

Stroke Magnetic Resonance Imaging Is Accurate in Hyperacute Intracerebral Hemorrhage

A Multicenter Study on the Validity of Stroke Imaging

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Background and Purpose—Although modern multisequence stroke MRI protocols are an emerging imaging routine for the diagnostic assessment of acute ischemic stroke, their sensitivity for intracerebral hemorrhage (ICH), the most important differential diagnosis, is still a matter of debate. We hypothesized that stroke MRI is accurate in the detection of ICH. To evaluate our hypotheses, we conducted a prospective multicenter trial.

Methods—Stroke MRI protocols of 6 university hospitals were standardized. Images from 62 ICH patients and 62 nonhemorrhagic stroke patients, all imaged within the first 6 hours after symptom onset (mean, 3 hours 18 minutes), were analyzed. For diagnosis of hemorrhage, CT served as the “gold standard.” Three readers experienced in stroke imaging and 3 final-year medical students, unaware of clinical details, separately evaluated sets of diffusion-, T2-, and T2*-weighted images. The extent and phenomenology of the hemorrhage on MRI were assessed separately.

Results—Mean patient age was 65.5 years; median National Institutes of Health Stroke Scale score was 10. The experienced readers identified ICH with 100% sensitivity (confidence interval, 97.1 to 100) and 100% overall accuracy. Mean ICH size was 17.3 mL (range, 1 to 101.5 mL). The students reached a mean sensitivity of 95.16% (confidence interval, 90.32 to 98.39).

Conclusions—Hyperacute ICH causes a characteristic imaging pattern on stroke MRI and is detectable with excellent accuracy. Even raters with limited film-reading experience reached good accuracy. Stroke MRI alone can rule out ICH and demonstrate the underlying pathology in hyperacute stroke. (*Stroke*. 2004;35:502-507.)

Key Words: hemorrhage ■ magnetic resonance imaging ■ magnetic resonance imaging, diffusion-weighted ■ stroke

Multisequence stroke MRI, an evolving routine in stroke centers for the diagnosis of hyperacute ischemic stroke, has the advantage of early lesion detection on diffusion-weighted images (DWI) compared with CT.^{1,2} Noncontrast CT is currently still widely considered necessary to rule out intracerebral hemorrhage (ICH) in hyperacute stroke patients.^{3,4} Besides the demonstration of the vascular and ischemic lesion in acute stroke, the exclusion of ICH is most important before initiation of thrombolysis. Primarily for safety reasons, many centers perform CT in addition to MRI to exclude ICH. To minimize pretreatment diagnostic delay and to optimize patient selection, stroke MRI must be able to reliably detect hyperacute ICH.

Although never formally assessed, CT is commonly considered the “gold standard” to demonstrate ICH. However,

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there are several case series of ICH patients imaged with MRI that indicate that MRI may be well suited to demonstrate ICH. Patel and coworkers⁵ presented a series of 6 ICH patients imaged within 5 hours of symptom onset. They were able to detect hemorrhage on MRI in all cases on T2*-weighted images at 1.0 or 1.5 T. In a prospective single-center study, we recruited 9 patients 3 to 5 hours 45 minutes after symptom onset.⁶ Compared with CT, ICH was 17.8% overestimated on T2*-weighted images and was visible on T2-weighted images, fluid-attenuated inversion recovery (FLAIR), and DWI. Lin and coworkers⁷ evaluated the sensitivity of gradient echo images and b=0 images obtained from DWI sequences. They failed to detect hemorrhage on these echo-planar T2-weighted images in 46% of 13 patients and

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MRI Protocol Parameters

	PD/T2-W TSE	3D TOF-MRA	T2*-W Flash	DWI	PWI
TR, ms	>2500	30–40	60	>3000	1300–1500
TE, ms	15–30 (TE1) 80–100 (TE2)	6.5–7.0	25–30	<120	50
b, s/mm ²	0–30 (b0) 1000 (b1)	...
Flip angle, °	90	15–20	30	90	90
Averages	1	1	1	1 at b0, 3 at b1000	1 each 1.3–1.5 s
FOV, mm ²	220–310	220–250	220–310	220–310	220–310
Matrix	256×192	256×128	256×192	128×64	128×64
Thickness, mm	6	1.0–1.2	6	6	6
Gap, mm	0.5	0	0.5	0.5	0.5
Slices, n	20	50	20	20	12 each 1.3–1.5 s

PD indicates proton density; W, weighted; TSE, turbo spin echo; 3D, 3-dimensional; TOF, time of flight; MRA, MR angiography; TR, repetition time; TE, echo time; and FOV, field of view.

suggested the use of gradient-echo images. However, the study presented by Lin and coworkers was not focused on the hyperacute phase of stroke. Linfante and coworkers⁸ presented the patient with the shortest delay from stroke to MRI in the literature: 23 minutes after ictus, they observed signal loss on T2*-weighted images in a patient with left hemispheric hemorrhage. On the basis of these findings and the advantages of MRI for therapeutic decisions in cerebral ischemia,⁹ several authors suggested using MRI as the prime imaging modality in hyperacute stroke.^{10,11}

Although these patient series rendered exemplary information of ICH appearance in stroke MRI during the hyperacute phase, a prospective study to evaluate the accuracy of stroke MRI in a large patient cohort under more realistic conditions for stroke centers is still pending. This was our motivation for conducting a multicenter stroke MRI study to prove the accuracy of MRI in patients with acute ICH.

Patients and Methods

Study Concept

In December 1999, the stroke MRI study group of the German competence network in stroke decided to image all hyperacute stroke patients according to a standardized protocol (the Table) in each participating center. This typical stroke protocol was designed to detect early infarction, vessel occlusion, and tissue at risk of infarction, as well as ICH and other differential diagnosis. For DWI, we chose a b value of 1000 mm/s² to reach a high sensitivity for early infarction. From February 2000 to April 2002, we prospectively conducted a multicenter study of ICH patients. Inclusion criteria were (1) known onset of symptoms, (2) focal neurological deficit with stroke severity of >3 points on the National Institutes of Health Stroke Scale (NIHSS), and (3) stable vital signs. Patients who did not give informed consent to the initial workup and those with general contraindications for MRI were not included. A total of 62 ICH patients admitted to the hospitals within the first 6 hours after ictus were investigated with MRI and diagnostic noncontrast CT. In every patient, diagnosis of ICH was confirmed by CT immediately before or after MRI, depending on the individual hospital stroke routine. A post hoc central CT reading was not performed. In Hamburg and Düsseldorf, all hyperacute stroke patients were first imaged with MRI; in Heidelberg, patients were randomized for the order of imaging modalities. In the other centers (Mannheim, Berlin, Mainz), CT was immediately followed by MRI. All MRI machines used had echo-planar capabilities but were different 1.5-T systems: Siemens

Vision (4), Siemens Symphony (1), and Marconi Edge (1). The study protocol was approved by the local ethics committees. Images from 62 ICH patients and 62 control subjects, all fulfilling the study inclusion criteria, were analyzed. Control subjects were not matched for age, time since onset, or severity of symptoms. Each center contributed control subjects in proportion to ICH patients. Control subjects were selected as a convenience sample in each center from the clinical routine, without any specified selection process except the study inclusion criteria. Randomization numbers were then assigned, and patient data were blinded at each study site before being sent to the principle investigators' site. The final clinical diagnosis was reported on separate data forms.

Evaluation and Statistic Analysis

Every center received a study instruction manual to adjust the stroke MRI protocol. The centers documented demographic data, imaging delay from symptom onset, and NIHSS score severity on a case report form and concealed patient identity with randomly assigned numbers. Each center printed hard copies of all images and sent them to the principal study center (Heidelberg). After patient recruitment was concluded, all image hard copies were evaluated in 1 reading session. T2- and T2*-weighted images and DWI from each patient were presented in the order of randomization numbers. Unaware of any clinical details and any CT findings, 3 readers (neurologists: A.G., P.S.; neuroradiologist, J.F.), all experienced in stroke imaging, separately read the images. An imaging diagnosis was noted for each patient, and image quality was rated (1=good quality, 2=of limited quality but of diagnostic value, 3=not suitable for diagnostic assessment). As recently suggested, further diagnostic information on residual tissue change after previous hemorrhage or signs of microbleeding on T2*-weighted images was recorded.¹² Three final-year medical students also rated the images with regard to ICH, ischemia, or neither. Before rating images, they had participated in a daily neuroradiological case conference for several weeks and had a 1-hour formal instruction session on how to read stroke MRI 1 week before the image evaluation. Because of their limited experience in image interpretation, they were asked only to rate the principal diagnosis.

All ICH images were analyzed separately with regard to their MRI appearance and size (J.F.). The signal intensities of the lesion core, periphery of the lesion, and surrounding tissue were compared with the contralateral tissue on T2- and T2*-weighted images and DWI. Hemorrhage volume was calculated with the bedside ABC/2 method as described by Kothari and coworkers¹³ on CT images. In this simple approach, the diameters in 3 spatial dimensions are multiplied and divided by 2. T2-weighted images were used for the hemorrhage volume assessment.

A sample size calculation was made before study conception. A minimum sample size of 50 patients per group was calculated to reach an acceptable (95% to 100%) confidence interval (CI) at a 100% sensitivity. Sensitivity, specificity, and accuracy, as well as positive and negative predictive values, were calculated for each rater. Binominal CIs were calculated for each rater as a rate of correct decisions as to whether ICH was diagnosed or excluded. The correlation between size of ICH and severity of NIHSS score was calculated as a Spearman signed-rank correlation.

Results

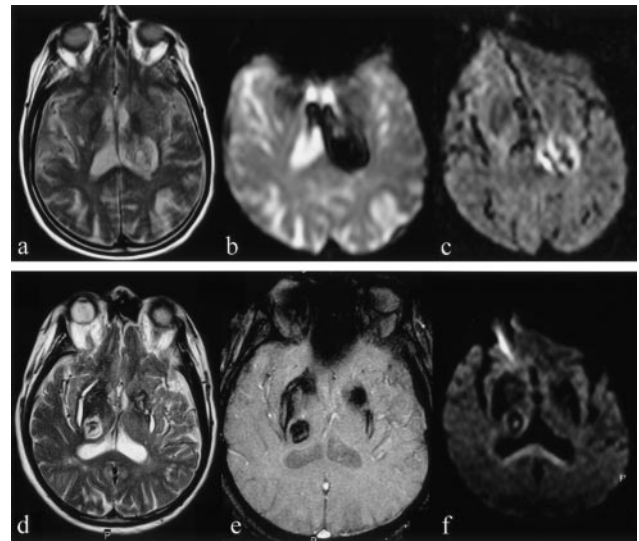
Patients

The median stroke severity of the 62 ICH patients was NIHSS score 9.5 (range, 4 to 31); 25% were female. The control cohort consisted of 58 ischemic stroke patients, 3 transient ischemic attack patients, and 1 patient with a postictal hemiparesis after a seizure caused by a temporal lobe tumor. Median NIHSS score of the control patients was 10 (range, 4 to 24). Mean age of the ICH group was 65.9 years (control group, 65.1 years). The first brain image had a mean delay of 198 minutes from symptom onset (SD, 89 minutes; range, 60 to 356 minutes). Twenty-nine ICH patients were imaged within the first 3 hours after symptom onset: 10 during the second hour and the remaining 19 during the third hour after symptom onset. The control group presented with similar delays from symptom onset: Brain imaging had a mean delay of 203 minutes (SD, 87 minutes; range, 69 to 358 minutes); 30 patients were imaged within the first 3 hours. The patient recruitment rates were as follows: Heidelberg, 88; Mannheim, 19; Hamburg, 10; Düsseldorf, 4; Berlin, 2; and Mainz, 1. Study screening logs were not kept, and there are no detailed data concerning the variability of recruitment rates. The mean hemorrhage volume was 17.3 mL (median, 10.1 mL). In 16 patients, hemorrhages were small, ie, <5 mL (range, 1 to 5 mL; mean, 3.1 mL); 15 ICH lesions ranged from 5.1 to 10 mL (mean, 7.5 mL); 17 ICHs were 10.1 to 25 mL (mean, 15.4 mL); and the remaining 14 cases showed large hemorrhage up to 101.5 mL (mean, 46.5 mL).

Ratings

Each expert identified all acute hemorrhages. In 4 patients, additional signs of old ICH residuals were reported in the comment section from at least 2 of the raters. In 2 cases, signs of microbleedings were described. The binominal CI of the experts' sensitivity was 97.07% to 100.00%. Specificity, predictive values, and accuracy were 100%. Imaging quality was judged as good in 83.1% of the examinations; 16.9% were of limited quality but sufficient for diagnostic assessment (ie, movement artifact in 1 sequence, susceptibility distortions). No rater judged any image set as not of diagnostic quality.

The final-year medical students reached a mean sensitivity of 95.2% (CI, 89.8 to 99.8). Mean specificity was 95.5 with a positive predictive value of 100% and a negative predictive value of 95.5%. They reached an accuracy of 97.6%. There was a significant correlation between NIHSS scores and hemorrhage size (Spearman's signed-rank correlation $r=0.53$, $P<0.0001$).



Small hyperacute thalamic hemorrhages on T2-weighted images (a, d), T2*-weighted images (b, e), and DWI (c, f) from different 1.5-T tomographs (a through c, Siemens Symphony; d through f, Marconi Edge). Patient in bottom row has also lesions from former hemorrhages at left lentiform nucleus and both external capsules (d, f).

ICH Appearance

ICH caused a hyperintense signal on T2-weighted images in 57 cases. The remaining 5 cases showed a slightly hypointense signal. The lesion core was surrounded by a rim isointense to normal brain tissue in 58 cases, and there was a hyperintense signal in the tissue adjacent to the hemorrhage in all cases (the Figure). On T2*-weighted images and DWI, we observed a hypointense rim surrounding a heterogeneous hemorrhage core. The surrounding tissue again showed an increased signal. Therefore, hemorrhage appearance was targetlike in all cases. In contrast to cerebral ischemia, there was a signal increase on T2-weighted images in each patient within the hyperacute phase.

Discussion

Hyperacute ICH is easily detectable on stroke MRI. On the basis of examinations of 124 patients examined within 6 hours of symptom onset, we reached the statistical power to prove our hypotheses. The 3 experienced raters separated the 62 ICH patients from a control group, while clinical status concerning time window and stroke severity were comparable for both patient groups. To stress our hypotheses, the images were also analyzed by 3 final-year medical students who also reached a substantial accuracy.

About 75% of hyperacute stroke patients with severe deficits suffer from cerebral ischemia.¹⁴ These patients have been examined with CT in the past to exclude ICH before initiation of thrombolytic therapy.⁴ In a prospective single-center trial, we observed a significantly higher accuracy of DWI in brain infarction compared with CT.¹⁵ In patients with cerebral ischemia, stroke MRI has been shown to delineate the infarcted tissue, a vessel occlusion if present, and hypoperfused tissue at risk that still could recover if cerebral blood flow was normalized.¹⁶ The longer the delay is from

stroke onset to initiation of thrombolysis, the larger the number of patients needed to treat to prevent 1 disabled or dead patient.¹⁷ On the basis of this study, CT for exclusion of hemorrhage may be omitted in centers that use MRI as the primary assessment of acute stroke patients.

Steinbrich and colleagues¹⁸ reported a sensitivity of 46% for MRI in acute ICH in the early 1990s. Recent studies described the appearance of hyperacute hemorrhage on stroke MRI under unblinded conditions.^{5,6} These studies presented data from 6 and 9 patients, respectively, imaged within the first 6 hours of symptom onset and contradicted the traditional opinion concerning a low sensitivity of MRI to ICH.^{19,20} Linfante and colleagues⁸ not only presented an ICH patient imaged 20 minutes after symptom onset but also described characteristic signal changes of ICH on T2- and T2*-weighted images. The phenomenology of acute ICH in our trial was identical to their descriptions regardless of the MRI system used in this multicenter trial. Morita and colleagues²¹ described a similar image pattern in 8 patients imaged from 40 minutes to 4 hours 30 minutes after symptom onset. Compared with cerebral infarction, they mentioned a hypointense rim as a characteristic sign of ICH. Some groups not only identified ICH on MRI but also evaluated signal changes in the perihematomal region.^{22,23} In 5 of 6 patients imaged with perfusion-weighted MRI, Kidwell and colleagues²² identified a diffuse hemispheric hypoperfusion of the affected hemisphere. A decreased apparent diffusion coefficient in 3 of 12 patients correlated with a poor clinical outcome. On the basis of data from 32 hyperacute ICH patients, we observed a mild prolongation of the mean transit time.²³ In contrast to the findings of Kidwell and colleagues, we did not observe any significant changes of apparent diffusion coefficient and perfusion maps. Warach²⁴ commented on both articles and indicated the methodological limitation of apparent diffusion coefficient and perfusion-weighted imaging measurement in perihematomal tissue. The value of perihematomal signal changes remains a matter of further studies. At the beginning of the study presented here, we did not have evidence to evaluate perfusion in a prospective manner.

We calculated lesion size according to the method suggested by Kothari and colleagues.¹³ Their comparison of volumetric measurements and the ABC approach in cerebral hemorrhage volumes was evaluated for CT. The results presented by Schellinger and colleagues⁶ suggest a 13% underestimation of lesion size on T2-weighted images compared with CT. Distortion artifacts hindered a volumetric comparison of MRI and CT data. Therefore, we assessed the intracranial bleeding volume by the ABC approach to describe the study cohort.

Both CT and MRI are prone to motion and other specific artifacts. Fast MRI sequences, commonly used for stroke MRI, reduce the likelihood of motion artifacts. Indeed, all of the MRI studies in this large patient population were of sufficient quality to provide a diagnostic assessment. This may be due to well-trained MRI personnel, but the multicenter approach of this study demonstrates that this degree of training can be achieved in stroke centers. However, the feasibility of stroke MRI was not formally assessed in this

study. One limitation of this study was the broad range of patient recruitment in the 6 centers. This was due mainly to logistic reasons concerning MRI (and CT) availability in those centers with lower recruitment rates. It has been shown that FLAIR sequences are sensitive to ICH and subarachnoid hemorrhage.²⁵ In this study, FLAIR was not performed to limit scan time but may indeed be a consideration when fast FLAIR imaging is available.

It has been suggested that the identification of signs of previous bleedings or so-called microbleedings increases the risk of hemorrhage after thrombolysis.¹² We were able to identify this subtle abnormality usually not visible on CT that may strengthen the value of MRI in patients considered for thrombolysis. Recent reports on microbleeds in stroke patients concentrated on T2*-weighted images.^{12,26} Therefore, we decided to focus our evaluation on susceptibility-sensitive sequences, as recently suggested by von Kummer.¹⁰

In MRI studies of patients with suspected stroke, it is possible to encounter individuals with poor clinical information and/or other underlying diagnoses like migraine, postictal states, and subarachnoid hemorrhage. Except for 1 control, such patients were not encountered in our study. All MRI studies in this cohort demonstrated positive findings explaining the acute symptoms. In the theoretical case of a completely negative MRI assessment, including perfusion-weighted sequences and MR angiography, potential “stroke mimics” should be considered.

Visual identification of ICH, even if small, is not difficult on MRI. From the findings of this study, we feel confident to examine patients with suspected acute cerebral ischemia with MRI only because MRI has a very high likelihood of a positive diagnosis of acute ischemia or ICH.

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Editorial Comment

Can MRI Reliably Detect Hyperacute Intracerebral Hemorrhage? Ask the Medical Student

Although never formally tested, a CT is required to exclude intracerebral hemorrhage (ICH) in acute stroke prior to thrombolysis. Therefore, centers that use MRI in acute stroke must in addition obtain a CT to safely rule out ICH.

Despite traditional skepticism, MRI is intrinsically able to detect hyperacute ICH. Such capability is based on the magnetic susceptibility effect of deoxyhemoglobin. In ICH, hemoglobin extravasates in an environment with a low O₂ concentration, low pH, and high CO₂. Because of the Bohr effect, such changes promote the formation of deoxyhemoglobin extending from the periphery of the hematoma toward the center. Deoxyhemoglobin has 4 unpaired electrons and is therefore paramagnetic ($\chi > 0$). As such, it produces magnetic inhomogeneities that result in local T2* relaxation enhancement. Obviously, the MR contrast of deoxyhemoglobin is highly dependent on the mode of imaging acquisition. For instance, deoxyhemoglobin induced signal loss (darkening) is most pronounced in sequences that are T2* weighted such as conventional gradient echo (GE) and both spin-echo and gradient-echo echo-planar sequences.¹

Atlas and Thulborn reported signal loss on long TR/TE, and GE images in a rat model of ICH.² Distinctive signal loss was present at the earliest imaging time point (1 hour after the induction of the hematoma). Several authors reported clearly detectable changes on T2*-weighted imaging in patients with ICH imaged between 23 minutes and 6 hours after symptom onset.^{3,4} In 5 patients with ICH imaged within 2 hours after symptom onset, distinctive patterns of hyperacute ICH and absence of signs of ischemic stroke were the hallmark features of this diagnosis. The hyperacute hematoma appears to be composed of 3 distinct areas: (1) center: isointense to hyperintense signal on T2* and T2-weighted imaging; (2) periphery: hypointense (deoxyhemoglobin) mostly on T2*-weighted imaging; (3) rim: hypointense on T1-weighted imaging and hyperintense on T2-weighted imaging, representing vasogenic edema encasing the hematoma.⁴

These preliminary clinical observations were put to test by Fiebach et al.⁵ This study is a prospective, multicentric, blinded, randomized trial involving 124 patients: 62 patients

with ICH and 62 controls. The authors measured sensitivity, specificity, accuracy, positive and negative predictive value of a multisequence MRI protocol in detecting ICH within 6 hours after symptom onset. Twenty-nine patients were imaged within the first 3 hours, 20 within the second hour. Three experienced readers identified ICH with 100% sensitivity and 100% accuracy. In addition, 3 students in the final year of medical school, who did not have formal training in MRI, identify ICH with a sensitivity of 95%.

This landmark article provides level I evidence that MRI can reliably detect ICH within 6 hours after symptom onset.

The data have critical implications for the care of acute stroke patients. Because ICH is a potentially lethal complication of thrombolytic treatment, evidence of prior hemorrhage is an absolute contraindication.⁶ Evidence of microbleeds on MRI is present in 38% to 66% of patients with primary ICH and in 26% of patients with ischemic stroke. Kidwell et al reported that 12% of 41 patients had microbleeds on MRI obtained pre-thrombolysis that were not visible on CT.⁷ Fiebach et al also reported that a T2*-weighted sequence identified microbleeds not visible on CT.⁵ Because all the major thrombolytic trials used CT before thrombolysis, the incidence of microbleeds in this patient population is not known. The data are worrisome since in the NINDS trial 20% of all symptomatic ICH occurred outside the arterial territory of the presenting stroke.⁸ The article of Fiebach et al provides further evidence that MRI should be “the gold standard” in screening for hematomas and microbleeds prior to thrombolysis.

Magnetic resonance imaging has proven to offer unique information in acute stroke.⁹ A multisequence MRI protocol is sensitive to early ischemia, can exclude nonstroke diagnosis, can predict the likelihood of hemorrhagic transformation, and can detect the arterial occlusion.^{9–11} In addition, by imaging the complex blood flow and tissue dynamics of early ischemia, MRI can guide therapeutic decisions based on tissue viability rather than rigid time intervals.^{9,12} Moreover, ultrafast MRI stroke protocols take only 5 to 20 minutes to perform and by reliably detecting hyperacute ICH, they can

now be used as the sole imaging study prior to thrombolysis.^{5,13}

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