Magnetic resonance imaging–monitored acute blood-brain barrier changes in experimental traumatic brain injury

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The authors posit that cellular edema is the major contributor to brain swelling in diffuse head injury and that the contribution of vasogenic edema may be overemphasized. The objective of this study was to determine the early time course of blood-brain barrier (BBB) changes in diffuse closed head injury and to what extent barrier permeability is affected by the secondary insults of hypoxia and hypotension. The BBB disruption was quantified and visualized using T1-weighted magnetic resonance (MR) imaging following intravenous administration of the MR contrast agent gadolinium–diethylenetriamine pentaacetic acid. To avoid the effect of blood volume changes, the maximum signal intensity (SI) enhancement was used to calculate the difference in BBB disruption.

A new impact-acceleration model was used to induce closed head injury. Forty-five adult Sprague–Dawley rats were separated into four groups: Group I, sham operated (four animals), Group II, hypoxia and hypotension (four animals), Group III, trauma only (23 animals), and Group IV, trauma coupled with hypoxia and hypotension (14 animals). After trauma was induced, a 30-minute insult of hypoxia (PaO2 40 mm Hg) and hypotension (mean arterial blood pressure 30 mm Hg) was imposed, after which the animals were resuscitated.

In the trauma-induced animals, the SI increased dramatically immediately after impact. By 15 minutes permeability decreased exponentially and by 30 minutes it was equal to that of control animals. When trauma was coupled with secondary insult, the SI enhancement was lower after the trauma, consistent with reduced blood pressure and blood flow. However, the SI increased dramatically on reperfusion and was equal to that of control by 60 minutes after the combined insult.

In conclusion, the authors suggest that closed head injury is associated with a rapid and transient BBB opening that begins at the time of the trauma and lasts no more than 30 minutes. It has also been shown that addition of posttraumatic secondary insult—hypoxia and hypotension—prolongs the time of BBB breakdown after closed head injury. The authors further conclude that MR imaging is an excellent technique to follow (time resolution 1–1.5 minutes) the evolution of trauma-induced BBB damage noninvasively from as early as a few minutes up to hours or even longer after the trauma occurs.

KEY WORDS • blood-brain barrier • magnetic resonance imaging • traumatic brain injury • gadolinium • secondary insult
change in the BBB in an experimental model of diffuse injury produced by impact acceleration and injury coupled with secondary insult. However, it was necessary to consider techniques that provide increased sensitivity and time resolution, especially in vivo.

The BBB impairment caused by head injury has been widely examined with qualitative and quantitative methods using light microscopic tracers such as Evans blue and trypan blue dyes, hydroperoxidase, radionuclides, and horseradish peroxidase. Although horseradish peroxidase and radionuclides methods have been found to be more sensitive than semiquantitative ratings using vital dyes, there still exist several limitations, such as radiation hazard and the need for in vitro evaluation. Therefore, currently available techniques are inappropriate for the repetitive in vivo assessment of the acute time course of the initial BBB breakdown. Currently, in vivo evaluation of the extent and site of BBB damage is possible using CT scans, although their sensitivity is not as good as that obtained with radionuclide methods. On the other hand, magnetic resonance (MR) imaging with gadolinium-diethylenetriamine pentaacetic acid (Gd-DTPA) provides a means for the noninvasive detection of BBB injury. The contrast agent Gd-DTPA, with a molecular weight of 938, does not normally cross the BBB, but has been shown to do so when the BBB is damaged, such as after cerebral infarction, tumors, infections, hyperosmotic shock, and brain contusion.

The objectives of this study were threefold: 1) to apply a noninvasive MR imaging method to in vivo quantification of BBB permeability; 2) to use this method to follow the time course of early BBB changes after diffuse closed head injury; and 3) to examine the effect of hypoxia and hypotension on BBB permeability.

Materials and Methods

Surgical Procedures

Forty-five adult Sprague–Dawley rats weighing 340 to 375 g, which were scheduled for MR imaging studies, were divided into four groups: Group I, sham-operated control (four animals), Group II, hypotension plus hypoxia and no trauma (HH) (four animals), Group III, trauma only (TO) (23 animals), and Group IV, trauma plus hypoxia coupled with hypotension (THH) (14 animals). A parallel bench series was also studied to document the changes in cerebral blood flow (CBF) and intracranial pressure (ICP) associated with each group (four animals each in the four groups).

The rats were initially anesthetized with halothane, then intubated and artificially ventilated with a gas mixture of N2O (70%) and O2 (30%) and halothane. Catheters (PE-50) were placed into a femoral artery and a femoral vein. Mean arterial blood pressure (MABP), rectal temperature, and arterial blood gas levels were monitored. Body temperature was maintained at 37°C ± 0.5°C by blowing warm air into the cylinder holder while the animal was in the magnet and by means of heat lamps when the animal was out of the magnet.

Induction of Hypotension and Hypoxia

In groups suffering from secondary insult, hypotension was induced by withdrawing arterial blood into a heparinized syringe during the first 5 minutes after trauma was induced until an MABP of 30 to 40 mm Hg was sustained for 30 minutes. After hypotension, all withdrawn blood was returned via a venous catheter. Hypoxia was obtained by reducing the oxygen content, so that the PO2 was maintained at approximately 40 mm Hg for 30 minutes. The rats in these groups were injected intravenously with 0.1 mg/kg of pancuronium bromide just before trauma to control ventilation.

Trauma Model

A new impact-acceleration head injury model was used to produce trauma. A midline scalp incision was made, the skin and periosteum were reflected, and the skull was carefully dried. A round stainless steel disk was mounted on the skull using superglue. When the bonding agent was dry, the rat was positioned under a hollow plexiglass tube disconnected from the respirator, and a section of the disk was weight dropped from a height of 2 m onto the center of the metal disk. Under these experimental conditions, in which the animals remained intubated, a mortality rate of less than 10% is obtained with a low incidence of skull fracture. The disk was used to prevent skull fracture. After trauma was induced, the rat was rapidly reconnected to anesthesia and artificially ventilated. The rats were injected intravenously with a 0.02-mg/kg dose of atropine sulfate before trauma to reduce mucus secretions. Rats that died on impact or experienced severe skull fractures were excluded from this study.

Magnetic Resonance Imaging

Experiments were performed using a 2.35-tesla, 40-cm bore magnet equipped with a 12-cm inner diameter, actively shielded gradient insert. Radiofrequency excitation and reception were performed using a 7-cm inner diameter, quadrature “bird cage” design resonator. To minimize any macroscopic motion artifacts, the rat was immobilized in the prone position within a plastic cylinder that included ear and mouth supports.

Both T1- and T2-weighted images were acquired from the same coronal slice (3-mm thickness) placed at a standardized anatomical plane 7.5 mm from the tip to the forebrain, using conventional single and multiecho spin-echo sequences, respectively. The T1-weighted images (repetition time 700 msec, echo time 22 msec) were sequentially acquired using an image matrix of 128 × 128 cm (1.5 minutes/image). The T2-weighted images (repetition time 3000 msec, echo time 160 msec) were acquired for elucidation of structures within the brain. All images were acquired using a 4-cm square field of view (FOV) corresponding to 0.3- × 0.3-mm pixels.

The average T1-weighted signal intensities (SIs) for six regions of interest (ROIs) within the brain (bilateral cortex, and caudate nucleus, corpus callosum, and whole brain) and one within the muscle, were determined for each image in both the control and posttrauma runs. These ROIs were drawn on the T1-weighted images because of the clear visualization of the above-mentioned regions and then transferred to the T2-weighted images for determining the SIs. The ROIs were normalized by dividing each ROI by the average ROI that was placed within the imaging FOV and had T1/T2 values similar to tissue relaxation times at this field strength. The SI variation across the central 3 cm of the FOV in the image of a uniform phantom was less than 2% of its value at the center. The animal was positioned so that the brain, typically 1.5 cm in diameter, was located at the radiofrequency coil’s center.

Five T1-weighted and one T2-weighted control images were collected prior to induction of trauma and injection of the Gd-DTPA. Following the acquisition of control images, the animals were removed and subjected to the insult. The Gd-DTPA was injected at a dose of 0.2 mmol/kg immediately before trauma via the femoral vein catheter. The animals were then repositioned in the magnet and data acquisition was conducted at 1.5-minute intervals from 4 to 73 minutes postinjury. In 15 animals from Group III (TO), Gd-DTPA was injected 15 (Group IIIb, five animals), 30 (Group IIIC, five animals), and 60 minutes (Group IIIId, five animals) after the trauma; whereas in six animals of Group IV (THH), Gd-DTPA was injected only 60 minutes postinjury (Group IVb).

The percentage change in SI of the previously described regions was calculated as follows:

$$\Delta SI (\%) = \left( \frac{SI_i - SI_0}{SI_0} \right) \times 100,$$

where SI is the normalized intensity t minutes after trauma, and SI0 is the normalized intensity before trauma.
Acute posttraumatic blood-brain barrier changes

We reasoned that the rate of movement of an intravascular marker to the extracellular space is a function of the BBB permeability–surface area product, the CBF, and the plasma volume. In this study we measured SI enhancement and plotted this value as a function of time (Fig. 1). The intensity enhancement is dependent on Gd-DTPA concentration in the tissue and, primarily, the blood volume as well as tissue relaxation times (T₁, T₂) and the image acquisition parameters. In the tissue contrast-enhancement curve, the initial rising slope after injection is primarily related to the blood volume or vascular volume fraction, the maximum enhancement ratio is related to the Gd-DTPA uptake (concentration) of the tissue, and the decay rate is related to the clearance of tracer from tissue.

To avoid the effect of blood volume changes, the maximal SI enhancement was used to calculate the severity of BBB disruption.

Measurements of ICP and CBF

Before trauma, epidural ICP was measured using a microsensor ICP transducer via a burr hole in the skull 5 mm anterior to the right coronal suture. Immediately after trauma, CBF was measured using laser Doppler flowmetry. Placement of the flowmetry probe in the cortex was performed through a burr hole placed 2 mm lateral from the midline, just caudal to the coronal suture. Throughout the experiment, the probe was kept in a fixed position and a constant flow signal was obtained. The laser Doppler flowmetry rate, ICP, and MABP were continuously monitored using a computerized recording system that recorded one value every 0.05 seconds. In the ICP/CBF bench study, ICP and CBF were continuously measured for 2 hours.

Water Content

Microgravimetric analysis was performed on the same slices for which MR imaging was performed. One-cubic millimeter brain pieces were sampled from both white and gray matter. Specific gravity and water content were obtained using a calibrated gravimetric column of kerosene and bromobenzene.

Sources of Supplies and Equipment

Elkins–Sinn, Inc. (Cherry Hill, NJ) provided the pancuronium bromide and the atropine sulfate, and Magnevist (Berlex Laboratories, Wayne, NJ) provided the Gd-DTPA. The Biospec magnet used for MR imaging was obtained from Bruker Instruments (Billerica, MA). To obtain ICP measurements we used a microsensor ICP transducer manufactured by Codman, Johnson and Johnson Professional, Inc. (Randolph, MA), and to obtain CBF measurements we used a Laser Pro, Model BPM 403, available from TSI, Inc. (St. Paul, MN).

Statistical Analysis

Values shown in figures are means ± standard deviation (SD) unless otherwise specified. Statistical analysis was performed using Student’s paired and unpaired t-test. Correlations between two parameters under study were calculated using linear regression analysis. A 95% confidence level was considered statistically significant.

Results

There were no significant differences in rectal temperature, MABP, arterial blood pH, PCO₂, or PO₂ between the experimental groups at baseline. The degree of PCO₂, PO₂, and MABP during secondary insult did not differ in the HH and THH groups.

Intracranial Pressure

The baseline ICP varied between 4 and 6 mm Hg before the impact and remained constant in the control group during the 2-hour period of study. The ICP in the TO and THH groups was not different at the time of impact (310 ± 124 mm Hg; 323 ± 112 mm Hg). However, after the injury, the ICP levels demonstrated different time patterns. The ICP in the TO group had a transient increase with a maximum value of 28 ± 3 mm Hg at 30 minutes, whereas the ICP in the THH group increased linearly with time following resuscitation, reaching 35 mm Hg at 90 minutes (Fig. 2 upper) and a plateau of 64 ± 24 mm Hg at 3 hours after trauma.

Mean Arterial Blood Pressure

The resting MABP of the rats in the four groups was 96 ± 9 mm Hg. At the moment of the impact, the MABP moderately increased and reached a maximum level within 5 seconds. In the TO group this transient increase was immediately followed by a period of hypotension and then a gradual return to control values within 16 ± 3 minutes. In the HH and THH groups, the MABP declined significantly during the 30-minute secondary insult. With resuscitation, the MABP in the HH group recovered to control levels within 30 minutes, whereas in the THH group, the recovery of MABP was significantly slower after the secondary insult (Fig. 2 center).

Cerebral Blood Flow

Cerebral blood flow remained constant throughout the 2 hours in the control group. In the TO group, the CBF decreased during posttraumatic hypotension, reaching levels of 60% of control, and then increased concurrently with the recovery of MABP. After 30 minutes a pronounced hyperemia was observed as levels reached 250%
to 300% (as compared to resting values), which lasted more than 2 hours. In the THH group, the animals did not respond in the same manner to resuscitation. In three of four cases, the reduction in CBF after the secondary insult was continuous except for a 15-minute transient increase after resuscitation. This low CBF value was due to the combined effect of the poor recovery of MABP and the elevation of ICP after resuscitation yielding a low cerebral perfusion pressure (CPP). Beyond 1 hour after trauma, the marked elevation in ICP was the cause of the low CBF (CPP ≤ 40 mm Hg) (Fig. 2 lower). In one case, CBF and CPP increased as a result of the recovery of MABP within 2 hours after trauma, but CBF decreased sharply after 2 hours due to the increased ICP.

**Fig. 2.** Graphs displaying time courses of intracranial pressure (ICP) (upper), mean arterial blood pressure (MABP) (center), and cerebral blood flow (CBF) (lower). Baseline measurements were obtained immediately before induction of trauma and/or secondary insult, which occurred 30 minutes later. Values are the means ± standard error (SE) of the mean. Upper: Note the rapid increase of ICP following reperfusion. Center: In the trauma only (TO) group the trauma was followed by a period of hypotension and then a gradual return to control values within 16 ± 3 minutes. In the hypoxia and hypotension (HH) group and in the trauma coupled with hypoxia and hypotension (THH) group, hypotension and hypoxia were induced in the rats. In the HH group, MABP immediately recovered, but in the THH group, MABP did not recover following resuscitation. Lower: The CBF did not change throughout the 4 hours in the sham-operated control group. In the TO group, CBF decreased during the posttraumatic hypotension period and then a hyperemic reaction was observed with a maximum value recorded at 2 hours postrecovery. In the THH group the reduction in CBF during secondary insult was continuous after resuscitation.

**Fig. 3.** Graphs displaying mean signal intensity (SI) changes in diffuse brain injury. Upper: Time course of SI changes in T₁-weighted magnetic resonance images of the trauma only (TO) groups. Lower: Time course of SI changes in T₁-weighted images of trauma with secondary insult and secondary insult groups. Control (Group I) = gadolinium–diethylenetriamine pentaacetic acid (Gd-DTPA) injection, no trauma. Hypoxia & hypotension (Group II) = hypoxia and hypotension. TO (Group IIIa) = trauma and Gd-DTPA injection at the same time; TO-15 (Group IIIb) = Gd-DTPA injection at 15 minutes postinjury; TO-30 (Group IIIc) = Gd-DTPA injection at 30 minutes postinjury. Trauma + hypoxia & hypotension (Group IVa) = trauma coupled with hypoxia and hypotension (trauma and Gd-DTPA injection in the same time). The maximum deviation for the experimental data is less than 6% and is therefore not shown in the figures.
Acute posttraumatic blood-brain barrier changes

**Dynamic Progression of BBB Damage**

The T₁-weighted images obtained as soon as 4 to 6 minutes after Gd-DTPA injection revealed a 32% SI increase in the muscles. There was no difference between the groups: it was 32% ± 8% in Group I, 26% ± 5% in Group II, 32% ± 12% in Group IIIa, 34% ± 9% in Group IIIb, 34% ± 6% in Group IIIc, and 32% ± 6% in Group IV.

Although the washing out of contrast from the muscle was faster in the sham-operated control group (16% enhancement was achieved 50 ± 3 minutes (half time) after injection) than in the TO (58 ± 4 minutes) or the THH group (92 ± 8 minutes), the intensity did not change significantly in the muscle during the first 30 minutes after trauma in either group. The SI enhancement changes in the brain for the four groups (Groups I–IV) are shown in Fig. 3. To illustrate more clearly the BBB disruption, the duration (as long as SI increased) and severity (maximum SI) of the BBB opening was calculated and plotted as described in Fig. 1. These data are summarized in Fig. 4.

**Group I (Control).** Signal intensity gradually increased in the brain during the first 13 minutes after Gd-DTPA injection and achieved a maximum value of 2% ± 1% between 13 and 75 minutes (Figs. 3–5).

**Group II (HH).** The Gd-DTPA injection did not alter the SI during the time of hypotension and hypoxia. At 30 minutes, however, a rapid and significant enhancement (6% ± 1%, p < 0.001) was observed, which paralleled the recovery of the blood pressure (Figs. 3 lower and 4). This transient enhancement may in part be explained by blood volume changes; however, the maximum intensity remains a function of barrier permeability.

**Group IIIa (TO, Trauma, and Gd-DTPA Injection at the Same Time).** Four minutes after the head injury and Gd-DTPA injection, significant bilateral increases in SI (9% ± 4%, p < 0.01) were visible on the MR images. During the next 20 minutes, the SI increased only slightly and reached its maximum value of 11.5% ± 6% at 26 minutes after trauma (Figs. 3 upper, 4, and 5). However, this enhancement was not homogeneous throughout the whole brain; that is, it was greatest (16% ± 4%) in the corpus callosum, less pronounced (11.5% ± 4%) in the cortex, and only moderate (6% ± 4%) in the caudate nucleus (Fig. 6). However, the differences between cortex and corpus callosum were not statistically significant. Throughout the remainder of the experiment, the SI did not change, remaining at the maximum value.

**Group IIIb (TO, Gd-DTPA Injection 15 Minutes After Trauma).** Following the injection of Gd-DTPA, a slight but significant increase in SI was visible corresponding to the whole brain (4% ± 2%). The cortex and the corpus callosum (5% ± 2%, and 6% ± 2%, p < 0.05) remained unchanged throughout the experiment (Fig. 3 upper).

**Group IIIc and Group IIId (TO, Gd-DTPA Injection 30 or 60 Minutes After Trauma).** The 10 animals in which Gd-DTPA was injected at 30 or 60 minutes postinjury showed SI changes similar to the sham-operated control group and no significant increase in SI was observed (Fig. 3 upper).

**Group IVa (THH, Trauma, and Gd-DTPA Injection at the Same Time).** A significant intensity enhancement was observed on the first images of Group IVa (6% ± 3%, p < 0.01); however, it was less pronounced when compared to the animals that were subjected to trauma alone. Although the further time-course study of MR signals showed gradually increased SIs during hypotension and hypoxia, the most definitive change occurred at the time of recovery (30 minutes postinjury). The SI increased 4% and reached its maximum value (12% ± 3%) within 3 minutes. As in the other groups, the SI did not change further and this high value was maintained during the entire duration of the experiment (Figs. 3 lower, 4, and 5). The
cerebral cortex and the corpus callosum showed the highest enhancement in each animal of this group and the mean value of the maximum percentage change was 13% ± 4% and 15% ± 6% in the two regions (Fig. 6).

Group IVb (THH, Gd-DTPA Injection 60 Minutes After Trauma). The six animals in which the Gd-DTPA was injected only 60 minutes postinjury showed SI changes similar to the rats in the control group and no significant increase was observed, indicating that the BBB was closed.

Water Content

In the control group, the water contents of the cerebrum, cerebellum, cortex, and thalamus were 78.76% ± 0.29, 75.73% ± 0.21, 79.5% ± 0.49, and 79.13% ± 0.18%, respectively. The water content of the cerebellum was significantly lower than that of the cerebrum (p < 0.001). In the HH group the cortex showed significantly higher water content (80.08% ± 0.36%, p < 0.05), whereas in the other regions in this group there was no change. The cortex in the TO and THH groups yielded significantly higher water content (80.12% ± 0.59%, p < 0.05; 80.76% ± 0.91%, p < 0.01) than that in the animals of the control group. The estimated water content of the cerebrum and cerebellum also increased in the TO and THH group animals at 90 minutes after the injury (79.24% ± 0.38%, p < 0.001; 76.22% ± 0.67%, p < 0.05, and 79.78% ± 0.69%, p < 0.001; 77.53% ± 1.55%, p < 0.01, respectively) (Fig. 7).

Discussion

The results of the present study indicate that the BBB opening in diffuse closed head injury is rapid and transient, beginning immediately after impact and closing within 30 minutes after impact. The addition of posttraumatic hypoxia and hypotension prolongs the duration of barrier opening by an additional 7 to 8 minutes; however, the permeability during this extended opening is not significantly different from animals subjected to trauma alone. Taken in concert, these findings lend support to the hypotheses that continued swelling beyond this relatively brief period of BBB compromise must be cellular in nature and that the contribution of vasogenic edema in traumatic diffuse injury may be overemphasized. Finally, MR imaging, due to its noninvasive character, is an excellent technique to follow (time resolution 1–1.5 minutes) the evolution of trauma-induced BBB damage from as early as a few minutes up to hours or even longer after the trauma.

Measurement of BBB Changes Using MR Imaging Techniques

The present findings are in agreement with previous reports that demonstrate that MR imaging with application of a T₁-shortening contrast agent is capable of monitoring in vivo the compromise of the BBB following hyperosmotic shock,30,34 hypoxia–ischemia,16 and brain tumors.23 However, only two studies have followed the early BBB changes quantitatively.30,34 Rhine, et al.,34 using hyperosmotic shock (arabinose, urea) and a similar method for demonstrating BBB disruption, found that Gd-DTPA injection enhances SI in the tissues outside the barrier by 17% to 33%, without affecting the intensity in normal brain tissue. These results are in accordance with our findings, which showed an insignificant (2%) increase in the SI of the normal brain (control animals) but a marked increase (32% ± 8%) in the muscles. However, it should be noted that the hyperosmotic barrier opening induced by a concentration of arabinose is not equivalent to the insult...
Acute posttraumatic blood-brain barrier changes
due to head injury. We think that this is one of the reasons
why we could not observe such a high increase (24%) in
the SI even in our THH group animals (12%). Moreover,
this difference suggests that the BBB breakdown observed
in the TO or THH group was only partial. This supports
the principal finding of this study, namely, that the BBB
opening is transient and rapidly reestablishes itself.

Transitory BBB Opening in Diffuse Injury

The evidence of the transient opening can be seen from
the time course of the intensity changes (Figs. 3 upper
and 4). The BBB for the TO group opens within a few minutes
after injury, gradually approaches a plateau at 26 minutes
posttrauma, and remains constant thereafter. Because the
elevated SI did not change during the next 60 minutes, we
also presume that the Gd-DTPA is trapped in the brain. At
15 minutes postinjury (Fig. 3 upper) Gd-DTPA injection
revealed only slight permeability disturbances; therefore,
we may also assume that the BBB breakdown is most severe
during the first 15 minutes after brain injury.

Effect of Secondary Insult on BBB Permeability

The fact that the BBB is closed 30 minutes after injury
in the TO group (Group IIc) and 60 minutes in the THH
group (Group IVb, Figs. 3 and 4) supports our contention
of the transient pattern of BBB opening in diffuse injury
and with secondary insult. Although many studies have
been published on BBB disruption caused by traumatic
brain injury, only very few investigations followed the
early changes.2,4,28,30,31 Our results are consistent with pre-
vious reports on the integrity of the BBB and the role of a
permeability deficit in the formation of cerebral edema
using other models of head injury.2,4,28,30,31 These studies
analyzed permeability defect of short duration and report-
ed increased permeability of BBB to trypan and Evans
blue, phosphate ion, and different proteins (M_r 44,000–
820,000) following trauma. Moreover, they also showed
that the percentage of the BBB leakage was seen between 0 and
30 minutes. Another study found no BBB breakdown at
30 seconds after moderate head injury.28 Our work cannot
exclude this possibility because our earliest measurements
were taken at 4 to 6 minutes following severe injury.
Although the 30-minute period of transient BBB opening
shown in our study is sufficient to produce signifi-
cant water content increase (0.5% in the cerebral and
cerebellum, 90 minutes postinjury), other features such as
delayed barrier opening and astrocytic swelling might also
contribute to further development of edema, particularly
as this late edema begins a few hours postinjury and has a
maximum effect between 3 and 8 days after trauma.2,4,28,30,31
Further studies are necessary to determine their applica-
tion to diffuse injury. Finally, it is important to empha-
size that the permeability changes observed in these stud-
ies were associated with a severe level of trauma and the
maximum duration of secondary insult possible, which in
combination would permit adequate resuscitation. It is
interesting to note the relatively rapid barrier closure
under these circumstances.

Regional Changes in BBB Permeability in Diffuse Injury

Based on these observations, we conclude that during
the transient breakdown of the BBB, Gd-DTPA may enter
both extracellular space and cellular compartments. After
the rapid closure of the barrier and sealing of the axons,21,22
Gd-DTPA is trapped intra- and extracellularly. It is rea-
sonable to assume that further studies are necessary to
clarify the predominant type of edema (cellular or vaso-
genic) that is associated with diffuse swelling following
traumatic brain injury. In addition, it is quite possible that
a delayed barrier opening could occur and additional stud-
ies are necessary to examine permeability changes beyond
3 hours. The relatively noninvasive nature of the methods
described here makes these types of studies practical and
allows each animal to serve as its own control.

As seen in Fig. 6, the gross breakdown of the BBB was
not uniform in the brain (it was most pronounced in the
corpus callosum and in the cortex) and was not even local-
ized at the site of the injury in contrast to other models of
head injury. This observation conforms to the concept that
trauma in this closed head injury model results in a gen-
eralized, diffuse injury and not a supratentorial focal brain
lesion.6 Nevertheless, further investigations are necessary
to identify the cause and the precise nature of the hetero-
genous BBB opening. In this regard, we must consider
that our measures of intensity in corpus callosum may be
influenced by partial volume artifacts due to the relatively
small size of the brain and the pixel size used in this study
(0.3 mm). Also it should be noted that the different relax-
ation times (T1/T2) for gray and white matter will have
some effect on the relative intensity magnitudes. For these
reasons, it is difficult to quantitate accurately regional dif-
fferences.

Effect of Initial Hypertensive Surge on the BBB

The mild and transient hypertension followed by a peri-
od of sustained hypotension seen in this closed head injury
model is in contrast to the documented prolonged surge of
arterial pressure after using the fluid-percussion model.5
Whereas in both models the barrier is compromised, in
closed head injury pathological events other than severe
hypertension are also responsible for the BBB disruption.
However, the difference in SI enhancement between the
TO and the THH groups (Fig. 3) during the first 30 min-
utes postinjury reflect the importance of blood pressure
and blood flow in the initial BBB breakdown.

In the THH group rapid enhancement in SI (Gd-DTPA
leakage) developed shortly after the trauma and during
the restoration of MABP and CBF. Others have reported a
similar early, transient opening and a delayed opening of
the BBB after transient ischemia due to vessel occlusion:
the first opening at the reactive hyperemia after reperfu-
sion and a second opening more than 5 hours after the
ischemic insult.12,15,39,40 Because we monitored the BBB
opening at 6 to 120 minutes postinjury we could only
demonstrate the additive effect of the first barrier opening.

Increase in Tissue Water With Secondary Insult

The water content measurement (Fig. 7) indicates an
increase of 1% for the THH group compared to 0.5% for
the trauma group 2 hours postinjury. These findings, in
accord with Kita and Marmarou’s work,13 also support the
hypothesis that secondary insult after brain injury pro-
longs the breakdown of the BBB.
Conclusions

Diffuse closed head injury is associated with a rapid and transient BBB opening to gadolinium that begins at the time of the trauma and approaches closure at approximately 25 to 30 minutes. Posttraumatic secondary insult prolongs the breakdown of the BBB. Magnetic resonance imaging, because of its noninvasive character, is an excellent technique to follow (time resolution 1–1.5 minutes) the evolution of trauma-induced BBB damage from as early as a few minutes up to hours or even longer after the trauma.

In summary, the rapid closure of the barrier observed in this experimental model provides further support for our hypotheses that the vasogenic component of edema may be overemphasized and that the predominant form of edema may be cellular in nature. Further studies are necessary to clarify this issue.

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