Imaging Evaluation of Acute Ischemic Stroke

Lawrence R. Wechsler, MD

Background and Purpose—Imaging is an important aspect of decisions regarding treatment for acute stroke. New imaging techniques using MRI and CT enable estimation of tissue viability. This information may be useful to select patients for acute stroke therapies.

Summary of Report—Several clinical trials identified patients with penumbra based on MRI or CT imaging. The results indicate patients with penumbra by imaging improve with reperfusion, but it is not yet clear that thrombolysis is beneficial when patients are selected on this basis. New quantitative techniques for assessing perfusion and diffusion may improve these results.

Conclusion—Identifying reversible patterns on MRI or CT perfusion imaging may ultimately yield better results than the mismatch concept that is currently under active investigation. (Stroke. 2011;42[suppl 1]:S12-S15.)

Key Words: acute care ■ acute Rx ■ acute stroke ■ imaging ■ magnetic resonance

Imaging plays a central role in the evaluation of patients with acute stroke. In the setting of acute stroke, CT or MRI imaging is used to differentiate ischemic from hemorrhagic stroke. CT may demonstrate evidence of early ischemic changes and diffusion-weighted MRI may show very early evidence of infarction. CT angiography and MR angiography add identification of large-vessel arterial occlusions. In addition to these traditional applications of imaging, perfusion studies provide insight into tissue viability in the setting of acute stroke. This information may be helpful for selecting patients likely to benefit from reperfusion therapy and excluding those who are likely to be harmed.

Acute stroke therapies in randomized trials and registries achieve good outcomes (modified Rankin Scale =2) in 25% to 45% of treated patients.1-5 Symptomatic hemorrhage in these studies occurred in 6% to 11% of patients. Although the probability of a good outcome may be greater than without treatment, the majority of patients remain disabled despite treatment. By selecting patients with imaging techniques, it may be possible to increase the yield of good outcomes and reduce the incidence of symptomatic hemorrhage.

Studies of the ischemic penumbra using a number of different methodologies demonstrate persistence of penumbral tissue in some patients as long as 24 hours after stroke onset.6 The frequency of penumbra declines with increasing time from stroke onset. The importance of imaging modalities to identify salvageable brain increases with greater time from onset of stroke. Identification of reversibly ischemic brain is possible with either CT or MRI imaging. A proposed MRI signature of penumbra is a mismatch between the area of abnormality on perfusion imaging (PWI) and diffusion imaging (DWI). DWI abnormality presumably indicates irreversible injury and the area of PWI abnormality that lies outside of the DWI abnormality represents tissue at risk but not yet infarcted. If reperfusion is achieved, the area at risk will not progress to infarction but without reperfusion, the infarct will grow to encompass the area of the previously identified perfusion abnormality. With CT perfusion, maps of cerebral blood flow (CBF), cerebral blood volume, and mean transit time are produced. Similar to MRI, the region of reduced cerebral blood volume presumably represents irreversible infarction and the area of reduced CBF that lies outside of the cerebral blood volume abnormality represents potentially reversible ischemia.

Several clinical trials used MRI or CT signatures of penumbra to either select patients for thrombolytic treatment or to test whether mismatch predicts recovery with reperfusion (Table). The Diffusion and Perfusion Imaging Evaluation For Understanding Stroke Evolution (DEFUSE) study was a prospective pilot study of 74 patients examining MRI patterns predictive of clinical response to early reperfusion.7 Patients with stroke between 3 and 6 hours from onset underwent MRI with diffusion and perfusion imaging followed by initiation of intravenous tissue plasminogen activator (tPA) at a standard dose. The MRI was then repeated 3 to 6 hours after the tPA and again at 30 days. Reperfusion was defined as ≥30% and ≥10 mL reduction in PWI lesion volume on the follow-up scan. In patients with >20% mismatch between the perfusion and diffusion abnormality, favorable clinical response defined as an >8-point improvement or 0 to 1 on the National Institutes of Health Stroke Scale at 30 days was achieved...
by 56% of patients who reperfused and only 19% of those who did not reperfuse (OR, 5.4; \( P = 0.039 \)). In addition, when patients with a malignant pattern defined as a PWI or DWI abnormality >100 mL were excluded, 67% of patients with target mismatch and reperfusion had a good clinical outcome, whereas only 19% of those with mismatch who did not reperfuse achieved such an outcome (OR, 8.7; \( P = 0.011 \)). In DEFUSE, all patients received tPA whether or not a mismatch pattern was identified. In the small number of patients with matched deficits, there was no clear pattern of response to reperfusion. Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET) was a randomized trial including 101 patients 3 to 6 hours from stroke onset who received either intravenous tPA or placebo. All patients underwent MRI both before and 3 to 5 days after treatment with tPA. The primary outcome measure of this trial was infarct growth on DWI between baseline and 90 days in patients with mismatch. There was a trend toward less infarct growth with patients receiving tPA; however, the difference between the tPA group and the placebo group did not reach statistical significance. Mismatch occurred in 86% of the patients entered into this trial. There was a trend toward more frequent good outcomes in all patients and mismatch patients treated with tPA, but the difference did not reach statistical significance. Only 11 patients had no mismatch (7 tPA, 4 placebo) and there were no significant differences between mismatch and nonmismatch patients in infarct growth or good clinical outcome. In DEFUSE and EPITHET, perfusion was quantified using Tmax, a deconvoluted estimation of time to peak. In contrast, the desmoteplase trials (Desmoteplase in Acute Ischemic Stroke Trial [DIAS], Dose Escalation of Desmoteplase for Acute Ischemic Stroke [DEDAS], DIAS 2) used visual assessment of mismatch based on mean transit time maps generated locally by standard MRI software.\(^9\) Patients were selected using MRI by identifying those with >20% mismatch between the PWI abnormality and the DWI lesion in patients 3 to 9 hours after stroke onset and then treated with either intravenous desmoteplase or placebo. It was hoped that the inclusion of patients with mismatch would improve outcomes by enriching the treatment group with those likely to benefit from reperfusion. Although DIAS and DEDAS showed greater good outcomes with higher doses of desmoteplase corresponding to the frequency of reperfusion, DIAS 2 did not confirm these results. In DIAS 2, the placebo group had much better outcomes than expected making it difficult for the treatment arms to demonstrate a benefit. However, a post hoc analysis indicated patients with an identified arterial occlusion responded favorably to increasing doses of desmoteplase. DIAS 3 and 4 are ongoing trials randomizing patients with arterial occlusion rather than mismatch. A recent meta-analysis of the desmoteplase studies in addition to EPITHET and DEFUSE demonstrated a highly significant response to reperfusion in mismatch patients with an OR of 5.19 (95% CI, 2.95 to 9.13).\(^12\) Although there was a trend toward a greater probability of a favorable outcome after thrombolysis in patients with mismatch, the difference did not reach statistical significance (OR, 1.28; 95% CI, 0.84 to 1.97). Because a significant response to thrombolysis could not clearly be demonstrated, a further refinement of the estimation of mismatch is necessary before imaging can be considered of established value in selecting patients likely to benefit from reperfusion therapy.

In addition to selecting patients likely to benefit, imaging can also be used to select those likely to be harmed. The DEFUSE study identified PWI or DWI volume >100 mL as a malignant mismatch pattern.\(^7\) In patients with this pattern, only 1 of 6 had a favorable outcome and all 3 patients with reperfusion had symptomatic hemorrhage. When the results of the DEFUSE and EPITHET studies were pooled, a perfusion abnormality of at least 85 mL with Tmax >8 seconds predicted a poor response to reperfusion.\(^13\) Patients with a malignant pattern were more likely to have a poor outcome (modified Rankin Scale score 5 to 6) with reperfusion than without. In this pooled analysis, a large perfusion lesion was a better predictor of outcome than a large diffusion abnormality.

To improve the predictability of mismatch, several challenges must be overcome. Not all DWI abnormality represents irreversible infarction and in some cases, DWI abnormality reverses with reperfusion without progressing to infarction on later fluid-attenuated inversion recovery or T2 imaging. Coregistered positron emission tomography and DWI images demonstrate that in areas of abnormal DWI on MRI, there are characteristic changes of both infarction and penumbra as defined by positron emission tomography criteria.\(^17,18\) Not all perfusion abnormalities represent ischemia. CBF may be reduced but not to the degree that irreversible changes occur without reperfusion. This “benign oligemia” may result in an overestimation of

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Patients</th>
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<td>≥5</td>
<td>Tmax</td>
<td>All patients treated</td>
</tr>
<tr>
<td>EPITHET</td>
<td>101</td>
<td>tPA</td>
<td>≥5</td>
<td>Tmax</td>
<td>All patients randomized</td>
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NIHSS indicates National Institutes of Health Stroke Scale; MTT, mean transit time.
mismatch in the absence of quantitation. Visual assessment of mismatch by MRI shows poor agreement with thresholding volumetric estimates of mismatch. In addition, visual assessment is less reliable using inexperienced readers. Finally, the optimal degree of mismatch that predicts response to reperfusion is unclear. In the DEFUSE trial, the frequency of favorable clinical response increased with increasing mismatch ratio reaching approximately 90% prediction of response to reperfusion with a mismatch ratio >4. In contrast, most studies consider a significant mismatch greater than a ratio of 1.2. Quantitative assessment with thresholding of both DWI/apparent diffusion coefficient and Tmax may help improve the predictability of response to reperfusion. Thresholding will also allow examination of different Tmax thresholds and the impact on measurement of mismatch and prediction of outcome. Several software programs have now been developed to automate the processing of quantitative perfusion, diffusion, and volumetric analysis of mismatch. Further studies using these rapid analysis techniques will hopefully help overcome some of the barriers to reliable selection of patients using MR or CT perfusion.

There is accumulating evidence that the size of the established infarct or core may be more important than penumbra in selecting patients for reperfusion. In 36 patients with acute middle cerebral artery occlusion, Jovin et al using xenon CT found that the percent of middle cerebral artery territory with CBF values consistent with penumbra was similar across all patients. However, the percent of middle cerebral artery territory with CBF in the range associated with infarction or core (CBF <8) varied from 5% to 50% of the middle cerebral artery territory. In multivariate analysis, the extent of core was a much stronger predictor of clinical outcome than penumbra. Other studies have shown that assessment of hypodensity on baseline CT by the Alberta Stroke Programme Early CT Score (ASPECT) predicts outcome after thrombolysis and response to intra-arterial therapy. In patients with large established infarcts, salvaging a small area of penumbra with reperfusion may have no clinical impact because the deficit is already determined by the infarct. In those with very little established infarct, salvaging the same degree of penumbra may have a much larger impact on the final clinical outcome.

Focusing completely on mismatch may be misleading in that the mismatch may not represent true penumbra and penumbra may not be the best predictor of clinical outcome. An alternative approach is defining a reversible pattern by either MR or CT. This pattern includes perfusion MR or CT values sufficiently reduced to cause infarction if not reperfused but results in normalization without infarction with reperfusion. Additionally, the DWI or cerebral blood volume abnormality should not be large enough to cause a severe deficit regardless of reperfusion. Patients with malignant pattern by either MR or CT should be excluded from therapy. By focusing on the concept of a reversible pattern rather than mismatch, greater success might be achieved with imaging as a tool for patient selection. It remains to be established that all or most patients without mismatch do not respond to reperfusion.

Disclosures

L.R.W. was an investigator in the DEFUSE trial and a Data Safety and Monitoring Board member of the DIAS study.

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8. Davis SM, Donnan GA, Parsons MW, Levi C, Butcher KS, Peeters A, Barber PA, Bladin C, De Silva DA, Byrnes G, Chalk JB, Fink JN, Kimber TE, Schultz D, Hand PJ, Frayne J, Hankey G, Muir K, Gobin YP, Jahan R, Vespa P, Kalafut M, Alger JR. Thrombolytic reversal of response to reperfusion. Additionally, the DWI or cerebral blood volume abnormality should not be large enough to cause a severe deficit regardless of reperfusion. Patients with malignant pattern by either MR or CT should be excluded from therapy. By focusing on the concept of a reversible pattern rather than mismatch, greater success might be achieved with imaging as a tool for patient selection. It remains to be established that all or most patients without mismatch do not respond to reperfusion.


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