The contribution of brain edema to brain swelling in cases of traumatic brain injury remains a critical problem. The authors believe that cellular edema, the result of complex neurotoxic events, is the major contributor to brain swelling and that vasogenic edema, secondary to blood-brain barrier compromise, may be overemphasized. The objective of this study, therefore, was to quantify temporal water content changes and document the type of edema that forms during the acute and late stages of edema development following closed head injury (CHI). The measurement of brain water content was based on magnetic resonance imaging—determined values of tissue longitudinal relaxation time (T₁-weighted imaging) and their subsequent conversion to percentage of water, whereas the differentiation of edema formation (cellular vs. vasogenic) was based on the measurement of the apparent diffusion coefficient (ADC) by diffusion-weighted imaging.

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In the animals subjected to trauma, the authors found a significant increase in ADC (10 ± 5%) and brain water content (1.3 ± 0.9%) during the first 60 minutes postinjury. This is consistent with an increase in the volume of extracellular fluid and vasogenic edema formation as a result of blood-brain barrier compromise. This transient increase, however, was followed by a continuing decrease in ADC that began 40 to 60 minutes postinjury and reached a minimum value on Days 7 to 14 (10 ± 3% reduction). Because the water content of the brain continued to increase during the first 24 hours postinjury (1.9 ± 0.9%), it is suggested that the decreased ADC indicated cellular edema formation, which started to develop soon after injury and became dominant between 1 and 2 weeks postinjury.

The study provides supportive evidence that cellular edema is the major contributor to posttraumatic swelling in diffuse CHI and defines the onset and duration of the increase in cellular volume.

**KEY WORDS** • traumatic brain injury • brain edema • brain water determination • posttraumatic ventriculomegaly • magnetic resonance imaging • diffusion-weighted imaging

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Contribution of vasogenic and cellular edema to traumatic brain swelling measured by diffusion-weighted imaging

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The contribution of brain edema to brain swelling in cases of traumatic brain injury remains a critical problem. The authors believe that cellular edema, the result of complex neurotoxic events, is the major contributor to brain swelling and that vasogenic edema, secondary to blood-brain barrier compromise, may be overemphasized. The objective of this study, therefore, was to quantify temporal water content changes and document the type of edema that forms during the acute and late stages of edema development following closed head injury (CHI). The measurement of brain water content was based on magnetic resonance imaging—determined values of tissue longitudinal relaxation time (T₁-weighted imaging) and their subsequent conversion to percentage of water, whereas the differentiation of edema formation (cellular vs. vasogenic) was based on the measurement of the apparent diffusion coefficient (ADC) by diffusion-weighted imaging.

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**T H E contribution of brain edema to brain swelling in cases of traumatic injury remains a critical problem. In head injury, the swelling and eventual rise in intracranial pressure (ICP) are frequent causes of death, and the poor prognosis in survivors with sustained ICP elevation has been well documented.**

**However, morphological and magnetic resonance (MR) imaging studies of edema formation following TBI cast new light on the swelling process and it is our hypothesis that the role of vasogenic edema may have been overemphasized.**

**Heretofore, cellular swelling has been termed “cytotoxic” and has usually been identified with the edema associated with ischemia. Recently, Klatzo categorized cellular swelling into “neurotoxic” and “isch-**
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In this study, we first identify whether these other types of edema play a significant role in the swelling process compared with the so-called vasogenic or “traumatic” edema, which is characterized by BBB compromise.

Two recently developed MR imaging techniques offer the opportunity of early detection and differentiation of the edema formation. The first of these novel imaging techniques is diffusion-weighted imaging. Because it has additional strong magnetic field gradients, this method is sensitive to the random, microscopic translational motion of water protons and provides an image of the apparent diffusion coefficients (ADCs). In our previous studies, a series of experiments was performed to follow the direction of ADC change to extracellular (vasogenic) and cellular (cytotoxic) forms of edema. The second imaging technique allows increased with vasogenic and decreased with cytotoxic forms of edema. The technique is based on precise estimates of the longitudinal relaxation time of tissue (T1) by MR imaging, and its subsequent conversion to water content.

In the present study, a combination of these two techniques (diffusion-weighted imaging and “water mapping”) was used to quantify temporal water content changes and document the type of edema that forms during both the acute and late stages of posttraumatic edema development.

Materials and Methods

Experimental Protocol

Thirty-six adult male Sprague–Dawley rats, each weighing 340 to 375 g, were used for the MR imaging studies. The rats were divided into two groups: a control group composed of six animals and a trauma group composed of 30.

Initially the rats were anesthetized with halothane, after which they were intubated and artificially ventilated, receiving a gas mixture of N2O (70%), O2 (30%), and halothane (0.5–1.5%). Rectal temperature was monitored and body temperature was maintained at 37 ± 0.5°C by blowing warm air into the magnet bore, and by using heat lamps when the animals were outside of the magnet.

Impact-Acceleration Injury

A new impact-acceleration head injury model was used to produce the trauma. A midline scalp incision was made, the skin and periosteum were reflected, and the skull was carefully dried. A sectioned 450-g brass weight was dropped from a height of 2 m onto the center of the metal disk. In these experimental conditions a mortality rate of 44% is obtained with a low incidence of skull fracture. After trauma, the disk was used to prevent skull fracture. After trauma, the rat was rapidly reconnected to the anesthetic agents, artificially ventilated, and the wound was closed.

Magnetic Resonance Imaging

Imaging System. 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 with a Gmax of 25 G/cm. Radiofrequency excitation and reception were performed using a 7-cm inner diameter quadrature “birdcage” design resonator. To minimize any macroscopic motion artifacts, the rat’s head was rigidly supported with a specially designed stereotactic device, including both ear and mouth supports mounted inside the cylinder.

Apparent Diffusion Constant Measurements. Apparent diffusion constant measurements were obtained using a two-dimensional spin-echo imaging technique or diffusion-weighted single voxel spectroscopy (SVS). For precisely defining anatomical regions, a two-dimensional diffusion-weighted image was used. Where time resolution was a critical factor, such as immediately after injury when fast water movement between compartments was expected, SVS was used.

Two-Dimensional Diffusion-Weighted Imaging. Two-dimensional diffusion-weighted imaging required a spin-echo sequence appropriately modified to include diffusion-sensitizing gradients along the readout (horizontal) direction with a duration of 4 msec and a gradient separation of 20 msec. Each data set consisted of two parallel, coronal slices (3-mm-thick, 4-mm center separation), a 128 × 128 cm matrix, a 1500-msec repetition time, a 33-msec echo time, and a 40-mm2 field of view. Diffusion weighting factors, or b values, of 10, 340, 670, and 1000 seconds/mm2 were used (maximum gradient strength of 23 G/cm); with two averages per data point, completion of the imaging series required 26 minutes. Pure ADC maps were calculated for each slice from the diffusion-weighted images by means of a pixel-by-pixel three-parameter least squares fit to the magnitude image data. The values of the frequency- and encoding gradients were included in the ADC calculations. The values of the ADCs were determined in the cortex, the caudate nucleus, and the thalamus under the disk.

Single Voxel Diffusion-Weighted Spectroscopy. For fast ADC measurements, diffusion-weighted SVS was used. Voxel dimensions (typically 5 mm × 5 mm × 5 mm) were selected to fit entirely within the brain in the same region in which the coronal sections of two-dimensional diffusion-weighted imaging were chosen. The voxel was located directly below the injury site and involved the unilateral cortical, caudate nucleus, corpus callosum, and thalamus. The technique required the use of a stimulated echo sequence appropriately modified to include diffusion-sensitizing gradients along one axis (the x-axis) with a duration of 4 msec and a separation of 25 msec. Each data set consisted of seven separate acquisitions, each of 2000-Hz spectral width, a repetition time of 1500 msec, and an echo time of 50 msec. An eighth acquisition was initially made to establish a steady state, but was eliminated prior to the ADC calculation. Diffusion weighting factors of 5, 225, 450, 675, 900, 1125, and 1350 were used (maximum gradient strength of 23 G/cm). Four scans were acquired at each b value for signal averaging. The data set was analyzed from the experimental decay of the peak amplitude as a function of the b factor corrected for cross terms. The SVS protocol was continuously repeated at approximately 1-minute intervals for the required experiment duration.

Before the experiments, we compared the two methods—SVS and two-dimensional diffusion-weighted imaging—for the measurement of ADC changes based on uniform diffusion calibration standards. We found that gels prepared from various concentrations of animal gelatin (#G-2625; Sigma Chemical Co., St. Louis, MO) in water, as well as aqueous solutions of polyethylene glycol (PEG, molecular weight 8000; #P-2139; Sigma Chemical Co.), constitute excellent primary standards for ADC calibration. The ADC values measured by the two methods agreed within 5%. In the animal studies, we observed that the percentage change in ADCs measured using the two methods was very close and the correlation was strongly significant (r = 0.84, p < 0.001). The differences in absolute ADC values are attributed to the inhomogeneous nature of the tissue encompassed by SVS, which crosses two slices, compared with the diffusion-weighted imaging technique with its well-defined anatomical regions.

Brain Water Determination by T2, Measurements. Our experience using MR imaging to measure brain water is based on laboratory and clinical studies involving noninvasive monitoring of brain edema formation and resolution. Briefly, pure T2 maps are generated and then converted to water maps by means of the following equation: 1/W = 0.907 + 0.407/T2, where T2 is expressed in seconds and W in grams of H2O per gram of tissue. Water maps were ana-
lyzed by obtaining global (whole-brain) and regional (cerebral cortex and caudate nucleus) tissue measures of edema with careful attention to excluding cerebrospinal fluid (CSF) spaces.

To confirm the validity of the MR imaging–based method in rodents, MR imaging–derived measures of water content were compared with gravimetry for control animals and for animals subjected to trauma at 1 hour and 3 days postinjury. As shown in Table 1, there was no statistically significant difference between the two methods.

Schedule of the Measurements. Baseline diffusion-weighted (both types) and T1-weighted images (water maps) were obtained. The rat was then removed from the magnet, subjected to head injury, and returned to the magnet immediately after the trauma. Fast diffusion-weighted images (SVS) were obtained sequentially (every minute) for 1 hour postinjury. Conventional diffusion-weighted images and T1-weighted images used for water content determination were obtained at the end of the 1st hour postinjury, at 4 hours, and on Days 1, 3, 7, 14, 28, and 42 in the animals in the trauma as well as the control group.

Determination of Ventricular Size. Using the MR imaging computer console at the level of the T1-weighted images, ventricular size was measured in the coronal section in square centimeters at different time points as mentioned earlier.

Water Content

Microgravimetric analysis was conducted on the same slices for which MR imaging was performed in those animals killed immediately after trauma occurred (control animals) and in those killed 1 hour or 3 days later (Table 1). One-cubic-millimeter brain pieces (Perfektum 14-gauge agar cutting needle; Popper & Sons, Inc., New York, NY) were sampled from the cortex. Specific gravity and water content were measured using a calibrated gravimetric column of kerosene and bromobenzene.10,27

Statistical Analysis

Values displayed in Table 1 and Fig. 1 are shown as means ± standard deviation. 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

Water Content Changes Measured by MR Imaging

In the control group, the water content of the whole
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<table>
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<th>TABLE 1</th>
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<td><strong>Water content measured in the cortex of nine rats by MR imaging and gravimetric techniques in a study of CHI</strong></td>
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<td>Method</td>
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<tr>
<td>MR imaging</td>
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* No statistically significant differences between methods.

Brain, cortex, and caudate nucleus was 79.05 ± 0.9%, 79.0 ± 0.9%, and 76.8 ± 0.4%, respectively. Water content of the cortex was significantly higher than that of the caudate nucleus (p < 0.001). The water content did not change during the 6-week period in any of the regions or in the whole brain (Fig. 1 upper left).

In the trauma group, the water content immediately increased after injury in each region as well as in the whole brain. This increase continued during the next 24 hours and reached its maximum value at the end of the 1st day (Fig. 1 upper right). During the next 2 weeks the water content was significantly higher than control values except on Day 3, when a transient decrease was observed. At the end of Week 6, we measured higher values in most animals; however, the difference was not significant in the whole brain. The brain swelling was diffuse, that is, the map did not show any regional differences in water content (Fig. 1 lower left and right).

Apparent Diffusion Coefficient Changes

Previous studies from our laboratories have confirmed that an increase in extracellular volume is associated with an increase in ADCs, whereas a decrease is associated with an increase in cellular volume.13

**Control Group.** The ADCs measured by SVS and diffusion-weighted imaging at baseline for the whole brain (0.70 ± 0.02 × 10⁻³ mm²/second and 0.57 ± 0.04 × 10⁻³ mm²/second, respectively) did not show any significant changes during the 6-week interval of the study (Fig. 2 upper).

**Trauma Group.** The baseline values in the rats subjected to trauma were not different from those of rats in the control group (SVS ADC: 0.70 ± 0.02 × 10⁻³ mm²/second; diffusion-weighted imaging ADC: 0.57 ± 0.04 × 10⁻³ mm²/second). During the first 45 minutes posttrauma, the ADC measured using the SVS technique showed a significant increase of 10% (p < 0.001) with a maximum value of 0.77 ± 0.04 × 10⁻³ mm²/second at 45 minutes. This transient elevation in the ADC was followed by a gradual decrease beginning 40 to 60 minutes postinjury, and the ADC crossed the baseline value at 24 hours. Beyond this time, the ADC change continued, reaching a 10% reduction 7 to 14 days postinjury (from 0.57 ± 0.04 × 10⁻³ to 0.52 ± 0.04 × 10⁻³ mm²/second). Interestingly, return of the ADC to normal value was only observed at 4 weeks after the trauma occurred (Fig. 2 lower). The cerebral cortex and caudate nucleus showed the most pronounced decrease (in the cortex from 0.58 ± 0.02 × 10⁻³ mm²/second to 0.53 ± 0.03 × 10⁻³ mm²/second, and in the caudate nucleus from 0.53 ± 0.02 × 10⁻³ mm²/second to 0.49 ± 0.03 × 10⁻³ mm²/second), with a mean value of 10 ± 3%. The ADC change in the thalamus (from 0.66 ± 0.05 × 10⁻³ mm²/second to 0.63 ± 0.04 × 10⁻³ mm²/second) was not significant.

**Ventricular Size**

**Control Group.** The ventricular size measured by MR imaging remained the same (0.33 ± 0.04 cm²) during the 6 weeks and did not show any significant change.

**Trauma Group.** The ventricular size changed during the 6-week period following head injury. Although it was smallest (0.24 ± 0.05 cm², p < 0.05) at 1 hour postinjury, it increased during the next 3 days and was significantly larger (0.47 ± 0.12 cm², p < 0.05) than that measured before the trauma occurred (0.32 ± 0.07 cm²). At 7 days postinjury, the ventricular size decreased again (0.26 ± 0.11 cm²); however, the difference, compared with the control value, was not significant. Throughout the remainder of the experiment, the ventricular size gradually increased and reached a significantly larger size at the end of the 6th week (0.36 ± 0.07 cm², p < 0.01) signifying the development of a postrumventriculomegaly (Fig. 3).

**Discussion**

**Changes in ADC and Tissue Water Content**

In this study the temporal course and type of diffuse brain swelling that predominates vasogenic or cellular edema was evaluated noninvasively by MR imaging following TBI. Our results show that closed head injury (CHI) is associated with a biphasic pathophysiological response. First, there is an increase in brain water content and water diffusion distance during the first 40 to 60 minutes postinjury, indicating an increase in the volume of the extracellular fluid and vasogenic edema formation. Second, a more widespread and slower edema formation caused by a predominately cellular swelling begins within 1 hour postinjury and becomes dominant at 1 or 2 weeks postinjury. These results taken in concert provide compelling evidence that the role of vasogenic edema may be overemphasized and that cellular edema is the major contributor to brain swelling in diffuse traumatic injury.

**Vasogenic Versus Cellular Edema in TBI**

Traumatic brain edema has usually been distinguished from other forms of edema by its origin, namely the leakage of plasma-borne substances from the vasculature as a result of a breakdown of the BBB.21 However, in light of more recent studies, it may be incorrect to assign the term “vasogenic” strictly to traumatic edema because other forms of edema are now considered to play an important role in the swelling process. Cellular edema associated with ischemia has been designated cytotoxic according to the original classification by Klatzo.21 Cellular swelling that occurs in the absence of ischemia is considered neurotoxic and may be a consequence of ionic disruption associated with traumatic injury.15,16 Thus at least
three forms of edema—vasogenic, ischemic, and neurotoxic—may contribute to increased tissue water following trauma.

In the present study the changes in the ADC after severe CHI suggest that the type of edema, cellular or vasogenic, changes with time after the traumatic insult. We found a significant increase in the ADC as well as in brain water content during the first 60 minutes postinjury. In a previous study, in which BBB permeability was tested by using contrast-enhanced (gadolinium–diethylenetriamine pentaacetic acid) MR imaging, we demonstrated that the BBB opens immediately after trauma and approaches closure approximately 30 minutes postinjury. In consideration of all these observations, we may conclude that these results are consistent with an increase in the volume of the extracellular fluid and vasogenic edema formation. It is possible that the vasogenic component may be exacerbated by systemic hypertension following trauma. However, it is important to note that previous studies have shown that impact acceleration results in only a brief hypertensive surge, not exceeding 25 mm Hg above baseline, followed by hypotension, which recovers by 30 minutes postinjury.

Blood pressure during the hypotensive period does not fall below 70 mm Hg. Thus, unlike fluid-percussion injury, which is associated with a marked hypertensive surge immediately posttrauma, it is unlikely that the mild increases in blood pressure seen in this model are a significant factor in the early production of the vasogenic edema component.

In the rat fluid-percussion brain injury model, Hansstock and colleagues evaluated the potential of diffusion-weighted imaging to differentiate cases of TBI in which there was no focal ischemia from those in which focal injury is a complication. They found an increased diffusion coefficient in cortical gray matter as early as 1 to 4 hours postinjury. Although they used a different model...
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and examined the type of edema in focal contusion, our combined results suggest that the increased water diffusion distance, as measured by our method, is consistent with the development of vasogenic edema a few hours postinjury. However, the mild and transient hypertension followed by a period of sustained hypotension seen in our CHI model contrasts with the documented prolonged surge of arterial pressure following trauma induced by the fluid-percussion model. Whereas in both models the barrier is compromised, in CHI pathological events other than severe hypertension are also responsible for the BBB disruption. Thus the role of hydrostatic brain edema (that is, transcapillary fluid filtration due to elevated arterial pressure) in edema formation or an exacerbation of edema by increased blood to the extracellular space gradient could be minimal or completely excluded in our model.

**Regional Differences in ADC**

Analysis of ADC changes from two different regions (cortex and caudate nucleus) as well as from the whole brain demonstrated that the transient increase in ADC was followed by a gradual decrease in ADC that began at 40 to 60 minutes postinjury and reached a minimum of $0.52 \pm 0.04 \times 10^{-3}$ mm$^2$/second at Day 7. Thereafter, the ADC remained negative until Day 14 and by Day 28 returned to baseline. Because the water content of the brain continued to increase during the first 24 hours, we posit that the fluid taken up by the cells must have origi-
ated either from the blood circulation or from the CSF space, both of which are in extensive diffusional contact with the tissue extracellular space.

Based on these observations, we conclude that cellular edema begins to develop 40 to 60 minutes postinjury and remains predominantly cytotoxic for up to 14 days (Fig. 2 lower). We use the term “predominantly” because the ADC measures the net difference between cellular and extracellular forms of edema, and it is entirely possible that a vasogenic component may contribute a small portion to the total tissue water. The initial vasogenic contribution can be estimated by measuring the total increase in brain water content on closure of the BBB; that is approximately a 0.3 to 0.4% increase if we consider that the BBB is closed at 30 minutes postinjury. It is also possible that a secondary opening of the BBB might have occurred. However, this was not studied in this series of experiments.

Mechanisms of Cellular Edema

The origin of cytotoxic brain edema is primarily related to disturbance of cellular osmoregulation, resulting in the intracellular uptake of water. The most commonly encountered cytotoxic edema is observed in cerebral ischemia, in which an interruption of energy supply leads to ionic pump failure and osmoregulation, resulting in an intracellular increase in sodium and water. Based on our blood flow measurements, the transient (20 minutes) and mild (30–40%) reductions in cerebral blood flow are not of a magnitude sufficient to cause metabolic failure and associated influx of water, which would be expected with failure of the adenosine triphosphate–dependent transmembrane ionic pumps. Furthermore, MR spectroscopy studies in the fluid-perfusion model in our laboratories have shown that there is no major energy failure after severe TBI. Further studies are required to clarify the issue in this diffuse injury model; however, our preliminary results are similar to those found in fluid-perfusion injury (unpublished data).

Potential for Development of Neurotoxic Edema

Although energy failure after trauma is less evident, the end result of ischemia and brain trauma is the same, that is, cell dysfunction and cell death. Therefore, it can be assumed that a sequence of events occurs, in which several different precipitating factors lead to the same final common pathway of injury progression. Although information about the process of cytotoxic damage in TBI is limited, considerable evidence exists that loss of cellular and potassium homeostasis, release of excitotoxic amino acids and free radicals, as well as acidosis, give rise to parenchymal damage. Based on these findings Siesjö and colleagues developed the notion that loss of cellular calcium homeostasis and enhanced production of free radicals are coupled events and that the detrimental effect of excessive tissue acidosis is, at least in part, secondary to the influence of hydrogen on calcium metabolism and free radical production. Therefore, in the absence of ischemia or barrier compromise (after > 30 minutes) and in the presence of a decreased water diffusion distance, it is reasonable to suspect that neurotoxic edema plays a major role in the swelling process.

On the basis of these results, we suggest that there is a biphasic pathophysiological response to CHI. First, there is a transient opening of the BBB caused by the direct effect of the trauma which produces predominantly vasogenic edema. Second, a more widespread and slower edema formation, caused by neurotoxic edema and astrocytic swelling, is initiated. Because we measured the BBB breakdown only 0 to 3 hours postinjury, we cannot exclude a second BBB breakdown in late edema formation, even though its role could be minimal.

With the exception of the thalamus (we were not able to measure water content in this region), changes in ADC were uniform and brain swelling was diffuse; that is, the water map did not show major regional differences in water content. This observation conforms to the concept that the trauma in this CHI model results in a massive diffuse injury and not in a more focal supratentorial brain lesion.

Changes in Ventricular Size During the Acute Swelling Process

We observed changes in ventricular size during the 6-week period following head injury. Although the ventricular size was smallest (0.24 ± 0.05 cm³, p < 0.05) at 1 hour postinjury, it increased during the next 3 days and was significantly larger (p < 0.05) than baseline measures. Seven days after trauma occurred, the ventricular size decreased again; however, the difference, compared with the control value, was not significant. Throughout the remainder of the experiment, ventricular size gradually increased and reached a significantly larger size at the end of the 6th week (p < 0.01) (Fig. 3). Our observations suggest that two types of postrumal ventriculomegaly may have occurred. First, the early ventricular dilation, which peaks on the 3rd day postinjury, may develop as a result of an obstruction in the CSF pathways caused by the formation of subarachnoid adhesion due to subarachnoid hemorrhage. Second, we believe that as the initial subarachnoid hemorrhage–induced hypertension subsides, another increase in ventricular volume occurs as a result of brain atrophy and the development of posttraumatic hydrocephalus, as has been shown in the studies by Foda, et al.

Conclusions

Development of edema after CHI is associated with a biphasic pathophysiological response. First, there is a brief period of increased water diffusion distance signifying a predominantly vasogenic edema formation that occurs immediately after injury. Second, at approximately 45 minutes postinjury, water diffusion distance begins decreasing because of the formation of a slower and more widespread cellular edema that becomes dominant and is sustained 1 or 2 weeks postinjury. These results provide compelling evidence that the role of vasogenic edema may be overemphasized in diffuse traumatic injury.

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