Prediction of Impending Hemorrhagic Transformation in Ischemic Stroke Using Magnetic Resonance Imaging in Rats

R.A. Knight, PhD; P.B. Barker, DPhil; S.C. Fagan, PharmD; Y. Li, MD; M.A. Jacobs, BS; K.M.A. Welch, MD

Background and Purpose—Hemorrhagic transformation (HT) of ischemic brain tissue may occur in stroke patients either spontaneously or after thrombolysis. A method to assess the risk of HT in ischemic tissue after stroke would improve the safety of thrombolytic therapy. As a means of predicting HT, we investigated the role of contrast-enhanced MRI at acute time points in a rat middle cerebral artery occlusion model with reperfusion.

Methods—Intraluminal suture occlusion of the middle cerebral artery was used to produce transient ischemia in male Wistar rats (n=11). Reperfusion was performed by withdrawal of the occluding filament after 2 (n=4), 3 (n=6), or 4 (n=1) hours. MRI studies were performed before and after reperfusion with the use of conventional T1-weighted imaging, with and without gadolinium (Gd-DTPA) contrast agent, and T2-weighted imaging. Follow-up MRI and histological studies were obtained at 24 hours.

Results—Petechial hemorrhage occurred by 24 hours in 9 of 11 animals. All animals showed brain swelling and cellular death throughout the ischemic region at 24 hours. A hyperintense region in the preoptic area became visible after Gd-DTPA injection within minutes after reperfusion in animals with subsequent HT. All animals showing acute Gd-DTPA enhancement subsequently developed petechial hemorrhage (or died) by 24 hours. In these animals, statistically significant differences in signal intensity (P=.0005) between the ipsilateral enhancing region and a homologous contralateral region were detected on post–Gd-DTPA T1-weighted imaging. There was also a statistically significant correlation (P=.01) between the rate of Gd-DTPA uptake and the size of the enhancing area. Two animals did not enhance with Gd-DTPA and did not exhibit hemorrhage on histological examination or MRI at 24 hours. No abnormalities were seen on precontrast T1-weighted images before and shortly after reperfusion or postcontrast T1-weighted images before reperfusion.

Conclusions—The primary finding of this study was the detection of early Gd-DTPA parenchymal enhancement in 82% of the animals after reperfusion. Enhancement was seen before any detectable hemorrhage, suggesting that early endothelial ischemic damage occurs before gross brain infarction and hemorrhage. Thus, we suggest that acute Gd-DTPA enhancement may provide an early prediction of petechial hemorrhage. (Stroke. 1998;29:144-151.)

Key Words: magnetic resonance imaging ▪ stroke, ischemic ▪ transformation, hemorrhagic ▪ rats

Hemorrhagic transformation of ischemic brain tissue can occur either spontaneously or after thrombolytic therapy. Recently, clinical treatment of acute ischemic stroke in humans with the thrombolytic drug rt-PA has shown success. While such clot-dissolving therapies may improve clinical outcome in some patients with ischemic stroke, there is an increased risk of developing fatal HT. For example, in the recently published National Institute of Neurological Disorders and Stroke rt-PA Stroke Trial, the risk of symptomatic HT during the first 36 hours after the onset of stroke was significantly higher in patients receiving rt-PA (0.6% versus 6.4%), and 61% of the patients with symptomatic HT died within 3 months.

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HT of ischemic stroke has a natural incidence of 15% to 26% during the first 2 weeks and up to 43% over the first month after cerebral infarction. The predisposing factor(s) responsible for HT are not well defined, although etiology (thrombotic versus embolic), collateral circulation, reperfusion, hypertension, size of the ischemic lesion, and the use of anticoagulants, thrombolytics, or both have been implicated. No precise predictors of HT have been determined, but caution is suggested when thrombolysis is considered in patients with early x-ray CT signs of major stroke such as sulcal effacement, mass effect, edema,
or possible hemorrhage or National Institutes of Health Stroke Scale score greater than 22.25.38

The sensitivity of CT for the detection of early cerebral ischemic damage remains controversial, and a significant proportion of stroke cases that subsequently develop large cerebral infarction have negative acute CT examinations.39 Currently, CT is the standard diagnostic test for identification of cerebral bleeding. However, while CT can readily diagnose hemorrhage once it has occurred, it cannot predict HT unless high-dose contrast-enhanced CT (possibly in conjunction with delayed scanning) is used.20,29

Increased acceptance of thrombolytic therapy will depend in large part on the ability of clinicians to identify patients at risk of developing hemorrhagic complications and the development of techniques to decrease such risks. Accordingly, we have studied the utility of Gd-DTPA contrast-enhanced MRI in a rat model of ischemia and reperfusion that reliably produces HT by 24 hours after reperfusion.20 Our data demonstrated that Gd-DTPA enhancement was visible shortly after reperfusion, occurring in brain regions that subsequently showed PH on MRI and histology at 24 hours. MRI results during ischemia, immediately after reperfusion, and at 24 hours after reperfusion were compared with histological data at the final time point.

Materials and Methods

Animal Preparation

All studies were performed in accordance with institutional guidelines for animal research under a protocol approved by the institutional Care of Experimental Animals Committee. Male Wistar rats (n=11) were anesthetized with halothane (0.7% to 1.5%) in a 2:1 mixture of N2O/O2, and core temperature was maintained at 36°C to 37°C throughout all surgical and MRI procedures. A polyethylene catheter (PE-50) was placed into the femoral vein for infusion of contrast throughout all surgical and MRI procedures. A polyethylene catheter

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<table>
<thead>
<tr>
<th>Selected Abbreviations and Acronyms</th>
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<tbody>
<tr>
<td>BBB = blood-brain barrier</td>
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<td>HT = hemorrhagic transformation</td>
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<tr>
<td>MCA = middle cerebral artery</td>
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<tr>
<td>PH = petechial hemorrhage</td>
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<tr>
<td>ROI = region of interest</td>
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<tr>
<td>rt-PA = recombinant tissue plasminogen activator</td>
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<td>TE = echo time</td>
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<td>TR = repetition time</td>
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Table: MRI and Histology at 24 Hours After Occlusion

<table>
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<tr>
<th>Reperfusion Time, h</th>
<th>Hemorrhage on 24-h MRI</th>
<th>Lesion Area, mm²</th>
<th>Hemorrhage Area, mm²</th>
<th>Plugged Microvessels, mm²</th>
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<td>41.49</td>
<td>0.32</td>
<td>2.49</td>
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<tr>
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<td>None</td>
<td>34.13</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>Present</td>
<td>24.61</td>
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<td>Died &lt;24 h</td>
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<td>Present</td>
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<td>4.84</td>
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<tr>
<td>4</td>
<td>Died &lt;24 h</td>
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Phantom or possible hemorrhage or National Institutes of Health Stroke Scale score greater than 22.25 or National Institutes of Health Stroke Scale score greater than 22.25.38

The sensitivity of CT for the detection of early cerebral ischemic damage remains controversial, and a significant proportion of stroke cases that subsequently develop large cerebral infarction have negative acute CT examinations.39 Currently, CT is the standard diagnostic test for identification of cerebral bleeding. However, while CT can readily diagnose hemorrhage once it has occurred, it cannot predict HT unless high-dose contrast-enhanced CT (possibly in conjunction with delayed scanning) is used.20,29

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Animals were placed in a supine position in an acrylic plastic holder assembly after the surgical procedure. The holder was equipped with a nose cone for administration of anesthetic gases and stereotaxic ear bars to minimize movement of the head. The holder was then placed inside the bore of the magnet and into a 5-cm-diameter birdcage transmit/receive coil tuned to the resonant proton frequency (~300 MHz). Once inside the magnet, a modified fast low-angle shot (FLASH) imaging sequence was used to validate the orientation of the head by adjusting the position of the animal, in an iterative manner, until the brain was in an inverted flat skull position with the central image slice located at the level of the bregma. The radiofrequency coil and animal holder were designed such that once the setup was positioned inside the magnet the animal holder assembly could be removed, with the radiofrequency coil remaining fixed within the bore of the magnet and subsequently reinserted such that the animal was returned to the same position. Reperfusion was performed by removing the animal from the magnet for withdrawal of the occluding filament. The holder was returned to the magnet immediately afterward, with the entire procedure requiring 2 to 3 minutes.

Imaging Protocol

All MRI measurements were performed with the use of a 7-T, 20-cm-bore superconducting magnet (Magnex Scientific, Inc) interfaced to an SMIS console (Surrey Medical Imaging Systems, Inc). MR images were acquired in a multislice mode (nine contiguous slices) with a 1-mm slice thickness and 32-mm field of view and were reconstructed with a 128×128 matrix (in-plane resolution approximately 0.25 mm). MR measurements included T1- and T2-weighted images. Multislice T1-weighted images were obtained with the use of both gradient-echo (TR=500 ms, TE=10 ms) and spin-echo (TR=500 ms, TE=20 ms) sequences. Spin-density and T2-weighted images were acquired with the use of a multislice, multiecho spin-echo sequence (TR=3000 ms, TE=30, 60, 90, and 120 ms). Improvements in the signal-to-noise ratio for the T1- and T2-weighted sequences were obtained by signal averaging (number of averages=4 and 2, respectively). Imaging time for the T1-weighted image sequences was approximately 5 minutes for each sequence and 13 minutes for the T2-weighted image sequence.

T1- and T2-weighted images were acquired during ischemia (ie, 1 to 1.5 hours before reperfusion) in all animals. The status of the BBB was qualitatively assessed during ischemia (n=3) and shortly after reperfusion (n=11) by injection of a gadolinium-chelate (Gd-DTPA) contrast material (Omniscan Gadodiamide, Sanofi-Winthrop Pharmaceutical, Inc; 0.1 mmol/kg IV bolus) followed by T1-weighted imaging. The protocol for acute time points (ie, <1 hour after reperfusion) consisted of multislice T2-weighted images and both gradient- and spin-echo T1-weighted images. Postcontrast images were obtained sequentially for approximately 30 minutes after injection with the T1-weighted image sequences. MRI study times for each animal are shown in the Table . Two animals died prematurely from postreperfusion complications, whereas the remaining nine were
studied at approximately 24 hours after MCA occlusion with the use of T1- and T2-weighted images without Gd-DTPA. These animals were then killed for histological evaluation.

MRI Data Analysis
MRI data were transferred to a SUN workstation (SUN Microsystems, Inc) for off-line processing. Images were baseline corrected and reconstructed with in-house software. All postprocessing of the reconstructed images was performed with Eigentool image analysis software. Smoothing of the processed images with a 5×5 gaussian filter and a uniformity correction algorithm, which corrects for image inhomogeneities, was applied to all images before analysis.

Gd-DTPA–enhanced MR images from the initial study time point from each animal were examined for regions of contrast enhancement and compared with conventional T1- and T2- weighted images obtained at 24 hours. ROIs that demonstrated contrast enhancement with Gd-DTPA were identified by subtracting the precontrast images from those obtained after the injection of contrast media. The subtracted images were then visually thresholded to identify enhancing regions from nonenhancing areas. Homologous ROIs were also measured from the contralateral side by transposing the regions identified on the ipsilateral side over to the contralateral side. Contrast enhancement within these ROIs was then evaluated by measuring the signal intensities from the original T1-weighted images. The initial rate of contrast enhancement was determined from the difference in signal intensities from images obtained before Gd-DTPA injection and those obtained immediately after. Analysis of images obtained at 24 hours was performed with both T1- and T2-weighted images to identify areas of ischemic damage and hemorrhage.

Histopathology
Nine animals were killed for histopathologic analysis at approximately 24 hours after the onset of MCA occlusion. These animals were deeply anesthetized with ketamine (44 mg/kg) and xylazine (13 mg/kg) shortly after the final MRI measurements and then killed by vascular washout with heparinized saline followed by transcardial perfusion fixation with 4% buffered paraformaldehyde. Brains were removed shortly after death and cut into 3-mm-thick coronal sections. The brains were also taken from the two animals that died prematurely and processed similarly, although it was not possible to perfuse one of the animals that died overnight (ie, <24 hours, but exact time of death unknown). Tissue blocks were embedded in paraffin for histological processing. Coronal sections (6 μm thick) were taken at 0.5-mm intervals through the brain region corresponding to the MRI sections and stained with hematoxylin and eosin for histopathologic evaluation. Light microscopy was performed blindly by a trained observer (Y.L.) for neuronal evaluation and identification of any hemorrhagic developments.

Areas of the lesion and contralateral and ipsilateral hemispheres were measured. Regions of infarction and PH were measured from digitized stained sections with a computerized digital imaging system (Global Laboratory Image Analysis Software, Data Translation). Area measurements were performed by tracing the outline of the ROIs on a computer screen. An indirect method, which partially corrects for edema and other deformations that can occur during tissue processing, was used to compute the lesion area.

Statistical Analysis
Statistical comparisons between ipsilateral and contralateral MRI signal intensity measurements were performed with a paired t test. Correlative analyses were performed between the initial rate of contrast enhancement and the measured area of enhancement and also between the area of acute enhancement and the area of hemorrhage measured by histology at 24 hours. Significance was inferred for P≤.05.

Results
Histopathology
Brain swelling and cellular death were identified throughout the ischemic region in the nine animals killed at 24 hours after MCA occlusion. The ischemic region was grossly identified on light microscopy as a region of pallor that contained shrunken eosinophilic neurons characteristic of neuronal death. The ischemic zone generally encompassed the entire preoptic region and striatum and often extended into the cortex. A summary of histopathologic measurements is presented in the Table.
HT of tissue within the ischemic region was characterized as petechial and denoted by extensive plugging of cerebral microvessels with red blood cells and the extravasation of blood around damaged blood vessels. PH appeared to occur spontaneously within selective areas of the preoptic region after reperfusion, with the probability of hemorrhagic involvement increasing as a function of duration of the ischemic event. Positive histological signs of PH in the preoptic brain region occurred in seven of nine animals that were examined at 24 hours (Fig 1A) and also in the two animals that died less than 24 hours after the onset of ischemia. Two animals did not develop HT.

Selective extravasation of blood distributed within the preoptic area and/or the leptomeninges denoted cerebral (brain parenchyma) or meningeal (subarachnoid) hemorrhage, respectively. Cerebral microvessels within the preoptic area were blocked by red blood cells, whereas microvessels appeared patent in other ischemic brain regions such as the striatum and cortex (Fig 1B and 1C). Two animals died prematurely after reperfusion (one approximately 1 hour after reperfusion and the other overnight). Histological examination of the animal that died 1 hour after reperfusion (animal No. S40, 4-hour MCA occlusion) revealed ischemic damage within the preoptic region and striatum. Extensive microvascular plugging was seen within the preoptic region, encompassing approximately 50% of the lesion, although there were few red blood cells present at this time within the parenchyma. Conversely, microvessels within the preoptic area appeared patent in the two animals that did not develop HT.

MRI T1-weighted imaging (gradient-echo and spin-echo) obtained before and shortly after reperfusion showed no abnormalities in any of the animals (Fig 2A and 2E), with the exception of a small, histologically confirmed subarachnoid bleed that occurred before reperfusion in one animal. Contrast enhancement was not visible with Gd-DTPA administration before reperfusion. After reperfusion, a hyperintense region developed in the preoptic region shortly after Gd-DTPA injection (Fig 2b through 2d and 2f through 2h), which corresponded to the area of hemorrhage identified by histology at 24 hours. All animals that displayed early postreperfusion contrast enhance-

Figure 2. Postreperfusion gradient-echo (A-D) and spin-echo (E-H) T1-weighted images, obtained from an animal with 3-hour MCA occlusion, shown before (A and E) and after (B-D and F-H) contrast media injection. Postcontrast images show the development of a hyperintense area in the preoptic region that is not seen on precontrast images.
ment subsequently demonstrated PH at histopathologic examination, whereas the two animals that failed to enhance did not develop HT. The anatomic distribution of Gd-DTPA enhancement matched the hemorrhagic region observed later, although the enhancing area was larger than the size of the bleed ($P = .004$). Postreperfusion spin-echo T1-weighted signal intensity measurements from the preoptic region of all animals immediately before and up to approximately 30 minutes after Gd-DTPA injection are shown in Fig 3. Differences in average signal intensity measurements (using the three post–Gd-DTPA measurements) between ipsilateral and contralateral ROIs were statistically significant in animals that developed petechial bleeding ($P = .0005$). Three distinct patterns of contrast enhancement were observed: (1) no enhancement, (2) slow initial uptake with steadily increasing enhancement over the 30-minute period after injection, and (3) rapid enhancement that remained constant or decreased slightly over the 30-minute period after injection. A significant correlation ($r^2 = .539$, $P = .01$) was found between the rate of Gd-DTPA uptake and size of the enhancing area (Fig 4). At 24 hours blood was evident in the preoptic region of animals that developed hemorrhage and was observed to be hypointense on noncontrast gradient-echo T1-weighted images and hyperintense on spin-echo T1- and T2-weighted images (Fig 5).

**Discussion**

The primary finding of this study was that early parenchymal enhancement was detected by Gd-DTPA enhancement in 9 of 11 animals after reperfusion of brain tissue previously ischemic for up to 4 hours. All animals that had acute Gd-DTPA enhancement subsequently developed PH within 24 hours, as detected by MRI and histopathology, or died. Conversely, those animals that did not enhance showed no evidence of petechial bleeding ($P = .0005$). Three distinct patterns of contrast enhancement were observed: (1) no enhancement, (2) slow initial uptake with steadily increasing enhancement over the 30-minute period after injection, and (3) rapid enhancement that remained constant or decreased slightly over the 30-minute period after injection. A significant correlation ($r^2 = .539$, $P = .01$) was found between the rate of Gd-DTPA uptake and size of the enhancing area (Fig 4). At 24 hours blood was evident in the preoptic region of animals that developed hemorrhage and was observed to be hypointense on noncontrast gradient-echo T1-weighted images and hyperintense on spin-echo T1- and T2-weighted images (Fig 5).

Early Gd-DTPA enhancement during the acute stages of ischemic stroke appeared to accurately predict subsequent PH. Enhancement was seen before any detectable hemorrhage. Precontrast T1- and T2-weighted spin-echo images and gradient-echo scans were all normal at the early reperfusion time point. From this we infer that early endothelial ischemic damage, with increased permeability to small molecules (ie, Gd-DTPA) across the BBB, occurs before gross tissue necrosis that is detectable by T2-weighted MRI. When reperfusion
ensues, complete disruption of the BBB may occur, resulting in HT. This point was confirmed pathologically in the animal that died less than 1 hour after reperfusion. This particular animal showed strong enhancement in the preoptic region but little histological evidence of bleeding, suggesting that enhancement can be seen before histological confirmation of hemorrhage is possible.

Acute contrast enhancement was readily apparent in some animals, while in others it was somewhat more subtle and delayed. The patterns of enhancement noted appeared predictive of evolving PH (or death) and based on preliminary histological analysis may be related to the severity of BBB damage and ultimately hemorrhage. Although the MRI appearance of hemorrhage is complicated, there is growing expectancy that MRI may be equal or superior to CT in detecting hemorrhage (with the possible exception of subarachnoid hemorrhage) once it has occurred. Elster and Moody described four phases of MRI contrast enhancement. The earliest phase consists of arterial enhancement only (generally seen in infarcts up to 3 days old and reflecting sluggish flow in the vessels). The second phase consists of meningeal enhancement (in cortical infarcts), followed by a transition phase with mixed arterial or meningeal and parenchymal enhancement. Finally, parenchymal enhancement alone is seen almost universally in patients with 1- to 4-week-old infarcts. Parenchymal enhancement in acute stroke (ie, <24 hours) is uncommon but has been seen as early as 2 hours after stroke onset.

In contrast to human stroke, parenchymal enhancement was consistently seen almost immediately after reperfusion in our animal model. A number of factors may account for this difference. The model of prolonged focal ischemia followed by rapid reperfusion may not be commonly encountered in human stroke and might cause hemodynamic differences as the stroke evolves. There are few reports of contrast-enhanced agents.

Figure 5. Gradient-echo T1- and spin-echo T1- and T2-weighted images, obtained without contrast media at approximately 24 hours after occlusion, from the same animal shown in Fig 2. The region of suspected hemorrhagic involvement is located in the area that displayed acute contrast enhancement and appears slightly hypointense on gradient-echo T1-weighted and hyperintense on spin-echo T1- and T2-weighted images.
MRI studies of stroke performed at hyperacute reperfusion time points as in our study. We also scanned for up to 30 minutes immediately after injection to detect delayed enhancement. For parenchymal enhancement to occur, the contrast agent must reach segments of the microvasculature where the BBB is damaged. If there is little or no reperfusion or insufficient collateral circulation, then enhancement may not occur. Therefore, it is possible that the “no-reflow” phenomenon may also account for the relatively scarce observation of contrast enhancement in acute human stroke. There were also some technical differences since our studies were conducted at 7 T, whereas most clinical studies are performed at fields of 1.5 T or lower. There is no proof, but it might be expected that studies at 7 T would be more sensitive to detecting subtle enhancement in acute ischemia than corresponding studies at 1.5 T. It is doubtful, though, that some degree of enhancement would not also be seen at 1.5 T, particularly with the use of higher doses of contrast agent and delayed scanning. Acute enhancement has in fact been reported in MRI studies of patients and could be combined with MRI techniques such as perfusion and diffusion-weighted MRI for identifying and assessing acute brain ischemia. Future studies will focus on whether early MRI contrast enhancement in stroke, with its implications for the risk of HT, should be a contraindication for thrombolytic therapy.

Acknowledgments

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References

Predicting risk of subsequent hemorrhage in acute ischemic stroke is of obvious importance regarding both prognosis and treatment. Previously, the risk of HT of ischemic stroke was usually be needed.

This study represents an important attempt by the investigators to use MRI as a predictive tool for hemorrhagic risk after ischemic stroke. The clinical utility of the observed relationship between contrast enhancement and HT will need to be explored in appropriately designed and performed clinical protocols. This investigation was performed with a 7-T magnet, and therefore its applicability to standard 1.5-T clinical magnets will also have to be established. Future confirmation that contrast enhancement on T1 MRI predicts risk of even PH transformation could be useful, especially in patients destined to receive thrombolytic therapy. This experiment could set the stage for exploring this relationship, but further animal experiments and then patient trials will obviously be needed.

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