AJNR

Early MR detection of experimentally induced cerebral ischemia using magnetic susceptibility contrast agents: comparison between gadopentetate dimeglumine and iron oxide particles.

W Reith, M Forsting, H Vogler, S Heiland and K Sartor

AJNR Am J Neuroradiol 1995, 16 (1) 53-60
http://www.ajnr.org/content/16/1/53

Early MR Detection of Experimentally Induced Cerebral Ischemia Using Magnetic Susceptibility Contrast Agents: Comparison between Gadopentetate Dimeglumine and Iron Oxide Particles

Wolfgang Reith, Michael Forsting, Hubert Vogler, Sabine Heiland, and Klaus Sartor

PURPOSE: To evaluate early patterns of MR changes in a rat model of cerebral ischemia using the first pass of two magnetic susceptibility contrast agents. **METHODS:** One hour after endovascular middle cerebral artery occlusion, all animals were examined in an experimental MR unit. After bolus application of gadopentetate dimeglumine and, 10 minutes later, of iron oxide particles, the MR changes of the first pass of these contrast agents were followed using a T2*-weighted fast low-angle shot sequence. Time-densitiy curves of both contrast agents were analyzed and compared. **RESULTS:** After bolus injection of either (paramagnetic) gadopentetate dimeglumine or superparamagnetic particles, nonischemic brain parenchyma decreased markedly in signal, whereas the ischemic brain area remained relatively hyperintense (and thus became clearly delineated). Only after application of gadopentetate dimeglumine did a mild reduction in signal occur in the ischemic hemisphere, although the main artery was occluded. An explanation for this phenomenon might be residual capillary perfusion (plasma flow), which is detectable only when the smaller (paramagnetic) contrast molecules are being used. **CONCLUSIONS:** Cerebral perfusion deficits can be detected 1 hour after vascular occlusion with T2*-weighted fast low-angle shot sequences and bolus injection of paramagnetic or superparamagnetic MR contrast agents. Gadopentetate dimeglumine may be used as a marker of microcirculatory plasma flow.

Index terms: Contrast media, comparative studies; Contrast media, paramagnetic; Brain, ischemia; Brain, magnetic resonance; Animal studies

AJNR Am J Neuroradiol 16:53–60, January 1995

The role of magnetic resonance (MR) imaging in the diagnosis of acute stroke is still unclear. Because parenchymal ischemic injury can be detected only 6 to 12 hours after the onset of symptoms and signs (1), standard MR seems to be unsuited for quantifying acute ischemic lesions, rendering the development of new therapeutic strategies difficult (2). Fast MR techniques combined with the use of contrast agents, however, may allow identification of ischemic lesions earlier and monitoring of the effects of therapeutic strategies (3–5). Contrast agents that cause a regional signal loss because of magnetic susceptibility–induced T2* shortening have been shown to provide a substantial contrast between ischemic and normally perfused brain areas (6, 7). In the present study we used superparamagnetic iron oxide particles as an intravascular contrast agent and gadopentetate dimeglumine, which readily crosses the vascular wall in tissues different from brain but cannot penetrate the intact blood-brain barrier. To our knowledge a direct comparison of a pure intravascular contrast agent, such as superparamagnetic iron oxide particles with gadopentetate dimeglumine using perfusion imaging has not been made.

We used FLASH (fast low-angle shot) sequences with an acquisition time of 1 second in sequential imaging (8), which have sufficient

Received December 1, 1993; accepted after revision April 25, 1994.

Supported in part by grant Ku 294/18–1 from the Deutsche Forschungsgemeinschaft of Germany. Presented at the 31st Annual Meeting of the American Society of Neuroradiology, Vancouver, Canada, May 1993.

From the Department of Neuroradiology, University of Heidelberg Medical School, Heidelberg, Germany (W.R., M.F., S.H., K.S.); and Schering, Berlin, Germany (H.V.).

Address reprint requests to Wolfgang Reith, MD, Department of Neuroradiology, University of Heidelberg Medical School, Im Neuenheimer Feld 400, D-69120 Heidelberg, Germany.

AJNR 16:53–60, Jan 1995 0195-6108/95/1601–0053

temporal resolution to make them suited for dynamic perfusion imaging. The purpose of this study was to evaluate, by using an experimental stroke model, the usefulness of T2*-weighted FLASH sequences combined with paramagnetic and superparamagnetic contrast enhancement for early detection of cerebral ischemia and compare the transit of the two susceptibility contrast agents in normal and acutely ischemic brain tissue.

Methods

Animal Preparation

The middle cerebral artery was occluded via a transvascular approach in 10 male Wistar rats weighing 270 to 320 g, which were allowed free access to food and water before the procedure (9). The animals were anesthetized with ketamine hydrochloride (4 mg/100 g) and xylazine hydrochloride (1.5 mg/100 g) by intramuscular injection. The right femoral artery was cannulated for measuring pH, oxygen pressure, and carbon dioxide pressure before ischemia, and for monitoring blood pressure during surgery. Rectal temperature was maintained at 37°C with a feedback-regulated heating pad.

For middle cerebral artery occlusion (Fig 1), the common carotid artery and the external cerebral artery were exposed through a midline neck incision. The distal common carotid artery and the external cerebral artery were first ligated with a 4–0 suture. A 4–0 monofilament nylon suture (length, 40 mm) with a tip that had been rounded by heating was then inserted through an arteriectomy of the common carotid artery and gently advanced into the internal carotid artery to a point approximately 17 mm distal to the carotid bifurcation. Mild resistance to this advancement indicated that the suture had entered the anterior cerebral artery, thus occluding the origins of the middle cerebral artery and the posterior communicating artery. To prevent bleeding, the common carotid artery was loosely ligated with a 4–0 silk suture just distal to the arteriectomy, after which the neck wound was rapidly closed.

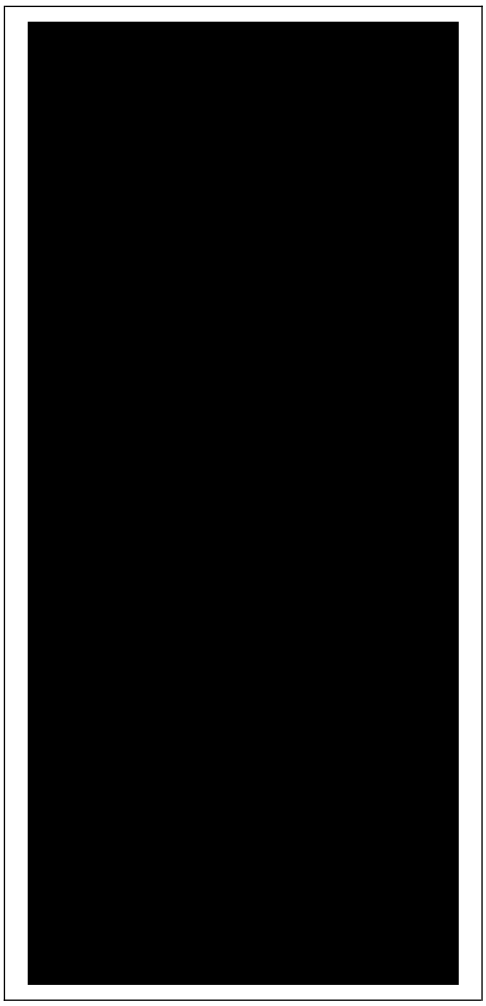


Fig 1. Schematic drawing of the endovascular occlusion technique: *1* indicates anterior cerebral artery; *2,* middle cerebral artery; *3,* posterior communicating artery; *4,* pterygopalatin artery, the only extracranial branch of the internal carotid artery; *5,* external carotid artery; and *6,* common carotid artery. The 4–0 nylon suture is advanced through an arteriectomy of the common carotid artery and then pushed into the A1 segment of the anterior cerebral artery. This way the blood flow into the middle cerebral artery is completely blocked.

Contrast Agents

Contrast material was injected manually into the tail vein by the same operator in less than 1 second at the beginning of data acquisition for image 4. Gadopentetate dimeglumine (Magnevist, Schering AG, Berlin, Germany) was used as the paramagnetic contrast agent. Its T1 relaxivity was 3.8 mmol/L per second at 20 MHz and 39°C, that is, a 1-mmol solution in water decreases T1 relaxation time by about 230 milliseconds.

Iron oxide particles (Schering AG) with diameters of about 40 nm as measured by laser light scattering were used as the superparamagnetic contrast agent. T1 relaxivity, measured at 39°C and 0.47 T with a nuclear MR spectrometer, was 25 mmol of Fe/L per second, and T2-relaxivity was 157 mmol of Fe/L per second.

Each animal received 0.2 mL of a contrast agent/saline solution, first one containing 0.3 mmol/kg of gadopentetate dimeglumine and then, in a second series, one containing 0.03 mmol/kg of iron oxide particles.

Scanning Procedure

Within 60 minutes after induction of ischemia, all animals were examined in a 2.0-T experimental MR unit (SISCO, Sunnyvale, Calif) under the same study protocol. First multisection coronal T2-weighted spin-echo images at 1700/90/2 (repetition time/echo time/excitations), with

a field of view of 7 cm, a section thickness of 3 mm, and an aquisition time of 8 min were obtained. Then contrast-enhanced perfusion MR studies were performed using T2*-weighted echo FLASH sequences with 3-mm-thick coronal sections through the optic chiasm (chiasmatic section). By applying a half-Fourier technique we were able to obtain 20 images within 32 seconds (25/21/1, flip angle of 20°, field of view of 10 cm × 10 cm, acquisition matrix of 128 × 256, and acquisition time of 1.6 seconds per image). Administration of the contrast medium was begun after the third image. The time for the bolus injection was approximately 1 second. The first set of perfusion images was obtained using a bolus injection of 0.2 mL of normal saline containing 0.3 mmol/kg of paramagnetic gadopentetate dimeglumine. Ten minutes later the same MR protocol was used to study the effects of a bolus injection of 0.2 mL of normal saline containing 0.03 mmol/kg of superparamagnetic iron oxide particles.

Microangiography

Immediately after the MR examination the animals were prepared for microangiography. All rats were transcardially perfused with a mixture of 20% barium sulfate (Micropaque) and gelatin in a ratio of 8:2 (10); 100 mL of this mixture was administered over a 30-minute period using a water pressure of 50 in, after which the brains were removed. Each brain was then cut into 2-mm-thick coronal blocks for a total of seven sections per animal using a rat brain matrix. After dehydration and embedding in paraffin, microangiograms were made of each tissue block. Microangiograms were analyzed both macroscopically and microscopically to correlate the areas of perfusion deficits on MR images with the state of the vascular network.

Data Analysis

All MR images were transferred to a Macintosh IIx computer (Apple Computer, Cupertino, Calif), and region-of-interest analysis was performed with an image-processing program (IMAGE 1.41, Wayne Rasband, National Institutes of Health, Bethesda, Md). The regional dynamics of intracerebral signal intensity were initially studied qualitatively by visual analysis in a cine mode. Then signal intensity was quantified by placing regions of interest (15 to 20 pixels) in identical areas of the occluded and nonoccluded hemisphere. In each animal, signal intensity in each region of interest was compared with the same region of interest before the arrival of the contrast agent. This way, relative signal intensity, $S = S_t/S_0$, was calculated, where S_t is the signal intensity measured at each time point and S_0 the signal intensity in the same region of interest on the first three images of the dynamic sequence (before arrival of contrast agent).

Resulting from animal studies (6) and numerical simulations (11, 12), the concentration of the contrast agent shows a linear dependency on the relative susceptibility change, ΔR2*. Considering this relationship and applying the equation:

$$S(t) = S_0 \times \exp(-TE \times \Delta R2^*),$$

which describes the dependency of the FLASH signal from ΔR2* (6), we calculated concentration-time curves from the relative signal intensity by:

$$C_S(t) \; \alpha \; -\ln(S[t]/S_0).$$

This conversion allowed calculation of the parameters relative regional cerebral blood volume (rrCBV) and mean transit time (MTT*), defined as:

$$\text{rrCBV} = \int C_S(t)\, dt$$

and

$$\text{MTT}^* = (\int t \times C_S[t]\, dt)/(\int C_s[t]\, dt).$$

The (absolute) regional cerebral blood volume (rCBV):

$$\text{rCBV} = (\int C_S[t]\, dt)/(\rho \times \int C_{AIF}[t]\, dt),$$

(where ρ is the density of brain tissue and C_{AIF} the arterial input function) as defined in indicator dilution theory (13, 14), could not be determined, because the arterial input function was unknown in our measurements. If C_{AIF} and ρ are approximately the same for all rats, however, rrCBV gives an approximate value for the regional cerebral blood volume. Especially for the comparison of ischemic and nonischemic tissue in one animal, C_{AIF} and ρ are constant.

MTT* is related to the mean transit time (MTT) (calculated for a hypothetical idealized bolus) by the equation:

$$\text{MTT}^* = \text{MTT} + \text{MTT}_{AIF},$$

where MTT_{AIF} is taken from the concentration-time curve $C_{AIF}(t)$ (13).

The evaluation of the functional tissue parameters was performed on a SUN Sparc Station (model GX 10, SUN Microsystems Mountainview, Calif). Regional cerebral blood volume (rrCBV) and MTT* were estimated by numerical integration and exponential extrapolation, respectively. In the first case, the upper integration limit was set to 16 seconds after bolus injection to eliminate the effects of the second pass of the bolus, which was observed more than 17 seconds after injection.

Results

All MR examinations were performed within 45 to 60 minutes after vessel occlusion. As expected, the initial conventional T2-weigthed spin-echo findings were normal in all animals; specifically, we did not observe any early signs of cerebral ischemia. The FLASH sequence revealed a marked signal decrease after contrast injection of both paramagnetic gadopentetate dimeglumine and superparamagnetic iron oxide particles in the nonischemic hemisphere

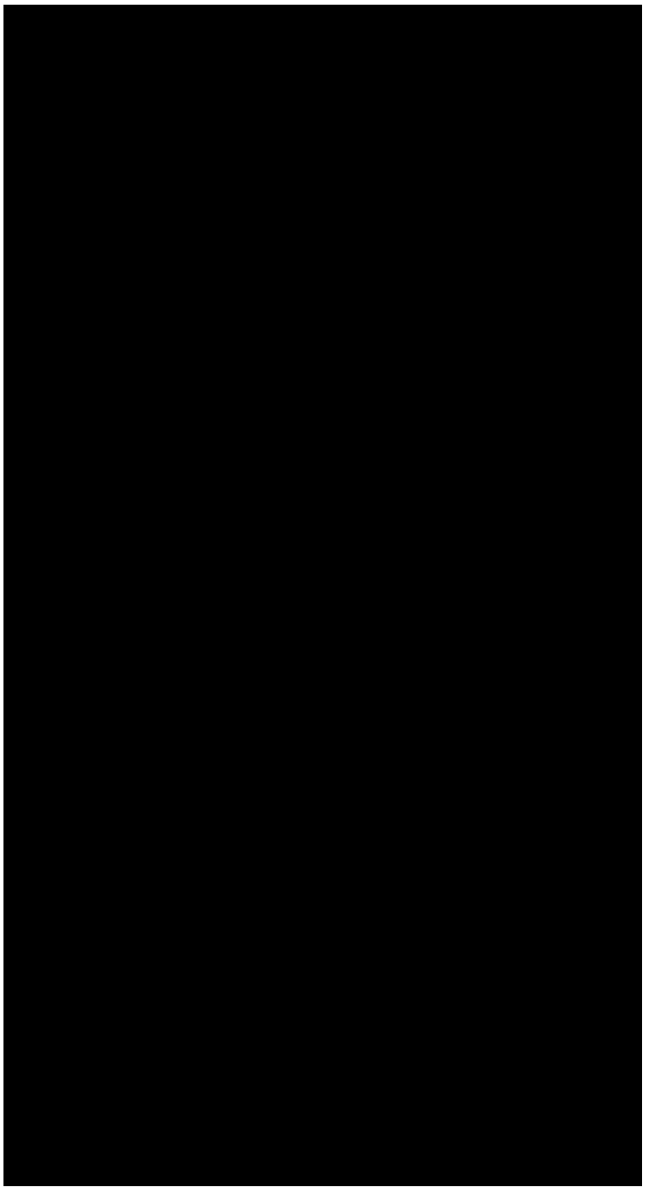


Fig 2. T2*-weighted MR image after bolus injection of paramagnetic (*A*) and superparamagnetic (*B*) contrast agents (4 of 20 images; order of acquisition, 1 to 4: *top left, top right, bottom left,* and *bottom right*). In the perfused brain area the signal decreases during the passage of the bolus. On the other hand, the ischemic area (left hemisphere in *A* and right hemisphere in *B*) is easily recognizable as a bright area with no signal decrease after injection of the contrast agents. The size of the visible ischemic area is independent of the type of contrast agent.

(Figs 2A and B). The ischemic area of the opposite hemisphere was easily recognizable as a bright area with no signal decrease after injection of the contrast agents. The size of the ischemic area remained the same regardless of whether the paramagnetic or the superparmagnetic contrast agent were injected.

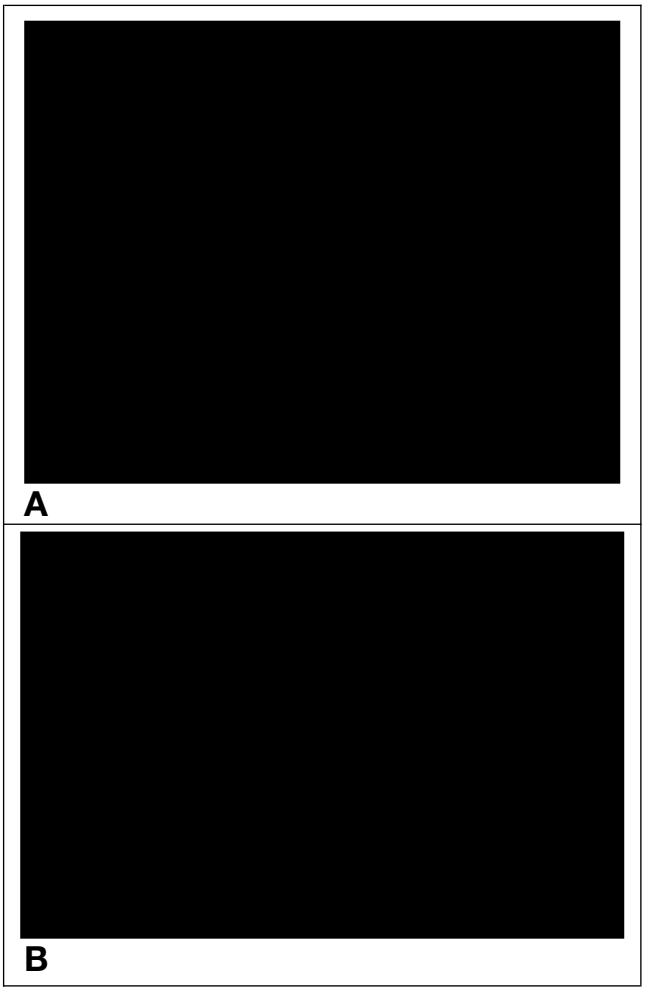


Fig 3. Time-density curves of the nonischemic hemisphere showed a first signal drop (MTT*) 5.88 seconds (gadopentetate dimeglumine, *A*) and 5.36 seconds (iron oxide, *B*) after contrast injection. Using superparamagnetic iron particles (*B*), there is nearly no signal decrease in the ischemic area, whereas there is a reduced and delayed (but significant) signal decrease in the same ischemic area when using paramagnetic gadopentetate dimeglumine (*A*).

Time density curves of the nonischemic hemisphere showed a physiologic circulation time of the contrast medium, with a first drop (MTT*) 5.88 seconds (gadopentetate dimeglumine; Fig 3A) and 5.36 seconds (iron oxide; Fig 3B), respectively, after contrast injection. By comparison, in the ischemic hemisphere MTT* was significantly longer (6.90 seconds) on gadopentetate dimeglumine; on iron oxide particles circulation time could not be estimated. In the nonischemic hemisphere a signal reduction of 21% was seen after the administration of paramagnetic gadopentetate dimeglumine and of 30% on administration of superparamagnetic

Functional tissue parameters relative regional cerebral blood volume (rrCBV) and mean transit time (MTT*) in ischemic and nonischemic hemispheres after administration of gadopentetate dimeglumine and iron oxide, respectively

	rrCBV, arbitrary units		MTT*, s	
	Gadopentetate Dimeglumine	Iron oxide	Gadopentetate Dimeglumine	Iron oxide
Normal hemisphere	2.04 ± 0.56 (2.32 ± 0.59)	2.58 ± 0.49 (2.94 ± 0.99)	5.88 ± 0.73 (7.03 ± 1.43)	5.36 ± 0.46 (6.79 ± 2.29)
Ischemic hemisphere	1.06 ± 0.48 (1.49 ± 1.09)		6.90 ± 1.17 (8.92 ± 2.49)	

Note.—Numbers without parentheses were calculated from numerical integration; numbers in parentheses were calculated with exponential extrapolation. Standard deviations in second case are high because time resolution is too poor to fit an exponential function exactly to the calculated concentration during bolus elimination (only four measurements without influence of second pass of the bolus).

iron oxide particles. In the ischemic hemisphere no significant signal reduction was visible on iron particles, whereas on gadopentetate dimeglumine a signal reduction of 12% was found.

The functional tissue parameters rrCBV and MTT* are given in the Table. When gadopentetate dimeglumine was used, rrCBV and rCBV were twice as high in the nonischemic hemisphere as in the ischemic hemisphere; the deduction from rrCBV to rCBV is allowed because ρ and C_{AIF} are identical for both hemispheres. MTT* was significantly longer in the ischemic hemisphere. Figure 3B demonstrates this fact qualitatively, showing that the bolus signal appeared about 3 seconds later in the ischemic than in the nonischemic hemisphere. When iron particles were used, the characteristic bolus signal disappeared in the ischemic hemispere (the signal increase of each postcontrast image was less than 3 SD of the precontrast images), and numerical integration and exponential extrapolation were thus not performed. Also, the signal drop was steeper and sharper on administration of iron particles than on gadopentetate dimeglumine. Approximately 17 seconds after bolus injection of the superparamagnetic iron particles a second, smaller signal drop—the second pass of the contrast agent—became visible. A second pass effect of gadopentetate dimeglumine was not seen.

Microangiographic studies (Fig 4) showed complete vascular occlusion in the territory of the occluded middle cerebral artery. The affected area corresponded exactly to the area of signal decrease on FLASH images in each animal.

Discussion

The treatment of acute ischemic stroke is still largely supportive rather than active. Furthermore, many problems still exist in the diagnosis of stroke. Established imaging methods such as computed tomography and MR do not fully reveal the extent or severity of cerebral ischemia within the first hours. Recent studies have shown that on computed tomography early parenchymal hypodensity reliably predicts ischemic brain damage but not the full extent of infarction (15). On MR both morphologic and vascular abnormalities unaccompanied by any parenchymal signal changes may be seen 2 hours after the onset of ischemia on T1-weighted images but are considered nonspecific (1). The ability to evaluate early ischemic changes would be useful for evaluating new therapeutic approaches to the treatment of acute stroke.

The results of the present study demonstrate that both magnetic susceptibility contrast agents, the intravascular superparamagnetic iron particles and the lanthanide chelate gadopentetate dimeglumine, provide a sensitive imaging method for the early differentiation of ischemic from normally perfused brain tissue. The dosages of both contrast agents used in this study are the same for humans (gadopentetate

Fig. 4. Microangiography with a complete absence of vessels in the territory of the occluded middle cerebral artery, corresponding to the nonperfused area on dynamic MR (Figs 2A and B).

dimeglumine) and considered to be safe (iron oxide particles). The signal decrease of 21% in the nonischemic hemisphere with gadopentetate dimeglumine is comparable to the results of Runge et al (16). This group found a 23% decrease in signal intensity in gray matter of cats after bolus administration of 0.25 mmol/kg of the lathanide chelate gadoteridol. Ten minutes after middle cerebral artery occlusion the change in signal intensity was 45% for normal gray matter compared with 20% for ischemic gray matter. This signal reduction is in the same range as our results, with a reduction from 21% (normal brain tissue; a differentiation between white and gray matter in rats is difficult and was not done) to 12% (ischemic hemisphere). The authors gave no explanation why there is still a signal decrease in the ischemic area. If we assume a complete occlusion of the middle cerebral artery, as we confirmed in our study by microangiography, no contrast agent should be able to enter the ischemic area. Thus no signal alteration should occur.

As previously shown, one way of detecting cerebral ischemia early is fast MR with intravenous bolus injection of contrast agents (dynamic MR). T2*-weighted dynamic imaging has several potential clinical applications. Whereas in the evaluation of ischemic stroke conventional T2-weighted spin-echo images show only areas of edema, necrosis or later gliosis, and Wallerian degeneration, dynamic T2*-weighted imaging provides additional functional information about regional cerebral blood flow. Contrast media based on dysprosium, gadolinium, or iron oxide particles cause regional signal loss (17, 18) because of magnetic susceptibiliy–induced T2* shortening. Enhancement with paramagnetic materials (lanthanide metal ions) exert their effects predominantly by dipole-dipole interactions (6). They are normally confined to the intravascular space of the brain. Therefore, in case of an intact blood-brain barrier, enhancement is caused by the intravascular space of the brain, with little or no enhancement of interstitial or intracellular tissue components. Dynamic MR using these contrast media measures both the microcirculation (capillaries and small venules) and the macrocirculation (predominately veins and, to a lesser degree, arteries), a volume that comprises merely 2% to 5% of brain tissue.

Regional cerebral blood flow, rCBF, can be derived from dynamic MR in the following manner. In indicator dilution theory (14), developed for nondiffusible tracers such as iodinated contrast agents and pure intravascular MR contrast agents, rCBF is defined as

$$rCBF = rCBV/MTT.$$

As mentioned above, the arterial input function must be known to calculate rCBV and MTT from rrCBV and MTT*. Because C_{AIF} depends not only on the shape of the injected bolus but also on the geometry and elasticity of the vascular network, it is necessary to acquire a T2*-weighted signal-time curve of the internal carotid arteries simultaneous to the signal-time curve of the brain region of interest. Such a noninvasive method for the derivation of C_{AIF} was presented by Perman et al (19) but is difficult to obtain in small vessels such as the internal carotid arteries of rats.

Because the contrast agents used in our study are nondiffusible and normally confined to the intravascular space of the brain, a signal loss occurred only in perfused parenchyma. In nonperfused brain regions no signal changes were seen after the administration of superparamagnetic iron oxide. The slight signal drop in ischemic brain on gadopentetate dimeglumine indicates that even after complete vessel occlusion residual perfusion exists in capillaries. Using intravascular fluorescence markers, Theilen et al (20) could show in forebrain ischemia that within 10 seconds after injection of the marker all capillaries were stained; compared with control animals there was only a filling delay. They suggested that despite drastic reduction in cerebral blood flow during forebrain ischemia, all cerebral capillaries remained perfused, although to a lesser degree. Reasons for our findings—partial reduction and delay of the bolus concentration in the ischemic area using paramagnetic gadopentetate dimeglumine, and total reduction using iron oxide particles—might be persistent capillary plasma flow and the fact that the small gadopentetate dimeglumine molecules (590 d) were able to pass through the capillaries, whereas the macromolecular iron particles (300 000 d), similar to red blood cells, were unable to pass. Looking at the signal curves obtained by Warach et al (21) and recently by Maeda et al (22), one can see the same phenomenon; there is a reduced and delayed signal drop in the ischemic hemisphere when using gadopentetate dimeglumine as contrast agent. Both groups did not explain their

findings, probably because they did not know the fact of persisting plasma flow. We now have to figure out how long after vessel occlusion this kind of flow persists and whether it can be used for therapeutic interventions.

The nonperfused region detected with T2*-weighted FLASH imaging after administration of gadopentetate dimeglumine and superparamagnetic iron oxide showed the same size as and corresponded well with the area of vascular occlusion in microangiograms. Microangiography allows the assessment of structural alterations in the microvasculature. Extravasation of micropaque was not observed in any of the animals, corresponding to the known fact that the blood-brain barrier remains intact within the first 2 days in rats (23). Crowell et al (10) found in experimental focal cerebral ischemia in the monkey that extravasation of micropaque was highly related to changes in the blood-brain barrier.

Optimal evaluation of new imaging techniques additionally requires the use of animal stroke models, which should fulfill two main conditions. First, they should simulate human stroke as closely as possible, and second, they should allow radiologically monitoring of the evolution of the infarct. One of the most commonly used stroke models is the diathermal occlusion of the middle cerebral artery of the rat, first described by Tamura et al (24). In this model the proximal middle cerebral artery is occluded by a subtemporal approach, resulting in an infarction of the frontal cortex and the lateral putamen. Although the size of the infarct is highly reproducible, this model has several disadvantages. The necessary craniectomy creates undesirable pressure gradients and traumatizes the sympathetic nerves that accompany the cerebral vessels. This may lead to changes in the vessel diameter and unpredictable changes in cerebral blood flow. In addition, the surgical approach causes artifacts, particularly in contrast-enhanced MR studies, such as surgically induced dural and parenchymal enhancement, which may be indistinguishable from ischemic blood-brain barrier disruption.

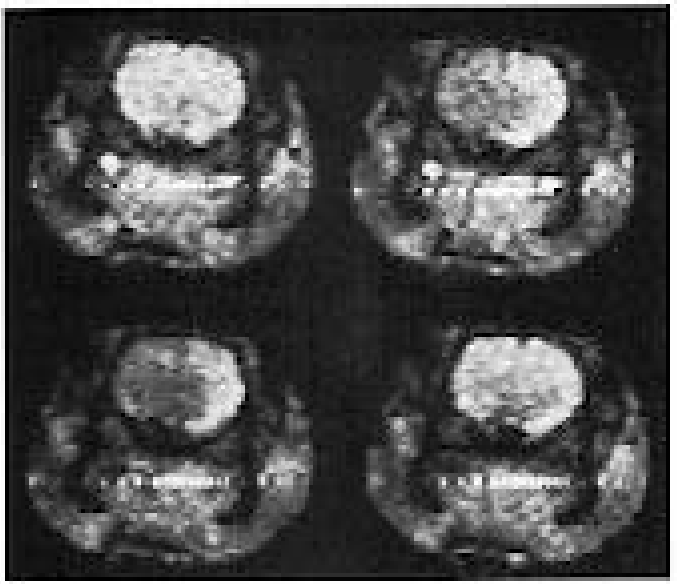
To avoid these disadvantages, we chose the model of transvascular middle cerebral artery occlusion, first described by Longa et al (9). This technique uses a nylon filament of just the right diameter necessary to occlude the internal carotid artery at the middle cerebral artery origin. This way, all sources of blood flow to the middle cerebral artery from the internal carotid artery and from the anterior and posterior cerebral arteries are blocked. Cerebral blood flow in the middle cerebral artery territory decreases to 2% to 30% of baseline levels (25). The advantage of this model—especially if used with MR—is that no craniotomy is required, and damage from brain retraction and vessel manipulation, temperature loss, and dessication of exposed brain are avoided. This minimizes unwanted pathologic enhancement on MR studies (23).

Our results suggest that dynamic MR using T2*-weighted FLASH sequences with intravenous bolus injection of gadopentetate dimeglumine or superparamagnetic iron particles allow detection of cerebral perfusion deficits immediately after vascular occlusion. In contrast to similarly sensitive imaging methods such as density-weighted imaging, dynamic T2*-weighted diffusion imaging FLASH imaging can be performed on most existing clinical MR systems. Additionally, it is possible to measure capillary plasma flow in ischemic areas if an arterial signal-time curve is acquired simultaneous to the signal-time curve of the brain region of interest.

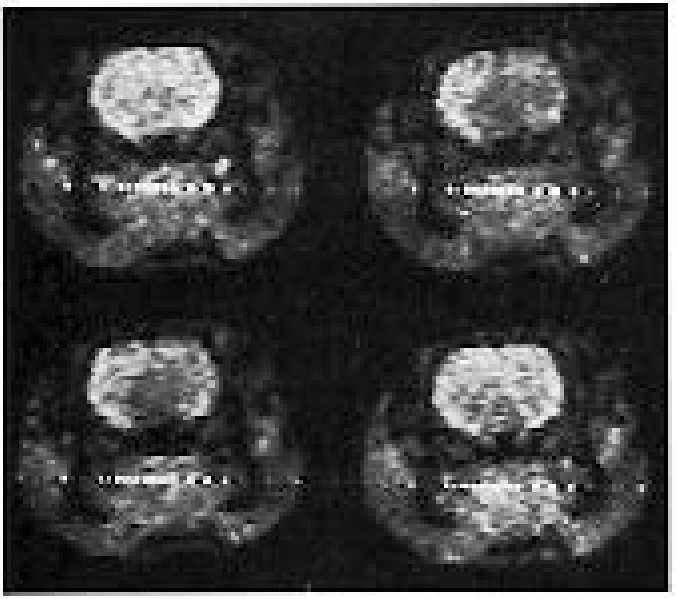
References

1. Yuh WTC, Crain MR, Loes DJ, Greene GM, Ryals TJ, Sato Y. MR imaging of cerebral ischemia: findings in the first 24 hours. *AJNR Am J Neuroradiol* 1991;12:621–629
2. WHO task force on stroke and other cerebrovascular disorders. Recommendations on stroke prevention, diagnosis and therapy. *Stroke* 1989;20:1407–1431
3. Rosen BR, Belliveau JW, Vevea JM, Brady TJ. Perfusion imaging with NMR contrast agents. *Magn Reson Med* 1990;14:249–265
4. Chenevert TL, Pipe JG, Williams DM, Brunberg JA. Quantitative measurement of tissue perfusion and diffusion in vivo. *Magn Reson Med* 1991;17:197–212
5. Gore JC, Majumdar S. Measurement of tissue blood flow using intravascular NMR contrast agents. *Magn Reson Med* 1990;14: 242–248
6. Villringer A, Rosen BR, Belliveau JW, et al. Dynamic imaging with lanthanide chelates in normal rat brain: contrast due to magnetic susceptibility effects. *Magn Reson Med* 1988;6:164–174
7. Moseley ME, Kucharczyk J, Mintorovitch J, et al. Diffusion-weighted MR imaging of acute stroke: correlation with T2-weighted and magnetic susceptibility-enhanced MR imaging in cats. *AJNR Am J Neuroradiol* 1990;11:423–429
8. Haase A. Snapshot FLASH MRI: applications to T1, T2, and chemical-shift imaging. *Magn Reson Med* 1990;13:77–89
9. Longa ZE, Weinstein PR, Carlson S, Cummins R. Reversible middle cererbal artery occlusion without craniectomy in rats. *Stroke* 1989;20:84–91

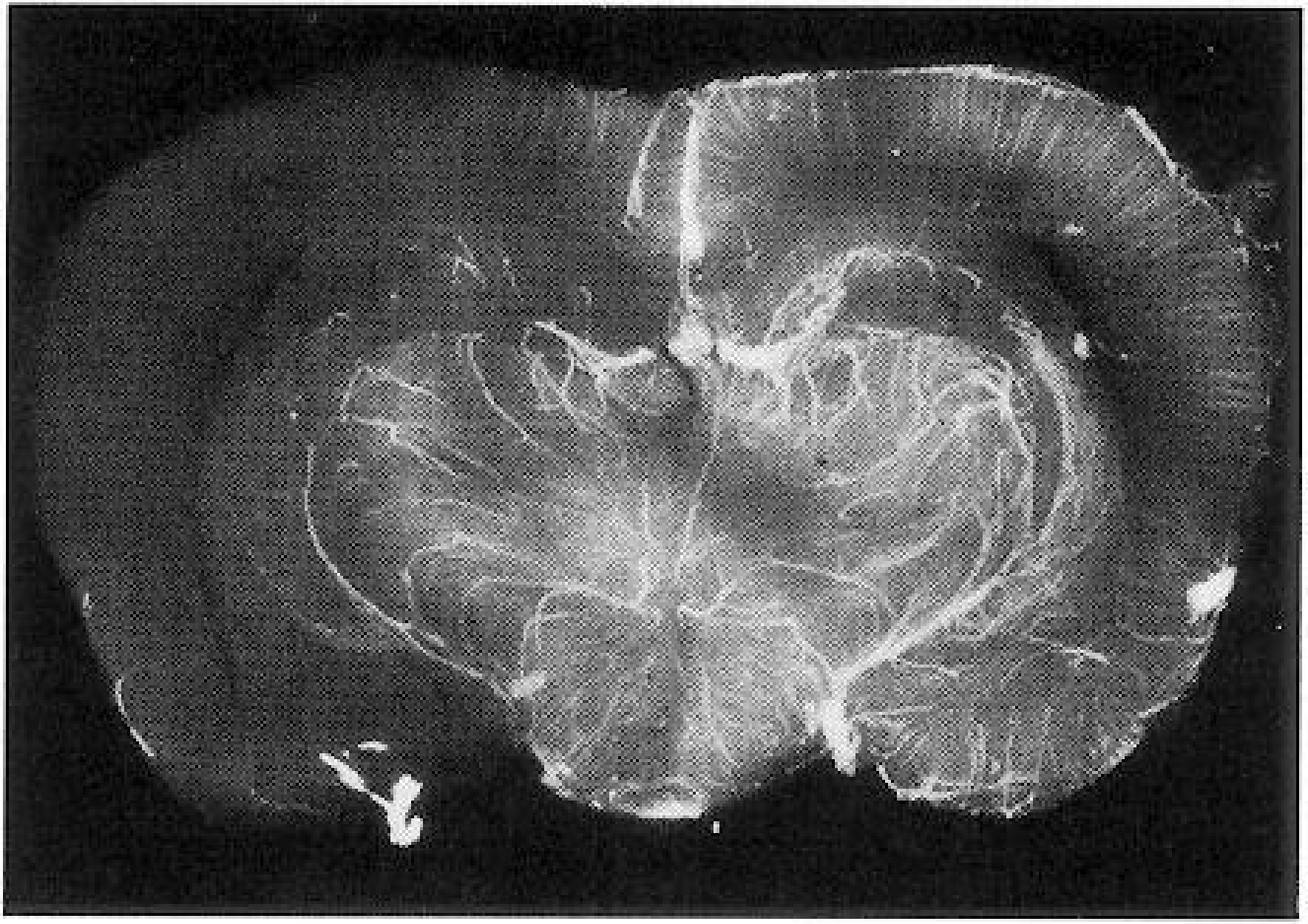
10. Crowell RM, Ollson Y, Ommaya AK. Angiographic and microangiographic observations in experimental cerebral infarction. *Neurology* 1971;21:710–719
11. Majumdar S, Gore JC. Studies of diffusion in random fields produced by variations in susceptibility. *J Magn Reson* 1988, 78: 41–55
12. Fisel CR, Ackerman JL, Buxton RB, et al. MR contrast due to microscopically heterogeneous magnetic susceptibility. *Magn Reson Med* 1991;17:336–337
13. Axel L. Cerebral blood flow determination by rapid sequence computed tomography. *Radiology* 1980;137:679–686
14. Zierler KL. Theoretical basis of indicator-dilution methods for measuring flow and volume. *Circ Res* 1962;10:393–407
15. Kummer Rv, Meyding-Lamadé U, Forsting M, et al. Sensitivity and prognostic value of early computed tomography in middle cerebral artery trunk occlusion. *AJNR Am J Neuroradiol* 1994;15: 9–15
16. Runge VM, Kirsch JE, Wells JW, Woolfolk CE. Assessment of cerebral perfusion by first-pass dynamic, contrast-enhanced, steady-state free-precession MR imaging: an animal study. *AJR Am J Roentgenol* 1993;160:593–600
17. Kucharczyk J, Mintorovitch J, Asgari HS, Moseley M. Diffusion/perfusion MR imaging of acute cerebral ischemia. *Magn Reson Med* 1991;19:311–315
18. White DL, Aicher KP, Tzika AA, Kucharczyk J, Engelstad BL, Moseley ME. Iron-dextran as magnetic susceptibility contrast agent: flow-related contrast effects in the T2-weighted spin-echo MRI of normal rat and cat. *Magn Reson Med* 1992;24:14–28
19. Perman WH, Gado MH, Larson KB, Perlmutter JS. Simultaneous MR acquisition of arterial and brain signal-time curves. *Magn Reson Med* 1992;28:74–83
20. Theilen H, Schröck H, Kuschinsky W. Capillary perfusion during forebrain ischemia and reperfusion in the rat brain. *Am J Physiol* 1993;265:H642–H648
21. Warach S, Li W, Ronthal M, Edelman RR. Acute cerebral ischemia: evaluation with dynamic contrast enhanced MR imaging and MR angiography. *Radiology* 1992;182:41–47
22. Maeda M, Itoh S, Ide H, et al. Acute stroke in cats: comparison of dynamic susceptibility-contrast MR imaging with T2- and diffusion-weighted MR imaging. *Radiology* 1993;189:227–232
23. Forsting M, Reith W, Dörfler A, Meyding-Lamadé U, Sartor K. MRI monitoring of experimental cerebral ischemia: comparison of two models. *Neuroradiology* 1994;36:264-268
24. Tamura A, Graham DI, McCulloch J, Teasdale GM. Focal cerebral ischemia in the rat, I: description of technique and early neuropathological consequences following middle cerebral artery occlusion. *J Cereb Blood Flow Metab* 1981;1:53–60
25. Nagasawa H, Kogure K. Correlation between cerebral blood flow and histologic changes in a new rat model of middle cerebral artery occlusion. *Stroke* 1989;20:1037–1043

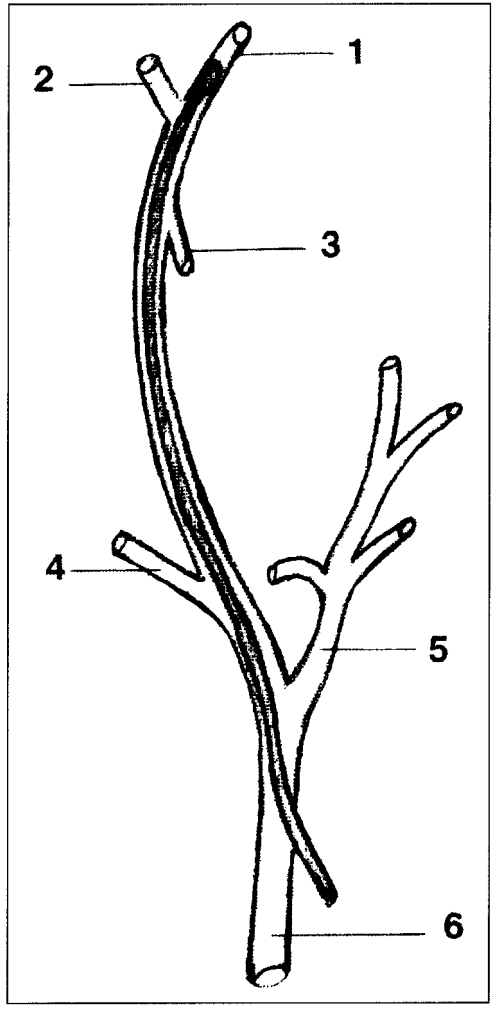


A

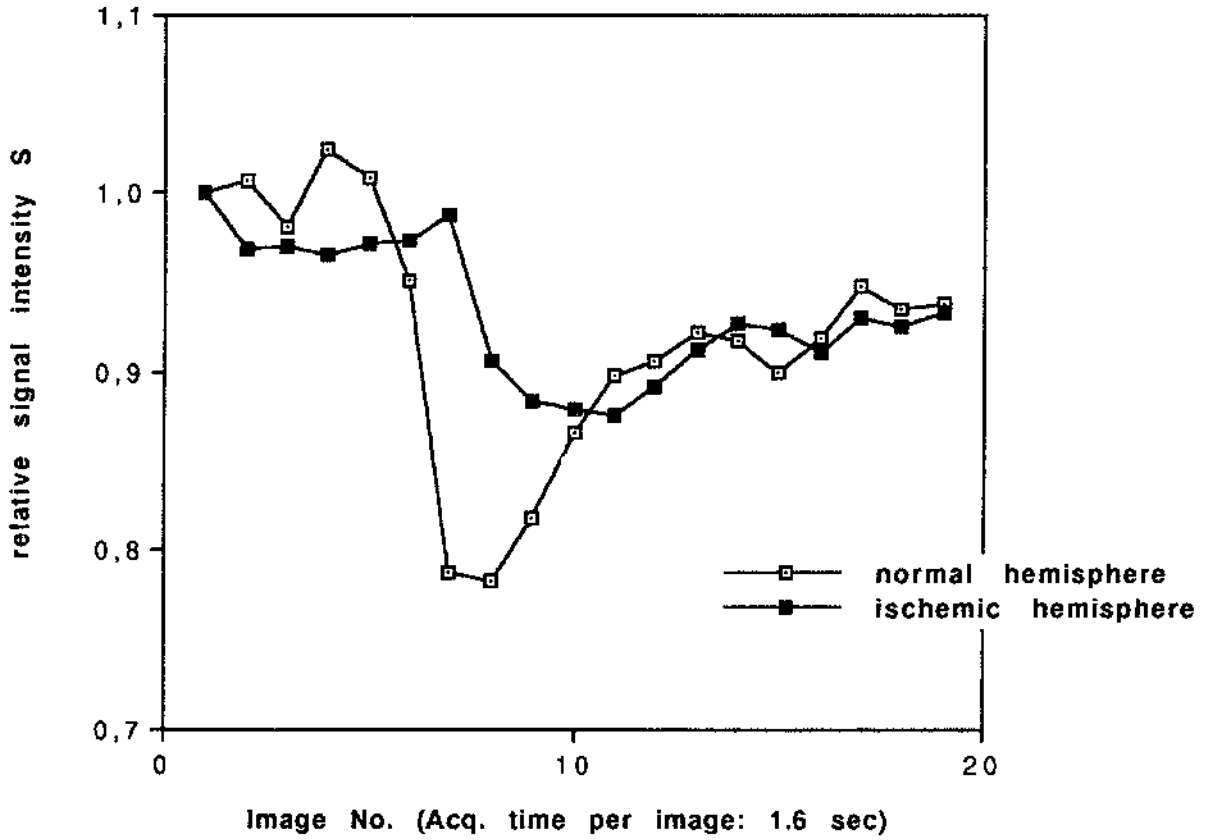


B



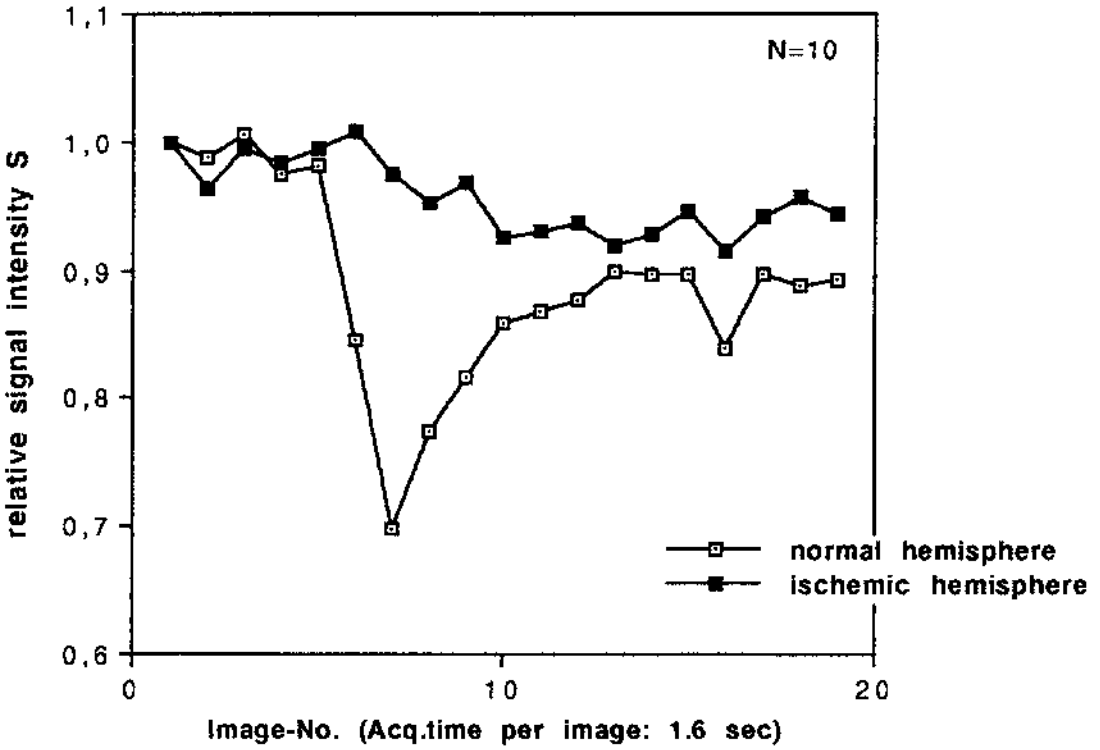

1
2
3
4
5
6

Signal curves obtained after application of paramagnetic Gd-DTPA



A

Signal curves obtained after application of superparamagnetic iron particles.



B