Predicting Infarction Within the Diffusion-Weighted Imaging Lesion
Does the Mean Transit Time Have Added Value?

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Background and Purpose—There is ample evidence that in anterior circulation stroke, the diffusion-weighted imaging (DWI) lesion may escape infarction and thus is not a reliable infarct predictor. In this study, we assessed the predictive value of the mean transit time (MTT) for final infarction within the DWI lesion, first in patients scanned back-to-back with $^{15}$O-positron emission tomography and MR (DWI and perfusion-weighted imaging; “Cambridge sample”) within 7 to 21 hours of clinical onset, then in a large sample of patients with anterior circulation stroke receiving DWI and perfusion-weighted imaging within 12 hours (85% within 6 hours; “I-KNOW sample”).

Methods—Both samples underwent structural MRI at approximately 1 month to map final infarcts. For both imaging modalities, MTT was calculated as cerebral blood volume/cerebral blood flow. After image coregistration and matrix resampling, the MTT values between voxels of interest that later infarcted or not were compared separately within and outside DWI lesions (DWI+ and DWI−, respectively) both within and across patients. In the I-KNOW sample, receiver operating characteristic curves were calculated for these voxel of interest populations and areas under the curve and optimal thresholds calculated.

Results—In the Cambridge data set (n=4), there was good concordance between predictive values of MTTpositional emission tomography and $\text{MTT}_{\text{perfusion-weighted imaging}}$ for both DWI+ and DWI− voxels of interest indicating adequate reliability of $\text{MTT}_{\text{perfusion-weighted imaging}}$ for this purpose. In the I-KNOW data set (N=42), the MTT significantly added to the DWI lesion to predict infarction in both DWI− and DWI+ voxels of interest with areas under the curve approximately 0.78 and 0.64 (both P<0.001) and optimal thresholds approximately 8 seconds and 11 seconds, respectively.

Conclusions—Despite the relatively small samples, this study suggests that adding $\text{MTT}_{\text{perfusion-weighted imaging}}$ may improve infarct prediction not only as already known outside, but also within, DWI lesions. (Stroke. 2011;42:00-00.)

Key Words: brain imaging ■ brain ischemia ■ cerebral blood flow ■ diffusion-weighted imaging ■ magnetic resonance ■ PET

In the diffusion-weighted imaging/perfusion-weighted imaging (DWI/PWI) “mismatch” model, the DWI lesion is assumed to represent the irreversibly damaged “core” and any tissue both outside the DWI lesion and with perfusion below the penumbra threshold the at-risk tissue.1 Recently, reasonably consistent PWI values predicting the penumbra flow threshold have been reported.2–10 Among PWI parameters, time-based parameters show the highest accuracy,3,11 particularly the mean transit time (MTT)7,8,10 as further supported by combined positron emission tomography (PET)/MR studies.12,13

The assumption that the DWI lesion equates with the core is, however, an oversimplification, especially early after stroke onset. The DWI lesion reflects variable disruption of energy metabolism14 and accordingly may depict both the penumbra and the core.14,15 In keeping with this and abundant experimental evidence, permanent reversibility of part or all of the DWI lesion may occur after early reperfusion,15,16 and

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The online-only Data Supplement is available at http://stroke.ahajournals.org/cgi/content/full/STROKEAHA.110.606970/DC1.

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the predictive value of the DWI lesion for final infarction is suboptimal. Surprisingly, whether perfusion improves prediction of infarction within the DWI lesion has been largely unaddressed despite clinical relevance. Although a study reported an inverse correlation between severity of hypoperfusion 3 to 6 hours after onset and DWI lesion reversibility, the actual predictive value of PWI within the DWI lesion was not assessed. Wu et al found a significant voxelwise predictive value of PWI over and above the DWI lesion but did not specifically assess this within the latter, and the added value of PWI resulted from cerebral blood flow (CBF), cerebral blood volume (CBV), and MTT together, which has unclear clinical relevance.

The MTT is of particular interest because it is directly assessable using $^{15}$O-PET as CBV/CBF. Before the advent of PWI, emphasis was placed on the reverse ratio (i.e., CBF/CBV), a validated surrogate for cerebral perfusion pressure. For instance, Marchal et al reported a strong trend ($P=0.087$) for CBV/CBV studied 5 to 18 hours after onset to predict infarction: as a reverse ratio, the MTT should behave similarly. Furthermore, PET-based MTT has recently been shown to be a good predictor of the penumbra threshold.

We aimed to compare voxelwise the predictive value of MTT for infarction within, relative to outside, the DWI lesion. To test the hypothesis that the MTT adds to the latter, we first assessed the use of PWI for this purpose by comparing the predictive value of PWI versus PET-based MTT obtained back to back in patients studied 7 to 21 hours after stroke onset. Although admittedly at these relatively late times the DWI lesion is expected to largely represent the core, and therefore the added value of MTT to be low, this unique sample was expected to provide support to the use of PWI-based MTT for the present purposes. The next, directly clinically relevant step was to assess the predictive value of PWI-based MTT within and outside the DWI lesion in a large hyperacute sample.

Methods and Patients

Cambridge Sample
This database consists of 7 patients with acute first-ever anterior circulation stroke prospectively enrolled in a protocol that involved back-to-back MR and $^{13}$O-PET and follow-up structural MRI 1 month later. Exclusion criteria included previous stroke, lacunar or hemorrhagic stroke, anticoagulation or thrombolysis (arterial cannulation was required for quantitative PET), organ failure, and recent myocardial infarction. Post hoc exclusion criteria for the present analysis included an incomplete data set and hemorrhagic transformation. The Regional Ethics Committee approved the protocol and informed consent was obtained from all patients.

I-KNOW Sample
The I-KNOW European consortium database (www.i-know-stroke.eu) consists of 62 patients with first-ever anterior circulation stroke. Inclusion criteria included National Institutes of Health Stroke Scale $\geq 4$ and onset-to-scan time $\leq 6$ hours or up to 12 hours if, respectively, intravenous tissue plasminogen activator or conservative treatment was contemplated. Patients had acute DWI/PWI and structural MRI approximately 1.5 months later and optional follow-up MRI at 2 hours and 24 hours. Exclusion criteria were as described previously save for thrombolysis. This multicenter protocol was approved by the respective Ethics Committees and informed consent was obtained.

Imaging

Cambridge Data Set

Diffusion-Weighted Imaging
Diffusion tensor MRI (12 directions) was obtained on a 3-T magnet (Med-spec $\times 300$, Bruker) using a single-shot spin-echo echoplanar image sequence with slice thickness $= 5$ mm, field of view $= 24 \times 24$ cm, and matrix $128 \times 128$.

Perfusion-Weighted Imaging
PWI was performed using single-shot gradient echo with repetition time 1390 to 1500 ms, echo time 23 to 36 ms, slice number 11 to 15, thickness $= 5$ mm, field of view $= 190$ mm, and matrix $64 \times 128$ or $128 \times 128$. Gadolinium-diethylenetriaminepentaacetic acid (0.1 mmol/kg) was injected intravenously as a bolus (3 to 4 mL/s) using an electric pump followed by 20 mL saline. Once MR acquisition was completed, the patient was moved to the PET suite and scanning started within 60 minutes.

Positron Emission Tomography
Transmission data (10 minutes $^{18}$F-FDG scan) followed by emission data (steady-state 10-minute $^{15}$O infusion and $^{18}$O2 inhalation and 5-minute $^{15}$O infiltration scans) were acquired (Advance scanner; GE Medical Systems, Milwaukee, WI). Images were reconstructed into $2.34 \times 2.34 \times 4.25$-mm pixels with corrections applied for attenuation, scatter, randoms, dead time, normalization, and sensitivity. During scanning, arterial blood samples were obtained for quantification.

Follow-Up MRI
The protocol included T1-weighted volume (spoil gradient-recalled acquisition), T2-weighted, and fluid-attenuated inversion recovery.

I-KNOW Data Set

Acute Imaging
The protocol included diffusion tensor MRI (12 directions; TR $> 6000$ seconds, field of view $= 24$ cm, matrix $128 \times 128$, thickness 3 to 5 mm), gradient echo, T1-weighted, T2-weighted, time of flight MR angiography, and PWI (TE 30 to 50 ms, TR 1500 ms, field of view $= 24$ cm, matrix $128 \times 128$, 18 slices, thickness 5 mm with gap $= 1$ mm; gadolinium contrast 0.1 mmol/kg at 5 mL/s followed by saline 30 mL). Repeat MRI at 2 hours and 24 hours included the same sequences except PWI, which was optional.

Follow-Up MRI
T1-weighted volume spoiled gradient-recalled acquisition, T2-weighted, fluid-attenuated inversion recovery, and DWI were acquired on 1.5- or 3-T magnets.

Data Analysis

Image Processing

Positron Emission Tomography
Parametric maps of CBF, CBV, cerebral metabolic rate for oxygen, and oxygen extraction fraction were calculated by inputting PET and arterial activities into standard models. An MTTPET map (in seconds) was then generated by voxelwise dividing CBV by CBF.

Perfusion-Weighted Imaging
CBF, CBV, and MTT maps were generated using a manually selected arterial input function derived from the contralesional middle cerebral artery using block-circulant deconvolution, in which MTTPET=$\text{CBV/CBF}$. Bolus passages were inspected and if necessary coregistered to the last image before bolus arrival. Penguin software (www.cfin.dk/software/penguin) was used for automatic brain masking, baseline detection, and concentration calculation. CBF corresponds to the peak of the deconvolved curve and CBV to the area under the curve (AUC).
Comparisons of means and ORs were performed also calculated to determine the risk of infarction for each 1-second MTT increase. This analysis was repeated among the DWI VOIs that progressed to infarction versus VOIs that did not. The reliability of MTT_{PWI} for the purposes of this study was judged by comparing on a per-patient basis the results for the PWI modality with those from the PET modality.

### I-KNOW Data Set

Subject to the outcome of the previously described analysis being positive, the following was planned.

#### VOIs Outcome Versus MTT
The same analyses as described previously were repeated, except that instead of performing them within patients, they were carried out across patients using means and paired t tests.

#### Receiver Operating Characteristic Curves
To quantify the predictive value of MTT_{PWI}, AUCs of the receiver operating characteristic (ROC) curves obtained separately for the DWI+ and DWI– VOIs were determined. The ROC analysis was first conducted using all VOIs across all patients and then on a within-patient basis; the predictive value of the observed AUCs was assessed against the neutral AUC=0.50 using CIs and 1-sample t tests, respectively. Standard optimal thresholds (OTs) were also determined together with their sensitivity and specificity. Two additional analyses were carried out for the DWI+ VOIs: (1) OTs were obtained separately for already reperfused and nonreperfused VOIs, determined using the mean+2 SDs of individual contralateral VOIs as threshold; and (2) in patients with initial occlusion and repeat MR angiography, within-subject AUCs and OTs were compared between the Thrombolysis In Myocardial Ischemia to 1 (nonrecanalizers) and Thrombolysis In Myocardial Ischemia to 2 to 3 (recanalizers).

### Results

#### Cambridge Data Set

**Patients**

Of the 7 patients in the database, 3 were excluded post hoc because of lack of acute DWI (n=1), hemorrhagic transformation (n=1), or too small infarct (n=1). The baseline characteristics of the retained patients are presented in online Table 1 (http://stroke.ahajournals.org).

**DWI Lesion Versus Final Infarct**

The number of VOIs in the prespecified tissue compartments in each patient are presented in online Table 2. The percentage of DWI+ VOIs that infarcted ranged from 44% to 89% (mean, 73%±19%) compared with 1% to 18% (mean, 7%±8%) for the DWI– VOIs (P<0.001). The proportion of final infarct that was initially DWI– ranged from 12% to 60%.

**MTT_{PWI} Versus MTT_{PET}**

An illustration of the acute DWI lesion, PET, and PWI MTT maps and final infarct is shown in Figure 1, and results are shown in the Table.

Among the DWI– VOIs, MTT_{PWI} was significantly higher in the VOIs that infarcted as compared with those that did not.
Among the 62 patients, 20 were excluded due to small infarct and/or DWI lesion (N=19) or hemorrhagic transformation (N=2). Among DWI− VOIs, there was good consistency of the findings between MTT\textsubscript{PWIs} and MTT\textsubscript{PETs}, with higher values in the VOIs that infarcted versus those that did not (P<0.001). This was also true, although less significant, for the DWI+ VOIs (12.5±3.9 seconds versus 10.9±4.3 seconds, respectively; P=0.01).

**ROC Analysis**

**Diffusion-Weighted Imaging− VOIs**

Using all VOIs across patients, the AUC for MTT\textsubscript{PWIs} to predict infarction was 0.78 (95% CI, 0.72 to 0.79) with OT=8.3 seconds (sensitivity, 69%; specificity, 74%; Figure 2). The mean AUC from the 42 individual ROCs was 0.77±0.16 (P<0.001 relative to neutral) and mean OT was 9.1 seconds (±2.1; sensitivity, 74%±18% [range, 20% to 100%]; specificity, 77%±11 [range, 54% to 96%]).

**Diffusion-Weighted Imaging+ VOIs**

Using all VOIs across patients, the AUC was 0.64 (95% CI, 0.61 to 0.66) with OT=11.3 seconds (sensitivity, 62%; specificity, 58%); the mean AUC from the 42 individual ROCs was 0.63±0.17 (P<0.001 relative to neutral), and mean OT was 11.4 seconds (±3.9; sensitivity, 69%±20% [range, 25% to 100%]; specificity, 66%±20% [range, 33% to 100%]). Comparing reperfused and nonreperfused VOIs, the OT across all patients was 7.51 seconds and 14.58 seconds (sensitivity, 62% and 62%; specificity, 53% and 54%), respectively. On repeat MR angiography, Thrombolysis In Myocardial Ischemia\textsubscript{3 to 5} scores were found in 18 and 5 of 23 patients at 2 hours and 9 and 19 of 28 patients at 24 hours, respectively. AUCs did not significantly differ at any time-point, whereas OTs did at 2 hours (12.5±4.1 seconds versus 8.0±3.0 seconds, respectively; P=0.03) but not at 24 hours (11.3±3.1 seconds and 11.3±4.6 seconds, P=0.9).

**Discussion**

Both for DWI+ and DWI− VOIs, there was good consistency in predictive value between MTT\textsubscript{PWIs} and MTT\textsubscript{PETs}, indicating adequate reliability of the former for present purposes. Assessing MTT\textsubscript{PWIs} in a reasonably large sample of hyper-

### Table. Cambridge Data Set: Mean (±1 SD) MTT (in Seconds) in VOIs That Progressed or Not to Infarction Among DWI− and DWI+ VOIs Separately in Each Patient*

<table>
<thead>
<tr>
<th></th>
<th>VOIs-Derived MTT</th>
<th>PET-Derived MTT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Noninfarcted</td>
<td>Infarcted</td>
</tr>
<tr>
<td>DWI− VOIs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient 1</td>
<td>9.2±4.6</td>
<td>13.9±0.6</td>
</tr>
<tr>
<td>Patient 2</td>
<td>9.2±3.8</td>
<td>16.1±1.6</td>
</tr>
<tr>
<td>Patient 3</td>
<td>10.2±3.0</td>
<td>12.8±1.3</td>
</tr>
<tr>
<td>Patient 4</td>
<td>7.7±3.2</td>
<td>7.3±3.3</td>
</tr>
<tr>
<td>DWI+ VOIs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient 1</td>
<td>14.2±5.4</td>
<td>13.6±3.8</td>
</tr>
<tr>
<td>Patient 2</td>
<td>12.6±4.8</td>
<td>13.1±5.9</td>
</tr>
<tr>
<td>Patient 3</td>
<td>10.8±3.9</td>
<td>13.4±7.7</td>
</tr>
<tr>
<td>Patient 4</td>
<td>10.8±4.1</td>
<td>9.6±2.7</td>
</tr>
</tbody>
</table>

MTT indicates mean transit time; VOI, voxel of interest; DWI, diffusion-weighted imaging; PWI, perfusion-weighted imaging; PET, positron emission tomography.

*P indicates mean transit time; VOI, voxel of interest; DWI, diffusion-weighted imaging; PWI, perfusion-weighted imaging; PET, positron emission tomography.

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**I-KNOW Data Set**

**Patients**

Among the 62 patients, 20 were excluded due to small infarct and/or DWI lesion (N=19) or hemorrhagic transformation (N=2), leaving 42 eligible (age, 67.8±11.9 years; 16 women; 17 right/25 left strokes; admission National Institutes of Health Stroke Scale 11.5±3.3). Thirty-three patients (79%) received intravenous tissue plasminogen activator. Acute MRI was performed 171±99 minutes after stroke onset (range, 50 to 462 minutes; 27 [64%] within 3 hours and 9 [21%] at 3 to 6 hours).

**DWI Lesion Versus Final Infarct**

The percentage of DWI+ VOIs that progressed from DWI− VOIs ranged from 9% to 100% (mean, 54%±26%) as compared with 0% to 12% (mean, 2%±3%) for the DWI− VOIs (P<0.001). The proportion of the infarct that was initially DWI− ranged from 0% to 89% (mean, 49%±25%).

**MTT in Infarcted Versus Noninfarcted VOIs**

Across patients, MTT\textsubscript{PWIs} was 11.4±3.2 seconds and 6.9±1.9 seconds in the DWI+ and DWI− VOIs, respectively (P<0.001). Across patients, MTT\textsubscript{PWIs} was higher in the DWI− VOIs that progressed relative to those that did not (10.9±2.7 seconds versus 6.9±1.8 seconds; P<0.001). This was also true, although less significant, for the DWI+ VOIs (12.5±3.9 seconds versus 10.9±4.3 seconds, respectively; P=0.01).

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**Discussion**

Both for DWI+ and DWI− VOIs, there was good consistency in predictive value between MTT\textsubscript{PWIs} and MTT\textsubscript{PETs}, indicating adequate reliability of the former for present purposes.
acute patients, we then found, supporting our hypothesis, that MTTPWI significantly added to the DWI lesion to predict infarction not only as expected among DWI/H11002 VOIs, but also, albeit to a lesser degree, for DWI/H11001 VOIs whether early recanalization occurred or not. These findings are strengthened by using voxel-based analysis, which is comprehensive and topographically accurate as compared with regions of interest.22

The combined PET/MR sample was small and thus our results may not be generalizable, yet useful conclusions could be reached. Among DWI− VOIs, MTTPWI was significantly higher in VOIs that progressed to infarction in 3 of 4 patients, of which 2 showed similarly significant findings with MTT-PET, whereas a trend was apparent ($P=0.14$) in the remaining patient. As anticipated with this late-scanned population, no significant predictive value prevailed among DWI/H11001 VOIs except in 1 patient using MTT PWI at a lowish $P=0.01$. Importantly, therefore, these data showed satisfactory concordance between the 2 imaging modalities.

Although MTTPWI has been previously validated as a predictor of the penumbra threshold against Xenon CT and PET,11−13,23 this study is the first to validate its use for infarct prediction. Given the delayed imaging, the Cambridge data set was, however, of limited use to address this value in the hyperacute setting. The analysis was therefore repeated on a larger sample in which DWI−PW1 was performed within 6 hours in 85% of patients and reperfusion therapy administered in 79%.

Outside the DWI lesion, MTTPWI was significantly longer for those VOIs that progressed to infarction, consistent with both the classic core/penumbra model in which perfusion is predictive of tissue outcome1 and studies assessing the predictive value of MTTPWI in the “mismatch.”3,5,7−10 Among time-based parameters, MTT, that is, the CBV/CBF ratio, has physiological validity compared with its surrogates and has proven reliability for infarct prediction2,3,7 and clinical correlation.24 Consistent with this, the ROC analysis also showed good predictive value, with AUCs $\geq 0.77$. This is consistent with 2 previous studies using ROC to assess the predictive value of MTTPWI independent of the DWI lesion3 or specifically in the “mismatch,”5 respectively. The OT of 9.1 seconds (8.3 seconds across all patients) was as expected longer than the OT of 5.3 seconds reported for the penumbra threshold.13

Within DWI lesions, almost half the VOIs escaped infarction, in keeping with published work,15,16 and MTTPWI was significantly higher in the VOIs that later infarcted, consistent with our hypothesis. Severity of hypoperfusion is increasingly recognized as an important determinant of tissue fate within DWI lesions. For instance, time-to-maximum (TMax) was found to inversely correlate with DWI lesion reversibility16; however, in this study, the added predictive value of PWI was not formally assessed and regions of interest were used, whereas TMax has limitations.3,25 In another study using generalized linear model, MTTPWI improved the predictive value of the DWI lesion,26 but again the role of the perfusion deficit within the latter was not directly assessed.

Again as expected, the ROC analysis showed lesser predictive value of MTTPWI within than outside the DWI lesion. Nevertheless, the observed AUCs $\geq 63%$ were significantly higher than neutral 50%, indicating useful, albeit modest, value. The OT of approximately 11.4 seconds was also expectedly longer and with lower sensitivity and specificity than outside the DWI lesion. Furthermore, as expected, the OT was almost twice as long for nonreperfused as compared with already reperfused VOIs. We cannot compare these results with previous work because the predictive value of PWI within DWI lesions had not been specifically looked at thus far.

This study suggests that adding the information provided by PWI may improve infarct prediction within the DWI lesion, which has potential implications for patient selection for thrombolysis.

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Disclosures
None.

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25. Calamante F, Christensen S, Desmond PM, Ostergaard L, Davis SM, Connelly A. The physiological significance of the time-to-maximum (Tmax) parameter in perfusion MRI. Stroke. 2010;41:1169–1174.
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SUPPLEMENTAL MATERIAL

**Supplemental Table 1.** Cambridge dataset: Patients characteristics.

<table>
<thead>
<tr>
<th>Gender</th>
<th>Age (yrs)</th>
<th>Side of stroke</th>
<th>Admission NIHSS</th>
<th>Onset to MR (hrs)</th>
<th>MR to PET (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>53</td>
<td>L</td>
<td>16</td>
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<tr>
<td>2</td>
<td>M</td>
<td>64</td>
<td>R</td>
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<td>F</td>
<td>84</td>
<td>R</td>
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<tr>
<td>4</td>
<td>F</td>
<td>73</td>
<td>L</td>
<td>17</td>
<td>21</td>
</tr>
</tbody>
</table>

NIHSS = National Institute of Health Stroke Scale.
**Supplemental Table 2.** Cambridge dataset: Progression of DWI+ and DWI− VOIs to infarction in each patient

<table>
<thead>
<tr>
<th>Patient</th>
<th>Final infarct</th>
<th>DWI−</th>
<th>DWI+</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Non-infarcted</td>
<td>Infarcted</td>
</tr>
<tr>
<td>1</td>
<td>104</td>
<td>286 (82%)</td>
<td>62 (18%)</td>
</tr>
<tr>
<td>2</td>
<td>44</td>
<td>445 (99%)</td>
<td>5 (1%)</td>
</tr>
<tr>
<td>3</td>
<td>101</td>
<td>346 (96%)</td>
<td>16 (4%)</td>
</tr>
<tr>
<td>4</td>
<td>60</td>
<td>554 (97%)</td>
<td>19 (3%)</td>
</tr>
</tbody>
</table>

Data presented are number of VOIs in each tissue compartment (%: percentage of VOIs in cell relative to sum of VOIs in the DWI+ and DWI− categories).