Characterization of edema by diffusion-weighted imaging in experimental traumatic brain injury

JUNKI ITO, M.D., ANTHONY MARMAROU, PH.D., PAL BARZÓ, M.D., PH.D., PANOS FATOUROS, PH.D., AND FRANK CORWIN, M.S.

Division of Neurosurgery and Department of Radiology, Medical College of Virginia, Richmond, Virginia

The objective of this study was to use diffusion-weighted magnetic resonance imaging (DWI) to help detect the type of edema that develops after experimental trauma and trauma coupled with hypotension and hypoxia (THH). Reduction in the apparent diffusion coefficients (ADCs) is thought to represent cytotoxic edema. In a preliminary series of experiments, the infarction edema model and middle cerebral artery occlusion models were used to confirm the direction of ADC change in response to purely extracellular and cytotoxic edema, respectively. The ADCs increased (p < 0.05) in the case of extracellular edema and decreased (p < 0.001) in cytotoxic edema.

Following these initial experiments, a new impact acceleration model was used to induce traumatic brain injury. Thirty-six adult Sprague-Dawley rats were separated into four groups: sham, trauma alone, hypoxia and hypotension (HH), and THH. Following trauma, a 30-minute insult of hypoxia (PaO2 of 40 mm Hg) and hypotension (mean arterial blood pressure (MABP) of 30 mm Hg) were imposed and the animals were resuscitated. The DWI was carried out at four 1-hour intervals postinjury, and MABP, intracranial pressure (ICP), cerebral perfusion pressure (CPP), and cerebral blood flow (CBF) were monitored. The ADCs in the control and HH groups remained unchanged. The ADCs in the THH group rapidly decreased from a control level of 0.68 ± 0.05 × 10−3 mm²/second to 0.37 ± 0.09 × 10−3 mm²/second by 3 hours posttrauma (p < 0.001). In this group, the decreased CBF and CPP during secondary insult remained low despite resuscitation, with the ICP increasing to 56 ± 7 mm Hg by 3 hours. In the trauma alone group, the rise in ICP reached a maximum value (28 ± 3 mm Hg) at 30 minutes with a significant and sustained increase in CBF despite a gradual decrease in CPP. The ADCs in this group were not significantly reduced. The data lead the authors to suggest that the rise in ICP following severe trauma coupled with secondary insult in this model is predominately caused by cytotoxic edema and that ischemia plays a major role in the development of brain edema after head injury.

KEY WORDS • brain edema • magnetic resonance imaging • traumatic brain injury • diffusion-weighted imaging • secondary insult • rat

In vivo diffusion-weighted magnetic resonance imaging (DWI) is a new magnetic resonance (MR) technique, which, by using additional strong magnetic field gradients, is sensitized to the random, microscopic translational motion of water protons. Apparent diffusion coefficient (ADC) maps can be derived from a series of DWI images obtained with varying magnetic field gradients. Recent findings in experimental cerebral ischemia models indicate that ADCs could provide earlier and more specific information about ischemic tissue damage and its characteristics of edema. In the past, a clear distinction was made between vasogenic and cytotoxic edema associated with ischemia. Cellular swelling often occurs as a result of ionic disruption, independent of the presence of edema. It appears now that all three forms of edema—vasogenic, cytotoxic, and cytogenic—may contribute to the increased tissue water that occurs following trauma and the often concurrent neurotoxicity. These considerations have prompted us to concentrate on identifying the contribution of each form to the brain-swelling process.

Raised intracranial pressure (ICP) subsequent to brain edema is the single most frequent cause of death in head-injured patients. In earlier studies Narayan and colleagues reported a 51% mortality rate in patients whose ICPs exceeded 20 mm Hg compared to a 16% mortality rate in patients with normal ICP. A recent analysis by the American Traumatic Coma Data Bank indicates that the probability of mortality and morbidity increases with time during elevated ICP levels above 20 mm Hg. Thus raised ICP continues to be a prominent feature of severe traumatic head injury. However, the mechanisms that lead to brain edema formation and subsequent ICP rise remain unclear.

The objective of this study was to use DWI to help
detect the type of edema that develops after experimental trauma and to follow the temporal course of the ensuing swelling process.

Materials and Methods

Preliminary Series

Prior to the studies of mechanical trauma, an initial series of experiments was performed to study the direction of ADC change in response to extracellular (vasogenic) and cellular (cytotoxic) forms of edema. To induce vasogenic edema, the infusion model was used to introduce slowly a fluid of known composition into the brain parenchyma of Sprague-Dawley rats anesthetized with halothane and mechanically ventilated to maintain normocapnic conditions. In these studies, a total of 45 µl of mock cerebrospinal fluid was introduced into the left basal ganglia of the rats at a rate of 20 µl per hour over a period of 1 hour. Previous studies have confirmed that the fluid is confined to the extracellular space. The ADCs were then determined 1 hour after the infusion ceased. The animals were allowed to recover and ADC measurements were again obtained at 24 hours.

In a second series of experiments using similarly prepared Sprague-Dawley rats, the middle cerebral artery (MCA) occlusion model was used to produce cytotoxic edema. Measurements of ADCs were obtained 3 hours after occlusion, when it has been shown that the cellular barrier remains intact and the edema produced is confined to the cells. Animals were allowed to recover and ADC measurements were obtained 24 hours after occlusion.

In each of these preliminary series, three animals, subjected to the same preparatory procedures but not infused or rendered ischemic, were used for control purposes. The ADC measures for these animals were obtained for purposes of comparison during the same time intervals as the animals undergoing infusion or occlusion.

Experimental Procedures: Impact–Acceleration Mechanical Injury

Sixteen adult male Sprague-Dawley rats were used for the ICP/cerebral blood flow (CBF) bench study, and 20 for the MR imaging studies. The rats, weighing 340 to 375 g, were divided into four subgroups within their major groups, ICP/CBF bench study and the MR imaging study, respectively, as follows: 1) control, four and six animals; 2) hypotension and hypoxia (HH); four and four animals; 3) trauma alone, four and four animals; and 4) trauma coupled with hypotension and hypoxia (THH), four and six animals.

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

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. Around stainless steel disk was mounted on the skull using a specially designed stereotactic device that included both ear and mouth supports mounted inside the cylinder. The disk was used to produce skull fracture. After trauma, the rat was rapidly reconnected to anesthesia and artificially ventilated. The animals were injected intravenously with a 0.02 mg/kg dose of atropine sulfate before trauma to reduce mucus secretions.

In the HH and the THH groups, hypotension was induced by withdrawing arterial blood into a heparinized syringe during the first 5 minutes following trauma until an MABP of 30 mm Hg was sustained for 30 minutes. After hypotension, all blood withdrawn 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 prior to trauma to control ventilation. Rats that died on impact or experienced severe skull fractures were excluded from this study.

Measurements of Intracranial Pressure and Cerebral Blood Flow

Before trauma, epidural ICP was measured using a microsensor ICP transducer (Codman, Johnson & Johnson Professional Inc., Randolph, MA) 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 (Laser Pro, BPM 403A; TSI Inc., St. Paul, MN). 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 4 hours. In the MR imaging study, only the ICP was measured until the rats were returned to the magnet and after the final DWI measurement.

Magnetic Resonance Imaging

Experiments were performed using a 2.35-tesla, 40-cm bore magnet ( Biospec; Bruker Instruments, Billerica, MA) equipped with a 12-cm inner-diameter actively shielded gradient insert. Radiofrequency excitation and reception were performed using a 7-cm inner-diameter “bird cage” design resonator. To minimize any macroscopic motion artifacts, each rat was placed prone and immobilized within a plastic cylinder; its head was rigidly supported with a specially designed stereotactic device that included both ear and mouth supports mounted inside the cylinder.

The DWI used either a stimulated-echo (STEAM) or spin-echo (SE) sequence appropriately modified to include diffusion-sensitizing gradients along the readout (horizontal) direction with a gradient duration (for the SE) of 3 msec and a gradient separation of 20 msec. Each dataset consisted of two parallel coronal slices (3-mm thick, 4-mm center-to-center separation), 256 × 128 matrix size, repetition time (TR) of 1500 msec (SE), and 40-mm field of view. Diffusion weighting factors, or b values, of 10, 200, 400, and 600 seconds/mm² were used (maximum gradient strength of 15 G/cm). Apparent diffusion coefficient maps were generated for each slice using a maximum entropy algorithm. The effect of the frequency encoding gradients was included in the ADC calculations. The values of the ADCs were determined in the chosen anatomical slice in the cerebral cortex corpus callosum and basal ganglia. Reference tubes that contained water were positioned beside the head to verify the system calibration and stability.

Baseline DWIs were first obtained. The rat was then removed from the MR imager, subjected to head injury and/or secondary insult, and returned to the magnet. Images were obtained sequentially for 4 hours. Prior to assessment of the ADCs, T₁ and T₂ images were obtained to confirm the absence of intracerebral hematoma in the region of interest.

Histological Examination

Immediately after the final DWI and measurement of ICP were obtained, the rats, maintained under deep anesthesia, underwent transcardiac perfusion with normal saline followed by 400 ml of 4% paraformaldehyde in Millonig’s buffer fixative solution. The brains were removed from the skull and stored in the same fixative overnight. Prior to cutting, the brains were placed in Millonig’s buffer for 1 hour. For light microscopy, the brains were cut into 2-mm thick coronal sections and embedded in paraffin blocks. Seven-micrometer-thick coronal sections, selected to correspond to the DWI slices, were cut and stained with hematoxylin and eosin.

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Statistical Analysis

Values provided in all tables and graphs are shown as the means ± standard error of the means. Statistical analysis was performed using Student’s paired and unpaired t-test. Correlations between the two parameters were calculated by using linear regression analysis. A 95% confidence level was considered statistically significant.

Results

Preliminary Series 1: Measurement of ADCs in Infusion Edema

The change in ADCs following the extracellular edema series is shown in Fig. 1 upper. With extracellular edema, ADC values measured at 1 hour postinfusion increased (p < 0.05) from baseline value. As the edema resolved, the ADCs returned to baseline by 24 hours postinfusion.

Preliminary Series 2: Measurement of ADCs in Cytotoxic Edema

The change in ADCs following middle cerebral artery occlusion is shown in Fig. 1 lower. With predominately cytotoxic edema, the ADC values decreased at 1 hour postocclusion and remained decreased over the 24-hour period (p < 0.001).

Impact Acceleration Injury

Physiological changes in each group are summarized in Table 1. There were no significant differences in rectal temperature, MABP, arterial blood pH, PCO₂ or PO₂ between the experimental groups at baseline. The degrees of hypoxia and MABPs during secondary insult did not differ in the HH (PCO₂ 32 ± 3 mm Hg; PO₂ 44 ± 14 mm Hg), and THH (PCO₂ 37 ± 4 mm Hg; PO₂ 43 ± 11 mm Hg) groups. There were significant intergroup differences in arterial pH during secondary insult (p = 0.03; THH 7.25 ± 0.07, p < 0.05).

Intracranial Pressure

The mean ICP ranged between 4 and 6 mm Hg before the impact and remained constant in the control group during the ensuing 4 hours. In the trauma alone group, the rise in ICP was immediate and reached a maximum value (28 ± 3 mm Hg) at 30 minutes, followed by a gradual decrease that remained above baseline. In the THH group,
ICP rapidly increased 30 minutes after resuscitation and remained elevated, reaching a plateau at 3 hours after trauma (Fig. 2).

Mean Arterial Blood Pressure

At the moment of impact, the MABP increased and reached a maximum level within 5 seconds. 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 trauma alone group, MABP significantly increased at 30 minutes after trauma and then gradually decreased. 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 near control levels within 30 minutes; however, in the THH group, MABP recovery was significantly slower (30 minutes after resuscitation) (Table 1).

Cerebral Perfusion Pressure and Cerebral Blood Flow

The cerebral perfusion pressure (CPP) was calculated as the difference between MABP and ICP. The CBF and CPP did not change within 4 hours in the control group. In the trauma alone group, a transient and slight decrease in ICP 30 minutes after trauma; however, because there was a similar increase in MABP the CPP remained unchanged. After 2 hours, the CPP gradually decreased in parallel with the MABP (Fig. 3 upper). The CBF decreased during posttraumatic hypotension and then a hyperemic reaction was observed with a maximum value at 2 hours postrecovery. In the THH group, the reduction in CBF during secondary insult was continuous after resuscitation, but the CPP decreased below 40 mm Hg after 2 hours due to the increased ICP.

Apparent Diffusion Coefficients

Control and the Hypotension and Hypoxia Groups. The ADCs at baseline were $0.68 \times 10^{-3} \pm 0.05 \times 10^{-3}$ mm$^2$/second in the cortex, $0.69 \times 10^{-3} \pm 0.07 \times 10^{-3}$ mm$^2$/second in the thalamus, and $1.11 \times 10^{-3} \pm 0.10 \times 10^{-3}$ mm$^2$/second in the corpus callosum. These results are in agreement with published values. The ADCs in these groups remained unchanged throughout the experiment.

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![Graphs showing the time course of the apparent diffusion coefficients (ADCs) acquired in the cerebral cortex (upper) and in the thalamus (lower). Baseline measurements were obtained immediately before the trauma and/or at secondary insult 30 minutes later. Values shown are the means ± standard error of the means. HH = hypotension and hypoxia; THH = trauma coupled with hypotension and hypoxia.](image)

reduction in ADCs occurred within the first 60 minutes. The ADCs reached their lowest values at 3 hours in the cortex \((0.37 \times 10^{-3} ± 0.11 \times 10^{-3} \text{ mm}^2/\text{sec})\) (Fig. 4 upper) and at 4 hours in the thalamus \((0.40 \times 10^{-3} ± 0.11 \times 10^{-3} \text{ mm}^2/\text{sec})\) (Fig. 4 lower). The reduction in ADC values in the thalamus (17%) at 2 hours was less than that in the cortex (44%).

**Apparent Diffusion Coefficient Image.** A set of three ADC images from the THH group is shown in Fig. 5. These images show a diffuse hypointense area in the cortex at the coronal level 2 hours and a diffuse hypointense area in the cortex and the thalamus 4 hours after trauma.

**Histological Findings**

Histopathological studies using light microscopy were performed 4 hours after trauma. Examination of bilateral areas of the supraventricular cerebral cortex directly under the helmet as well as of the thalamus revealed neuronal injury. Perineurial astrocytic swelling accompanied by vacuolation was observed in those animals with decreased ADCs, that is, those in the THH group (Fig. 6 right). Groups that did not show a reduction in ADCs did not exhibit astrocytic changes (Fig. 6 left and center).

**Discussion**

One objective of these studies was to use ADCs to examine the temporal course and type of edema that occur with traumatic brain injury coupled with secondary insult. In this process, it was essential to determine if the ADCs were of sufficient sensitivity and specificity to detect different forms of edema. Importantly, our initial studies of models that produce purely extracellular and cytotoxic edemas indicated that ADCs increase with vasogenic and decrease with cytotoxic forms of edema. These studies provide further confirmation that ADC measurements can distinguish among edema types.

**Changes in ADCs in Cortex and Thalamus**

Several previous studies of brain ischemia have shown that ischemic tissue is characterized by reductions in ADC values.1,2,5,14,15 Although the precise mechanisms underlying the reduction in ADCs in ischemia are uncertain, it is thought to represent the onset of intracellular water accumulation or cytotoxic edema.1,3,21 After the onset of ischemia, tissue–adenosine triphosphate reserves are depleted, and the subsequent failure of the Na+/K+-adenosine triphosphatase pump causes water protons and ions to migrate from the faster-diffusing, extracellular space into the...

![Apparent diffusion coefficient (ADC) images of coronal sections at baseline (left) and at 2 hours (center) and 4 hours (right) after trauma in the trauma coupled with hypotension and hypoxia group. The ADC images reveal hypointensity in the cortex at 2 hours (arrows), and in the cortex and the thalamus at 4 hours after trauma.](image)
The most striking features are the swelling of the perineural astrocytic processes in the THH group (arrows). H & E, original magnification × 300.

Fig. 6. Photomicrographs showing histological sections obtained from control tissues (left) and at 4 hours after trauma from the trauma alone group (center) and the trauma coupled with hypotension and hypoxia (THH) group (right). The most striking features are the swelling of the perineural astrocytic processes indicating cytotoxic edema.

Marmarou8 reported that the THH group showed the same increase in ICP as the trauma alone group and the trauma coupled with hypotension and hypoxia (THH) group, but this increase was less than in the cortex. This result was consistent with the conclusion reached in this work that the major component of the increased ICP in the THH group was brain edema. In our study, the change in ICP, which reached a plateau after 3 hours, correlated with changes in ADCs. Using the same trauma model, Kita and Marmarou9 reported that the THH group showed an increase in ICP after recovery from secondary insult with the reduction of tissue energy metabolism as detected by 31P spectroscopy. Our results support the belief that brain ischemia associated with severe trauma may play a large role in the reduction in ADCs, as reflected by the disruption of tissue energy metabolism. However, further studies are necessary to clarify this issue, particularly chronic experiments in which tissue atrophic factors are also involved.

Changes in ICP After Head Trauma

In the THH group, a rapid increase in ICP occurred just after recovery from secondary insult with the reduction in ADCs. Using the same trauma model, Kita and Marmarou9 reported that the THH group showed the same increase in ICP (36 ± 6 mm Hg) and that water content significantly increased in the cortex 2 hours after trauma. According to this study, cerebral blood volume decreased. The conclusion reached in this work was that the major component of the increased ICP in the THH group was brain edema. In our study, the change in ICP, which reached a plateau after 3 hours, correlated with changes in ADCs. The reduction in ADCs in the thalamus at 2 hours was less than that in the cortex. This result was consistent with the conclusion that vasogenic edema is compatible with either a normal or reduced extracellular space, at least within 4 hours after trauma. Taking these factors in concert, we must conclude that in this model, cytotoxic edema prevailed over vasogenic edema. Recently, cytotoxic edema has been further classified based on etiology: ischemic edema is caused by reduction in blood flow, and neurotoxic edema is caused by excessive neurotransmitter release. However, we could not differentiate in this work between these two distinct forms of cellular edema.

Our results show that the secondary insult in trauma was the cause of the reduced ADC values. After resuscitation, CPP and CBF did not recover in the THH group. Yuan, et al.,25 reported that brain trauma suppresses MABP recovery after hemorrhage, mainly by inhibiting cardiac contractile performance. Traumatic head injury causes a transient decline in high-energy phosphates,9 and cerebral ischemia after trauma could be a major factor contributing to the consumption of high-energy phosphates in brain.5 Moseley and colleagues10 reported that a good correlation is found between ADCs and ischemic disturbances of energy metabolism as detected by 31P spectroscopy. Our results support the belief that brain ischemia associated with severe trauma may play a large role in the reduction in ADCs, as reflected by the disruption of tissue energy metabolism. However, further studies are necessary to clarify this issue, particularly chronic experiments in which tissue atrophic factors are also involved.

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with the earlier report of Kita and Marmarou that water content in the thalamus is less than that in the cortex. Our results and those obtained earlier support the hypothesis that brain edema is the major component of the increased ICP in this group. In conclusion, our data indirectly support the hypothesis that the rise in ICP and the associated reduction in ADCs are predominately caused by cytotoxic edema.

In the trauma alone group, the rise in ICP did not coexist with a significant reduction in ADC values. Thus it is difficult to regard the main cause of the increased ICP in this group as a cytotoxic edema. In the high level–fluid percussion injury, Miller and Corales reported that increased ICP at 15 minutes after injury is not due to brain edema but to a transient increase in intravascular pressure and CBF volume. In our model, the CBF that increased after posttraumatic hypotension was not necessarily coincident with the changes in ICP. Subarachnoid hemorrhage extended to the subarachnoid spaces over the cerebral hemispheres, but the severe ventricular dilation could not be detected in the MR imaging. We speculate that the increase in ICP during the 30 minutes following trauma may have been due to the effects of vascular engangement and/or extravasation through a transiently disrupted blood–brain barrier.

Conclusions

The rise in ICP following trauma coupled with secondary insult at the acute stage in this model is predominately caused by a cytotoxic edema. We suggest that cellular swelling plays a major role in the sequence of events leading to brain swelling after head injury.

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