Diffusion-Weighted Imaging Studies of Cerebral Ischemia in Gerbils
Potential Relevance to Energy Failure
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Background and Purpose: Diffusion-weighted magnetic resonance imaging has been shown to be particularly suited to the study of the acute phase of cerebral ischemia in animal models. The studies reported in this paper were undertaken to determine whether this technique is sensitive to the known ischemic thresholds for cerebral tissue energy failure and disturbance of membrane ion gradients.

Methods: Diffusion-weighted images of the gerbil brain were acquired under two sets of experimental conditions: as a function of cerebral blood flow after controlled graded occlusion of the common carotid arteries (partial ischemia), as a function of time following complete bilateral carotid artery occlusion (severe global ischemia), and on deocclusion after 60 minutes of ischemia.

Results: During partial cerebral ischemia, the diffusion-weighted images remained unchanged until the cerebral blood flow was reduced to 15-20 ml • 100 g⁻¹ • min⁻¹ and below, when image intensity increased as the cerebral blood flow was lowered further. This is similar to the critical flow threshold for maintenance of tissue high-energy metabolites and ion homeostasis. After the onset of severe global cerebral ischemia, diffusion-weighted image intensity increased gradually after a delay of approximately 2.5 minutes, consistent with complete loss of tissue adenosine triphosphate and with the time course of increase in extracellular potassium. This hyperintensity decreased on deocclusion following 60 minutes of ischemia.

Conclusions: The data suggest that diffusion-weighted imaging is sensitive to the disruption of tissue energy metabolism or a consequence of this disruption. This raises the possibility of imaging energy failure noninvasively. In humans, this could have potential in visualizing brain regions where energy metabolism is impaired, particularly during the acute phase following stroke. (Stroke 1992;23:1602-1612)

KEY WORDS • cerebral ischemia • energy metabolism • magnetic resonance imaging • gerbils

The use of nuclear magnetic resonance imaging (MRI) to depict the early events in cerebral ischemia has been hampered by the apparent lack of changes in the MRI-observable parameters using standard imaging techniques. However, it has become clear recently that MR images that have been specifically sensitized to the translational diffusion of tissue water (diffusion-weighted images) can reveal tissue contrast based on properties essentially very different from those exploited in standard (i.e., T₁- or T₂-weighted) images. For instance, the anisotropic nature of water diffusion in the brain has been studied using such diffusion-sensitizing techniques, and it is now becoming apparent that these methods play an important role in the study of cerebral ischemia, giving information that is complementary to that obtained from standard images. See Editorial Comment, p 1612

The precise mechanisms underlying the changes observed in diffusion-weighted images during ischemia are uncertain. It has been postulated that these changes reflect the development of cellular edema, with the reduction in the apparent diffusion coefficient (ADC) of water being the result of movement of water from the (relatively) unrestricted diffusion environment in the extracellular space to the (relatively) diffusion-restricted intracellular space. It is not clear, however, that the amount of water that is postulated to be redistributed can in itself be sufficient to account for the degree of change seen in diffusion-weighted images, even though there are reports that the extracellular space in the brain can be reduced by up to 50% during severe cerebral ischemia.

Understanding the causes of diffusion-weighted image changes is therefore important in determining how effective this technique will be in unraveling the progress of cerebral ischemia, especially the early events that are an immediate consequence of energy failure. To this end, we have studied the progressive changes in diffusion-weighted images in the gerbil model of cerebral...
ischemia, either as a function of blood flow during partial carotid artery occlusion or as a function of time after complete bilateral carotid artery occlusion. We interpret our results in terms of the known blood flow thresholds and time dependence of failure of energy metabolism in this model.

Materials and Methods

All animals used were adult male gerbils (60–70 g) anesthetized with halothane/oxygen. After dissection of both common carotid arteries, nylon snares (Ethibond 2/0, Ethicon) were guided around both arteries and attached to individually manually controlled screw systems to allow unilateral or bilateral occlusion with the animal in the MRI magnet.

Rectal temperature of the animals was monitored and maintained at 35.5–37°C by blowing warm air into the sealed magnet bore. Respiratory rate was also monitored, as all animals were allowed to breathe spontaneously throughout the experiments.

For the measurement of cerebral blood flow (CBF), two platinum electrodes (one in each hemisphere) were inserted into the parietal cortex to a depth of 1 mm through burr holes made in the skull with a dental drill and fixed in place with cyanoacrylate adhesive. The position of the electrodes in the brain was subsequently confirmed during the imaging experiments; because of the susceptibility gradients caused by the metal of the electrodes, the images showed lack of signal at the position of the electrodes. The position of the electrodes was always 2–3 mm posterior to the slice on which attention was focused. As has already been described, CBF was measured using the hydrogen clearance polarographic technique. The platinum electrodes were polarized to 400 mV with respect to a reference silver/silver chloride electrode placed subcutaneously in the flank. After baseline stabilization, hydrogen gas was mixed with the inspired gas/anesthetic mixture to a final concentration of approximately 5% and the electrode currents were monitored continuously to determine the point of saturation. The hydrogen was withdrawn, the oxygen/halothane mixture was restored to the baseline level, and the electrode currents were then sampled every 15 seconds, digitized, and routed to a computer. The digitized currents were then used to calculate the time-averaged CBF over the preceding 15 seconds according to the equation

$$I_t - I_{t+\delta t} = \frac{1}{\delta t} \times 100 \text{ ml} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$$

where $I_t$ and $I_{t+\delta t}$ are the electrode currents at $t$ and $t+\delta t$ seconds, respectively.

The CBF was displayed graphically on the computer monitor (as CBF versus washout time) and thus gave a near-immediate, real-time indication of the blood flow in response to the partial or complete carotid artery occlusion produced by manually turning the screws connected to the snares. Data were stored for later analysis. The analysis and assumptions underlying this technique have been more thoroughly covered in a previous paper. Briefly, as long as the electrode currents decay monoexponentially, the calculated blood flow remains constant and the display of CBF as a function of washout time will have a slope of 0. Subsequently, at the end of the experiment, to calculate the blood flow against which image changes were plotted, all points on the flat part of the CBF versus washout time plot were used to calculate a mean flow over the complete washout period. Variation over the monoexponential part of the washout curve was always <10%, which indicates the stability of blood flow during the course of each measurement. Compared with manual calculation based on the $t_{1/2}$ method, assuming monoexponential decay of the electrode currents, the method is accurate to ±10%. Our previous data have shown that CBF measured by the $t_{1/2}$ method in control animals is stable for at least 5 hours.

The screw/snare system described above, in combination with the real-time graphic display of CBF, allows the production of reversible unilateral or bilateral cerebral ischemia of controlled duration, the severity being determined by the degree of carotid artery occlusion.

Imaging was performed at 100 MHz using a horizontal, 2.35-T magnet fitted with 12-cm i.d. homemade gradient coils. These gradients are capable of 100 mT·m⁻¹ output over ±2 cm from the center of the magnet. With this size of gradient coil in the 27-cm clear magnet bore, shielded gradients were not necessary. Images were acquired using a 7-cm whole-body transmit coil and a separate 1.2-cm surface receive coil, decoupled as described by Styles and Bendall et al, respectively. The platinum electrodes were within the sensitive volume of the surface coil.

Images were acquired using a standard $T_2$-weighted spin-echo sequence. Diffusion-weighted images were acquired using the same $T_2$-weighted sequence incorporating pulsed gradients, based on the method of measuring diffusion coefficients described by Stejskal and Tanner. The diffusion-weighted images were therefore also $T_2$ weighted. The diffusion-sensitizing gradients were applied in the read (vertical) direction.

A single $b$ value of 2,459 sec · mm⁻² (28-msec gradient pulses; leading edge separation, 56.5 msec; amplitude, 30 mT·m⁻¹) was used throughout in the diffusion-weighted sequences, yielding heavily diffusion-weighted images. Coronal images were acquired by applying the slice-selective gradient in the z direction (parallel to the magnet bore). The left and right sides of the images represent the left and right thalamus and left and right cortex. Data are presented as signal intensity ratio (SIR), defined in the present studies as image intensity after ischemia/image intensity before ischemia.

In the first part of the study (eight gerbils), diffusion-weighted images were acquired as a function of CBF during partial ischemia. First, pres ischemia (control) images were collected while CBF was measured. Blood flow was then reduced by gradually occluding the right carotid artery while CBF was measured. The computer display showed whether this was producing a unilateral reduction in blood flow. If not, the right carotid artery was occluded completely, followed by partial occlusion of the left carotid artery, again while monitoring the computer display for changes in CBF. This technique was successful in reducing blood flow in all of the
animals in this study and took <30 seconds. Once CBF was lowered, blood flow was allowed to stabilize further for 20–30 minutes before imaging. The CBF was then determined during image acquisition, if possible more than once (i.e., when blood flow was relatively high, so that the electrode currents quickly returned to baseline levels), and the mean value was calculated.

Images were acquired using the combination of a Bruker AM100 spectrometer and a Picker MR Vista system. Radio frequency output and waveform shaping were carried out by the Bruker system and an Oxford Research Systems selective excitation unit; gradient control, signal acquisition, and image processing were performed on the Picker equipment. The use of this equipment has already been described.8,10,17

 Imaging parameters were relaxation time (TR), 3,300 msec; echo time (TE), 140 msec; sweep width, 25 kHz; 256 samples×64 views, four averages; field of view, 3 cm; and slice thickness, 2 mm. Total imaging time was thus 14.5 minutes. Diffusion-sensitizing gradients were applied in the read direction. All data were zero filled to 256x256 before processing.

The second part of the study (six gerbils), investigating the time course of changes during and following severe global ischemia, was carried out in a separate group of animals using an SMIS imaging console (Surrey Medical Imaging Systems, Guildford, UK). CBF was not measured in these experiments.

To overcome the high level of mortality that would follow from completely occluding or releasing both carotid arteries simultaneously in this second set of experiments, the protocol was as follows: after stabilization of the gerbils and acquisition of control diffusion-weighted images, the right carotid artery was occluded and five sets of diffusion-weighted images were acquired over the next 12–13 minutes, followed by one T2-weighted (i.e., not diffusion-sensitized) image. This was followed by occlusion of the left carotid artery, and five further diffusion-weighted images and one T2-weighted image were acquired. There were transient disturbances observed in the respiratory trace immediately after bilateral occlusion, followed by restoration of the normal breathing pattern for the remainder of the ischemic period. The total time that both arteries were occluded was 60 minutes, during which time diffusion-weighted and T2-weighted images were interleaved approximately every 10 minutes. After this, the right carotid artery was released, one diffusion-weighted image was acquired, and then the left carotid artery was released. Five diffusion-weighted images and one T2-weighted image were acquired immediately on deocclusion, and then interleaved diffusion-weighted and T2-weighted images were acquired at approximately 10-minute intervals. There were transient changes in the breathing pattern following complete deocclusion, indicating restoration of CBF, which stabilized after 2–3 minutes.

After 1 hour of reperfusion, the gerbils were killed by nitrogen/halothane asphyxiation and five diffusion-weighted images and one T2-weighted image were collected, the acquisition commencing as soon as the breathing motions stopped (approximately 30–45 seconds after the administration of nitrogen).

The imaging parameters in these experiments were adjusted to provide usable images within the shortest possible time, taking into account saturation and T1 effects and image resolution and the signal to noise ratio. In this case, diffusion-weighted and T2-weighted images were acquired with a TR of 915 msec, a TE of 140 msec, a sweep width of 10 kHz, 128 samples×64 views, two averages, a field of view of 3 cm, and a slice thickness of 2 mm. The diffusion-sensitizing gradient pulses were applied in the read direction. Total imaging time was thus 2.25 minutes. All data were zero filled to 128×128 before processing.

Results

Control and immediate postischemia (60 minutes)

T2-weighted images showed clear detail, with gray and white matter clearly differentiated and the cortex and thalamus well defined (Figure 1A and 1B). The lateral and dorsal third ventricles were clearly visible due to the long T2 of the cerebrospinal fluid. Control diffusion-weighted images (Figure 2A) were much less clear than the corresponding T2-weighted images; the heavy diffusion weighting and T2 weighting almost completely attenuated the signal, with the exception of signals from the trigeminal nerves at the base of the brain, which were highlighted.3,4,16 Figure 1C shows an outline of the slice taken from Figure 1A and shows the typical ROIs from which the SIRs for all subsequent experiments were calculated.

The first set of experiments was aimed at determining the relation between diffusion-weighted image intensity and CBF. Figure 2 shows the changes occurring in diffusion-weighted images in a single gerbil at different stages of controlled partial unilateral reduction in CBF. In this particular animal, partial occlusion of the right carotid artery resulted in a unilateral reduction in CBF, so that it was not necessary to proceed to occlusion of the left carotid artery as described in “Materials and Methods.” After stabilization, CBF was measured while diffusion-weighted images were being acquired; the values are shown superimposed above each hemisphere in Figure 2. This unilateral effect was seen in only one of the eight animals investigated in this set of experiments.

In the example shown in Figure 2, as blood flow to the right hemisphere was reduced there was an increased relative intensity in that hemisphere in the diffusion-weighted images (Figure 2B). Note that as CBF fell further to 7 (Figure 2C) and 4 (Figure 2D) ml·100 g⁻¹·min⁻¹ the signal intensity in the right hemisphere increased.

The SIRs determined from ROIs placed in the thalamus and cortex from eight gerbils are plotted as a function of cortical CBF in Figure 3. In these animals, control CBF ranged from 46 to 73 (mean±SEM, 61.4±3.1) ml·100 g⁻¹·min⁻¹. Thus all CBFs of <46 ml·100 g⁻¹·min⁻¹ were obtained after partial occlusion. At CBFs of ≥30 ml·100 g⁻¹·min⁻¹, the SIR remained stable close to unity (mean±2 SD, 0.99±0.22; dotted lines in Figure 3). As CBF was reduced below 15–20 ml·100 g⁻¹·min⁻¹, the SIR increased sharply, reflecting an increase in the relative concentration of water with a lower ADC.

The second set of experiments was designed to investigate the time course of diffusion-weighted changes following complete bilateral carotid artery occlusion; CBF was not measured. Images from one gerbil and data obtained from six animals in this part of the study are shown in Figures 4–7. In contrast to the example
Figure 1. T₂-weighted magnetic resonance images acquired from same gerbil before (panel A) and immediately after (panel B) 60 minutes of profound cerebral ischemia. Lateral ventricles (small arrows) and dorsal third ventricle (large arrow) are indicated. TG, trigeminal nerves (see Figure 2). Panel C: Outline, taken from image in A, showing major structures: Cx, cortex; Th, thalamus. Regions of interest from which signal intensity ratios were calculated are shown in C as shaded areas. Left and right sides of images correspond to left and right sides of animal, respectively.

Images of Figure 2, there were no marked changes in diffusion-weighted signal intensity in any animal in this study after occlusion of the right carotid artery alone (data not shown). Therefore, the last diffusion-weighted image acquired during this part of the experiment, immediately before bilateral carotid artery occlusion, was used as the reference image from which the SIR was calculated for all subsequent diffusion-weighted images for each animal.

Figure 4, top, shows the changes occurring in diffusion-weighted images following complete bilateral carotid artery occlusion with a time resolution of approximately 2.5 minutes (2.25 minutes acquisition time, 0.2–0.25 minutes sequence download and initialization time). The SIR in the measured brain ROIs began to increase following complete bilateral occlusion (Figure 4, bottom panel), but not immediately; during the first acquisition the SIR increased only slightly, or not at all, followed by a more rapid rise.

Figure 5 shows that these changes are reversible on reperfusion, when the SIR was seen to decrease following bilateral deocclusion. There were no significant changes in the single diffusion-weighted image acquired after unilateral deocclusion. There was a gradual decline in the SIR during the first 20 minutes after bilateral deocclusion and restoration of blood flow. In some cases, however, the SIR in the thalamus, particularly on the right side, then began to increase as a postischemic intrathalamic lesion began to develop. This lesion was subsequently visible on T₂-weighted images, but only after at least 60–90 minutes of reperfusion (data not shown). It is possible that the development of this unilateral lesion is due to occlusion and deocclusion of the right carotid artery before the left.

Postmortem changes in the SIR from diffusion-weighted images following asphyxiation by nitrogen/halothane are shown in Figure 6. Image acquisition was begun as soon as the respiratory movements ceased. In this case, the SIR was calculated relative to the last image acquired before administration of nitrogen. Changes in the SIR were qualitatively similar to those seen after bilateral carotid artery occlusion, i.e., there was an increase in the SIR (Figure 4, bottom). The first time point after death had a higher SIR than the first point immediately after occlusion, probably because prior to death there is an additional short period of hypoxia after the introduction of nitrogen into the anesthetic gases.

In contrast to the effects observed in the diffusion-weighted images, the SIR of T₂-weighted images did not...
change markedly during any stage of this protocol (Figure 7).

Discussion

The use of T2-weighted imaging to visualize tissue edema after experimental ischemia is well established. However, it is not normally possible to detect any changes in T2-weighted images until some time (up to several hours) after the insult.

In agreement with previous studies, our observations show that diffusion-weighted imaging is far more sensitive to ischemia than T2-weighted imaging in that changes can be observed even during incomplete ischemia. In the studies reported here, the degree of hyperintensity in the diffusion-weighted images shows an interesting relation with CBF. Above 15-20 ml·100 g·min⁻¹, the diffusion-weighted image intensity remains relatively constant. At these values and below, the intensity gradually increases as CBF is reduced. CBF thresholds have been reported for various neurologic and neuroimaging criteria; our own studies in gerbils have shown that there is a major decline in the concentration of high-energy phosphates when CBF falls below 20 ml·100 g·min⁻¹. Others have also shown that the phosphocreatine (PCr) concentration decreases as CBF falls below 18-25 ml·100 g·min⁻¹ and is accompanied by electrical failure, while the adenosine triphosphate (ATP) concentration begins to decline as CBF falls below 12-15 ml·100 g·min⁻¹. This latter threshold is associated with progressive failure of the energy-dependent ion pumps and failure of evoked potentials. Below this value, when CBF is 7-10 ml·100 g·min⁻¹, there is massive accumulation of extracellular potassium, which correlates with total energy failure. Our observation that the diffusion-weighted images do not change until CBF falls below the critical threshold for energy maintenance is therefore highly significant. The fact that there is still measurable perfusion would largely exclude the postulated contribution of at least three factors (i.e., cessation of capillary perfusion, cessation of macroscopic pulsatile motion, or fall in brain temperature) to the increased diffusion-weighted image intensity during ischemia. The first two points can probably be excluded by the fact that the appearance of the diffusion-weighted images does not begin to change as soon as
CBF is altered; the last point can probably be excluded by the facts that the brain is still being perfused and the temperature of the magnet bore is elevated by the warm air necessary to maintain the animal's body temperature. Mintorovitch et al. have shown that temperature changes during focal brain ischemia are not sufficient to account for the degree of hyperintensity seen in diffusion-weighted images. Also, in agreement with the results presented here, Moseley et al. reported that there is a dissociation between the immediate drop in cerebral perfusion following induction of ischemia and the delayed changes observed by diffusion-weighted imaging.

It is important to take into account the possible heterogeneity of regional CBF during ischemia and how this would affect the results presented here. In gerbils, the carotid arteries supply the whole of the forebrain, including the thalamus (although there may be some constant supply from the posterior circulation). This leads to a generalized reduction in CBF following carotid artery occlusion. Avery et al. found that CBF ranged from 3 ml • 100 g⁻¹ • min⁻¹ in the frontal cortex to 10 ml • 100 g⁻¹ • min⁻¹ in the thalamus during profound cerebral ischemia in gerbils. Such a discrepancy between cortical and thalamic regional CBF may in part explain the results in Figure 3, in which the cortex (where the electrodes were placed and thus where CBF was measured) showed a greater increase in the SIR than the thalamus, where the severity of ischemia may have been partly overestimated. Further support for the validity of the hydrogen clearance method for measuring global CBF comes from the work of Avery et al., who showed that this method of measuring CBF in gerbils gave a representative indication of CBF in the majority of the cortex, and of Branston et al., who correlated regional CBF with cortical evoked potentials in baboons.

The screw/snare technique, reported in this and other papers, in which the animal is not removed from the magnet, enables us to begin to acquire images immediately after carotid artery occlusion. In addition, we have acquired images sufficiently quickly to be able to resolve the changes following the onset of ischemia, though at the expense of the signal to noise ratio and resolution. Despite the resulting signal loss and taking into account the very severe signal attenuation due to the diffusion-weighting gradients, the images were of sufficient quality to allow analysis.

The SIRs calculated from the diffusion-weighted images following complete bilateral carotid artery occlusion show a delayed (approximately 2.5 minutes) increase (Figure 4). As with the changes in the SIR at CBFs below 15–20 ml • 100 g⁻¹ • min⁻¹ seen in the CBF study, this is also a significant observation. Under normoglycemic conditions, the ATP store is rapidly depleted following cessation of blood flow to the brain. Kobayashi et al., using a similar gerbil model, reported a 70% loss of ATP within 1 minute after ischemia and a 92% loss by 5 minutes. Loss of ATP is accompanied by collapse of the transmembrane ion gradient. Hansen has shown that the extracellular potassium concentration ([K⁺]ₑ) changes by only a small amount during the 1–2 minutes following the onset of ischemia or anoxia, but that this is followed by a steep increase in [K⁺]ₑ, as depolarization ensues. Both Eleff et al. and Pekar et al. have measured intracellular ATP and sodium by nuclear magnetic resonance (NMR) spectroscopy following complete ischemia. The observations reported by Pekar et al. using both phosphorus-31 and multiple quantum-filtered sodium-23 NMR spectroscopy show that upon production of cerebral ischemia there is a delay of approximately 2 minutes before the ATP level begins to fall and that of intracellular sodium begins to increase. An inevitable consequence of sodium influx is intracellular accumulation of osmotically obliged water, resulting in cellular swelling and a decrease in the extracellular space, as has been shown chemically and by tissue impedance measurements. It has been postulated that this redistribution of tissue water may result in a reduction in the ADC of the water molecules, resulting in hyperintense regions on diffusion-weighted images, though the exact mechanism of the reduction in ADC remains unexplained.

Reperfusion of ischemic brain tissue is followed in the majority of cases by a brief hyperemic phase and results in restoration of intracellular ATP and the transmembrane ion gradients. Eleff et al. have suggested that the initial phase after reperfusion consists of energy-driven sodium extrusion (and thus, presumably, accumulation of potassium), such that full ATP recovery is delayed until this process reaches a steady state, and this is then followed by normalization of intracellular pH. The rate of energy recovery following ischemia depends on the duration of ischemia. For example, Kobayashi et al. reported a very rapid (<5 minutes) recovery of PCr and ATP following 5 minutes of bilateral ischemia in gerbils, whereas ATP recovery was considerably slower following 60 minutes of ischemia. Our own NMR observations show that recovery of cerebral energy metabolites is almost complete by 12
FIGURE 4. Top panel: Diffusion-weighted magnetic resonance images in a gerbil acquired (A) before and (B) 0–2.5 minutes, (C) 5–7.5 minutes, and (D) 10–12.5 minutes after complete bilateral carotid artery occlusion. Bottom panels: Signal intensity ratio (SIR) plotted as function of time following onset of complete cerebral ischemia in four regions of interest. SIR was determined relative to preischemia images. Time-axis data have been plotted midway between each acquisition cycle (i.e., 1.25 minutes following beginning of image acquisition). Results are mean±SEM (n=6). Arrows indicate time of bilateral carotid artery occlusion.
FIGURE 5. Top panel: Diffusion-weighted magnetic resonance images in a gerbil acquired (A) before and (B) 0–2.5 minutes, (C) 5–7.5 minutes, and (D) 10–12.5 minutes following deocclusion. Bottom panels: Signal intensity ratio (SIR) versus time following reperfusion on carotid artery deocclusion. Arrows indicate time of release of both carotid arteries. Results are mean±SEM (n=6) from same region of interest in same animals as in Figure 4.
FIGURE 6. Top panel: Post-mortem diffusion-weighted magnetic resonance images in a gerbil acquired (A) before and (B) 0–2.5 minutes, (C) 5–7.5 minutes, and (D) 10–12.5 minutes after respiratory movements stopped. Bottom panels: Signal intensity ratio (SIR) versus time following introduction of nitrogen gas into anesthetic gases in same regions of interest in same animals in Figures 4 and 5. SIR was calculated relative to last image acquired immediately prior to administration of nitrogen. Arrows indicate time at which respiratory movements stopped.
minutes of reperfusion after 15 or 30 minutes of bilateral ischemia. The time course of ATP recovery noted by Eleff et al\textsuperscript{33} and Allen et al\textsuperscript{38} resembles that of the diffusion-weighted image changes that we have seen on reperfusion (Figure 5). Mintorovitch et al\textsuperscript{39} have noted similar changes on reperfusion after cerebral ischemia in rats. Williams et al\textsuperscript{33} noted a similar time course in their tissue impedance. A reason for this is that the extracellular space returns to its preischemic state as cellular energy processes recover.

The time course of diffusion-weighted image changes that we saw after death adds support to the hypothesis concerning the dependence of diffusion-weighted image intensity on cellular energy metabolism. However, it is not immediately apparent why the first postmortem time point showed a greater hyperintensity than the first postocclusion time point. It is feasible that the preceding period of ischemia exacerbated the effects of a second ischemic insult, as Alger et al\textsuperscript{39} have suggested. On the other hand, the increased intensity could be due to the effects of hypoxia before respiration stops.

We do not yet fully understand the events at the cellular and molecular levels that are responsible for the hyperintensity in diffusion-weighted images during ischemia. Nevertheless, the evidence is strong that these changes are a consequence of energy failure. If this hypothesis is correct, then such a technique offers the exciting possibility of being able to image noninvasively the events associated with energy failure and recovery, at much higher resolution than is achievable with spectroscopic measurements of tissue metabolites. This in turn has implications for the evaluation and management of patients with acute stroke.

References

Diffusion-weighted imaging (DWI) by magnetic resonance is an important advance for the rapid detection (within minutes) of an ischemic focus. Because high-speed imaging techniques are required, there are problems using this method in clinical patients because of head movement. Nevertheless, DWI now has been accomplished in stroke patients and undoubtedly will soon become routine in stroke evaluation. Early stroke detection will become an imperative if combined thrombolysis and cytoprotection becomes an established method of therapy for cerebral ischemia. The biological basis of DWI is still not understood, and controversies exist concerning the significance of the fall in the diffusion coefficient that is translated into increased signal intensity. Some consider this a result of cytotoxic edema and others impaired cell membrane permeability with limitation of water diffusion because of rigidity of the cell membrane. The study by Busza et al is important because it demonstrates a relation between DWI signal enhancement and the cerebral blood flow threshold we have come to recognize at which energy failure, ion homeostasis, and functional deficits occur. The same relation of diffusion coefficient with cerebral blood flow does not remain over time, however. Over time, the diffusion coefficient returns to normal and even increased values, probably because of the onset of breakdown of cell membranes, cellular necrosis, and a freer diffusion of cellular water as cerebral ischemia persists. The literature will soon see an explosion of other papers on the biological basis of DWI, but this article represents an early seminal study.

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