Sensitivity of Diffusion- and Perfusion-Weighted Imaging for Diagnosing Acute Ischemic Stroke Is 97.5%

Claus Z. Simonsen, MD, PhD; Mette H. Madsen, MD; Marie L. Schmitz, MD; Irene K. Mikkelson, MSc, PhD; Marc Fisher, MD; Grethe Andersen, MD, DMSc

Background and Purpose—MRI using diffusion-weighted imaging (DWI) is the most sensitive diagnostic imaging modality for early detection of ischemia, but how accurate is it and how much does perfusion-weighted imaging (PWI) add to the sensitivity have to be known.

Methods—In this single-center study, we collected epidemiological, imaging, and outcome data on all patients with stroke undergoing MRI-based treatment with intravenous tissue-type plasminogen activator at our center from 2004 to 2010. The DWI negative patients were identified, and we calculated the sensitivity and specificity of DWI and additional PWI for diagnosing acute ischemic stroke. We compared DWI positive and negative patients to identify characteristics associated with DWI negativity.

Results—Five hundred sixty-nine consecutive patients were treated with intravenous tissue-type plasminogen activator on the basis of an acute MRI. A DWI lesion was evident in 518 patients. Forty-seven patients were DWI negative; however, a relevant PWI lesion was found in 33 of these patients. Four stroke mimics were treated with intravenous tissue-type plasminogen activator and 1 of these patients had a DWI lesion. Thus, 8% of all patients with stroke were DWI negative. The combination of DWI and PWI resulted in a sensitivity of 97.5% for the ischemic stroke diagnosis. DWI negativity was associated with less severe strokes, location in the posterior circulation, a longer time from onset to scan, and an improved 90-day outcome. The cause of small-vessel disease was more likely to be DWI negative.

Conclusions—The combination of DWI and PWI before intravenous tissue-type plasminogen activator confirms the diagnosis in 97.5% of all ischemic strokes. (Stroke. 2015;46:98-101. DOI: 10.1161/STROKEAHA.114.007107.)

Key Words: diffusion magnetic resonance imaging ■ perfusion imaging ■ stroke ■ tissue-type plasminogen activator

Intravenous tissue-type plasminogen activator (tPA) is the only approved treatment for acute ischemic stroke. Imaging is required to exclude intracerebral hemorrhage before thrombolytic therapy, and computerized tomography scanning is the standard imaging selection tool. MRI can also reliably exclude intracerebral hemorrhage, and diffusion-weighted imaging (DWI) is more sensitive in showing ischemia. However, DWI can occasionally be negative in acute ischemic stroke. We aimed to determine whether perfusion-weighted imaging (PWI) provides further diagnostic information to the evaluation of patients with ischemic stroke who were DWI negative.

We retrospectively examined our database of intravenous tPA-treated patients who were initially evaluated by MRI to establish the rate of DWI negative and DWI positive strokes and to identify factors associated with DWI negativity. The contribution of PWI in confirming the diagnosis of ischemic stroke was also evaluated.

Materials and Methods

MRI is the preferred imaging modality for patients presenting with symptoms of acute stroke at our hospital. Only in cases of a contraindication to MRI (eg, pacemaker), if the patient is too unstable (eg, vomiting, respiratory concerns) or if the patient cannot fit into the MRI scanner (eg, obesity, severe cervical kyphosis), a computerized tomographic scan is obtained. MRI was done on either a 3.0- or 1.5-Tesla machine. The MRI protocol included DWI, T2*-weighted imaging, fluid-attenuated inversion recovery imaging, and dynamic susceptibility contrast PWI during infusion of a bolus of gadolinium-based contrast agent. Perfusion parameters were calculated using in-house perfusion software. Detection and delineation of the DWI and PWI lesions were done by an experienced neuroradiologist and neurologist, who were blinded to the final diagnosis, but knew the lesion side.

Eligible patients were treated with intravenous tPA, according to the national clinical guidelines in the study period. Patients had to have an acute, focal neurological deficit, hemorrhage should be excluded on MRI and treatment had to be initiated <3 hours after symptom onset. The treatment window was extended to 4.5 hours from January 2010, where the upper age limit of 80 years was also...
eliminated. A DWI lesion larger than one third of the middle cerebral artery territory was also an exclusion criterion for intravenous tPA. No higher or lower cutoff of the National Institute of Health Stroke Scale was applied. PWI was done unless there was a medical contraindication to the injection of the contrast agent.

The patients were followed up after 90 days to establish outcome using the modified Rankin Scale, and the stroke subtype was determined according to the TOAST criteria.9

Statistical Analysis
Standard descriptive statistics were used to summarize the baseline clinical and imaging variables. None of the continuous variables were normally distributed; so the Mann–Whitney test for ordinal, non-normal continuous data was used. The χ² test was used for categorical variables. Statistical significance was defined at 2-tailed P<0.05. All analyses were performed using MedCalc software (version 13.2.2; Ostend, Belgium).

Results
A total of 569 patients received intravenous tPA on the basis of clinical and MRI criteria from 2004 to 2010. Clinical and imaging follow-up identified 4 stroke mimics among the intravenous tPA-treated patients. In one of them, a DWI lesion was seen on the acute MRI study. All 4 had a normal perfusion scan initially and a normal 24-hour scan (3 of these were MRIs). Subsequently, the symptoms were determined to be inconsistent with stroke on a more carefully performed examination than was possible in the acute situation.

Of the 565 patients with stroke, 518 had a DWI lesion. The sensitivity of DWI for identifying ischemic stroke is, therefore, 92%; specificity 75%; and the positive predictive value given the presence of a DWI lesion is 99.8% (Table 1).

Of the 47 patients who had a stroke but were DWI negative, 43 had an interpretable perfusion scan. (The remaining 4 did not have a scan because of a medical contraindication or the scan failed technically or was uninterpretable because of artifacts.) Hyperperfusion corresponding to location of the symptoms was detected in 33, increasing the sensitivity of combined DWI and PWI to (518+33)/565=97.5% for identifying ischemic stroke in the hyperacute time period.

We performed univariate analysis comparing the DWI positive patients with the DWI negative patients. Having a DWI negative scan was not related to any vascular risk factors. But DWI negative scans were associated to having a less severe stroke (median National Institute of Health Stroke Scale, 4 versus 7; P=0.0008) and a better outcome (percentage with modified Rankin Scale, 0–1; 80.9% versus 61.8%; P=0.015; Table 2). However, a negative DWI did not always correspond to a benign course. The Figure illustrates a patient who presented with a negative DWI and only a PWI lesion, but who ultimately had a large infarct and a poor outcome.

Table 1. Distribution of All the Patients Between the Presence of a DWI Lesion or Not, and the Final Diagnosis Being a Stroke or Not

<table>
<thead>
<tr>
<th></th>
<th>DWI positive</th>
<th>DWI negative</th>
<th>Stroke, Yes</th>
<th>Stroke, No</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=518</td>
<td>n=47</td>
<td>518</td>
<td>1</td>
</tr>
<tr>
<td>DWI positive</td>
<td>518</td>
<td>1</td>
<td>519</td>
<td></td>
</tr>
<tr>
<td>DWI negative</td>
<td>47</td>
<td>3</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td></td>
<td>n=565</td>
<td></td>
<td>565</td>
<td>4</td>
</tr>
</tbody>
</table>

DWI indicates diffusion-weighted imaging.

Table 2. Univariate Analysis Comparing the DWI in Patients With Positive and Negative Stroke

<table>
<thead>
<tr>
<th>Variable</th>
<th>DWI Positive (n=518)</th>
<th>DWI Negative (n=47)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline variables</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (IQR), y</td>
<td>67 (58–74)</td>
<td>62 (56–70.75)</td>
<td>0.085</td>
</tr>
<tr>
<td>Baseline National Institute of Health Stroke Scale (IQR)</td>
<td>7 (4–13)</td>
<td>4 (3–8)</td>
<td>0.0008</td>
</tr>
<tr>
<td>Men, %</td>
<td>322 (62.2)</td>
<td>28 (59.6)</td>
<td>0.85</td>
</tr>
<tr>
<td>Risk factors, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>55 (10.6)</td>
<td>1 (2.1)</td>
<td>0.11</td>
</tr>
<tr>
<td>Hypertension</td>
<td>284 (54.8)</td>
<td>25 (53.2)</td>
<td>0.95</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>103 (19.9)</td>
<td>5 (10.6)</td>
<td>0.18</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>229 (44.2)</td>
<td>21 (44.7)</td>
<td>0.93</td>
</tr>
<tr>
<td>Current smoking</td>
<td>185 (35.7)</td>
<td>23 (48.9)</td>
<td>0.10</td>
</tr>
<tr>
<td>Prior antiplatelet treatment</td>
<td>174 (34.7), n=502</td>
<td>15 (32.6), n=46</td>
<td>0.91</td>
</tr>
<tr>
<td>Imaging</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time to scan, min</td>
<td>109 (80–140)</td>
<td>120 (98.5–154.25)</td>
<td>0.047</td>
</tr>
<tr>
<td>Posterior circulation, %</td>
<td>79 (15.3)</td>
<td>15 (34.9)</td>
<td>0.0019</td>
</tr>
<tr>
<td>Causes of stroke, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Large vessel disease</td>
<td>193 (37.1)</td>
<td>13 (27.7)</td>
<td>0.26</td>
</tr>
<tr>
<td>Cardioembolic</td>
<td>147 (28.4)</td>
<td>8 (17.0)</td>
<td>0.13</td>
</tr>
<tr>
<td>Small vessel disease</td>
<td>93 (18.0)</td>
<td>17 (36.2)</td>
<td>0.0047</td>
</tr>
<tr>
<td>Other/undetermined</td>
<td>86 (16.6)</td>
<td>9 (19.1)</td>
<td>0.81</td>
</tr>
<tr>
<td>Outcome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Good outcome (modified Rankin Scale, 0–1), %</td>
<td>320 (61.8)</td>
<td>38 (80.9)</td>
<td>0.0147</td>
</tr>
</tbody>
</table>

DWI indicates diffusion-weighted imaging; and IQR, interquartile range.

The posterior circulation was more often the stroke location when DWI was negative (34.9% versus 15.3%; P=0.0019.) The location of the stroke for the 47 DWI negative strokes was determined by the PWI in the 33 patients who had interpretable scans. In 7 cases, the location was seen on a follow-up scan. In 2 cases, it was clinically apparent that the stroke was in the posterior circulation (internuclear ophthalmoplegia). In 5 cases, it was not possible to determine the location. Small-vessel disease was more prevalent in the DWI negative group (36.2% versus 18.0%; P=0.0047).

The time from symptom onset to imaging was longer in the DWI negative patients (120 versus 109 minutes; P=0.047). There was a trend toward younger patients in the DWI negative group (Table 2).

Discussion
In this study, on the basis of MRI-selected intravenous tPA-treated patients, an acute DWI lesion was present in 92% of the study population and the addition of PWI verified the ischemic stroke diagnosis in 97.5% of all patients. The patients who were DWI negative often had milder strokes and better 90-day outcomes although scanned in later time windows. The DWI negative strokes were more often in the posterior circulation and more often caused by small-vessel disease.

A computerized tomographic scan is the usual imaging modality in selecting patients for reperfusion therapy because of availability and the short imaging time. Although MRI
takes longer time, it has been shown that patients treated on the basis of MRI have similar outcomes compared with computerized tomography, and some studies have even found a better outcome and a lower rate of symptomatic intracerebral hemorrhage for the MRI selected patients. In addition, MRI gives a better estimate on stroke pathogenesis and better prognostication. Seeing the lesion makes it easier to decide about treatment resulting in 43% of our patients having a pretreatment National Institute of Health Stroke Scale of ≤5. This mild baseline severity is the explanation of our good outcome rates with intravenous tPA.

In agreement with our findings, a previous study found a sensitivity of 90.4% of DWI on stroke diagnosis, and a smaller study found a false-negative rate of 5.8% when imaging was performed within 48 hours. Another study was using MRI and showed negative DWI in 33% of patients, but these patients were scanned with a median time of 12 days after the symptom onset and had mild strokes with a median National Institute of Health Stroke Scale of ≤5. This mild baseline severity is the explanation of our good outcome rates with intravenous tPA.

PWI increases sensitivity from 92% to 97.5%, but it is time consuming and infusion of gadolinium-based contrast agent is potentially harmful for some patients. Because PWI is not recommended routinely before administration of intravenous tPA, we suggest to perform PWI in patients with a negative DWI, or if the patient is outside the treatment window, or part of a study.

Strokes in the posterior circulation can be DWI negative more often than strokes in the anterior circulation, which was observed previously and in our study. In a recent study, the rate of DWI negativity was 9% and similar to our finding. But the rate between anterior and posterior strokes was equal. In our study, we found that DWI negative strokes occur twice as often in the posterior circulation than in the anterior circulation (34% versus 15%).

That DWI negativity is associated with mild strokes and good outcomes is not surprising because a study has shown that small DWI lesions before intravenous tPA is associated with a good outcome. Also, in patients with transient ischemic attack, DWI negativity predicts a more benign outcome with a lower risk of stroke in the future. It is surprising that the time to imaging was longer for the DWI negative patients. We think that this indicates that robust collaterals can ensure survival of the penumbra for a longer time period.

We used both 3.0- and 1.5-Tesla scanners in this study. A previous article has compared the performance of these scanners and found that the 1.5 Tesla had a higher sensitivity (98.8%) than the 3.0-Tesla scanner (90.9%) in diagnosing ischemic stroke. We do not think that using 2 different field strengths MRI scanners affected our study.

Four patients were ultimately judged as having stroke mimics. A closer evaluation of the history, neurological examination, and the results of follow-up imaging led to the conclusion of a stroke mimic diagnosis. One of them had migraine and another was found to be intoxicated (blood ethanol level of 70 mmol/L), and these factors could account for their presenting symptoms. The other 2 were diagnosed with functional symptoms. The neuroradiologist, who was blinded to the final diagnosis, read one of the scans as DWI positive. We acknowledge that there is no true gold standard for the stroke diagnosis either than the clinical impression together with support from imaging.

**Conclusions**

Our study from a routine clinical setting finds, as previously shown, that a substantial minority (8%) of patients with intravenous tPA-treated stroke are DWI negative, but as a novel finding that, by adding PWI, diagnostic sensitivity increases to 100%. Accordingly, the use of MRI evaluation before intravenous tPA ensures acute treatment on the basis of a valid diagnosis with only a minimal risk of treating stroke mimics. DWI negative strokes are more likely to affect the posterior circulation and are more often lacunar syndromes.

**Disclosures**

None.

**References**

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