Regional Cerebral Blood Flow After Cortical Impact Injury Complicated by a Secondary Insult in Rats

Bala K. Giri, MD; Indra K. Krishnappa, MD; Robert M. Bryan, Jr, PhD; Claudia Robertson, MD

Background and Purpose—Traumatic injury makes the brain susceptible to secondary insults. An uncomplicated mild lateral cortical impact injury (3 m/s, 2.5-mm deformation) that causes little or no permanent sequelae results in a large contusion at the impact site when the traumatic injury is complicated by a secondary insult, such as 40 minutes of bilateral carotid occlusion.

Methods—To determine whether the increased sensitivity to secondary insults in this model is caused by a vascular mechanism, cerebral blood flow (CBF) was measured with 14C-isopropyliodoamphetamine quantitative autoradiography, and brain tissue PO2 (PbtO2) was measured at the impact site and in the contralateral parietal cortex.

Results—In animals that underwent bilateral carotid occlusion 1 hour after the impact injury, CBF and PbtO2 were lower at the impact site than they were in animals that had either the impact injury or the carotid occlusion alone. In the immediate area of the impact, CBF was 14±6 mL · 100 g−1 · min−1 in the animals with the impact injury followed by carotid occlusion compared with 53±24 mL · 100 g−1 · min−1 in the animals with the impact injury alone and 74±14 mL · 100 g−1 · min−1 in the animals with the carotid occlusion alone (P<0.001). At the time of this very low CBF value in the animals with the carotid occlusion after the impact injury, PbtO2 at the impact site averaged 1.3±1.6 mm Hg and was <3 mm Hg in 5 of the 6 animals. In contrast, PbtO2 in the animals with the impact injury alone averaged 9.3±2.9 mm Hg, and none of the animals had a PbtO2 of <3 mm Hg (P=0.008).

Conclusions—The CBF and PbtO2 findings in this model suggest that the reduced CBF after traumatic injury predisposes the brain to secondary insults and results in ischemia when confronted with a reduction in cerebral perfusion pressure. (Stroke. 2000;31:961-967.)

Key Words: brain injuries ■ cerebral blood flow ■ cerebral ischemia ■ trauma

Secondary ischemic insults are an important cause of damage to the brain after traumatic brain injury (TBI). In a number of clinical studies, a poor outcome has consistently been associated with prehospital hypotension or hypoxia,1–6 with intraoperative hypotension,7 and with hypoxia and hypotension in the intensive care unit.2–8–10

In the laboratory, a mild lateral cortical impact injury (3 m/s, 2.5-mm deformation) that causes little or no permanent sequelae results in a large contusion at the impact site when the traumatic injury is complicated by 40 minutes of bilateral carotid occlusion (BCO).11 A similar sensitivity to secondary insults has been observed in the fluid percussion injury model12–14 and the weight-drop model.15

Two general mechanisms may be responsible for the increased sensitivity of the traumatized brain to ischemic insults.16 First, it is likely that trauma impairs the ability of the brain to regulate cerebral blood flow (CBF), and for any given insult, the cerebrovascular response after TBI may be inadequate. In many studies, both clinical and experimental, impaired autoregulation has been observed after TBI.17–22 Second, trauma may induce cellular processes that make the brain more sensitive to an additional insult. This mechanism is supported by studies in which the CBF response is similar in the trauma and the nontrauma animals12 and by in vitro studies in which CBF is not a factor.23

To determine whether the vascular mechanism is a factor in the cortical impact injury model, regional CBF (rCBF) was measured with quantitative autoradiography in a group of animals that underwent a 3-m/s impact injury followed 1 hour later by 40 minutes of carotid occlusion. The measurement of reduced CBF does not necessarily indicate oxygen depletion and, therefore, ischemia. Because reduced CBF associated with TBI may be simply a manifestation of a reduced metabolic rate, brain tissue PO2 (PbtO2) was measured continuously during the uncomplicated cortical impact injury and during the cortical impact injury followed by 40 minutes of BCO.

Materials and Methods

Male Long Evans rats that weighed approximately 350 g and were fasted overnight were used in the experiments: 15 for the measure-
ment of CBF and 12 for the measurement of PbtO\textsubscript{2}. The protocol for this study was approved by the Animal Protocol Review Committee of Baylor College of Medicine. For both experiments, the rats were anesthetized with 3.5\% isoflurane in 100\% oxygen in a vented anesthesia chamber. After endotracheal intubation with a 16-gauge Teflon catheter, the rats were mechanically ventilated with 2\% to 3\% isoflurane in 100\% oxygen for the remainder of the experiment. Rectal temperature was monitored and maintained at 37\°C with a heating pad. The ventilator was adjusted to maintain arterial PCO\textsubscript{2} near 35 mm Hg.

For both studies, a catheter was placed in the left femoral artery to monitor blood pressure and to draw blood samples. Arterial blood was periodically sampled and analyzed for PO\textsubscript{2}, PCO\textsubscript{2}, and pH. For the measurement of CBF, catheters were also inserted into the right femoral artery and vein.

Both carotid arteries were exposed via a vertical midline incision and carefully dissected free from the other contents of the carotid sheath. The head of each rat was fixed in a stereotaxic frame with ear bars, and a 10-mm-diameter craniectomy was performed in the right parietal skull adjacent to the midline in preparation for the cortical impact injury. The dura was left intact. For the PbtO\textsubscript{2} experiment, a PO\textsubscript{2} catheter and thermocouple catheter (Licox PO\textsubscript{2} catheter and thermocouple catheter; GMS) were placed into the brain parenchyma at the exposed impact site and in the contralateral parietal lobe via a small burr hole. The PO\textsubscript{2} catheter was calibrated before insertion, and the calibration was checked again at the end of the experiment. The PO\textsubscript{2} values were temperature corrected to the brain temperature indicated by the adjacent thermocouple catheter.

The animals were randomly assigned to 1 of 3 treatment groups: (1) TBI+BCO group (3 m/s, 2.5-mm deformation impact injury, followed 1 hour later by 40 minutes of BCO), (2) TBI group (3 m/s, 2.5-mm deformation impact injury, followed 1 hour later by 40 minutes of sham carotid occlusion), and (3) BCO group (sham impact injury, followed 1 hour later by 40 minutes of BCO).

In 15 of the animals (5 in each of the 3 treatment groups), CBF was measured at the end of the 40-minute BCO or sham carotid occlusion period. CBF was measured with \textsuperscript{14}C-isopropylidoamphetamine (IPIA) and quantitative autoradiography.\textsuperscript{24} IPIA is useful as a flow tracer because it is extracted 100\% in the brain during a single pass.\textsuperscript{25} The IPIA (29 \textmu Ci/mmol) was custom synthesized at Du Pont-New England Nuclear. IPIA (50 \textmu Ci/0.5 mL) in normal saline was injected quickly into the right femoral vein. Blood was withdrawn from the right femoral artery at a rate of 0.4 mL/min beginning at the time of IPIA infusion and continuing until the rat was sacrificed 30 seconds later with the use of a guillotine. After death, the brain was rapidly removed, frozen in isopentane chilled to −40\°C, and stored at −70\°C until it was sectioned. Each brain was cut into 20-\mu m-thick sections with a cryostat (−18\°C). Representative sections were mounted onto glass slides and placed in contact with radiograph film in light-tight cassettes. After a 15-day exposure, the film was developed, producing autoradiographic images. Concentrations of the tracer (radioactivity/g brain tissue) were determined by comparing the optical densities of various brain regions with the optical densities produced with calibrated standards packed with tissue sections in the cassettes. The total radioactivity in the blood withdrawn was calculated according to the following equation:

\[
\text{Total radioactivity in blood sample} = \frac{\text{Radioactivity in aliquot}}{\text{Mass of entire blood sample}} \times \frac{\text{Mass of aliquot}}{\text{Mass of entire blood sample}}
\]

Blood flow for individual regions was calculated according to the following equation:

\[
\text{Blood flow} = \frac{\text{Radioactivity/g in brain region} \times 0.4 \times 100}{\text{Total radioactivity in blood sample withdrawn}}
\]

where blood flow is given in mL·100 g\textsuperscript{−1}·min\textsuperscript{−1}, and 0.4 mL/min is the rate of blood withdrawal from the femoral artery. The rate of withdrawal (0.4 mL/min) was chosen to provide sufficient blood to measure radioactivity without altering arterial blood pressure. The equation for the calculation of blood flow is the same basic equation for the calculation of blood flow with the microsphere method.\textsuperscript{25} CBF was graphically displayed and calculated with the use of an

<p>| TABLE 1. Baseline Physiological Parameters in Animals With CBF Measurement |
|--------------------------|--------------------------|--------------------------|--------------------------|</p>
<table>
<thead>
<tr>
<th>BCO Group</th>
<th>TBI Group</th>
<th>TBI+BCO Group</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight, g</td>
<td>335±33</td>
<td>364±45</td>
<td>348±10</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>106±10</td>
<td>117±26</td>
<td>94±15</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>66±8</td>
<td>84±15</td>
<td>70±14</td>
</tr>
<tr>
<td>Mean BP, mm Hg</td>
<td>79±8</td>
<td>98±18</td>
<td>81±14</td>
</tr>
<tr>
<td>Arterial pH</td>
<td>7.31±0.05</td>
<td>7.38±0.17</td>
<td>7.36±0.08</td>
</tr>
<tr>
<td>Arterial PO\textsubscript{2}, mm Hg</td>
<td>36±6</td>
<td>36±5</td>
<td>35±5</td>
</tr>
<tr>
<td>Arterial PCO\textsubscript{2}, mm Hg</td>
<td>193±62</td>
<td>221±87</td>
<td>214±35</td>
</tr>
</tbody>
</table>

BP indicates blood pressure.

Figure 1. Examples of typical autoradiographs from these studies. Top, from an animal in the TBI group, showing marked reduction in rCBF at the impact site, with normal CBF in the remainder of the brain. Middle, from an animal in the BCO group showing a reduction in CBF throughout the forebrain. Bottom, from an animal in the TBI+BCO group showing a reduction in CBF throughout the forebrain but, in addition, a very marked reduction in rCBF at the impact site.
image analysis system (MCID MI; Imaging Research Inc). The identification of rat brain regions for rCBF measurements was made according to a standard atlas.26

In 12 animals (6 randomized to the TBI+BCO group and 6 randomized to the TBI group), PbtO$_2$ was measured before the impact injury, with 45 minutes allowed for the catheter readings to stabilize. The catheter at the impact site was removed for the impact injury and then immediately replaced into the same area of the brain. PbtO$_2$ was then monitored after the impact injury for 3 hours. The PbtO$_2$ on the injured side was compared with the values obtained for the contralateral uninjured side of the brain.

Data are reported for all groups as mean±SD. Analyses of CBF data were performed with 2-way ANOVA with treatment group and side of the brain as factors. The PbtO$_2$ data were analyzed with repeated measures ANOVA with time and side of the brain as factors. Tukey’s test was used for multiple comparisons, and Fisher’s exact test was used for categorical data.

Results

CBF Measurements

Physiological measurements, including mean blood pressure, arterial pH, P$_{CO_2}$, and P$_{O_2}$, were made in each rat before injury and are presented in Table 1. There were no significant differences in the physiological measurements among the 3 groups. Arterial P$_{CO_2}$ in the TBI+BCO group, which tended to be slightly lower than that in the other 2 groups at baseline, was normalized during the experiment and averaged 35±3 mm Hg, a value similar to that of the other groups at the time of the CBF measurement.

Representative examples of the autoradiographs for the 3 experimental groups are shown in Figure 1. A summary of all of the CBF data is given in Table 2.

In the animals that underwent only the impact injury (TBI group), CBF tended to be less on the impacted right side in all of the cortical areas (frontal, parietal, temporal, occipital) and in the hippocampus. However, these right–left differences were significant only in the parietal cortex (motor area), in the occipital cortex (areas A18 and A18a), and in the hippocampus (Table 2). CBF was reduced to 54±24 and 42±33 mL·100 g$^{-1}$·min$^{-1}$ in the parietal cortex (motor area) and in the occipital cortex, respectively, on the impacted side. In the hippocampus, CBF was 254±33 mL·100 g$^{-1}$·min$^{-1}$ on the impacted side compared with 319±44 mL·100 g$^{-1}$·min$^{-1}$ on the uninjured side. In the remainder of the brain regions, there were no significant differences in CBF between the right and left sides after adjustment for multiple comparisons with Tukey’s method.

In the animals that underwent only the BCO (BCO group), CBF was moderately reduced in the forebrain on both sides. Regions in the hindbrain were less affected. There were no significant right–left differences in CBF in any areas of the brain (Table 2). CBF was not reduced to ischemic levels in any area of the brain.

In the animals that underwent BCO 1 hour after the impact injury (TBI+BCO group), CBF was significantly lower than that in either the TBI group or the BCO group at the impact site. In the immediate area of the impact, CBF was reduced to

Table 2: Regional Values for CBF

<table>
<thead>
<tr>
<th>Region</th>
<th>BCO Group</th>
<th>TBI Group</th>
<th>TBI+BCO Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Left</td>
<td>Right</td>
<td>Left</td>
</tr>
<tr>
<td>FrONTAL CORTEX (motor)</td>
<td>74±11</td>
<td>73±10</td>
<td>330±71</td>
</tr>
<tr>
<td>FrONTAL CORTEX (somatosensory)</td>
<td>109±14</td>
<td>101±11</td>
<td>421±85</td>
</tr>
<tr>
<td>CINGULATE GYRUS</td>
<td>74±8</td>
<td>77±6</td>
<td>400±110</td>
</tr>
<tr>
<td>PARietal CORTEX (motor)</td>
<td>73±9</td>
<td>74±14</td>
<td>292±40</td>
</tr>
<tr>
<td>PARietal CORTEX (somatosensory)</td>
<td>109±7</td>
<td>103±15</td>
<td>393±95</td>
</tr>
<tr>
<td>TEMPORAL CORTEX</td>
<td>90±12</td>
<td>93±11</td>
<td>360±63</td>
</tr>
<tr>
<td>Occipital cortex A18</td>
<td>71±9</td>
<td>75±6</td>
<td>314±40</td>
</tr>
<tr>
<td>Occipital cortex A18a</td>
<td>87±7</td>
<td>85±11</td>
<td>315±44</td>
</tr>
<tr>
<td>Caudate-putamen</td>
<td>104±13</td>
<td>100±9</td>
<td>301±29</td>
</tr>
<tr>
<td>Hippocampus</td>
<td>134±14</td>
<td>135±10</td>
<td>319±44</td>
</tr>
<tr>
<td>Lateral geniculate</td>
<td>123±5</td>
<td>118±9</td>
<td>336±87</td>
</tr>
<tr>
<td>Medial geniculate</td>
<td>138±11</td>
<td>128±16</td>
<td>343±73</td>
</tr>
<tr>
<td>Other thalamus</td>
<td>119±12</td>
<td>132±20</td>
<td>261±49</td>
</tr>
<tr>
<td>Substantia nigra</td>
<td>218±19</td>
<td>220±14</td>
<td>340±100</td>
</tr>
<tr>
<td>Red nucleus</td>
<td>267±30</td>
<td>275±30</td>
<td>365±117</td>
</tr>
<tr>
<td>Reticular nucleus</td>
<td>239±18</td>
<td>228±31</td>
<td>337±50</td>
</tr>
<tr>
<td>Superior colliculus</td>
<td>138±15</td>
<td>204±20</td>
<td>415±107</td>
</tr>
<tr>
<td>Inferior colliculus</td>
<td>195±29</td>
<td>206±16</td>
<td>401±106</td>
</tr>
</tbody>
</table>

Values are mean±SD in mL·100 g$^{-1}$·min$^{-1}$.

*Areas of the brain in which there was a significant group×side interaction and in which the CBFs in the right and left sides were significantly different (P<0.05, Tukey’s test). Comparisons of the areas of the brain in which there were significant group differences are shown in Figures 2 and 3.
In 2 areas of the brain, the parietal cortex (motor area) and occipital cortex A18, there were significant group differences in CBF ($P<0.05$ by Tukey’s test), and a reduction in CBF to $<18 \text{ mL} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$ was observed in the TBI+BCO group. In the parietal cortex, this reduction in CBF was significantly greater in the TBI+BCO group than in the BCO or TBI group. In the occipital cortex, this reduction in CBF was significantly greater in the TBI+BCO group than in the BCO group.

![Figure 2](image1)

![Figure 3](image2)

In 2 additional areas of the brain (occipital cortex A18a and hippocampus), there were significant differences in CBF among the 3 experimental groups ($P<0.05$. Tukey’s test), but CBF did not decrease to $<18 \text{ mL} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$. In the occipital cortex A18a, the CBF was lower in both the TBI+BCO and BCO groups than in the TBI group, but none of the values were $<18 \text{ mL} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$. In the hippocampus, the CBF was lower in the TBI+BCO group than in either of the other 2 groups, but none of the values were $<18 \text{ mL} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$.

**PbtO2 Studies**

The results of the PbtO2 studies are illustrated in Figures 4 and 5 for the TBI and TBI+BCO groups, respectively. In each figure, the arrow labeled CBF illustrates the timing of the autoradiographic CBF studies discussed earlier. PbtO2 averaged 24.6±8.3 mm Hg before the impact injury and changed significantly during the TBI experiment (side effect $P=0.011$, time effect $P<0.001$, side×time interaction $P=0.015$) and during the TBI+BCO experiment (side effect $P=0.002$, time effect $P<0.001$, side×time interaction, $P<0.001$).

The animals that received only the 3-m/s impact injury (TBI group) had a significant reduction in PbtO2 to $<10$ mm Hg immediately after the impact injury. The PbtO2 gradually increased but was still less than control values and less than that of the contralateral side at 2 hours after the impact injury. At the time of the CBF measurement discussed earlier (rCBF in the impact site $53\pm24 \text{ mL} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$), the average PbtO2 at the impact site was $9.3\pm2.9$ mm Hg.

In the animals that received the combined impact injury followed by carotid occlusion (TBI+BCO group), the PbtO2 also decreased to $<10$ mm Hg at the impact site after the impact injury. During the carotid occlusion, the PbtO2 at the impact site decreased to $1.3\pm1.6$ mm Hg at the time of the
CBF measurement discussed earlier (CBF 14±3 mL·100 g⁻¹·min⁻¹) compared with 5.5±2.5 mm Hg on the contralateral side. At this time, 3 of 6 animals had a PbtO₂ of 0 mm Hg and 5 of 6 animals had a PbtO₂ of <3 mm Hg at the impact site. In contrast, PbtO₂ was ≥3 mm Hg on the contralateral side in all animals (P<0.008, Fisher’s exact test).

There were no changes in the measured physiological parameters during the experiment that account for the differences in PbtO₂ observed in the 2 treatment groups. Arterial blood gases, rectal temperature, and mean arterial blood pressure did not significantly vary throughout the study or between groups. The calibration check of the PO₂ catheters at the end of the study showed minimal drift of the PO₂ readings during the experiment. In zero oxygen solution, the average PO₂ was 0.1±0.2 mm Hg, and in room air, the average PO₂ was 155.7±3.6 mm Hg.

Discussion

TBI results in a reduction in CBF in many experimental models. However, it has never been clear whether this reduction in CBF causes any additional damage to the brain. CBF in the present study either was not sufficiently reduced to be considered ischemic or was markedly reduced only at the impact site, where tissue was badly damaged. The reduction in CBF in this circumstance may simply be a reflection of the severity of the primary damage to the cortical tissue. Finally, ischemic thresholds for CBF may be different after TBI, because cerebral metabolic requirements may be altered by the tissue response to the trauma.

In the fluid percussion injury, global CBF is reduced to approximately 50% of normal levels by 30 minutes to 1 hour after injury.27–29 By 2 hours after lateral fluid percussion injury, CBF returned to near normal values in all areas except at the actual impact site.30

In the controlled cortical impact injury model, CBF is reduced primarily at the impact site in mild injury 24,31 With more severe injury, the reduction in CBF is global, although the greatest decrease in CBF is always at the impact site31,32 CBF does decrease to <18 mL·100 g⁻¹·min⁻¹ at the impact site in this model, and there is a tendency for the volume of tissue with CBF values of <18 to 20 mL·100 g⁻¹·min⁻¹ to increase from 30 minutes to 4 hours after injury.31

CBF must be considered within the context of cerebral metabolic requirements, which are known to be altered after TBI. Studies that have measured the glucose metabolic rate after experimental TBI suggest that the metabolic rate is initially increased as large amounts of energy are expended in the regain of ionic concentration gradients.33 Later, cerebral metabolic rate is decreased.33,34 Similar findings have been observed in human brain injury.35 The initial increased metabolic requirements tend to increase the CBF threshold, which would result in energy depletion, and the later decreased metabolic rate tends to

Figure 4. In the TBI group, PbtO₂ values (mean±SD) at the impact site decreased immediately after the impact and then gradually increased toward normal levels (side effect P<0.011, time effect P<0.001, side×time interaction P<0.015). *PbtO₂ values in the injured brain that were significantly lower than those in the contralateral hemisphere (Tukey’s test). Arrow labeled CBF marks the time of the CBF measurement. PbtO₂, although lower at the impact site than on the contralateral side, never decreased below 3 mm Hg in any animal.

Figure 5. In the TBI+BCO group, PbtO₂ values (mean±SD) at the impact site decreased immediately after the impact and again during BCO (side effect P<0.002, time effect P<0.001, side×time interaction P<0.001). *PbtO₂ values in the injured brain that were significantly lower than that in the contralateral hemisphere (Tukey’s test). Arrow labeled CBF marks the time of the CBF measurement. At this time, near the end of the carotid occlusion period, the PbtO₂ was <3 mm Hg at the impact site in 5 of the 6 animals. In contrast, PbtO₂ was ≥3 mm Hg in all animals on the contralateral hemisphere (P=0.008).
increase the CBF threshold, which would result in energy depletion. Therefore, the ischemia threshold of 18 mL · 100 g⁻¹ · min⁻¹, which was established in normal brain, may not apply after trauma. In such circumstances, the measurement of cerebral oxygenation can provide additional information about the relative adequacy of the CBF.

The present study contributes information to two issues regarding the CBF response to TBI in the cortical impact injury model. First, the reduction in CBF at the impact site to an average value of 53 ± 24 mL · 100 g⁻¹ · min⁻¹ is not simply a physiological response to reduced cerebral metabolic requirements caused by the 3-m/s impact injury. The PbtO₂, which averaged 9.3 ± 2.9 mm Hg at the time of the low CBF measurement at the impact site, was significantly lower than the normal value of 24.6 ± 8.3 mm Hg measured before the impact injury and was significantly lower than that on the contralateral side throughout most of the postimpact period of monitoring. The surface area of the P₀₂ probe used for these measurements is sufficiently large for the resulting measure to be an average tissue P₀₂ in the region surrounding the probe. The local variability in tissue P₀₂ observed with microelectrode measurements is not found with this probe. Normal PbtO₂ measured with these probes is typically 20 to 40 mm Hg, and reductions to 8 to 10 mm Hg are generally thought to be critical reductions in cerebral oxygenation. 36–38

Because previous studies have documented that the injury level used in the present study does not result in histological changes, 11 it may be assumed that the observed reduction in CBF and oxygenation can be tolerated at least transiently without causing ischemic damage. However, if the reduction in CBF were an appropriate and physiological response to reduced cerebral metabolic requirements, then tissue oxygenation should not have decreased. Although the level of PbtO₂ found in the impacted brain is not sufficiently low to result in permanent damage by itself, it does indicate a degree of hypoperfusion and perhaps also a vulnerability to additional ischemic insults.

Second, when the injured brain, which already has a reduced baseline CBF value, is confronted with a secondary ischemic insult, the cerebral vasculature is not able to maintain an adequate level of perfusion at the impact site. CBF in the impacted brain tissue fell during the carotid occlusion period to levels that would normally be considered ischemic (<18 mL · 100 g⁻¹ · min⁻¹). PbtO₂ also fell to very low values (<3 mm Hg) during the carotid occlusion period, indicating that the reduced CBF was inadequate to prevent oxygen depletion. Finally, because previous studies have found that 40 minutes of BCO after a 3-m/s, 2.5-mm deformation impact injury causes a large contusion (median volume 15.5 mm³) at the impact site and a decrease in the neuron density of both CA1 and CA3 regions of the hippocampus, 11 the present CBF and PbtO₂ findings suggest that ischemia may be associated with the tissue necrosis that develops at the impact site.

There were no systemic factors that might have contributed to the CBF findings. Past studies in which the cardiovascular response to impact injury of varying degrees of severity was studied suggested that this very mild impact injury causes only a small decrease in blood pressure and no increase in intracranial pressure. 33 This was consistent with the blood pressure and blood gas findings of the present study, suggesting that the CBF findings were due to local factors.

Isoflurane has important effects on CBF and metabolism, and it should be considered whether the results were influenced by the anesthetic agent used in the present study. Isoflurane typically increases CBF in a dose-response manner. 39, 40 PbtO₂ increases with CBF during isoflurane anesthesia. 41 Therefore, it is unlikely that the reductions in CBF that occur with trauma or during carotid occlusion can be explained by anesthetic effects. Isoflurane may contribute to the relatively high CBF values measured in the noninjured areas of the brain in the TBI group, but the normal PbtO₂ values in this group suggest that the measured CBF values are probably appropriate for metabolic requirements.

In summary, the results of the present study suggest a mechanism for increased susceptibility to secondary injury caused by trauma. Cerebrovascular dysfunction at the site of trauma puts the injured area at risk for secondary injury. Although cellular processes, which are independent of flow, may be involved, its relative contribution in this model is uncertain.

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References

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**Editorial Comment**

The article by Giri et al represents the thoughtful execution and presentation of these animal data concerning secondary brain injury. This study provides compelling and interesting evidence of dysfunction of cerebral blood flow regulation at the site of a mild brain injury that renders that area of the brain unable to accommodate a global drop in blood flow. Their findings are of interest to those of us who have puzzled over the grave consequences of systemic hypotension after head injury or stroke, and they provide data that are important pieces of that puzzle. Specifically, the presence of a mild cortical impact injury results in a local impairment of blood flow and oxygen tension. The next step is to elucidate the pathophysiology of this phenomenon and attempt to prevent its occurrence.

Also, having worked with the Licox probe in animals, I know the difficulties involved in using bilateral probes in a rat brain. One should be skeptical in interpreting these types of data, because, in my hands at least, it is very easy to corrupt the data due to technical factors alone. This results in wide variation in the PO2 data from rat to rat and even from hemisphere to hemisphere. However, the data presented here are very clean. Clearly, the authors have a talent for it.

The take-away message for clinicians is that it is the local environment in the brain due to the injury that makes the brain susceptible to secondary insults and not the secondary insult per se. For me personally, it provides further hope that there will be intervention, pharmacological or otherwise, that may ameliorate the consequences of traumatic brain injury.

**Joe Watson, MD, Guest Editor**

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