Identification of Major Ischemic Change
Diffusion-Weighted Imaging Versus Computed Tomography

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Background and Purpose—Thrombolytic therapy is not recommended in patients with CT changes of recent major infarction, which has been defined as reduced attenuation or cerebral edema involving >33% of the middle cerebral artery territory (European Cooperative Acute Stroke Study [ECASS] criteria). Diffusion-weighted imaging (DWI) is more sensitive than CT in detecting acute ischemia, and the combination of DWI, MR perfusion imaging, and MR angiography provides additional information from a single examination. We sought to determine whether DWI could identify the presence and extent of major ischemia as well as CT in hyperacute stroke patients.

Methods—Seventeen suspected hemispheric stroke patients were studied with both CT and DWI within 6 hours of symptom onset. None received thrombolytic therapy. The scans were examined separately by 2 neuroradiologists in a blinded fashion for ischemic change and cerebral edema, graded as normal, <33%, or >33% of the MCA territory. Final diagnosis of stroke was determined with the use of standard clinical criteria and T2-weighted imaging at day 90.

Results—Sixteen of 17 patients had a final diagnosis of stroke. Acute ischemic changes were seen in all 16 on DWI (100% sensitivity) and in 12 of 16 on CT (75% sensitivity). DWI identified all 6 patients with major ischemia on CT, with excellent agreement between the 2 imaging techniques (κ=0.88). One patient eligible for thrombolysis on the ECASS CT criteria had major ischemia on DWI.

Conclusions—DWI is more sensitive than CT in the identification of acute ischemia and can visualize major ischemia more easily than CT. (Stroke. 1999;30:2059-2065.)

Key Words: magnetic resonance imaging, diffusion-weighted stroke, ischemic tomography, x-ray computed tomography, x-ray computed tomography, x-ray computed tomography

Thrombolytic therapy with tissue plasminogen activator (tPA) improves outcome if given within 3 hours of ischemic stroke onset.1 However, not all treated patients obtain benefit, and avoidance of tPA has been recommended in patients with CT evidence of major infarction because of the increased risk of hemorrhagic transformation.2,3 A number of acute stroke therapy trials, beginning with the European Cooperative Acute Stroke Study (ECASS) I, have defined major infarction as parenchymal hypointensity or cerebral edema exceeding one third of the middle cerebral artery (MCA) territory on CT.4–9 Such change is associated with worse acute neurological state and worse outcome and may identify patients less likely to respond to t-PA.10,11

CT has been the investigation of choice for the triage of stroke patients. The early ischemic changes of parenchymal hypointensity and cerebral edema on CT correspond to an increase in the intracellular and extracellular water components of affected brain tissue.12,13 However, these changes are subtle, and CT is frequently normal in the first hours after stroke onset.14,15 Thus, in the emergency setting, CT is still primarily used to exclude intracerebral hemorrhage.15,16

Significant advantages are offered by newer rapid MR techniques, particularly diffusion-weighted imaging (DWI),17–22 which has a high sensitivity and specificity for ischemic stroke.22–24 Increased DWI signal intensity is evident within minutes of the onset of ischemic injury and occurs as the result of a reduction in the apparent diffusion coefficient of water and the development of cytotoxic edema.25 Acute DWI lesions can also be clearly delineated from surrounding normal brain tissue and from areas of old infarction.17,18,20 While very early restoration of blood flow to an ischemic region may lead to a reversal of DWI lesions in animal studies,26 there has been only 1 human case report in which the initial DWI lesion was very small.27 We suggest that DWI lesions remain useful markers of tissue that is likely to die without prompt intervention.

The therapeutic time window for thrombolytic and other acute stroke therapies is likely to vary between patients,28,29 and not all patients will respond equally well to therapies.
regardless of time from symptom onset. When DWI is used in combination with MR perfusion imaging (PI), different lesion patterns may be identified from which predictions can be made concerning stroke evolution and likely outcome.\textsuperscript{29–32} Such DWI/PI patterns may provide a template on which a more rational selection of acute stroke therapy can be based.\textsuperscript{29,30,32–40} However, the use of both CT and MRI is time consuming and expensive.

In this prospective serial study we compared the sensitivity and positive predictive value of CT and DWI for detecting early infarction. We also determined whether DWI could identify all cases of major ischemia as defined by the ECASS criteria (>33% MCA territory).\textsuperscript{4,5} The purpose of the study was to decide whether DWI, as part of a single-modality acute ischemia protocol, can be used together with accepted clinical criteria to screen and select stroke patients for thrombolytic therapy.

**Subjects and Methods**

We studied 17 consecutive patients (9 men; mean age, 68.5±12.8 years) presenting to the Royal Melbourne Hospital with suspected acute hemispheric cerebral infarction (9 right sided) and who had DWI and CT studies within 6 hours of stroke onset. This was defined as the time the patient was last known to be without neurological deficit. This time window was used because there is evidence to suggest that some patients treated between 3 and 6 hours may benefit from thrombolytic therapy.\textsuperscript{2,3} In addition, we and others have found that hypoperfused tissue at risk of infarction may persist beyond 3 hours.\textsuperscript{29,32,41} None of the patients were treated with thrombolytic therapy, although 11 patients were enrolled in trials of putative neuroprotective agents. Patients had T2-weighted imaging (T2-WI) performed at 90 days. A final diagnosis of stroke was made on the basis of the standard clinical criteria in conjunction with T2-WI studies. The study was performed with the approval of our institution’s Ethics Committee, and written informed consent was obtained from the patient or next of kin.

Only patients with symptoms and signs consistent with hemispheric ischemic stroke were included because these are the most frequent stroke subtypes and are the easiest to study with combined DWI and PI. Other exclusion criteria were preexisting significant nonischemic neurological deficits (including dementia or extrapyramidal disease) or a history of prior stroke, which would hamper interpretation of clinical and radiological data. Seven of the 17 patients have been previously described in 2 studies investigating the utility of echo-planar PI and DWI and MR angiography (MRA).\textsuperscript{29,32} The Canadian Neurological Scale (CNS), a validated neurological impairment scale,\textsuperscript{42} was performed just before the acute imaging studies. Outcome clinical assessments were performed on the same day as the final MR study and consisted of a repeated CNS score, the Barthel Index (BI), and the modified Rankin Scale (RS).\textsuperscript{43} The BI is a validated functional disability scale, and the RS is a validated handicap scale. Outcome was dichotomized into excellent or poor

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...was defined as in the CT scans. The extent of the parenchymal hemorrhage and parenchymal hyperintensity. Cerebral edema was defined as a circumscribed effacement of cortical sulci, compression of ventricles, and shift of midline structures. The presence of edema and parenchymal hypodensity were noted and graded (normal, <33%, or >33% of MCA territory), as previously reported in the ECASS I and II trials.\textsuperscript{4,5} The isotropic DWI scans were examined for evidence of intracerebral hemorrhage, the hyperdense middle cerebral artery sign (HMCAS), parenchymal hypodensity, and cerebral edema. The HMCAS was defined as a part of the MCA that was denser than other parts of the vessel or any other visualized vessel of similar size as shown by unenhanced CT, in which density could not be attributed to calcification. Parenchymal hypodensity was defined as increased radiolucency of cerebral tissue relative to other parts of the same structure or to its contralateral counterpart.
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Demographic and time of scan data are presented as mean±SD values. Dependent variables were compared with nonparametric techniques except when normality of data could be proven, in which case parametric equivalents were preferred, and are presented as mean difference with 95% CIs. Results were considered statistically significant at the 5% level.
Results

There was a mean time of 3 hours and 18 minutes (±1 hour and 30 minutes) to the acute CT scan and 4 hours and 1 minute (±1 hour and 1 minute) to the DWI scan (mean difference, 0.7 hours; 95% CI, −0.3 to 1.7 hours; \( P=0.16 \)). Fourteen patients had outcome T2-WI studies (83.5 ±25.5 days; range, 29.3 to 125.0). Two patients had died by day 90 giving a positive predictive value of 100%. Thus, 25% of patients with a final diagnosis of stroke had normal CT scans, all of which were seen in all 16 patients with a final diagnosis of stroke, giving a sensitivity and positive predictive value for DWI of 100%. Changes consistent with ischemia were seen on CT in 12 of 16 stroke patients, giving a sensitivity of 75%. All 12 patients with CT changes of ischemia had a final diagnosis of stroke, giving a positive predictive value of 100%. Thus, 25% of patients with a final diagnosis of stroke had normal CT scans, all

The HMCAS was seen on CT in 5 of 17 patients (29%). Occlusion of the M1 segment of the MCA was seen on MRA in 6 patients (35%). The HMCAS was seen in conjunction with MCA stem occlusion on MRA in 4 patients; however, 2 had MCA stem occlusion on MRA with no evidence of a HMCAS (Table). A fifth patient with a HMCAS was unable to tolerate an MRA. Thus, CT was unable to identify all cases of occlusion on MRA. In addition, 5 of 6 patients with MCA occlusion on MRA had evidence of major ischemia on DWI, while only 2 of 5 patients with a HMCAS had evidence of major ischemia on CT. This difference was not significantly different (\( P=0.20 \), Fisher exact test), possibly because of the small patient numbers.

A final diagnosis of stroke was made in 16 of 17 patients on the basis of standard clinical criteria and imaging results. The remaining patient (patient 13) presented with sudden onset of a left upper limb monoparesis. An initial diagnosis of ischemic stroke was made, and he was admitted to the stroke unit. Normal acute imaging studies prompted further investigation, which led to a final diagnosis of a brachial plexopathy. However, because of his initial treatment as a stroke patient, he has been included in this analysis.

Hyperintense lesions on DWI consistent with acute ischemia were seen in all 16 patients with a final diagnosis of stroke, giving a sensitivity and positive predictive value for DWI of 100%. Changes consistent with ischemia were seen on CT in 12 of 16 stroke patients, giving a sensitivity of 75%. All 12 patients with CT changes of ischemia had a final diagnosis of stroke, giving a positive predictive value of 100%. Thus, 25% of patients with a final diagnosis of stroke had normal CT scans, all

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### Results in 17 Suspected Hemispheric Stroke Patients Studied With Both CT and DWI

<table>
<thead>
<tr>
<th>Patient</th>
<th>Time to Scan, h/min</th>
<th>MCA Occlusion</th>
<th>Evidence of Ischemia</th>
<th>Major Ischemia</th>
<th>Acute DWI Lesion, cm³</th>
<th>Final Infarct Size, cm³</th>
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*Final infarct volume brought forward from T2-WI at 3–5 days after stroke onset as patient died (patients 2 and 6) or was unable to tolerate imaging studies (patient 8).
of whom had evidence of ischemia on DWI. This difference in ischemia detection rate is significant (relative difference, 0.24; 95% CI, 0.0 to 0.50; McNemar $\chi^2$ = 4.00; $P < 0.05$). Thus, DWI is better able than CT to detect signs of ischemia in the first 6 hours after stroke onset. The Figure shows CT and MRA/DWI studies in patient 17.

The ECASS criteria of major ischemia were then applied to the CT studies and extended to DWI. Evidence of ischemia involving >33% of the MCA territory (major ischemia) was detected in 6 patients by CT and 7 patients by DWI (difference, 0.06; 95% CI, −0.11 to 0.23; McNemar $\chi^2$ = 1.0; $P = 0.32$). Thus, there was no difference in the detection of major ischemia between CT and DWI in the first 6 hours after stroke onset. In addition, there was excellent agreement between the 2 imaging modalities ($k = 0.88; P = 0.0001$). However, the hyperintense DWI ischemic lesions were visually more distinct and easier to identify than the ischemic lesions on CT.

In 1 patient (patient 2), the CT scan was normal despite evidence of major ischemia on DWI. The CT scan in this particular case was performed at 2 hours after symptom onset, while the DWI was performed at 4 hours. It is therefore possible that the ischemic changes seen on the DWI developed in the 2 hours after the CT scan was performed. This patient subsequently died.

We then examined the relationship between the presence of major ischemia on both CT and DWI with the final infarct size (T2-WI) and clinical outcome, which was dichotomized into excellent and poor. The presence of major ischemia on DWI was associated with larger final infarct size (mean volume difference, 83.5 cm$^3$; 95% CI, 21.3 to 153.2 cm$^3$; $P = 0.01$) and worse clinical outcome (CNS, $Z = 2.65$, $P = 0.008$; BI, $Z = 2.12$, $P = 0.03$; RS, $Z = 1.67$, $P = 0.10$; Wilcoxon signed rank test).

Similarly, patients with major ischemia on acute CT had worse clinical outcome (CNS, $Z = 2.83$, $P = 0.005$; BI, $Z = 2.33$, $P = 0.02$; RS, $Z = 1.90$, $P = 0.058$; Wilcoxon signed rank test). There were also trends in those with major ischemia on CT to have larger acute DWI volumes (mean volume difference, 42.9 cm$^3$; 95% CI, −9.6 to 91.5 cm$^3$; $P = 0.08$) and larger final infarct size (mean volume difference, 71.7 cm$^3$; 95% CI, −2.4 to 145.9 cm$^3$; $P = 0.06$).

**Discussion**

DWI was able to detect major ischemia, defined as ischemic changes involving >33% of the MCA territory, as well as CT. However, these changes were more easily visualized on DWI than CT. The presence of major ischemia on DWI was also associated with a larger final infarct size and worse
functional outcome. We and others\textsuperscript{29,40,46} have previously found that acute DWI lesion volumes are correlated with both acute neurological state and eventual stroke outcome. However, to our knowledge, this is the first study to show an association between major ischemic change on DWI and stroke outcome.

In a report by von Kummer et al.,\textsuperscript{10} the extent of hypointensity on acute CT correlated with both acute and outcome clinical states. This group also found that the beneficial effect of tPA treatment is most pronounced in patients with ischemic changes on CT involving <33% of the MCA territory. Those with normal CT scans or evidence of major ischemia obtained no benefit from tPA and had an increased risk of fatal hemorrhage. Thus, the presence and extent of ischemic changes appear to have significant implications for prognosis and treatment and should therefore be determined as rapidly as possible.

There was greater interobserver agreement regarding the extent of ischemia on DWI than CT. Hyperintense ischemic lesions on DWI were comparatively easy to identify and grade. In contrast, early ischemic changes on CT are often subtle and can be difficult to appreciate.\textsuperscript{10,47} One of the reasons for this superiority of DWI over CT in the detection of acute ischemia is the significantly greater contrast-to-noise ratio for DWI.\textsuperscript{24} As a result, the reliability and reproducibility of CT in the detection and estimation of the degree of ischemic change is controversial, von Kummer et al.\textsuperscript{10} found an interobserver agreement on the extent of parenchymal hypointensity of 86%, but the chance-adjusted agreement was low ($\kappa=0.36$). Similarly, Marks et al.\textsuperscript{11} found an interobserver agreement on the estimation of the extent of MCA territory ischemia of 72%, with pairwise $\kappa$ coefficients of 0.44 to 0.65. These results are similar to those of the present study. However, in all 3 studies, CT scans have been read by neuroradiologists in the nonacute setting and are therefore unlikely to represent standard clinical practice.\textsuperscript{10}

DWI had greater sensitivity in the detection of hyperacute ischemia than CT and had a positive predictive value of 100%. All patients with a final diagnosis of stroke had evidence of ischemia on DWI. In contrast, 25% of stroke patients had normal acute CT scans. These results confirm the high sensitivity of DWI to hyperacute ischemia in earlier investigations, which has ranged from 94% to 100%.\textsuperscript{22,24} Previous studies have also found that DWI is superior to T2-weighted and proton-density MR sequences in the detection of ischemia.\textsuperscript{23,24}

In this study there was only 1 DWI scan in which there was no evidence of ischemia. This was a true-negative result since the patient was subsequently found to have a brachial plexopathy. This patient was the only subject in this series without a region of hypoperfusion that is of greater volume than the a region of infarction.\textsuperscript{23} We suggest that the CT sign of a hyperdense MCA was inferior to MRA in identifying MCA occlusion. The presence of the HMCAS is associated with severe brain ischemia and poor functional outcome. However, while the HMCAS may identify patients who may benefit from tPA, it has no significant independent prognostic value when compared with acute clinical state and early CT changes.\textsuperscript{30} Of interest, the Pro-urokinase in Acute Cerebral Thromboembolism (PROACT) trial has found that intra-arterial thrombolysis is of benefit in patients with occlusion of the MCA.\textsuperscript{9} We have previously shown that the absence of MCA blood flow on MRA predicts the presence of a region of hypoperfusion that is of greater volume than the diffusion-weighted lesion and as such may identify hypoperfused tissue at risk of infarction.\textsuperscript{12} We suggest that the positive results of the PROACT trial may in part be a result of the selection and treatment of only patients with MCA occlusion and therefore those with greater likelihood of having potentially salvageable penumbral tissue.

None of the patients studied had intraparenchymal hematoma. However, 2 patients had small areas of hypointensity consistent with minor petechial hemorrhage on the MR studies. Neither of these patients had a history of hypertension, and the areas of hypointensity occurred within the region of infarction. Changes consistent with hemorrhage were not seen on CT, possibly as the result of partial volume effects. With the advent of thrombolytic therapy for acute ischemic stroke, the detection of hyperacute hemorrhage has
become critical. There is increasing evidence that multimodal MRI, particularly susceptibility-weighted sequences, are as reliable as CT in the detection of acute intraparenchymal hemorrhage. At higher field strengths, a hypointense rim is characteristically seen surrounding a central isointense or heterogeneous region of hyperacute hematoma on T2-WI and to a lesser extent T1-WI. This rim is thought to be the result of a transitional stage in which there is rapid deoxygenation of hemoglobin within erythrocytes at the periphery of the hematoma. This causes an increase in magnetic susceptibility with resultant signal loss, best seen on gradient echo sequences. This rim is thought to be the result of thrombolytic therapy. However, it remains to be proven that MRI is as sensitive as CT in the detection of acute hemorrhage.

In summary, this study has shown that DWI is able to identify the presence of early infarction with greater sensitivity than CT. In addition, DWI can visualize major ischemia more easily than CT. Should the ability of MRI to identify acute hemorrhage be confirmed in further studies, it could safely replace CT in the investigation of stroke patients being considered for thrombolytic therapy. This hypothesis requires further investigation with randomized controlled trials.

Acknowledgments
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References


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