MRI-Based Selection for Intra-Arterial Stroke Therapy

Value of Pretreatment Diffusion-Weighted Imaging Lesion Volume in Selecting Patients With Acute Stroke Who Will Benefit From Early Recanalization

Albert J. Yoo, MD; Luis A. Verduzco, BS; Pamela W. Schaefer, MD; Joshua A. Hirsch, MD; James D. Rabinov, MD; R. Gilberto González, MD, PhD

Background and Purpose—Recent studies demonstrate that an acute diffusion-weighted imaging lesion volume $>70$ cm$^3$ predicts poor outcome in patients with stroke. We sought to determine if this threshold could identify patients treated with intra-arterial therapy who would do poorly despite reperfusion. In patients with initial infarcts $<70$ cm$^3$, we sought to determine what effect recanalization and time to recanalization had on infarct growth and functional outcome.

Methods—We retrospectively studied 34 consecutive patients with anterior circulation stroke who underwent pretreatment diffusion-weighted imaging and perfusion-weighted imaging and subsequent intra-arterial therapy. Recanalization success and time to recanalization were recorded. Initial diffusion-weighted imaging and mean transit time lesion and final infarct volumes were determined. Patients were stratified based on initial infarct volume, recanalization status, and time to recanalization. Statistical tests were performed to assess differences in clinical and imaging outcomes. Good clinical outcome was defined as a 3-month modified Rankin Scale score $\leq 2$.

Results—Among patients with initial infarcts $>70$ cm$^3$, all had poor outcomes despite a 50% recanalization rate with mean infarct growth of 114 cm$^3$. These patients also had the largest mean transit time volumes ($P<0.04$). Patients with initial infarct volumes $<70$ cm$^3$ who recanalized early had the best clinical outcomes ($P<0.008$) with a 64% rate of modified Rankin Scale score $\leq 2$ and the least infarct growth ($P<0.03$) with mean growth of 18 cm$^3$.

Conclusion—This study supports the use of an acute diffusion-weighted imaging lesion volume threshold as an imaging selection criterion for intra-arterial therapy. It also confirms the importance of early reperfusion in selected patients. (Stroke. 2009;40:2046-2054.)

Key Words: cerebral infarction ■ cerebral revascularization ■ magnetic resonance imaging

With the advent of advanced MRI such as diffusion-weighted imaging (DWI) and perfusion-weighted imaging (PWI), the concept of using imaging criteria as opposed to strict time limits to identify patients likely to benefit from thrombolysis has demonstrated growing promise. Multiple studies have demonstrated that intravenous thrombolysis can be safely and effectively given beyond the 3-hour window when patients are selected based on a perfusion-diffusion mismatch on MRI.1,3

The purpose of this study is to explore the use of advanced MRI in the setting of anterior circulation large vessel occlusion treated with intra-arterial therapy (IAT). Using the imaging selection criterion used in the Desmoteplase in Acute Ischemic Stroke trial of a PWI-DWI mismatch of at least 20% appears to have little discriminatory power for these patients with large vessel occlusion, because the vast majority will satisfy this requirement.4

The use of a DWI lesion volume threshold appears to hold more promise. It has been demonstrated in recent studies that in anterior circulation strokes, an acute DWI lesion volume $>70$ cm$^3$ has a high specificity for poor outcomes with or without therapy.5-7 We sought to determine whether this DWI threshold could be applied to the pretreatment MRI to identify patients who would do poorly despite recanalization. Furthermore, in those patients with an acute DWI lesion volume of $<70$ cm$^3$ at the time of intervention, we sought to evaluate whether recanalization status and time to recanalization predicted infarct growth and long-term functional outcome.

Methods

Patient Selection

We reviewed our acute stroke database for patients who presented to Massachusetts General Hospital between February 2005 and July...
2007 and underwent IAT or a combination of intravenous tissue plasminogen activator and IAT. Inclusion criteria for analysis were: (1) acute occlusion of the intracranial internal carotid artery (ICA) and/or proximal middle cerebral artery (MCA), including stem (M1) and proximal branch lesions (M2), on CT angiography; (2) pretreatment MRI; (3) follow-up CT or MRI performed within 1 week of stroke onset; and (4) available neurological follow-up at approximately 3 months after the stroke. Medical records were reviewed for clinical data. Our Institutional Review Board approved the study.

Imaging

Computed Tomography

The noncontrast head CT scan was acquired with contiguous 5-mm thick axial sections (140 kV, 300 mAs). The CT angiography was performed from the vertex to the aortic arch using a 1.25-mm slice thickness, 0.625-mm reconstruction interval, 140 kV, and 300 to 500 mAs. Isovue 370 (Bracco Diagnostics) was injected through an 18-gauge intravenous line using a power injector (Medrad) at a rate of 3.5 mL/s for a total volume of 100 mL followed by a saline “chaser” (4 mL/s for 40 mL). SmartPrep (GE Medical Systems) was used with a region of interest centered over the aortic arch. Scanning was triggered once the region of interest reached 500 HU with a 10-second scan delay.

In our emergency department stroke imaging protocol, CT angiography is performed to document the level and extent of intracranial vessel occlusion. If an occlusion is identified, the neurointerventional and stroke services consult on possible endovascular intervention. Because the CT angiography includes the aortic arch and neck, valuable information regarding the cervical vasculature (eg, occlusion or severe stenosis) is provided before the procedure.

Magnetic Resonance Imaging

The DWI sequence was a balanced spin-echo echoplanar sequence acquired in the axial plane with the following parameters: TR 5000 ms; TE 80 to 110 ms; b-value 1000 s/mm²; field of view 22 cm; matrix size 128×128, zero-filled to 256×256; and slice thickness 5 mm with a 1-mm interslice gap. Five images per slice were acquired with the diffusion gradients turned off followed by 30 images with the diffusion gradients applied in 6 different directions, for a total imaging time of 3 minutes 5 seconds. Isotropic DWI images, apparent diffusion coefficient maps, and echoplanar T2-weighted images were generated on the scanner console at the time of imaging.

For the PWI sequence, serial gradient echo echoplanar images were acquired with TR/TE of 1500/40 ms. Slice thickness and spacing were as specified previously: 14 to 16 slices were acquired for each patient. Images were acquired at each of 46 or 80 time points. After a 10-second preinjection delay during which baseline images were obtained, 20 mL gadopentetate dimeglumine 0.5mol/L (Magnevist; Bayer HealthCare Pharmaceuticals) was injected at 5 mL/s followed by 20 mL normal saline bolus. PWI images were converted to DR2 maps, and for each pixel, the area under each DR2 point was calculated to derive cerebral blood volume. Relative cerebral blood flow was calculated using singular value decomposition deconvolution, with the arterial input function derived from the middle cerebral artery ipsilateral to the infarct. Mean transit time (MTT) was calculated by dividing cerebral blood volume by cerebral blood flow for each pixel.

Fluid-attenuated inversion recovery imaging was performed using the following parameters: TR 10000 ms, TE 140 ms, field of view 22 cm, matrix size 256×192, slice thickness 5 mm, and interslice gap 1 mm.

Acute Stroke Therapies

Intra-Arterial Reperfusion Therapy

Inclusion criteria for IAT are: (1) large vessel occlusion (internal carotid artery, MCA M1 or M2 branches) on CT angiography; (2) noncontrast CT without hemorrhage; (3) noncontrast CT with parenchymal hypodensity less than one third of the MCA territory or a PWI–DWI mismatch >20% with a DWI abnormality less than one third of the MCA territory; and (4) ability to navigate a microcatheter to the level of the thrombus. Exclusion criteria are comparable to IV tPA criteria.

Cerebral angiography is performed under general anesthesia to document the occlusion level. Mechanical means of clot retrieval/dissolution include the MERCI Retrieval System, microwire macroagulation, balloon angioplasty, and stent placement. For chemical thrombolysis, urokinase (Abbott Laboratories) is mixed to a dose of 5000 U/mL and is administered through the microcatheter into the clot. Typical doses are 250 000 to 750 000 U. Of the previously mentioned stroke treatment tools, only the MERCI retrieval device is a US Food and Drug Administration-approved treatment. The remainder of the mechanical tools and the use of urokinase represent off-label uses in the treatment of stroke.

Reperfusion was graded with the Mori scale: Grade 0, complete occlusion; 1, distal movement of thrombus without reperfusion; 2, partial recanalization with reperfusion in <50% of the ischemic area; 3, partial recanalization with >50% reperfusion; and 4, complete recanalization/reperfusion. This scale has been validated in the setting of large vessel occlusions treated with IAT and has been shown to be more refined in its prognostic usefulness than the modified Thrombolysis in Myocardial Infarction scale, especially when reperfusion is partial. The Thrombolysis in Cerebral Infarction scale has been recently modified and is now equivalent to the Mori scale with both scales dividing partial reperfusion into less than and more than 50% of the occluded territory. We defined recanalization as a Mori score ≥2, because it has been shown that even partial reperfusion improves clinical outcome for patients undergoing IAT.

Imaging Analysis

Volume measurements of the lesion on admission DWI and MTT maps and follow-up MRI or noncontrast CT images were performed with a semiautomated commercially available image analysis program (Analyze; Biomedical Imaging Resource at the Mayo Foundation). A research assistant (L.V.) first outlined the regions of abnormality. Subsequently, the contours were edited by an experienced neuroradiologist (A.Y.) blinded to treatment and clinical outcome, and volume calculations were performed.

Clinical and Imaging Scoring

The National Institutes of Health Stroke Scale (NIHSS) score was used to assess the neurological status of patients with acute stroke on presentation to the emergency department. A modified Rankin Scale score at 3 months after the stroke was the primary clinical end point and was obtained through retrospective review of the 3-month clinic visit with the stroke neurologist or by phone interview by a nonblinded interventional neuroradiologist. A modified Rankin Scale score ≤2 was considered a good outcome. The rate of parenchymal hematoma type 2 (PH2, hemorrhage in >30% of the infarction with substantial mass effect) was assessed as a safety end point on follow-up CT or MRI. PH2 has been used as an imaging surrogate for symptomatic hemorrhage. Among the 34 patients, an European Cooperative Acute Stroke Study (ECASS) score could not be obtained for 3. The mean time from ictus to follow-up imaging used for ECASS scoring was 2.4±2.1 days.

Statistical Analysis

Patients with an initial DWI lesion volume >70 cm³ were termed the “futility group,” comprising those patients who were likely to have a poor outcome regardless of successful recanalization. Patients with initial DWI volumes <70 cm³ were divided by recanalization status and then by time to recanalization in which the mean time between pretreatment MRI and vessel opening was used as a cutoff to
Table 1. Baseline Clinical and Demographic Variables, Imaging Characteristics, and Outcomes

| Male sex  | 50% |
| Age, years | 68.8±17.1 |
| Left hemisphere | 62% |
| NIHSS | 18 (14–21) |
| Atrial fibrillation | 44% |
| Diabetes mellitus, Type II | 18% |
| Hypertension | 62% |
| Blood pressure,* mm Hg | 153±32 |
| Glucose level,* mg/dL | 139±47 |
| Occlusion site |
| ICA | 16 |
| M1 segment, MCA | 15 |
| M2 segment, MCA | 3 |
| IV tPA | 35% |
| Time onset to admission DWI, hours | 4.1±2.3 |
| Time onset to follow-up MR or CT, days | 2.3±2.1 |
| Admission DWI volume, cm³† | 21.4 (11.9–41.2) |
| Admission MTT volume, cm³ | 212.5±81.9 |
| Follow-up infarct size, cm³† | 60.8 (31.6–180.9) |
| Recanalization (Mori grade ≥2) | 76% |
| Time onset to recanalization, hours | 7.4±3.1 |
| Time imaging to recanalization, hours | 3.4±1.4 |
| Good outcome | 26% |
| PH2 incidence | 3% |

*Most recent value before the procedure. Continuous variables are means (±SD), except for that noted by the daggers (†), which are given as medians (IQR).

separate the recanalizers into early and late groups. This yielded 3 additional groups: “early recanalizers,” “late recanalizers,” and “nonrecanalizers.” The 4 groups were compared for several variables. Categorical variables were analyzed using the 2-tailed Fisher exact test (VassarStats: http://faculty.vassar.edu/lowry/VassarStats.html), and continuous variables were analyzed using one-way analysis of variance (Statistics to Use, T.W. Kirkman, www.physics.csbsju.edu/stats/). Normality was tested with the Kolmogorov-Smirnov test (MedCalc Software, Version 9.3.9.0). Statistical significance was considered at \( P<0.05 \).

Results

Thirty-four patients met our study criteria. Seventeen (50%) were male and 21 (62%) involved the left hemisphere. The mean patient age was 68.8±17.1 years. The median NIHSS score was 18 (interquartile range [IQR], 14 to 21). Occlusions were in the following vessels: 16 ICA, 15 M1 segment, and 3 M2 segment. All of the ICA occlusions extended into the MCA, of which 11 also extended into the proximal anterior cerebral artery. Nine (26%) patients had a good outcome at 3 months, 2 of whom had ICA occlusions. Nine patients died, 5 of whom had ICA occlusions. Full-dose IV tPA was administered in 12 (35%) patients, 2 of whom had a good outcome.

The average time from stroke onset to MRI was 4.1±2.3 hours. The median admission DWI lesion volume was 21.4 cm³ (IQR, 11.9 to 41.2), and the mean admission MTT lesion volume was 212.5±81.9 cm³. A total of 26 of 34 patients (76%) demonstrated partial to complete recanalization (Mori grade 2 to 4) after IAT. For these patients, the average time from stroke onset to recanalization was 7.4±3.1 hours and from imaging to recanalization was 3.4±1.4 hours. Time from stroke onset to follow-up imaging averaged 54.2±50.2 hours, and CT was the follow-up imaging modality in 18 (53%) patients. The median follow-up infarct size was 60.8 cm³ (IQR, 31.6 to 180.9). Mean infarct growth (final lesion minus initial lesion volume) was 63.0±71.5 cm³.

When the 34 patients were dichotomized by 3-month outcome (Table 2), patients with good outcome (modified Rankin Scale score ≤2) had significantly lower NIHSS scores (15 [IQR, 9 to 17] versus 19 [IQR, 16 to 21], \( P<0.02 \)), smaller follow-up lesion volumes (39.9±35.2 cm³ versus 127.6±103.0 cm³, \( P<0.02 \)), and less infarct growth (16.4±19.7 cm³ versus 79.8±76.1 cm³, \( P<0.02 \)). They were also more likely to have M1 and M2 occlusions than ICA occlusions (\( P<0.01 \)) and more likely to have diabetes mellitus Type II (44% versus 8%, \( P<0.03 \)). There was a trend for higher recanalization rates in patients with good outcome (100% versus 68%, \( P<0.08 \)). There were no statistical differences in the remainder of the variables compared. Multiple logistic regression could not be performed due to the small number of patients in the study.

Only one patient had a PH2 hemorrhage. This was a 74-year-old woman with a right terminal ICA occlusion extending into the MCA. Her admission NIHSS score was 16. Her initial DWI lesion volume was 12.2 cm³. She underwent mechanical embolectomy using the MERCI device with Mori 2 reperfusion at 5 hours 26 minutes after imaging. She did not receive intravenous or intra-arterial thrombolytic. Her final infarct volume was 17.0 cm³. This patient had a good outcome with a 3-month modified Rankin Scale score of zero.

Stratification Based on Initial DWI Lesion Volume and Time to Recanalization

Six patients had admission DWI volumes >70 cm³, termed the “futile.” The mean admission DWI and MTT lesion volumes in this group were 140.7±54.7 cm³ and 293.5±51.3 cm³, respectively. Three of 6 patients underwent successful recanalization (Mori grades 2 to 4), but all 6 had a poor outcome, including 3 deaths.

There were 28 patients with initial DWI lesion volumes <70 cm³. Mean admission DWI and MTT lesion volumes were 20.0±12.8 cm³ and 197.1±78.5 cm³, respectively. Twenty-three of the 28 patients (82%) had partial or complete recanalization (Mori ≥2). Nine of the 23 recanalizers had a good outcome. All 5 patients without recanalization had a poor outcome. Six patients died. The mean time from imaging to vessel opening was 3.3 hours. There were 11 “early recanalizers” (< 3.3 hours), 12 “late recanalizers” (>3.3 hours), and 5 “nonrecanalizers.”

Table 3 compares the baseline variables among the 4 groups. There was a significant difference in the distribution of the levels of occlusion (\( P<0.001 \)). All patients in the futile group had ICA occlusions. More ICA occlusions were also seen in the late versus early recanalizers (\( P<0.008 \)).
There was a significant difference in 3-month outcome among the 4 groups. Seven of 11 (64%) early recanalizers, 2 of 12 (17%) late recanalizers, zero of 5 nonrecanalizers, and zero of 6 futile group patients achieved a good outcome ($P<0.008$, Figure 1). Pairwise comparisons demonstrated that the early recanalizers had significantly better outcomes than the other groups. Furthermore, there was a difference in mortality among the 4 groups: zero of 11 early recanalizers, 4 of 12 (33%) late recanalizers, 2 of 5 (40%) nonrecanalizers, and 3 of 6 (50%) futile group patients died ($P<0.04$). The one PH2 hemorrhage was seen in the late recanilizer group, and as previously mentioned, this patient had a good outcome.

Interestingly, the futile group had the largest initial MTT lesion volumes ($P<0.044$, Figure 2). There was no statistical difference in mean admission DWI ($P<0.88$) and MTT ($P<0.53$) lesion volumes among early, late, and nonrecanalizers.

There was a significant difference in infarct growth among the 4 groups ($P<0.03$, Figure 3). The greatest infarct growth was seen in the futile group, which had a mean infarct growth of 114±30 cm$^3$. Infarct growth for early, late, and nonrecanalizers were 18±16 cm$^3$, 67±76 cm$^3$, and 93±90 cm$^3$, respectively. The difference in infarct growth between early and late recanalizers was statistically significant ($P<0.05$).

The 23 recanalized patients with initial DWI lesion volumes <70 cm$^3$ were similarly divided into early and late recanalizers by mean time from stroke symptom onset to vessel opening (7.5±3.1 hours). There was no statistically significant difference in clinical outcome among the 4 groups when divided by this method ($P<0.13$). In fact, there was no time point cutoff from symptom onset to vessel opening that was associated with a significantly better outcome for early recanalizers.

**Discussion**

Patients with large vessel occlusion of the anterior circulation represent a relatively homogeneous population, which accounts for the majority of the morbidity and mortality related to stroke. Intra-arterial therapy appears to be more favorable than IV tPA for these proximal occlusions. A major advantage in studying patients undergoing IAT is that the degree and timing of recanalization are known. These data are largely lacking in patients with stroke treated with IV tPA, in which time to treatment is used as a surrogate variable.
This study demonstrates that in patients with acute anterior circulation stroke undergoing IAT, those with initial infarct volumes ≤70 cm³ who undergo early recanalization have the best clinical outcomes and the least infarct growth. These findings are consistent with the data from a number of prior IV tPA studies. In the Diffusion and perfusion imaging Evaluation For Understanding Stroke Evolution (DEFUSE) trial, the best clinical outcomes were seen in those patients who had a PWI–DWI mismatch ≥20%, an initial DWI lesion volume <100 cm³, and early reperfusion,18 defined as at least 30% reduction in the PWI lesion volume at 3 to 6 hours after IV tPA administration. In the EchoPlanar Imaging

Table 3. Comparison of the Baseline Clinical and Demographic Variables Among the 4 Study Groups

<table>
<thead>
<tr>
<th></th>
<th>Early RC (N=11)</th>
<th>Late RC (N=12)</th>
<th>Non-RC (N=5)</th>
<th>DWI &gt;70 cm³ (N=6)</th>
<th>Statistical Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>72.4±11.9</td>
<td>69.6±18.1</td>
<td>72.2±15.0</td>
<td>57.8±23.7</td>
<td>&lt;0.38*</td>
</tr>
<tr>
<td>Male sex</td>
<td>7</td>
<td>5</td>
<td>3</td>
<td>2</td>
<td>&lt;0.63†</td>
</tr>
<tr>
<td>Left hemisphere</td>
<td>6</td>
<td>9</td>
<td>2</td>
<td>4</td>
<td>&lt;0.56†</td>
</tr>
<tr>
<td>NIHSS</td>
<td>15 (10–21)</td>
<td>18 (17–20)</td>
<td>19 (16–21)</td>
<td>21 (16–22)</td>
<td>&lt;0.43‡</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>6</td>
<td>5</td>
<td>2</td>
<td>2</td>
<td>&lt;0.89†</td>
</tr>
<tr>
<td>Diabetes mellitus, Type II</td>
<td>5</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>&lt;0.06†</td>
</tr>
<tr>
<td>Hypertension</td>
<td>7</td>
<td>8</td>
<td>3</td>
<td>3</td>
<td>&lt;0.92†</td>
</tr>
<tr>
<td>Blood pressure, § mm Hg</td>
<td>154.5±26.3</td>
<td>157.8±35.1</td>
<td>152.6±40.7</td>
<td>142.5±33.7</td>
<td>&lt;0.83*</td>
</tr>
<tr>
<td>Glucose level, § mg/dL</td>
<td>133.7±39.7</td>
<td>142.1±52.8</td>
<td>175.6±51.0</td>
<td>113.0±26.1</td>
<td>&lt;0.16*</td>
</tr>
<tr>
<td>Occlusion site</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICA</td>
<td>1</td>
<td>8</td>
<td>1</td>
<td>6</td>
<td>&lt;0.001†</td>
</tr>
<tr>
<td>M1 segment, MCA</td>
<td>7</td>
<td>4</td>
<td>4</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>M2 segment, MCA</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Time onset to DWI, minutes</td>
<td>193±74</td>
<td>304±180</td>
<td>305±107</td>
<td>169±74</td>
<td>&lt;0.07*</td>
</tr>
<tr>
<td>Time onset to follow-up MR or CT, days</td>
<td>2.9±2.1</td>
<td>2.5±2.6</td>
<td>2.1±1.5</td>
<td>0.9±0.4</td>
<td>&lt;0.29*</td>
</tr>
<tr>
<td>IV tPA</td>
<td>4</td>
<td>2</td>
<td>2</td>
<td>4</td>
<td>&lt;0.24†</td>
</tr>
<tr>
<td>IA urokinase dose, 1000 IU</td>
<td>150 (70–200)</td>
<td>250 (180–280)</td>
<td>300</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time onset to VO, hours</td>
<td>7.0 (5.5–8.5)</td>
<td>5.3 (4.8–7.6)</td>
<td>3.6 (2.3–5.2)</td>
<td></td>
<td>&lt;0.42</td>
</tr>
<tr>
<td>Time imaging to VO, hours</td>
<td>3.3 (2.3–4.2)</td>
<td>3.6 (2.3–5.2)</td>
<td></td>
<td></td>
<td>&lt;0.78</td>
</tr>
<tr>
<td>Mori grade ≥2¶</td>
<td>23</td>
<td></td>
<td>3</td>
<td></td>
<td>&lt;0.13†</td>
</tr>
<tr>
<td>CT follow-up</td>
<td>4</td>
<td>7</td>
<td>3</td>
<td>4</td>
<td>&lt;0.65†</td>
</tr>
<tr>
<td>PH2 hemorrhage</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>&lt;1.00†</td>
</tr>
<tr>
<td>Mortality, %</td>
<td>0</td>
<td>33</td>
<td>40</td>
<td>50</td>
<td>&lt;0.04†</td>
</tr>
</tbody>
</table>

Values given are means (±SD), medians (IQR), or presence of a characteristic.
*Analysis of variance.
†Fisher exact test.
‡Kruskal-Wallis.
§Most recent value before the procedure.
||Mann–Whitney U test.
¶Comparison between patients with a DWI >70 cm³ and the other 3 groups combined.
RC indicates recanalizer; VO, vessel opening.

Figure 1. Clinical outcome by imaging selection and time to recanalization. There was a significant difference in outcome among the 4 groups (P<0.008). Early recanalizers had the best outcomes (64% good outcome). Good outcome, 3-month modified Rankin Scale score ≤2.
bolytic Evaluation Trial (EPITHET), patients with a PWI–DWI mismatch >20% who underwent reperfusion, defined as >90% reduction in the PWI lesion volume on the Day 3 to 5 MRI scan, had significant infarct growth attenuation and better clinical outcomes. In a third study of 113 patients, those who had a PWI–DWI mismatch of >20% and a shorter time to recanalization, as measured by transcranial Doppler ultrasound for 2 hours after IV tPA administration, had a better 3-month clinical outcome. Our study extends these findings to proximal intracranial vessel occlusions treated with IAT.

By selecting patients on the basis of an acute DWI lesion volume threshold and early recanalization, we were able to identify a population of patients with large vessel occlusion with a 64% rate of good clinical outcome. This rate is similar to the 67% rate of favorable clinical outcome in the target mismatch group with early reperfusion in the DEFUSE study. It also compares favorably with published studies of IAT-treated patients. Recanalizers in the MERCI and Multi MERCI trials achieved good functional outcomes 46% and 49% of the time, respectively. Although the MERCI and Multi MERCI trials included patients with intracranial vertebral and basilar artery occlusions, there was no significant difference in outcomes between anterior and posterior circulation strokes in these studies.

This study supports the hypothesis that there is an acute DWI lesion volume threshold above which patients do poorly despite treatment. Our futile group is similar to the “malignant profile” group in the DEFUSE trial, which was defined as those patients having initial DWI lesion volumes >100 cm³ and/or a PWI lesion volume >100 cm³ with at least 8 seconds of Tmax delay. Of 6 patients with a malignant profile, only one had a favorable outcome despite early reperfusion in 3. Unlike the malignant profile group in which 3 patients had symptomatic intracranial hemorrhage, none of our futile group patients had PH2 hemorrhage. Furthermore, the DWI threshold may be lower than the often used “one third of the MCA territory,” or approximately 100 cm³. Three recent studies have identified a volume of >70 cm³ as highly predictive of a poor clinical outcome. Among our 6 patients with DWI lesion volume >70 cm³ (futile group), all had a poor clinical outcome despite a 50% recanalization rate. In addition, the futile group had a significantly larger mean MTT lesion volume compared with those subgroups with initial DWI volumes <70 cm³. These findings suggest that the futile group patients have the worst pial collateral flow, another factor that has been associated with functional outcome.

A DWI lesion volume threshold does not imply that the initial infarct volume alone determines clinical outcome for all patients. In fact, the initial DWI lesion volume was not a predictor of outcome in univariate analysis (Table 2). This is
because patients below the cutoff value of 70 cm$^3$ had both good and poor outcomes depending on recanalization and time to recanalization. The majority of the early recanalizers (64%) and a minority of the late recanalizers (17%) had a good outcome, whereas none of the nonrecanalizers had a good outcome ($P<0.016$). This finding suggests that in selected patients (those below the threshold), recanalization may be necessary but not sufficient for a good outcome, and that earlier recanalization leads to better clinical outcomes.

Although reperfusion status and time to reperfusion appear to be the major determinants of clinical outcome in patients with relatively small initial DWI lesions ($<70$ cm$^3$), 36% (4 of 11) of the early recanalizers still had a poor outcome. This is likely related in part to the eloquence of the brain tissue that could not be salvaged in these patients. Of the 4 early recanalizers that had a poor outcome, 3 had infarcts involving the basal ganglia and/or the motor strip resulting in dense hemiplegia. The fourth patient had an infarct involving the left inferior frontal gyrus and anterior operculum (Broca’s area) resulting in an expressive aphasia. In addition, comorbidities probably play an important role, because one patient had longstanding Parkinson disease and another had severe coronary artery disease complicated by cardiac arrest during the stroke admission.

An immediately available quantitative DWI lesion volume threshold would provide a more precise and discriminatory means over current criteria to select IAT-eligible patients who would likely benefit from reperfusion therapy. Thus far, excluding patients based on initial infarct size has been imprecise at best. The “greater than one third of the MCA territory” rule used in studies of intravenous and intra-arterial therapies is determined by visual inspection of the lesion on a baseline noncontrast CT or DWI scan. The other commonly used MRI selection criterion is a PWI–DWI mismatch $>20%$. This does not have adequate discriminatory power in the setting of large vessel occlusion because most patients with terminal ICA and M1 segment occlusions have a $>20\%$ mismatch. In one study of patients with acute M1 occlusion, Jovin et al. used xenon-enhanced CT to demonstrate that the amount of noninfarcted, hypoperfused tissue (the mismatch) is relatively constant.4

Interestingly, there was no time point cutoff from symptom onset to vessel opening that was associated with a significantly better outcome for early versus late recanalizers. This suggests the possibility that time from imaging, rather than time from stroke symptom onset, may be more clinically meaningful for patients who are selected for IAT based on a favorable PWI–DWI profile. This finding is supported by the DEFUSE study in which early reperfusion (based on MRI performed 3 to 6 hours after IV tPA administration, which occurred immediately after the initial MRI scan) essentially represented time from initial imaging rather than stroke onset.18 Because the ischemic penumbra may persist in the majority of patients with proximal occlusions for up to 24 hours,29 this finding may allow us to extend the time window for IAT. Imaging selection criteria may also have important implications for patients with wake-up strokes, whose times of symptom onset are unknown.

It is important to stress that the additional time required for DWI and PWI imaging never delayed treatment for our patients with stroke. Because we have a MR scanner in the emergency department, our MRI evaluation for hyperacute stroke occurs within 10 minutes, which is within proposed guidelines.10 We believe that institutions should not pursue MRI studies for hyperacute stroke if it will result in a delay in IAT. In the future, it may be possible to obtain information that is similar to that provided by DWI using processed CT perfusion maps.

In our study, follow-up imaging parameters mirrored the differences in clinical outcome among the 4 subgroups. There was significantly less infarct growth in patients who recanalized earlier versus later ($P<0.03$). This corroborates findings of the study by Delgado-Mederos et al., in which patients who took longer to recanalize had more DWI lesion growth at 36 to 48 hours.20 The variation in the amount of infarct growth within each subgroup, especially the nonrecanalizers, is likely related in part to interindividual differences in the strength of the collateral circulation. In addition, differences in the level of occlusion also may contribute to this variation. Both infarct growth ($P<0.02$) and final lesion volume ($P<0.02$) were associated with clinical outcome in univariate analysis in our study.

Among the baseline variables studied, the only significant difference among the 4 groups was the level of occlusion ($P<0.001$). All patients in the futile group had ICA occlusions. This is consistent with one study, which demonstrated that carotid-T occlusions present with larger initial infarct volumes than MCA occlusions.26 Also, more ICA occlusions were seen in the late recanalizers (8 of 12 patients) versus the early recanalizers (one of 11 patients). This is also in agreement with well-documented evidence that terminal ICA occlusions are more difficult to recanalize than MCA occlusions.26–28 It is probably for these reasons that terminal ICA occlusions historically have the poorest outcomes among anterior circulation strokes.27,28

It is important to note that our study population had an unfavorable vessel occlusion profile with the majority of patients having ICA occlusions (47%) and a small minority with M2 occlusions (9%). This likely contributes to our low rate of good clinical outcome (26%) despite good reperfusion rate (76%). In fact, the level of occlusion was significantly associated with clinical outcome ($P<0.01$). Patients with poor outcomes had more proximal occlusions.

An interesting and unexpected finding in this study was the significant association between the presence of diabetes mellitus Type II and a good outcome. The literature is conflicting regarding the effect of diabetes on stroke outcome with some studies demonstrating worse outcomes in patients with diabetes and other studies that refute this.29 A direct influence of hyperglycemia at the time of ischemia is likely to be important. There are many studies that demonstrate that patients with acute stroke with admission or pretreatment hyperglycemia have worse outcomes, particularly in nonlacunar strokes in which hyperglycemia may lead to lactic acid buildup and cell death in the ischemic penumbra.30,31 However, in the absence of hyperglycemia, diabetes may actually limit infarct growth. In one study, diabetic rats undergoing 3
hours of MCA occlusion had less infarct expansion (and more hemorrhagic conversion) than similarly treated control rats. The authors hypothesized that this may be secondary to cerebrovascular remodeling because the diabetic rats also demonstrated an increased vascular tortuosity index. In our patients, it is potentially this second factor of limiting infarct growth that may explain the better outcomes in patients with diabetes. There was no difference in admission glucose levels between patients who did well and those who did poorly. There was no increase in hemorrhagic conversion in the patients with diabetes, because the one patient with PH2 hemorrhage in this study did not have diabetes.

The limitations of this study are primarily related to its retrospective design as well as to the lack of control patients. In addition, the relatively small number of patients, especially those with larger initial DWI volumes, limited our ability to better characterize a DWI lesion volume threshold for patients undergoing IAT. This latter limitation is largely related to the small number of patients with stroke who satisfy clinical criteria to undergo IAT. Furthermore, our patient population was heterogeneous with regard to the method of intra-arterial recanalization. Although this limits evaluation of specific recanalization techniques, it reflects clinical practice where multiple techniques are routinely used to achieve reperfusion.

Conclusion

This study provides further evidence for using an acute infarct volume threshold to identify patients who likely will not benefit from reperfusion therapy. This is particularly important for patients with proximal vessel occlusion, most of whom satisfy current imaging criteria of a PWI–DWI mismatch of >20%. Furthermore, this study reinforces the importance of early recanalization in achieving the best outcomes in selected patients. These findings need to be verified in larger studies addressing the role of advanced imaging in selecting patients for intra-arterial stroke therapies. Further investigation should also address whether we can prospectively identify which patients will recanalize early.

Sources of Funding

A.J.Y. was the 2007 recipient of the Neuroradiology Education and Research Foundation/Boston Scientific Fellowship in Cerebrovascular Disease Research. L.A.V. was a 2007 recipient of the Howard Hughes Medical Institute Research Training Fellowships for Medical Students. This study was supported in part by the National Institutes of Health through a grant from the National Institute of Neurological Disorders and Stroke NS050041 (to R.G.G.).

Disclosures

J.A.H. is on the MERCI Registry Steering Committee but receives no financial compensation. R.G.G. is affiliated with Bayer and GE.

References


Albert J. Yoo, Luis A. Verduzco, Pamela W. Schaefer, Joshua A. Hirsch, James D. Rabinov and R. Gilberto González

_Stroke_. 2009;40:2046-2054; originally published online April 9, 2009;
doi: 10.1161/STROKEAHA.108.541656

_Stroke_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2009 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/40/6/2046

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/