Magnetic Resonance Imaging Criteria for Thrombolysis in Acute Cerebral Infarct

N. Hjort, MD; K. Butcher, MD, PhD, FRCP(C); S.M. Davis, MD, FRACP; C.S. Kidwell, MD; on behalf of the UCLA Thrombolysis Investigators; W.J. Koroshetz, MD; J. Röther, MD; P.D. Schellinger, MD; S. Warach, MD, PhD; L. Østergaard, MD, MSc, PhD

Background and Purpose—Magnetic resonance imaging (MRI) selection of stroke patients eligible for thrombolytic therapy is an emerging application. Although the efficacy of therapy within 3 hours after onset of symptoms with intravenous (IV) tissue plasminogen activator (tPA) has been proven for patients selected with computed tomography (CT), no randomized, double-blinded MRI trial has been published yet.

Summary of Review—MRI screening of acute stroke patients before thrombolytic therapy is performed in some cerebrovascular centers. In contrast to the CT trials, MRI pilot studies demonstrate benefit of therapy up to 6 hours after onset of symptoms. This article reviews the literature that has lead to current controlled MRI-based thrombolysis trials. We examined the MRI criteria applied in 5 stroke centers. Along with the personal views of clinicians at these centers, the survey reveals a variety of clinical and MRI technical aspects that must be further investigated: the therapeutic consequence of microbleeds, the use of magnetic resonance angiography, dynamic time windows, and others.

Conclusion—MRI is an established application in acute evaluation of stroke patients and may suit as a brain clock, replacing the currently used epidemiological time clock when deciding whether to initiate thrombolytic therapy. MRI criteria for thrombolytic therapy are applied in some cerebrovascular centers, but the results of ongoing clinical trials must be awaited before it is possible to reach consensus. (Stroke. 2005;36:388-397.)

Key Words: diffusion magnetic resonance imaging • magnetic resonance imaging • perfusion magnetic resonance imaging • stroke management • thrombolysis

The use of magnetic resonance imaging (MRI) for selecting acute stroke patients suitable for intravenous (IV) or intra-arterial (IA) thrombolysis is a growing application. Randomized, double-blind, placebo-controlled trials of acute stroke therapies have so far been based on computed tomography (CT).1–4 Only the National Institute of Neurological Disorders and Stroke (NINDS) trial1 demonstrated efficacy of IV tissue plasminogen activator (tPA) has been proven for patients selected with computed tomography (CT), no randomized, double-blinded MRI trial has been published yet.

Smaller, nonrandomized MRI studies have suggested more sophisticated ways of selecting patients for thrombolysis.6–19 In contrast to CT, diffusion-weighted MRI (DWI) can demonstrate ischemic changes within minutes of the onset.20,21 Perfusion-weighted MRI (PWI) defines areas of hypoperfusion.22 A PWI–DWI mismatch, which indicates tissue with decreased perfusion extending beyond that of diffusion abnormalities, is thought to represent tissue at risk of infarction yet potentially salvageable.23,24 PWI–DWI mismatch is seen in 80% to 86% of stroke patients examined in the acute phase14,25 and is a strong predictor of infarct growth.24,25 MR angiography (MRA) can localize the vascular lesion and susceptibility-weighted T2* imaging acute or chronic intracerebral hemorrhage (ICH).26 Hence, MRI alone may refine selection of thrombolytic candidates.

Studies involving MRI selected stroke patients receiving thrombolytics are reviewed (Table 1). These pilot studies form the scientific rationale for ongoing trials. Until now, no randomized placebo-controlled trials using MRI selection of patients for thrombolysis have been published to our knowledge. Although placebo-controlled trials will define how to implement the abundant MRI parameters within some years, the clinical practice at present is based on local experience, expert opinions, and the published open-label studies. Along with the current state-of-the-art workup, this article presents...
the views and personal experience of 5 stroke centers with extensive experience using MRI in the decision process before administration of thrombolytics, most commonly tPA (Tables 2–6). We hope this will further the research, clinical development, and debate in the community.

MRI Thrombolysis Studies

The PWI–DWI Mismatch in Thrombolysis

The first results of monitoring patients receiving tPA by MRI were published in 1999 by Marks et al.6 evaluating 6 patients with acute PWI and DWI after tPA treatment in the 0- to 3-hour time window. Six other patients (admitted <6 hours) were used as controls. Only 1 of 6 treated patients showed mismatch after treatment compared with 5 of 6 controls, suggesting that recanalization already had occurred. Early reperfusion, defined as resolution of PWI abnormalities after 24 to 36 hours, was most frequent in the treatment group (5 of 6 versus 1 of 5 controls).

Jansen et al.18 found mismatch and arterial occlusion in 21 of 35 acute stroke patients before therapy with IV tPA up to 6 hours from symptom onset. Eleven of 21 patients with mismatch were treated, 6 within 3 hours. MRA on day 2 showed recanalization in 8 of 21 mismatch patients, 6 of whom received tPA (<5 hours), whereas 2 had spontaneous recanalization. Growth of infarcts was less in the tPA group.

Sunshine et al.19 used DWI and PWI to triage 41 acute stroke patients to therapy. Patients without DWI lesions were treated conservatively, whereas those with DWI abnormalities received IV and/or IA tPA dependent on occlusion type and time of admission. No clinical or follow-up MRI data were published, but the study demonstrated the feasibility of MRI in an acute stroke setting.

Schellinger et al.22 included 24 patients in a noncontrolled study of the feasibility of PWI, DWI, and MRA to select patients for thrombolytic therapy (<6 hours). Eleven of 24 patients were treated with tPA within 3 hours. Eleven of 20 patients with initial occlusion showed recanalization on day 2 MRA. Patients without recanalization experienced significant growth of infarct from day 1 to 5, with lesion volumes being significantly greater than those of the recanalization group on days 2 and 5. The recanalization group had significantly better outcome scores. The authors concluded that MRI is a practical and safe tool in monitoring of tPA treatment. This study provides pathophysiological insight into vessel status in a stroke thrombolysis setting.

Röther et al.14 presented 139 stroke patients (<6 hours). Seventy-six patients were selected for tPA treatment (NINDS inclusion criteria,1 <3 hours; ECASS II criteria,3 3 to 6 hours). PWI–DWI mismatch was present in 120 of 139 patients. Recanalization (minimal, incomplete, or complete recanalization by Thrombolysis in Myocardial Infarction [TIMI] criteria) was significantly more frequent in the tPA group. Treatment initiated <3 hours yielded higher rate of recanalization than in the 3- to 6-hour time window. Thrombolysis improved clinical outcome irrespective of time window. Outcome was similar among groups. One would expect worse outcome with delayed time window because of smaller volumes of tissue at risk of infarction, worse initial National Institutes of Health Stroke Scale (NIHSS) score, larger initial DWI volumes, or larger final infarct volumes. However, differences in these parameters in the subgroups in the 0- to 3-hour and 3- to 6-hour time windows were not found. Because of the small cohort of nonmismatch, thrombolysis patients (9 of 19 without mismatch), the role of PWI–DWI mismatch in deciding tPA treatment could not be established.

The effect of PWI–DWI mismatch on outcome was examined by Parsons et al20 in 19 stroke patients (<6 hours) before tPA and compared with 21 historical controls. Notably, of 32 patients with mismatch, only 24 had visible occlusion on MRA. They found no statistical difference in clinical outcome between the tPA and control group but significantly improved outcome in the subgroup of mismatch patients. Infarct growth and final infarct size were significantly smaller in treated patients compared with controls. PWI–DWI mismatch tissue not progressing to infarction, “penumbral salvage,” was larger in the mismatch tPA group compared with mismatch controls. This was especially pronounced in mismatch tissue with mean transit time (MTT) delays >6 seconds (severe hypoperfusion) compared with MTT delays >4 seconds (moderate hypoperfusion), pointing to MTT prolongation as a quantitative marker of infarct risk, possibly providing thresholds of significance in clinical decision-making. As described here14 and as described by Kuelkens,27 time of treatment influenced neither MRI nor clinical parameters. They concluded that PWI–DWI mismatch represents tissue at risk and that thrombolysis should therefore be considered, even if occlusion on MRA is not visible.

Butcher et al.16 further analyzed the data of Parsons2 to find perfusion thresholds for infarcting tissue, expressed in MTT prolongation beyond that of the unaffected hemisphere. Acute MTT delay was 22% longer in regions of infarction compared with salvaged regions. MTT delay threshold for infarction was greater for patients showing reperfusion on subacute MRI than patients without. Thus, reperfusion made salvage of tissue with relatively more severe hypoperfusion possible. Reperfusion was observed more frequently in treated patients than controls (13 of 17 versus 5 of 18). The MTT threshold for infarction was inversely correlated with time to treatment.

Fiehler et al.15 also found correlation between severity of perfusion deficit and subsequent infarction using perfusion thresholds. Thirty-two acute stroke patients were examined with DWI and PWI before thrombolytic therapy within 6 hours. Recanalization was seen in 20 of 32 patients. A volume of ≥50 mL with cerebral blood flow value of ≤12 mL/100 g per minute predicted growth of DWI lesion. Absolute flow measures were obtained by normalization to literature positron emission tomography values. Proximal occlusion of median cerebral artery (MCA) and internal carotid artery (ICA) was correlated with growth of infarct.

To determine perfusion thresholds for irreversible infarcted tissue from penumbral tissue, Shih et al.12 analyzed a cohort of 14 successfully recanilized patients examined before IV and/or IA thrombolytic therapy. The fate of all voxels with a pretreatment perfusion deficit (defined as time to peak of the residue function: Tmax ≥2 seconds; Figure) were analyzed during follow-up DWI on day 7. The Tmax threshold values that most successfully determined fate of voxels were 6 and 8 seconds. Tmax ≥6 seconds identified 71% of the voxels that
went on to infarction on day 7. Nine of 14 patients showed regression of DWI lesion from the pretreatment to the follow-up DWI. The same threshold was found earlier by Neumann-Haefelin et al28 in an observational study.

Nighoghossian et al10 performed PWI and DWI before and after thrombolysis (<7 hours). Correlations were found between acute PWI and DWI lesion volume and outcome NIHSS in contrast to acute PWI–DWI mismatch volume and outcome. Recanalization was seen in 15 of 29 patients on MRA on day 2, which correlated strongly to a positive outcome. Please find summary of MRI thrombolysis studies in Table 1.

**DWI Reversibility**

The apparent diffusion coefficient (ADC) provides a quantitative measure of the acute reduction in water diffusion observed as hyperintensities on DWI immediately after symptom onset. Infarcted tissue appears hyperintense in DWI images, initially because of diffusion restriction in cell swelling, later caused by the inherent T2-weighting and the cytotoxic edema, tissue necrosis. ADC values reflect these cellular changes, remaining low for 3 to 5 days before slowly increasing to supernormal values because of tissue edema and necrosis. During this course, values appear normal: pseudo-normalization.29 Animal studies have shown reversal of DWI and ADC abnormalities after reperfusion,30 with some suggesting that ADC thresholds may exist in reperfusion.31 Observations of ADC threshold for salvage/infarction in (nonthrombolyzed) humans by Fiehler et al32 do not support this. Tissue displaying ADC values ≲50% were seen to return to normal values on day 7 T2-weighted imaging. In a cohort of 68 patients admitted <6 hours, ADC normalization of >5 mL tissue volume was subsequently observed in 20.6%.33 ADC normalization was most frequent in the 0- to 3-hour time window and was associated with at least partial reperfusion. Tissue with severe initial ADC decrease was less likely to normalize. Brain tissue with initially decreased ADC may include “tissue at risk,” and PWI–DWI mismatch may not be essential in the 3-hour time window.

In the study by Marks,6 ADC increase within the ischemic zone was observed only in the 5 of 6 patients with early reperfusion, remaining high within the first week.

Kidwell et al8 studied the course of diffusion parameters in 7 humans after IA urokinase or a combination of IV and IA tPA, leading to partial or complete recanalization. Six patients showed significant decrease in DWI and ADC abnormality volume (ADC map threshold <550 μm2/s) after therapy. Nonetheless, half of the patients displayed secondary growth of DWI and ADC lesion volume, which was speculated to be a result of reperfusion injury.

In a later publication by Kidwell et al,11 12 additional patients were included for a further analysis of DWI reversal. Eight of 18 patients showed reversal of DWI, and 13 of 18 showed reversal of ADC abnormalities after treatment. Three of 18 patients had sustained DWI reversal (day 7), and 5 had early reversal followed by secondary reappearance. Regional analysis of all patient data demonstrated that mean pretreatment ADC values were lowest for voxels without reversal and highest for those with sustained reversal. Patients with sustained reversal had the best clinical outcome. Based on the observation of partial reversal of diffusion lesions, Kidwell et al34 have proposed a modified view of the ischemic penumbra in which parts of the initial diffusion abnormality are included.

Uno et al13 examined 10 patients with PWI and DWI before and after IA thrombolysis (<6 hours). Three of 7 recanalized patients showed DWI reversibility. Initial PWI–DWI ratio was correlated with initial NIHSS score and initial PWI–DWI volume was correlated with rescued volume.

Clinical implications of DWI and PWI lesion reversal by thrombolysis were addressed by Chalela et al.17 To determine predictive factors for excellent neurological outcome, patients were examined before and 3 hours after therapy. Of 37 patients with acute MTT lesions, 16 showed MTT lesion reduction >30%, whereas 8 of 42 with acute DWI lesion showed a comparable shrinkage of the DWI lesion. Unlike DWI lesion volume reduction, MTT lesion reduction correlated to an excellent outcome, suggesting that DWI lesion reversal is not immediately accompanied by functional improvements. Complete or partial recanalization occurred in 14 of 24 patients. Interestingly, residual perfusion deficits were observed in the majority of patients with complete recanalization at the 3-hour examination, suggesting that distal

The measured tissue concentration time curve gives rise to various measures of the transit time that all depend on the local shape of the arterial input function: arrival time (AT) of the bolus, which mainly reflects collateral circulation, time-to-peak, which to some extent reflects tissue transit time (TTP), and, if arrival delay is included, collateral circulation (TTP). First moment (the center of gravity of the tissue concentration time curve (FWHM) mainly depend on tissue mean transit time. Deconvolution removes the dependence on the arterial input curve. With arterial delays, the deconvolved curve is not maximum at t=0, but after a certain delay it is at maximum, T:\max. Cerebral blood flow is usually taken as the curve height at this time. MTT is calculated as CBV/CBF, where CBV is determined as the area under the deconvolved curve (or the tissue concentration time curve; however, this requires laborious corrections for tracer recirculation). CBF indicates cerebral blood flow.
perfusion deficits caused by lysis of the main clot may be observed. Parsons reported 2 additional patients showing reversal of DWI lesions after thrombolytic therapy. With the potential for functional recovery of tissue initially lesioned on DWI suggested by these studies, the metabolic and hemodynamic characteristics of DWI abnormalities remain a topic of further study.

Ongoing and Completed Unpublished Trials
A Melbourne-based placebo controlled MRI trial, EPITHET (Echoplanar Imaging Thrombolysis Evaluation Trial) is currently including patients in the 3- to 6-hour window to determine whether the presence and extent of the PWI–DWI-mismatch identifies patients who benefit from tPA. The trial also tests whether large DWI lesions are associated with increased risk of hemorrhagic transformation after tPA. MRI is performed before randomization but is not used in patient selection.

The National Institutes of Health-funded DEFUSE (DWI Evolution for Understanding Stroke Etiology) study includes patients in the 3- to 6-hour window to open-label treatment with IV tPA. The aim is to define PWI and DWI parameters predicting favorable response to tPA.

The now-completed DIAS (Desmoteplase In Acute Stroke) trial included 102 patients in a 3- to 9-hour window with the following MRI selection criteria: PWI abnormality ≥2 cm in diameter involving the hemispheric gray matter plus PWI–DWI mismatch >20%. This trial was the first to exclude patients with isolated ICA occlusion. The aim was to test efficacy of IV desmoteplase in a placebo-controlled design. Patients were randomized to treatment with different doses or placebo. A significant dose-response on reperfusion 4 to 8 hours from onset and 90-day clinical outcome was observed up to 125 μg/kg. Of note, with sample sizes of ≈15 to 20, statistically significant positive clinical response was observed in the mismatch patients. Both frequency of ICH and clinical outcome appeared to be independent of time.

The NINDS-based ROSIE (ReoPro Retavase Reperfusion of Stroke Safety Study—Imaging Evaluation) proof of principle trial compares the effect of a combination of standard-dose ReoPro with an increasing dose of reteplase in patients 3 to 24 hours after symptom onset. A lesion on PWI is required, whereas patients with acute or chronic hemorrhage, microbleeds, or DWI lesion more than one-third of MCA territory are excluded. Primary outcome is trichotomized into response (complete reperfusion without toxicity), toxicity (symptomatic ICH or other major bleeding), or neither. The ROSIE-2 trial tests the effect of tinzaparin, acetylsalicylic acid, and an increasing dose of eptifibatide added on standard tPA (3 hours). Endpoint is early, near complete, or complete reperfusion.

Clinical and Methodological Issues
Detection of ICH on MRI
The sensitivity of modern stroke MRI protocols for the detection of ICH, the most important differential diagnosis of
acute ischemic stroke, is still a matter of debate. Although many experts consider noncontrast CT the definite test to rule out ICH in hyperacute stroke patients, others challenge this rule of CT within MRI stroke protocols to minimize pretreatment diagnostic delay. The largest prospective, blinded, multicenter trial was presented by Fiebach et al, evaluating MRI accuracy in 62 ICH patients and 62 nonhemorrhagic patients (<6 hours). Three readers experienced in stroke imaging and 3 interns each evaluated sets of diffusion-weighted, T₁-w, and T₁*-weighted images. Experienced readers identified ICH with 100% sensitivity and 100% overall accuracy, whereas interns reached a mean sensitivity of 95%. The authors concluded that hyperacute ICH causes a characteristic imaging pattern on stroke MRI and is detectable with excellent accuracy even in less experienced raters.

Based on these findings, MRI may be used as the sole imaging modality in hyperacute stroke without requiring additional CT.

Implications of Microbleeds on MRI

Cerebral microbleeds (CMBs) may be indicative of a higher risk of primary ICH and risk of symptomatic ICH after thrombolytic or other antithrombotic therapies. Susceptibility-weighted gradient echo is, in contrast to other MRI sequences and CT, able to show small chronic hemorrhages as focal areas of signal loss. These are most likely hemosiderin deposits caused by minor bleeding from small fibrohyalinized arterioles.

Lee et al examined 227 consecutive acute stroke patients. CMBs were counted using T₁*-weighted imaging gradient echo, and old lacunes and leukoariosis were evaluated. The degree of CMB and leukoariosis were moderately correlated with the presence of ICH. Location of CMB in the corticomedial area or deep gray matter was strongly associated with ICH in the same area, whereas no associations were observed for CMB in the infratentorial area or for old lacunes in any area.

Kidwell et al presented 41 IA thrombolysis patients, of which 5 had CMB on pretreatment MRI. Major symptomatic ICH occurred in 1 of 5 patients with CMB compared with 4 of 36 patients without.

Nighoghossian et al found CMB on T₁*-weighted imaging in 24 of 100 acute stroke patients. Age, diabetes, previous use of antithrombotic drugs, and lacunar infarcts were associated with CMB. ICH was diagnosed in 26 patients (18 acutely on T₁* gradient echo). Baseline NIHSS, diabetes, and CMB were significant and independent predictors of ICH. Risk of secondary ICH after IV thrombolysis in patients with CMB was recently addressed by the same group. Pretreatment MRI demonstrated CMB in 8 of 44 patients. There was no difference in bleeding between patients with and without CMB.

In conclusion, there is CLASS III (Lee et al) and CLASS IV evidence that multiple CMB are associated with higher risk of primary ICH. Whether presence of CMB is indicative of a high risk for predicting secondary ICH after thrombolysis is unclear and the data are inconsistent. A prospective study of incidence and severity of hemorrhagic complications and clinical gains from thrombolysis in such a subgroup is needed.

Vessel Imaging in Thrombolysis

MRA allows noninvasive assessment of vascular status. Although digital subtraction angiography remains the gold standard for vascular imaging, MRA yields comparable sensitivity and good correlation with patterns of infarction. Visibility or nonvisibility of M2 branches reliably differentiates MCA stenosis and occlusion. Contrast-enhanced MRA improves vascular MRI. CT angiography (CTA) by spiral CT is a widely available tool to evaluate the circle of Willis and provides accurate information on stenoses or occlusions in the basal arteries of the brain. CTA compares favorably with Duplex ultrasound, allowing reliable detection of intracranial stenosis, emboli, and aneurysms of a moderate or larger size. CTA is superior to Doppler sonography in the assessment of basilar artery patency in patients with acute basilar artery ischemia, particularly in distal basilar occlusion. CTA may provide information of collateral circulation. The degree of enhancement in postocclusion vessels can be taken as an estimate of the blood flow of leptomeningeal collaterals. CTA is less reliable in showing branch occlusions of the MCA or other smaller vessels distally to the circle of Willis.

Comparative trials of CTA and MRA with Doppler sonography/Doppler ultrasound or angiography in the intracranial circulation are limited. Both techniques are very reliable in the assessment of the distal ICA and proximal MCA including the trifurcation. CTA, unlike MRA, shows leptomeningeal collaterals. This information may, however, be gleaned in part from the timing of dynamic PWI images. MRA is susceptible to low flow rates and may overestimate stenoses.

Whereas patients with isolated ICA occlusion were excluded in the DIAS trial, neuroradiological intervention or
TABLE 3. MRI Criteria for Thrombolysis Used at Department of Neurology, Heidelberg, Germany

<table>
<thead>
<tr>
<th>Time Interval</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–3 hours: Standard CT-based tPA without loss of time. If feasible, MRI is performed directly after CT, and if a contraindication such as large DWI lesion or no PWI lesion, stroke mimic, lacunar infarct with match, beginning hemorrhage is found, then tPA infusion is ended. After 3 hours: First priority is to include patients in therapeutic trials. If possible and not part of the protocol, MRI is performed for academic reasons. 3–9 hours: Patients who are not eligible for any study are included in an open MRI trial, in which tPA is indicated in patients with PWI/DWI mismatch and/or vessel occlusion or PWI/DWI match (ie, PWI lesion present and PWI = DWI) without hyperintensity on FLAIR/T2, NIHSS 4–25, or disabling neurological deficit, DWI lesion &lt;one-third the MCA territory. Individual cases with unknown time window are also treated if there is a large mismatch suggesting an early time window or excellent collaterals and no hyperintensity on FLAIR/T2. IA thrombolysis plus ResPro is only performed in basilar artery occlusion and in rare exceptions (carotid T-occlusion, large thrombus) IV/IA combined thrombolysis is tried. ICA occlusions are treated by percutaneous transluminal angioplasty (with or without stenting) or emergency thromboendarterectomy. If distal ICA occlusion, presence of a PWI/DWI mismatch, small DWI lesion, and lack of interventional options, the patient should either be included in a therapeutic trial or be given IV tPA despite a lower probability of recanalization as opposed to MCA occlusions. In general, it is felt that PWI deficit rather than DWI lesion should be the most important indicator for thrombolysis because of potential reversibility of DWI lesions.</td>
<td></td>
</tr>
</tbody>
</table>

MRI Versus Advanced CT

The lessons learned from applying diffusion–perfusion MRI with MRA can be used to markedly enhance the information obtained from CT.

Demonstration of reversibility of DWI lesions places hypodensity on CT in a more secure position as a marker of irreversible ischemic injury. CTA provides reliable means of rapidly identifying patients with vascular lesions amenable to IA thrombolysis or carotid endarterectomy/angioplasty stent. Interestingly, continued imaging of the whole brain during a CTA study yields a “poor mans” cerebral blood volume (CBV) map. Whether quantitative or qualitative, this map of abnormal CBV is very predictive of tissue that dies despite reperfusion.

CT has advantages and drawbacks in determining tissue at risk for infarction without reperfusion. Because signal intensity is more directly related to contrast dye concentration, CT has advantages over MRI in quantifying perfusion. Single-slab CT provides quantitative MTT, cerebral blood flow, and CBV, allowing absolute thresholds in delineating penumbral tissue (thresholded cerebral blood flow lesion minus thresholded CBV lesion). When contrast CT and MRI are performed in sequence, the CT CBV abnormality correlates extremely well with DWI lesion size. CT scanners are not sensitive enough to scan the entire brain for whole-brain perfusion. Instead, the contrast bolus is tracked through a 2-cm tissue slab for each dye injection. CTA demonstrates arterial occlusions that place specific territories at high risk for infarction. A “mismatch” can then be defined as the difference between the abnormality on CBF CT perfusion study and the expected core infarct based on CBV abnormality. Recent data suggest that for a given vascular occlusion, it is only the amount of “core” that is important in making treatment decisions.

The Perfusion–Diffusion Mismatch: How and When?

The MTT is ideally inversely proportional to the regional perfusion pressure and, hence, closely related to the regional risk of ischemic injury in areas of normal DWI (mismatch). The mismatch volume depends on how MTT is determined and its significance seems to depend on the time of its measurement.

Methodologically, “true” MTT is defined as area divided by height of the impulse response (tissue concentration curve
TABLE 5. MRI Criteria for Thrombolysis Used by Department of Neurology and UCLA Stroke Center, Los Angeles, California

<table>
<thead>
<tr>
<th>Time Window</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–3 hours</td>
<td>Patients can be screened with either MRI or CT for standard IV tPA. Treatment should not be delayed by multimodal imaging if the patient otherwise qualifies for therapy. In theory, the only MRI exclusion criterion is previous or acute ICH. Mismatch should not necessarily influence treatment in this time window as this phenomenon was not analyzed in the NINDS trial. Moreover, because early presentation is likely a good surrogate marker for the presence of penumbra, most patients presenting &lt;3 hours will have salvageable tissue. Patients should not be excluded for treatment based on ADC or perfusion volumes or thresholds until accurate MRI ICH risk markers are validated. In the future, MRI may identify patient subgroups who are not candidates for even early therapy (eg, carotid T-occlusions with extensive, severe drops in cerebral blood flow, leaving no penumbral tissue even &lt;3 hours). In addition, the role of CMB in determining eligibility for thrombolytic therapy is not yet known. In practice, presence of ≥4 CMBs could cause hesitation to treat. Ultimately, this is left to the discretion of the treating physician until definitive data are available to address this issue.</td>
</tr>
<tr>
<td>After 3 hours</td>
<td>IV and IA thrombolytic therapies have not been approved by regulatory agencies; therefore, treatment is undertaken as part of a clinical trial or protocol or as compassionate care. Patients presenting &gt;3 hours are preferentially enrolled in clinical trials when available. For patients who may be candidates for therapy &gt;3 hours and are not eligible for a trial, a multimodal screening MRI is performed and endovascular treatment (mechanical embolectomy and/or IA thrombolysis) is considered in any patient with a target vessel occlusion on MRA plus presence of substantial mismatch or absence of mismatch without severe and extensive ADC declines (eg, &gt;40 mL volume of ADC values &lt;550 μm²/s). Patients with basilar artery occlusions and severe neurologic deficits are considered for treatment up to 24 hours or more because of the poor prognosis and the hypothesized differential vulnerability to ischemia in the brainstem. Because our group believes therapies can be effective regardless of time window as long as penumbral tissue is present and risk of treatment low, we are willing to consider therapies in patients with unknown time of onset as long as their imaging suggests there is a likelihood of benefit (large vessel occlusion, small or faint diffusion lesion, substantial mismatch). Until such criteria are prospectively validated, these patients should be enrolled in clinical trials to definitively answer these questions.</td>
</tr>
</tbody>
</table>

if contrast was delivered as an infinitely narrow pulse), found by deconvolving the tissue concentration time curve with an arterial input. Acute stroke, the contralateral MCA is generally chosen to represent the arterial delivery of tracer to all brain tissue. Deconvolution techniques are, however, sensitive to dispersion and, in some cases, delays of the arterial input downstream of where it is measured. In cases in which blood reaches tissue through collaterals, the chosen arterial input is not truly representative and causes underestimation of MTT, and bias mismatch volumes. Current deconvolution algorithms are less sensitive to delays, and methods by which the arterial input function is determined locally are being developed to overcome the problems of dispersion in collaterals. With these technical advances, the problems of sensitivity of MTT maps to the choice of arterial input will hopefully be overcome. The complexity of deconvolution causes some to prefer methods that involve only analysis of the tissue concentration time curve. The figure shows some popular choices used in the literature. Although these pseudomeasures of transit time do not reflect “true” MTT and may overestimate perfusion deficits, they may reflect the extent of collateral circulation and hence be of diagnostic importance. A number of methodological issues need to be addressed before clinicians are able to consistently and accurately determine the region of significant hyperperfusion in real time.

The probability of infarction in acute ischemic stroke is related to the severity of cerebral hypoperfusion. Positron emission tomography studies have identified absolute perfusion thresholds for neuronal electrical failure and structural integrity in animal models. PWI thresholds in stroke would theoretically allow the rapid prediction of the response to reperfusion strategies (eg, thrombolysis) in individual patients. Butcher et al addressed perfusion thresholds and found that the degree of prolongation of MTT and decrease in relative cerebral blood flow predict infarction of oligemic regions. Tissue salvage occurred in areas of greater MTT prolongation in patients in whom reperfusion occurred, ie, restoration of blood flow altered the PWI threshold for infarction. Thresholds for infarction/salvage varied widely between individual patients, attributable to the finding that the severity of MTT prolongation compatible with tissue salvage was inversely correlated with the duration of hypoperfusion. As has been found in animal studies, perfusion threshold for infarction are time-dependent.

The change of thresholds for infarction, whether absolute or relative, over time makes prediction of tissue fate based on PWI alone problematic. Thus, prediction of outcome in acute stroke patients becomes a matter of forming predictive models analyzing many variables, of which PWI measures and duration of symptoms are only 2, albeit important, independent variables. These models also include the extent and severity of bioenergetic compromise indicated by DWI and ADC maps and vulnerability according to tissue type (gray and white matter have different thresholds for infarction). The development of these models will require large numbers of patients studied by PWI and DWI at different time points after symptom onset.

Conclusion

In summary, MRI is feasible in acute stroke management. The pathophysiological information obtained may be viewed as a brain clock replacing the presently used epidemiological time clock when deciding whether to initiate thrombolytic therapy. Unlike the CT-based trials, MRI pilot studies demonstrate the benefits of thrombolytic treatment up to 6 hours after symptom onset. Significant PWI–DWI mismatch is common, up to 6 hours, suggesting many individual patients may benefit from treatment in that time window. PWI and DWI thresholds delineate areas with higher probability of infarction or salvage, but their precise role in therapy selection remains to be determined.

We report the practice patterns in 5 MRI research stroke centers. There is a tendency to use PWI–DWI as a selection tool after 3 hours. Only one center requires perfusion deficit (or occlusion on MRA) before...
thrombolysis in the 0- to 3-hour window. There is no clinical trial evidence to date that acute stroke patients within 3 hours from onset should be excluded from treatment with IV tPA based on MRI findings as long as they meet other treatment criteria. This article mainly reviewed the experience of MRI and thrombolysis within the first 6 hours after symptom onset. Meanwhile, a variety of diagnostic and therapeutic practices applied beyond 6 hours (even up to 24 hours) are reported by some centers; also, here PWI–DWI is decisive. Whether mismatch in a given time window is a valuable criterion cannot be answered by the present studies. Likewise, there is no firm scientific evidence for using one of the presented lesion volume or occlusion site criteria. Importantly, there is no consensus, and a sixth center interviewed (Department of Neurology, Royal Melbourne Hospital, authors K.B., S.D.) uses only established CT criteria in patient selection while conducting the EPITHET trial and pursues the solution to some of the more methodological issues (see The PWI–DWI Mismatch: How and When?). The exact clinical role of MRI in acute stroke awaits the results of ongoing clinical trials.

**TABLE 6. MRI Criteria for Thrombolysis Used by Department of Neurology, Massachusetts General Hospital, Boston, Massachusetts**

<table>
<thead>
<tr>
<th>Time Interval</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–3 hours: Decisions to treat with IV tPA are based on a noncontrast CT scan without hypodensity large enough to match the territory supplied by the occluded vessel(s) seen on CTA. MRI is performed as soon as possible after administration of IV tPA to gauge degree of perfusion and diffusion abnormality and presence of CMB, which would elevate consideration of proceeding to IA lysis with limited infusion of thrombolytic drug. MRI is postponed if it entails delay to IA treatment. MRI is used as a second test to identify mismatch or to identify small regions of infarct that are essential in making the diagnosis of stroke or TIA. In patients treated with IV tPA, CTA is used to identify patients for ‘salvage’ IA lysis. Those patients with proximal MCA, ICA, or basilar artery occlusion accessible to catheter-based therapy undergo catheter angiography and IA lysis as soon as possible after IV tPA.</td>
<td></td>
</tr>
<tr>
<td>3–6 hours: CTA is used to identify patients with major vessel occlusion for IA lysis. CT perfusion is undergoing study as a means to threshold tissue at risk vs tissue unlikely to survive despite recanalization. As noted, MRI is used as a second test to gauge extent and location of mismatch that factor into decision-making in the catheterization laboratory; ie, use of clot retrieval device vs lytic drug, targeting vessels for recanalization, when to halt the procedure, how much urokinase to infuse, etc. MRI is used after the procedure to distinguish contrast extravasation vs hemorrhage. After 6 hours: Aggressive intervention is applied for patients with MR DWI/PWI mismatch or CT low-density/PWI mismatch. The presence of functionally important neurologic deficits attributable to ischemia in DWI normal regions positively influences decisions to proceed with interventions such as IA clot retrieval (the United States Food and Drug Administration has recently approved a device used within an 8-hour time window), neurointensive care admission for optimal blood pressure management, emergent endarterectomy, or even extracranial to intracranial bypass surgery. Patients with unknown time of onset are currently not treated.</td>
<td></td>
</tr>
</tbody>
</table>

ICA indicates internal carotid artery; MCA, middle carotid artery.

**Acknowledgments**

This study was supported by The Danish National Research Foundation and The Danish Medical Research Council.

**References**


56. Alsop DC, Schlaug G. Defining a local input function for perfusion quantification with bolus contrast MRI. Presented at International Society for Magnetic Resonance, 10th Scientific Meeting and Exhibition, Honolulu, Hawaii; May 18–22, 2002. (Abstract).


Magnetic Resonance Imaging Criteria for Thrombolysis in Acute Cerebral Infarct
on behalf of the UCLA Thrombolysis Investigators

Stroke. 2005;36:388-397; originally published online December 23, 2004;
doi: 10.1161/01.STR.0000152268.47919.be
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2004 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://stroke.ahajournals.org/content/36/2/388

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org/subscriptions/