Expanding the Window for Thrombolytic Therapy in Acute Stroke

The Potential Role of Acute MRI for Patient Selection

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Background—Effective therapy was not available for treatment of acute stroke until 1995, when tissue plasminogen activator (tPA) was shown to improve neurological and functional outcome in stroke patients who were treated within 3 hours of symptom onset.

Summary of Review—Currently, many patients do not qualify for tPA therapy because they present for evaluation beyond 3 hours after stroke onset. Attempts to expand the treatment window to 6 hours, using CT to select patients, have failed. Use of early MR imaging may provide significant advantages over CT for identification of patients who are likely to benefit from thrombolytic therapy because (1) the early perfusion-weighted imaging (PWI) lesion estimates the region of acute dysfunctional brain tissue, whereas the acute diffusion-weighted imaging (DWI) lesion appears to correspond to the core of the early infarction; (2) the mismatch between the acute PWI lesion and the smaller DWI lesion represents potentially salvageable brain tissue (an estimate of the ischemic penumbra); and (3) in patients with a PWI/DWI mismatch, early reperfusion is often associated with substantial clinical improvement and reversal or reduction of DWI lesion growth.

Conclusions—Clinical trials that use new MRI techniques to screen patients may be able to identify a subset of acute stroke patients who are ideal candidates for thrombolytic therapy even beyond 3 hours after stroke onset. (Stroke. 1999;30:2230-2237.)

Key Words: magnetic resonance imaging, diffusion-weighted ■ magnetic resonance imaging, perfusion-weighted ■ stroke, acute ■ thrombolysis

Tissue plasminogen activator (tPA) is an effective therapy for acute stroke when administered within 3 hours of symptom onset. This medication can open occluded cerebral arteries before irreversible brain injury has occurred. No clear benefit of tPA therapy has been demonstrated for patients treated between 3 and 6 hours after stroke onset, a time period when a substantial number of patients present for evaluation. This therapeutic failure may have occurred because some patients treated 3 to 6 hours after symptom onset have already sustained severe, irreversible brain injury and others have already undergone spontaneous recanalization of their occluded arteries. Treatment of these patients is unlikely to produce beneficial effects and may result in harm secondary to brain hemorrhage. Inclusion of these patients in clinical trials may have masked beneficial effects of tPA in other patient subgroups.

Robust new MRI techniques are now available that allow early identification of ischemic brain regions and cerebral perfusion deficits. Diffusion-weighted imaging (DWI) can rapidly detect ischemic brain lesions, and perfusion-weighted imaging (PWI) can identify blood flow abnormalities. Preliminary data indicate that patients who present with a large PWI deficit and a small DWI lesion (DWI/PWI mismatch) may be more likely to have a favorable clinical response to thrombolytic therapy, even beyond 3 hours after symptom onset. These patients demonstrate substantial improvements in neurological function and have smaller final infarct volumes after successful thrombolysis.

Benefit of tPA for Stroke Treatment

Currently, intravenous tPA is the only widely available therapy for acute ischemic stroke that has proved to be beneficial. This therapy is effective for reducing neurological disability in selected patients who can be treated within 3 hours of stroke onset. The cost effectiveness of tPA therapy for acute stroke has been demonstrated. The Food and Drug Administration (FDA) approved tPA for stroke treatment within 7 months of the publication of the NINDS rt-PA Acute Stroke Study, and guidelines endorsing the use of tPA for appropriate stroke patients have been issued by the National Institutes of Health, American Academy of Neurology,
American Heart Association, and the American College of Chest Physicians.\textsuperscript{5–7}

Unfortunately, at present only a small percentage of stroke patients in the United States are receiving tPA treatment. The most common reason that patients are not eligible for this therapy is the inability to meet the strict 3-hour treatment window. Studies have suggested that if the treatment window could be expanded to six hours, a considerably larger number of patients would be eligible for tPA therapy. For example, in a recent study 21\% of ischemic stroke patients arrived at a hospital between 3 to 6 hours of symptom onset.\textsuperscript{8}

**Trials of Thrombolytic Therapy Beyond 3 Hours**

Three large randomized trials have studied the effectiveness of intravenous tPA in patients treated beyond 3 hours after stroke onset. The European Cooperative Acute Stroke Study (ECASS) randomized 620 patients with a presumed middle cerebral artery (MCA) distribution ischemic infarct to treatment with intravenous tPA (1.1 mg/kg) or placebo.\textsuperscript{9} Treatment was begun within 6 hours of symptom onset. Patients with evidence of substantial early infarct signs on the baseline CT scan were not eligible for enrollment in this trial. The study failed to show a statistically significant benefit of tPA over placebo for the primary end point of a difference of 15 points on the Barthel Index at 90 days after treatment. However, 109 of the patients enrolled (18\%) did not meet the inclusion or exclusion criteria for the study (these patients had “major protocol violations”). The clinical outcome of these “protocol violation” patients who received tPA was extremely poor. The most common protocol violation was the failure to recognize substantial early infarct signs (usually a region of hypodensity >one third of the MCA territory on the baseline CT scan. A post hoc analysis of the baseline CT scan data from ECASS found that patients with early infarct signs that were <one third of the MCA territory were the most likely to have a favorable clinical response to tPA.\textsuperscript{10}

Patients with normal baseline CTs appeared to have a small benefit from tPA therapy, and patients with substantial early infarct signs (>one third of the MCA) had a very unfavorable response, with a high risk of intracranial hemorrhage and a 50\% mortality rate.

Based on the findings of ECASS, the ECASS II trial was designed. A major difference between the studies was that the ECASS II investigators received extensive training in how to recognize early infarct signs (>one third of the MCA territory) on CT scans. The goal was to exclude as many patients with these CT findings as possible. In addition, the dose of tPA was reduced from 1.1 mg/kg to the 0.9-mg/kg dose that was successful in the NINDS 3-hour window trial.

Of the patients enrolled in ECASS II, 4.6\% were later judged to have CT scan violations, with early hypodensity in >one third of the MCA territory, compared with 8.3\% in the first ECASS trial. Unfortunately, despite this improvement, ECASS II also failed to show a statistically significant benefit of tPA over placebo for the primary end point of achieving a very favorable outcome (Rankin Scale score of 0 or 1) at 90 days, although there was a trend favoring the tPA group.\textsuperscript{11} One of the secondary outcomes (median improvement in National Institutes of Health Stroke Scale [NIHSS]) did show a statistically significant benefit for tPA; however, the absolute degree of benefit was small (only 1 point on the NIH scale). A post-hoc secondary analysis, which evaluated the number of patients who were nondependent (Rankin score of 0, 1, or 2) at 90 days, demonstrated a statistically significant benefit in favor of tPA, with an absolute risk reduction of 8\%.

Recently, the results of the Alteplase Thrombolysis for Acute Non-Interventional Therapy in Ischemic Stroke (ATLANTIS) study were presented.\textsuperscript{12} This trial had a study design similar to that of the NINDS trial but evaluated a longer time-to-treatment window. Originally, the study enrolled patients within 6 hours of stroke onset but was modified in 1993 to a 0- to 5-hour treatment window. Following the announcement of the NINDS trial results, the study was modified to a 3- to 5-hour treatment interval, and additional CT scan exclusion criteria, similar to those used in the ECASS trials, were added. A total of 761 patients were enrolled in the ATLANTIS study; the majority (579) were enrolled between 3 and 5 hours of stroke onset. This study found no differences in the primary end point (NIHSS score 0 or 1 at 90 days) between the tPA and the placebo groups. One of the secondary end points (≥11-point improvement in the NIHSS) did reveal a significant benefit for tPA.

Therefore, although tPA has been demonstrated to be effective for treatment of acute ischemic stroke within 3 hours of symptom onset, 3 large studies have failed to find substantial benefit of this therapy beyond 3 hours after stroke onset. All 3 of these studies relied heavily on CT scan–based criteria to exclude patients who had substantial evidence of early infarct signs on the baseline CT scan in conjunction with clinical criteria that were similar to those used in the NINDS trial. A variety of secondary end points and post hoc analyses of these trials revealed encouraging results, suggesting that some patient subgroups may benefit from tPA beyond 3 hours.

More definitive evidence that specific subgroups of ischemic stroke patients can benefit from delayed thrombolytic therapy was recently demonstrated in the PROACT II study.\textsuperscript{13} In this study, 180 patients with angiographically proved MCA occlusions were treated with intra-arterial prourokinase plus low-dose intravenous heparin versus intravenous heparin alone within 6 hours of stroke onset. Forty percent of the patients who received prourokinase were functionally independent at 3 months compared with 25\% in the control group ($P<0.05$). This study demonstrates that the therapeutic window for acute stroke intervention extends beyond 3 hours when patients are selected on the basis of direct imaging of an occluded MCA. However, it is not clear how much of the success of PROACT II is related to optimal patient selection versus other factors, such as improved recanalization rates with intra-arterial administration of the thrombolytic agent. In addition, conventional angiography, which is a cumbersome invasive procedure, was required to identify these patients, and intra-arterial therapy requires the expertise of a highly skilled interventional neuroradiologist. Therefore, this therapy is available at only a limited number of specialty centers.

Considerable data are now available indicating that novel MRI techniques may be effective for identifying subgroups of
patients who are likely to benefit from thrombolytic therapy beyond 3 hours after stroke onset. These new techniques include DWI, PWI, and high-speed magnetic resonance angiography (MRA).

**DWI in Acute Stroke**

Diffusion-weighted MR imaging is a new application of MRI technology that is capable of generating images based on a quantitative assessment of the random movement of water protons (diffusion) within tissues.14,15 This technique is ideal for assessment of acute brain ischemia, because the random movements of water protons are rapidly attenuated in regions of significant acute brain ischemia.16–19 Although the pathophysiological explanation for the reduced diffusion of water within ischemic tissue is not completely understood, substantial experimental data indicate that this change is mediated by water movement from the extracellular to the intracellular space.19,20 Water within the extracellular space has relatively unrestricted diffusion, whereas the intracellular environment provides greater restriction to the random movements of water protons. During acute brain ischemia, it is well accepted that water moves from the extracellular to the intracellular environment after activation of excitatory amino acid receptors. In addition, loss of ion homeostasis occurs after significant energy depletion.21 Experimental evidence suggests that cytotoxic edema which results from early energy depletion during acute experimental ischemic stroke is the key factor responsible for the changes seen on DWI during acute stroke.19,22–24 Mild degrees of ischemia, insufficient to produce energy failure and cytotoxic edema, do not produce changes on DWI in experimental models.25

Early ischemic lesions seen on DWI expand over time in experimental stroke models. This expansion can be attenuated in animal models with effective neuroprotective agents or thrombolytic therapies.26–32 In some models, early DWI lesions decrease in size or completely reverse with effective therapies. The size of the ultimate DWI lesion correlates very closely with conventional measures of infarct volumes in sacrificed animals.20,33–36

Clinical evidence also indicates that lesion volumes visualized on early DWI scans in stroke patients also have a strong correlation with final infarct volumes and clinical neurological outcomes.37–43 Serial DWI imaging during the first several days after stroke onset frequently reveals progressive enlargement of the DWI lesion, and the eventual DWI lesion volume correlates closely with the final T2-weighted (T2W) lesion volume (which is generally accepted to correlate closely with the volume of infarcted brain tissue).37,39,40 Therefore, many investigators believe that DWI is an ideal method for assessing the evolution of ischemic brain tissue during the early hours and days after stroke onset.

**PWI in Acute Stroke**

PWI is another new MR technique that is complementary to DWI. Using a rapidly injected bolus of a contrast agent, a qualitative map of brain perfusion can rapidly be generated.15,44,45 Brain regions that are substantially hypoperfused are identified by the delayed arrival of the contrast agent to the vascular bed. A variety of hemodynamic maps can be created using PWI. In animal models, PWI lesions can be seen immediately after vessel occlusion and resolve rapidly after successful thrombolysis or reperfusion.46,47 In stroke patients, serial PWI studies can document the evolution of PWI lesions over time and help clarify if and when reperfusion occurs (Figure 1). Most stroke patients who do not receive thrombolytic therapy have PWI lesions that persist for at least 24 hours; patients who receive thrombolytics frequently demonstrate early reversal of PWI lesions.1,2,43,48

In both animal models and acute stroke patients, early PWI lesions are typically larger than early DWI lesions.31,46,49 In studies of acute stroke patients, the volume of the early PWI lesion correlates more closely with the acute neurological deficit, suggesting that the early PWI lesion provides a more accurate estimate of the volume of dysfunctional brain tissue than does the early DWI lesion.37,40 However, if the patient does not experience rapid reperfusion, the DWI lesion will typically expand to fill most or all of the volume of the early PWI lesion, and this volume will correlate closely with both the patient’s chronic neurological deficit and final infarct volume as displayed on T2W imaging (Figure 2).43 In contrast, if a patient experiences early resolution of the PWI lesion (which often occurs after successful thrombolysis), the early DWI lesion usually does not enlarge significantly (Figure 3), and in some cases, reversal of DWI abnormalities may occur.2 In addition, these patients frequently experience substantial early clinical improvement.1,2,48
Use of DWI and PWI to Identify Optimal Candidates for Thrombolytic Therapy

It is apparent that multiple MRI profiles can occur in acute stroke patients; these early profiles predict both clinical outcomes and final infarct volumes and have the potential to predict the response to thrombolytic therapy. The most common MRI profile in patients with acute stroke is a PWI lesion that is larger than the DWI lesion (Figure 4). Approximately 70% of patients imaged within the first 6 hours after stroke onset will demonstrate this PWI/DWI mismatch.39,40,43,50,51 These patients may respond favorably to thrombolytic therapy, even when it is administered beyond 3 hours after stroke onset.1,2 For example, in a recently reported series1 of 21 stroke patients with an acute PWI/DWI mismatch, almost half demonstrated early resolution of the PWI lesions (typically following intravenous tPA therapy administered between 3 to 5 hours after symptom onset). The group with early reperfusion experienced substantial improvements in NIHSS scores and had statistically significantly improved 90-day outcomes compared with the patients who had persistent PWI lesions.

Some patients may undergo rapid irreversible injury to large brain regions after the onset of stroke symptoms because of poor collateral circulation. These patients may present with large early DWI lesions that are similar in size to the acute PWI lesion and are probably unlikely to benefit from thrombolytic therapy (Figure 4).

Another MRI pattern encountered in acute stroke patients is an early DWI lesion that is larger than the PWI lesion (or no PWI lesion is present) (Figure 4). These patients may have experienced partial or complete spontaneous recanalization, and it has been speculated that they will have little or no benefit from thrombolytic therapy.52 Rarely (in <10% of patients presenting with symptoms of an acute stroke) no DWI or PWI lesion is seen on early imaging.43,53 In this situation, spontaneous early resolution of the neurological deficit (transient ischemic attacks) or very small infarcts with limited clinical deficits often occur. Therefore, only marginal benefits could be expected from thrombolytic therapy in these patients.52,54
The hypotheses discussed above are supported by recent observations\textsuperscript{1,43,55} that patients with PWI/DWI mismatch who have early resolution of PWI deficits typically have smaller final infarct volumes than patients with persistent PWI lesions (see Figure 5). For example, 2 recent series have shown reduced growth of DWI lesions and significantly smaller final infarct volumes in patients with an acute DWI/PWI mismatch who experience early resolution of PWI lesions.\textsuperscript{1,55} The majority of these “early reperfusion” patients received intravenous tPA, many beyond 3 hours after symptom onset.

**MRA in Acute Stroke**

An additional MRI technique, MRA, may also predict which patients respond favorably or unfavorably to thrombolytic therapies. Several investigators have reported that patients with complete occlusion of the distal internal carotid artery are unlikely to recanalize with intravenous thrombolytic therapy.\textsuperscript{56} In contrast, patients with occlusions of proximal MCA branches are more likely to have early recanalization after thrombolysis. MRA can reliably differentiate these subgroups as well as identify patients who have evidence of intracranial or extracranial occlusions of other major vessels. Patients who have normal MRA studies may have undergone early spontaneous recanalization or have occlusions of small, deep penetrating branches.\textsuperscript{54} Although it is unknown whether these patients will benefit from thrombolytic therapy, it has been hypothesized that substantial benefits are unlikely.\textsuperscript{52}

Combining PWI and MRA may also provide insights into cerebrovascular hemodynamics. For example, a patient with an MCA occlusion who has a large PWI deficit may have poor collateral circulation and be at higher risk for developing a large infarction than a patient with a similar MCA occlusion who has only a small PWI lesion because of excellent collateral circulation. MRA also has the potential to identify the patient subgroups likely to have final infarct volumes that are substantially larger than the initial DWI lesions. Rordorf et al\textsuperscript{50} recently reported that patients with MCA stem (M-1) occlusions documented on MRA within 12 hours of stroke onset typically had early DWI lesions that were substantially smaller than their final infarct volumes. In contrast, 6 of 7 patients who had an open M-1 segment on the initial MRA had final infarct volumes that matched the size of the early DWI lesion. Early recanalization of MRA-documented MCA occlusions has also been associated with a favorable clinical response and reduced final infarct volumes in a recently reported series.\textsuperscript{1}
MRI for Detection of Acute or Chronic Brain Hemorrhage

A final potential advantage of MR imaging for screening candidates for thrombolytic therapy is that MR may be more sensitive for detecting both acute and chronic brain hemorrhages compared with CT. At present, both a clinical history of previous brain hemorrhage as well as evidence of an acute brain hemorrhage demonstrated by CT are contraindications to tPA therapy. The sensitivity of MRI for identification of hyperacute brain hemorrhage has not yet been adequately evaluated. However, preliminary data suggest that MR is extremely sensitive for detecting acute interparenchymal hemorrhages, particularly if specific sequences such as gradient recall echo (GRE) are used. In addition, fluid-attenuated inversion-recovery MR images appear to be sensitive for detection of subarachnoid hemorrhage. Because of the occurrence of subarachnoid hemorrhage in patients receiving thrombolytic agents, the role of MRI in the decision to administer thrombolytic agents is likely to increase.

Chronic, small brain hemorrhages are not well detected by CT but are detected on MRI, particularly with GRE sequences. This provides a theoretical benefit of MR over CT for screening candidates for thrombolytic therapy. For example, one of the most common causes of brain hemorrhage in elderly individuals is amyloid angiopathy. Patients with this disorder may be at higher risk for brain hemorrhage if treated with thrombolytic agents. These patients frequently have small, asymptomatic brain hemorrhages that are undetected by CT but easily seen on MRI. Whether patients with small, asymptomatic cerebral microbleeds should be excluded from receiving thrombolytic agents will require investigation.

Limitations of MRI for Assessment of Acute Stroke

At present, the greatest impediment to the widespread use of MRI for assessment of acute stroke is limited emergency access to MRI scanning. MRI access is likely to improve as more data become available to document the clinical relevance of acute MRI in stroke. MRI studies are also more difficult to obtain than CT scans in acutely ill or uncooperative patients. In addition, excluding contraindications to MRI (such as metal fragments or implants) can be challenging in the acute stroke setting. Patient monitoring and administration of intravenous therapies requires specialized MRI-compatible equipment, and the cost of MRI exceeds that of CT in most hospitals. Additional studies are required to convincingly establish that the sensitivity of MRI for detection of acute brain hemorrhage is at least as good as that of CT.

Preliminary data suggest that patients with a PWI/DWI mismatch are likely to be optimal candidates for thrombolysis; however, numerous issues require clarification. For example, how does the size of the mismatch influence therapeutic response? What are the implications of a large DWI lesion on the baseline scan? Which MRI profiles are most likely to respond favorably to intra-arterial thrombolysis? Many of these issues are under investigation in ongoing studies.

Conclusion

Although intravenous tPA is beneficial when administered within 3 hours of stroke onset, large clinical trials have failed to document significant benefits when given in later time windows. This failure may have resulted in part because of inclusion of subgroups of patients who were unlikely to benefit from thrombolytic therapy. Preliminary data indicate that new MRI techniques are likely to be more effective than CT for identifying patients who may respond favorably to thrombolytic therapy between 3 and 6 hours after symptom onset. Clinical trials designed to convincingly establish whether specific MRI profiles are predictive of a favorable or unfavorable response to thrombolytic therapy are needed.

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References

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