF values were only partially compensated for, and normal oxygen availability could not be maintained. The combined data, including cerebrospinal fluid pressure measurements, indicated primary cerebrovascular effects of the concussive trauma. These vasomotor effects may induce critical cerebral ischemia and thus profoundly influence posttraumatic cerebral function, and cause irreversible damage.

KEY WORDS • experimental concussion • cerebral blood flow • cerebral oxygen consumption • vasoconstriction

In head trauma, the mechanical influence upon the cerebrovascular system may be as important as the direct neural effects. Vasomotor reactions observed in different experimental models include dilatation of capacitance vessels and changes in the tone of resistance vessels, including failure of autoregulation as well as vasoconstriction. Similar vascular reactions have been found in clinical studies. These changes of vasomotor function may be prime causes of cerebral edema and ischemic lesions. However, changes of the cerebral blood flow (CBF) also appear as adjustments to changes of tissue function. Thus, especially in the clinical situation, it may be difficult to assess to what extent the circulatory alterations are primary or secondary.

In our previous studies the pathophysiology of cerebral concussion was analyzed in rats subjected to a defined, standardized impact acceleration. With this
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model, it was found that concussion symptoms were elicited above a threshold impact velocity of 6 m/sec. With 7 m/sec impacts, there were short-lasting concussion symptoms with rapid recovery. Trauma of 8 or 9 m/sec produced more intense and long-lasting responses, sometimes leading to prolonged comatose states with incomplete or total lack of recovery. The immediate concussive response may involve an excitation of neurons. However, provided no systemic complications (respiratory failure) occurred, the 7 m/sec concussion was usually not accompanied by changes of the energy state of the tissue. Acceleration with 9 m/sec impacts, on the other hand, could give rise to rapidly progressing energy depletion, signifying an imbalance between production and utilization of energy. Angiographic studies showed early vascular narrowing, indicating reduction of CBF as a possible constituent of the immediate trauma reaction.12

The present study was designed to determine CBF and oxygen consumption (CMRO2) in the immediate posttraumatic period, and thereby to evaluate the significance of vascular factors in the pathophysiology of concussive head trauma, severe enough to induce prolonged coma and energy failure.

Material and Methods

Animal Preparation

In male Wistar rats weighing 350 to 420 gm, anesthesia was induced with halothane (2% to 3%). The rats were intubated endotracheally, or tracheotomized, and suxamethonium chloride (Celocurin) was injected intravenously into the femoral vein. When paralyzed, the animals were artificially ventilated with 75% N2O and 25% O2. In all animals, one femoral artery and one femoral vein were cannulated for arterial blood sampling and blood pressure monitoring, and for injection of drugs, respectively. Before experimental or control procedures were started, a respiratory steady state of 20 to 30 minutes was maintained as controlled by repeated determinations of arterial pO2, pCO2 and pH by means of microelectrodes.*


The body temperature was kept close to 37°C. Small amounts of a heparin solution diluted to 50 units/ml, were used for flushing of the catheters.

Acceleration Trauma

Concussive head trauma was delivered as described by Nilsson, et al.4 The animal was placed unrestrained on its back in a plaster bed. The occipital crest was hit from below by a piston weighing 600 gm with a velocity of 7 or 9 m/sec. The impact caused an upward acceleration combined with a backward rotation of the head, and a marked retroflexion of the head-neck junction and upper cervical spine. The concussive response, as estimated from the blood pressure reaction in the anesthetized and paralyzed animal, correlated well with other criteria of experimental concussion. The 7 m/sec trauma usually gave rise to a short-lasting response with complete recovery within a few minutes, while the response to the 9 m/sec trauma was more pronounced and lasted longer, sometimes followed by coma without recovery within the observation periods of 30 to 60 minutes. Subarachnoid effusion of blood, particularly in the cisterna magna, complicated the concussion in about 50% of rats with 7 m/sec impact and in about 90% of those with 9 m/sec impact. Gross intracerebral lesions were not seen.

Regional Cerebral Blood Flow Measurement

Regional cerebral blood flow (rCBF) was determined in 27 animals. Measurement of rCBF lasted for 60 seconds. Four groups of animals were studied at different intervals after a 9 m/sec trauma: four rats at 9 to 15 seconds after the impact, six rats at 2 to 4 minutes, six rats at 10 to 20 minutes, and four rats at 40 minutes after trauma. Seven animals were studied as controls.

The method of rCBF measurement used was a modification of the method of Reivich, et al., using 14C-ethanol as tracer substance, and liquid scintillation counting on dissolved pieces of tissue dissected from various cerebral regions. For this procedure, the rats were provided with additional femoral vein and artery catheters for intravenous isotope infusion and serial arterial sampling, respectively. About 20 μC of 14C-ethanol was infused intravenously during a period of 60 seconds. The integral of the arterial 14C-
ethanol concentration was determined from blood samples collected at 5-second intervals in 50 μl glass capillaries. At 60 seconds, the CBF was stopped by intravenous injection of 1 ml of a saturated potassium chloride solution, which induced instantaneous heart standstill. The rat was immediately decapitated, and the head was frozen in liquid nitrogen.

For counting of arterial 14C-ethanol activity, 25 μl of the blood samples were pipetted into glass vials, and the proper scintillation fluids were added. The frozen brains were dissected in a refrigerated glove box at −15°C. Tissue was taken from eight regions: three cortical regions (corresponding to the territories of the anterior, middle, and posterior cerebral arteries), the caudate nucleus, the thalamus, and cross sections of the mesencephalon, pons, and medulla oblongata. The tissue pieces, weighing 20 to 60 mg, were dissolved in vials, and treated as the blood samples. The beta-activity of the blood and tissue samples was determined in a Nuclear Chicago scintillation counter.† The CBF was calculated from the integrated arterial curve and the tissue activity, using a partition coefficient of 1.14.18 The blood pressure was continuously monitored. Samples were taken for measurements of arterial pO₂, pCO₂, and pH during the CBF measurement.

Cerebral Blood Flow and Cerebral Metabolic Rate for Oxygen

Cerebral blood flow and oxygen consumption (CMRO₂) were measured 20 minutes after acceleration concussion with a 7 m/sec impact in six animals, and with a 9 m/sec impact in seven animals. Serial determinations of arterial and cerebral venous (from the retroglenoid vein42) blood oxygen content were made in 11 animals (seven of which were the same as used for CBF and CMRO₂ measurements), from 30 seconds to 30 minutes after a 9 m/sec trauma. Two to six determinations were performed in each animal.

A xenon-133 (133Xe) desaturation technique was used for these measurements, essentially a modification of the original Kety and Schmidt technique,28 as described by Norberg and Siesjö,44 and Nilsson and Siesjö.42 The animals were prepared with an additional femoral artery catheter for arterial blood sampling, and with a catheter in the retroglenoid vein on one side for cerebral venous blood sampling.42 The acceleration concussion was delivered as described above. During the following 20 minutes, the animals were saturated with 133Xe, administered via the insufflated gas mixture from a rubber balloon containing about 10 mC of 133Xe in 75% N₂O and 25% O₂. After 20 minutes, desaturation was started by disconnecting the rubber balloon; artificial respiration was continued with 75% N₂O and 25% O₂. Arterial and cerebral venous 133Xe activity were determined at the end of the saturation period and at intervals during the desaturation period, usually 20, 40, 60, and 90 seconds, and 2, 4, 7, 10, 15, and 20 minutes after the start of the desaturation. Samples for determination of the total oxygen content in arterial and cerebral venous blood were taken at the end of the saturation period, and at 2 and 10 to 20 minutes after the start of desaturation. The CBF method requires that flow is constant during the period of measurement. The experiment was therefore discarded if the arteriovenous differences in oxygen content (AVDO₂) changed more than 10%. The blood for determination of 133Xe and oxygen content was sampled in 50 μl glass capillaries with both ends drawn into fine tips (acting as a self-sealing device). Donor blood was infused during the period of repeated sampling to keep blood pressure constant. Arterial pO₂, pCO₂, and pH were determined immediately before, and once or twice during, the desaturation period.

The 133Xe activity of the blood samples was determined in a Wallac gamma counter,‡ and the CBF calculated from the integrated arterial and venous desaturation curves,45,44 and with a tissue/blood partition coefficient for 133Xe of 0.82. The oxygen content was determined with the method of Fabel and Lübbers14 (see Borgström, et al.), and the CMRO₂ was calculated from the CBF and AVDO₂.

† Scintillation counter manufactured by Nuclear-Chicago, 2954 Peachtree Road, N.E., Atlanta, Georgia.
‡ Gamma counter manufactured by Wallac OY, Turko, Finland.
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Cerebrospinal Fluid Pressure

For measurement of cerebrospinal fluid pressure (CSFP), we used eight of the animals used for rCBF measurement, and the six measured for CBF and CMRO₂ after 9 m/sec injury. The cisterna magna was punctured just before or during the CBF measurement for determination of CSFP. In five additional animals, the cistern was punctured 5 minutes after trauma, and CSFP was measured during the following 10 minutes. In four animals measurements were performed during the impact acceleration.

After the trauma, CSFP was measured isovolumetrically in the occipital cistern, which was punctured with a fluid-filled thin needle connected to a strain gauge transducer. The needle was left in place for the rest of the experiment to diminish the leakage. The CSFP was also monitored during the impact acceleration through a thin (PE 50), saline-filled catheter, introduced transversely through the cisterna magna and bilaterally fixed with sutures in the neck muscles. The catheter had its tip sealed and was equipped with a side hole which opened into the subarachnoid space. In all measurements free communication was checked by recording the pressure response to manual pressure applied for a short time to the vertex region of the skull.

Statistical Methods

The nonparametric Mann-Whitney U test was used to evaluate differences between the groups. For summarizing data within groups, mean values and SEM are usually given.

Results

Regional Cerebral Blood Flow

The physiological variables and control values for rCBF are shown in Table 1. The rCBF values for cortical regions were about 100 ml/100 gm/min. The lower values obtained on central cerebral hemisphere and brain-stem tissues represented mean values of regions, which were not homogeneous and contained various proportions of gray and white matter. Table 2 shows the correspond-

<table>
<thead>
<tr>
<th>Physiological Variables</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>temperature (°C)</td>
<td>37.4 ± 0.1</td>
</tr>
<tr>
<td>MABP (mm Hg)</td>
<td>128 ± 5</td>
</tr>
<tr>
<td>arterial pO₂ (mm Hg)</td>
<td>128 ± 5</td>
</tr>
<tr>
<td>arterial pCO₂ (mm Hg)</td>
<td>37.0 ± 1.3</td>
</tr>
<tr>
<td>arterial pH</td>
<td>7.31 ± 0.1</td>
</tr>
<tr>
<td>regional cerebral blood flow*</td>
<td></td>
</tr>
<tr>
<td>cortex†</td>
<td></td>
</tr>
<tr>
<td>ACA</td>
<td>102 ± 5</td>
</tr>
<tr>
<td>MCA</td>
<td>100 ± 8</td>
</tr>
<tr>
<td>PCA</td>
<td>97 ± 6</td>
</tr>
<tr>
<td>mean</td>
<td>99 ± 6</td>
</tr>
<tr>
<td>central</td>
<td></td>
</tr>
<tr>
<td>caudate nucleus</td>
<td>87 ± 4</td>
</tr>
<tr>
<td>thalamus</td>
<td>81 ± 4</td>
</tr>
<tr>
<td>mesencephalon</td>
<td>82 ± 1</td>
</tr>
<tr>
<td>mean</td>
<td>83 ± 4</td>
</tr>
<tr>
<td>brain stem</td>
<td></td>
</tr>
<tr>
<td>pons</td>
<td>75 ± 3</td>
</tr>
<tr>
<td>medulla</td>
<td>68 ± 4</td>
</tr>
<tr>
<td>mean</td>
<td>71 ± 4</td>
</tr>
</tbody>
</table>

*Values for rCBF are mean (ml/100 gm/min) ± SEM.
†Regions refer to the cortical territories of the anterior (ACA), middle (MCA), and posterior (PCA) cerebral arteries.

ing data obtained after concussive trauma. Since the rCBF values of the different regions within cortical, "central," and brain-stem regions, were very similar in both the control and experimental groups, only the mean data are given. The "immediate" rCBF, as measured during the acute concussive response, was significantly increased in the cortex. All regions showed significantly reduced flow values 2 to 4 and 10 to 20 minutes after trauma. This time course is illustrated in Fig. 1, which gives individual values. The results show that rCBF was consistently increased immediately after trauma, and consistently reduced at 2 to 4 minutes. After post-concussive periods of longer than 10 minutes there was considerable variability, with some animals having rCBF close to normal and others showing a marked reduction in flow.

The CBF changes did not show any specific regional preferences, except that both the immediate increase and the subsequent decrease of flow were more extensive in the cortex than in the brain-stem regions.
### TABLE 2
Regional cerebral blood flow values in four trauma groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Period of BP Response* (min)</th>
<th>Start of rCBF Measurement† (min)</th>
<th>Physiological Variables‡</th>
<th>Mean rCBF§</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cortex</td>
</tr>
<tr>
<td>immediate (4 rats)</td>
<td>1.1 ± 0.1</td>
<td>0.23 ± 0.03</td>
<td>36.9 ± 0.1</td>
<td>147** ± 9</td>
</tr>
<tr>
<td>2–4 min (6 rats)</td>
<td>1.4 ± 0.3</td>
<td>2.3 ± 0.2</td>
<td>36.9 ± 0.2</td>
<td>32*** ± 5</td>
</tr>
<tr>
<td>10–20 min (6 rats)</td>
<td>1.5 ± 0.3</td>
<td>15.7 ± 1.7</td>
<td>36.9 ± 0.1</td>
<td>49** ± 11</td>
</tr>
<tr>
<td>40 min (4 rats)</td>
<td>1.5 ± 0.5</td>
<td>41.0 ± 0.6</td>
<td>37.5 ± 0.2</td>
<td>75 ± 12</td>
</tr>
</tbody>
</table>

*The trauma response was evaluated from the duration of the blood pressure reaction.
†The intervals between impact and start of the 60-second period of measurement of rCBF.
‡Physiological variables taken at the time of rCBF measurement. MABP = mean arterial blood pressure, CSFP = cerebrospinal fluid pressure, PaO2 = arterial oxygen pressure, PaCO2 = arterial carbon dioxide pressure.
§All rCBF values are given as mean (ml/100 gm/min) ± SEM. Significance of differences from the control values of rCBF (Table 1) determined with the Mann-Whitney U test (* = p < 0.05, ** = p < 0.01, *** = p < 0.001).

### TABLE 3
Physiological variables, arterial and cerebral venous oxygen content, CBF, and CMRO2 in control group and 20 minutes after trauma*

<table>
<thead>
<tr>
<th>Group (No.)</th>
<th>Temp (°C)</th>
<th>MABP (mm Hg)</th>
<th>CSFP (mm Hg)</th>
<th>PaO2 (mm Hg)</th>
<th>PaCO2 (mm Hg)</th>
<th>pH</th>
<th>Arterial O2 (ml/100 ml)</th>
<th>Venous O2 (ml/100 ml)</th>
<th>AVDO2 (ml/100 ml)</th>
<th>CBF (ml/100 gm/min)</th>
<th>CMRO2 (ml/100 gm/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>control</td>
<td></td>
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<td></td>
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<tr>
<td>(n = 8)</td>
<td>37.1 ± 0.1</td>
<td>138 ± 2</td>
<td>—</td>
<td>126 ± 4</td>
<td>34.9 ± 0.6</td>
<td>7.37 ± 0.2</td>
<td>21.1 ± 0.5</td>
<td>11.5 ± 0.5</td>
<td>9.6 ± 5.0</td>
<td>79.5 ± 2.4</td>
<td>7.6 ± 0.2</td>
</tr>
<tr>
<td>7 m/sec</td>
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<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>(n = 6)</td>
<td>37.0 ± 0.2</td>
<td>155 ± 4</td>
<td>—</td>
<td>103 ± 5</td>
<td>37.4 ± 1.9</td>
<td>7.31 ± 0.1</td>
<td>23.5 ± 0.6</td>
<td>13.6 ± 1.5</td>
<td>9.9 ± 1.2</td>
<td>83.3 ± 11.5</td>
<td>8.2 ± 0.3</td>
</tr>
<tr>
<td>9 m/sec</td>
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<tr>
<td>A (n = 3)</td>
<td>36.9 ± 0.1</td>
<td>162 ± 4</td>
<td>20–40</td>
<td>123 ± 7</td>
<td>35.3 ± 1.7</td>
<td>7.28 ± 0.2</td>
<td>21.7 ± 0.6</td>
<td>9.6 ± 0.4</td>
<td>12.1 ± 0.7</td>
<td>68.3 ± 3.3</td>
<td>8.3 ± 0.9</td>
</tr>
<tr>
<td>B (n = 4)</td>
<td>37.2 ± 0.2</td>
<td>138 ± 4</td>
<td>28 ± 5</td>
<td>119 ± 13</td>
<td>40.1 ± 0.8</td>
<td>7.22 ± 0.5</td>
<td>19.3 ± 0.8</td>
<td>4.5† ± 1.0</td>
<td>14.8† ± 0.9</td>
<td>30.5† ± 3.3</td>
<td>4.5† ± 0.4</td>
</tr>
</tbody>
</table>

*MABP = mean arterial blood pressure, CSFP = cerebrospinal fluid pressure, PaO2 = arterial oxygen pressure, PaCO2 = arterial carbon dioxide pressure, AVDO2 = arteriovenous differences in oxygen content, CBF = cerebral blood flow, CMRO2 = cerebral oxygen consumption. Values are mean ± SEM.
†Significant difference from control values (p < 0.01).
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Postmortem examination revealed various degrees of pulmonary edema in one animal of the "immediate" group, three of the 2- to 4-minute group, and two of the 40-minute group. In addition, six animals were excluded from the three last groups (two, one, and three animals, respectively) since they had pulmonary edema with secondary circulatory failure. All animals but one in the 2- to 4-minute group, and in the 10- to 20-minute group, had subarachnoid hemorrhage (SAH) in the occipital cistern.

Cerebral Blood Flow and Cerebral Metabolic Rate for Oxygen

The CBF values, as determined with the $^{133}$Xe desaturation technique, and AVDO$_2$ values are shown graphically in Fig. 2. For comparison the normal correlation between these variables is shown based on data from Nilsson and Siesjö showing CMRO$_2$ 7.6 ml/100 gm/min ± 2 SD. After a 7 m/sec trauma the CBF varied more than in the normocapnic control series but the CMRO$_2$ was kept constant (Fig. 2 and Table 3).

In the 9 m/sec injury group as a whole, there was a low CBF and a high AVDO$_2$, but two subgroups could be identified. Thus, four animals showed very low CBF values, significantly different from the other three, and from the controls. Despite a very high oxygen extraction, the resulting CMRO$_2$ in this group was only 4.5 ml/100 gm/min as compared to the control value of 7.6. In the remaining three animals, AVDO$_2$, CBF, and CMRO$_2$ were close to normal.

Four of the animals in the 7 m/sec injury group and all in the 9 m/sec injury group had SAH in the posterior fossa, most pronounced in the occipital cistern.

Cerebral Arteriovenous Differences in Oxygen Content

The results of the repeated determinations of arterial and cerebral venous oxygen content during the acute posttraumatic course after 9 m/sec impact in 11 animals are summarized in Fig. 3. The venous oxygen content decreased and the AVDO$_2$ increased significantly in the 2- to 5-minute and 6- to 10-minute groups.

Cerebrospinal Fluid Pressure

The results of the measurements are partly shown in Tables 2 and 3 and summarized in
FIG. 3. Arterial and cerebral venous oxygen content, determined repeatedly in a total of 11 animals at various time intervals after 9 m/sec trauma. The values are grouped 0 to 1, 1 to 6, 6 to 10, 10 to 20, and 20 to 30 minutes after trauma. + and ++ show AVDO₂ values significantly higher than control (+: p < 0.05, ++: p < 0.01). ** and *** show [O₂]v values significantly lower than control (**: p < 0.01, ***: p < 0.001).

Fig. 4. There was an immediate increase of CSFP following the 9 m/sec impact, reaching its maximum about 30 seconds after the immediate blood pressure peak, and starting to decrease after about 1 minute. In the continuously monitored animals there was a decrease during the period of measurement. The value obtained initially at puncture (CBF groups) were in the range of 10 to 50 mm Hg, median value 30 mm Hg (Fig. 4). In these animals no correlation between the elevation of CSFP and the reduction of blood flow was indicated. All animals had SAH as described in the previous groups.

Discussion

Methods

A detailed description of the trauma model used in the study is given previously.40,41
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Essentially, trauma of 7 m/sec velocity elicits concussion, usually followed by a rapid and uncomplicated recovery, while the 9 m/sec trauma used in the present study induces a more massive, immediate concussive response and also a prolonged posttraumatic coma. Subarachnoid hemorrhage occurs at both trauma levels, but more frequently after 9 m/sec injury (90%) than after 7 m/sec injury (50%). In the present series, the concussive responses, as estimated from the blood pressure reaction, were similar to those previously described.

In a previous series, the effects of a 7 m/sec trauma upon the rCBF was studied using the method of Reivich, et al., with $^{14}$C-antipyrine as a tracer substance and autoradiographic assessment of tissue activity. The modification of the rCBF method used in the present study, with $^{14}$C-ethanol as tracer, and determination of tissue activity from dissected, anatomically defined pieces of tissue, gives more consistent and reproducible results. The method requires constant flow during the period of saturation, in this case, 60 seconds. In the present series, the "immediate" group did not fulfill these conditions, since the last part of the saturation probably took place during a period of decreasing blood flow, due to a fall in blood pressure, and possibly, an increasing narrowing of the cerebral vessels. Thus, the rCBF figure probably underestimates the peak flow value. Furthermore, diffusion limitation of the tracer may exaggerate this error. At later intervals after the trauma, such flow changes should not be suspected to occur during the period of saturation.

The modification of the Kety and Schmidt method for determination of CBF and CMRO$_2$ in the rat, with the retroglenoid vein used for cerebral venous sampling, has been described previously. The measurements were performed 20 minutes after the trauma, and constant AVDO$_2$ values (within 10% limits) were demanded. A steady-state situation was probably at hand, and the CBF and CMRO$_2$ values thus obtained should be accurate.

Measurement of CSFP by puncture of the occipital cistern may be influenced by leakage around the needle or the catheter. The continuous recordings (Fig. 3) showed a progressive decrease. Thus slight leakage probably occurred. Taking into consideration only the initial pressures after the puncture, there was no significant difference in the cisternal pressure between 3 and 30 minutes. The pressure in the occipital cistern should be an accurate indicator of the pressure in the posterior fossa. No direct supratentorial pressure measurements were performed for technical reasons. However, since the trauma model caused its most pronounced effects in the brain-stem region, and no localized expansive lesions occurred, it is unlikely that the supratentorial pressure was higher than that measured in the cistern.

Results

Cerebral Blood Flow. The finding of an initial, short-lasting increase of flow after trauma is in agreement with findings in other studies. Thus, an immediate increase of jugular outflow was noted already by Polis, and confirmed by Denny-Brown and Russell. Brown and Brown found that CBF increased parallel to the rise in arterial blood pressure, indicating a pressure-passive flow increase. Similar patterns were found by Langfitt, et al., Meyer, et al., and ourselves in 7 m/sec trauma.

The results showing a global decrease of rCBF 2 to 4 and 10 to 20 minutes after the 9 m/sec trauma are consistent with the angiographic and metabolic findings previously reported. The results obtained in "whole brain" 20 minutes after trauma in the CBF/CMRO$_2$ series are compatible with the rCBF results. Probably the period of flow reduction was short in those animals with a tendency to normalization during the 20 to 40-minute period (see also Fig. 3).

Flow studies in other trauma models have not invariably confirmed this finding. Polis, in his early studies, suggested arterial spasm as a possible component of the cerebrovascular response to trauma. This, however, was not confirmed by others. The less severe 7 m/sec trauma of the present model did not elicit this flow pattern. Lin, et al., and McCullough, et al., found vascular narrowing in concussion complicated by SAH. Interestingly, gunshot injury can elicit a decrease of carotid blood flow, very similar to that of the present study. Mechanisms related to those of compression concussion may be involved.

Clinical angiographic studies have provided increasing evidence that vasospasm is a common phenomenon in head in-
jury, Its pathogenetic importance is supported by the morphological studies by Graham and Adams, in which a high proportion of ischemic brain lesions were found after head trauma.

Various mechanisms may elicit the CBF abnormalities. The cerebral blood flow is determined by the cerebrovascular resistance (CVR) and the cerebral perfusion pressure (CPP). The CPP, which is the pressure head available to force blood through the brain vessels, equals the difference between the mean arterial blood pressure (MABP) and the mean venous pressure (MVBP). The cortical venous pressure is very close to the pressure in the subarachnoid fluid surrounding these veins. Provided there is free communication, the CSFP will be equal in the whole CSF space and close to the brain tissue pressure. The following relation will then hold for the entire brain:

\[
\text{CBF} = \frac{\text{CPP}}{\text{CVR}} = \frac{\text{MABP} - \text{MVBP}}{\text{CVR}} = \frac{\text{MABP} - \text{CSFP}}{\text{CVR}}.
\]

With normal autoregulatory vasomotor function, CVR in this equation varies to keep CBF constant within a wide range of CPP changes.

Calculations of the CPP and CVR show that changes in MABP and CSFP alone could not explain the posttraumatic flow pattern. Thus, there was an immediate vasodilatation, followed within 2 minutes by a pronounced increase in vascular resistance, which tended to normalize over the following 30 minutes.

The initial increase of flow probably reflects absence of autoregulation and/or vasodilatation (calculated decrease of CVR 20% to 40%), caused by the direct vascular trauma, or by the rapid increase of blood pressure.

Failure of autoregulation may also explain part of the subsequent low-flow reaction. In addition to the vascular trauma mechanisms referred to, the pattern of ICP increase may contribute to failure of autoregulation. It is known that the autoregulation can be abolished if an increase of ICP occurs very rapidly or with repeated maneuvers of ICP increase. In such situations vasodilatation does not develop with decreasing CPP, that is, vasomotor tone remains high and flow decreases. However, in the present series evidently a vasoconstriction developed, since the calculated CVR showed a two- to threefold increase.

The vasoconstriction is interpreted to be essentially a primary event, that is, it does not reflect a depression of the metabolic demands, since the low-flow values were associated with an increase of the oxygen extraction (see below).

Vasoconstriction is known to be elicited by both mechanical stimuli and SAH. Thus, touching or stretching of intracranial arterial branches leads to vasospasm, as shown experimentally, or noted during operations. Local application of blood to the vessel wall and SAH have similar effects.

A rapid increase of MABP implies a mechanical stimulus, which may not only induce passive vasodilatation but also trigger an intense vasoconstruction.

The paramount clinical importance of arterial spasm associated with hemorrhage has given rise to many reports concerned with the possible biochemical and neurogenic mechanisms involved. Such mechanisms might well operate in the present model.

However, SAH per se in 7 m/sec trauma did not seem to elicit ischemia as judged from angiography and determinations of CBF and the cerebral metabolic state. These facts indicate that the direct mechanical effects of trauma may be critical. The distortion of the vessels in situ during impact acceleration might well induce vasoconstriction similar to that elicited by direct manipulation of vessels. Such distortion was recently demonstrated with high-speed angiographic technique.

Finally, in addition to the possible vasomotor effects of mechanical trauma and hemorrhage, the effects of "leaking transmitters," or other vasoactive substances released from the tissue by trauma, may be involved.

Cerebral Metabolic Rate for Oxygen. Although the present results do not permit quantitative calculations of the CMRO₂ during the acute concussive response, a high metabolic rate is indicated (Table 2 and Fig. 3). The energy depletion and lactacidosis developing during the first minute after injury, despite a high CBF, further indicate a high energy consumption. Such findings have previously been made in compression-trauma
Experimental head injury in the rat models. Thus, Nelson, et al., found an increase in energy consumption immediately after trauma, and Meyer, et al., found an increase of CMRO$_2$ 1 minute after light concussion. The results support the theory of Walker, et al., implying excitation, seen initially and after discharge, as the general response of neuronal cells to concussive trauma.

The subsequent reduction of CBF to about one-third of normal must critically reduce oxygen availability, since at this level of flow even maximum oxygen extraction is insufficient to maintain CMRO$_2$ at normal levels. The present results strongly indicate that the decrease of CBF was a primary event, that is, that it did not reflect a post-concussive depression of neuronal activity (and metabolism). Thus, there was a decrease of CBF combined with a high oxygen extraction. In some animals the venous oxygen content was below 3 ml/100 ml (Fig. 3). The 9 m/sec injured animals of the CBF/CMRO$_2$ series also had a high oxygen extraction, although in some it was not sufficiently high to keep oxygen availability at normal levels (Fig. 2, Table 3). In contrast, a primary reduction of the metabolic rate by hypothermia or barbiturates is known to induce a harmonic reduction of CBF, keeping venous oxygen content and AVDO$_2$ values constant. We conclude that following acceleration trauma of 9 m/sec CBF is reduced to values that are insufficient to supply the tissue with adequate amounts of oxygen.

Vasogenic edema due to vasodilatation and high perfusion pressure has been proposed to be one cause of traumatic brain dysfunction and damage. The present data support the suggestion that early traumatic ischemia may be another factor explaining the finding that prolonged coma, or the clinical syndrome of primary brain-stem damage may occur without obvious gross morphological changes. On the other hand, low CBF and CMRO$_2$ values in other posttraumatic states, may mainly reflect the low metabolic demands of the injured brain and thus not elucidate the initial pathogenetic mechanisms. Meyer, et al., interpreted their findings of reduced CBF and CMRO$_2$ after severe experimental compression concussion this way, and so did Lindquist and LeRoy. This dual significance of CBF and CMRO$_2$ changes, thus complicates the interpretation of data from most clinical studies.

Summary

The present study emphasizes that concussive head injury not only elicits the well known neuronal reactions, but also may have profound direct effects upon the function of the cerebrovascular system. The most important change that appeared with 9 m/sec trauma was an early reduction of CBF. This could critically reduce the oxygen availability in the brain, so that the normal or initially increased metabolic demands could not be met. Similar primary vascular reactions probably appear in clinical situations.

References

40. Nilsson B, Pontén U: Experimental head in-


This study was supported by grants from the Swedish Medical Research Council (project 14X-00263), and from USPHS Grant 2 R01 NS07838-07 from the National Institutes of Health.

Address reprint requests to: Bengt Nilsson, M.D., Forskn. Avd. 4, E. Blocket, Lasaretet, 221 85, Lund, Sweden.