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 MTT$_{\text{PET}}$ and MTT$_{\text{PWI}}$ for both DWI+ and DWI− voxels of interest indicating adequate reliability of MTT$_{\text{PWI}}$ 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 MTT$_{\text{PWI}}$ may improve infarct prediction not only as already known outside, but also within, DWI lesions. (Stroke. 2011;42:1602-1607.)

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
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 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 (ie, CBF/CBV), a validated surrogate for cerebral perfusion pressure. For instance, Marchal et al reported a strong trend (P=0.087) for CBV/CBF 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 $^{15}$O-PET and follow-up structural MRI 1 month later. Exclusion criteria included previous stroke, lacunar or hemorrhagic stroke, anticoagulation or thrombolysis (arterial cannulation), 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 ≥4 and onset-to-scan time ≤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 (Medspec s300, Bruker) using a single-shot spin-echo echoplanar image sequence with slice thickness=5 mm, field of view=24×24 cm, and matrix 128×128.

**Perfusion-Weighted Imaging**

PWI was performed using single-shot gradient echo with repetition time 1500 to 1500 ms, echo time 23 to 36 ms, slice number 11 to 15, thickness=5 mm, field of view=190 mm, and matrix 64×128 or 128×128. Gadolinium-diethylenetriaminepentaacetic acid (0.1 mmol/kg) was injected intravenously as a bolus (3 to 4 mLs) 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 $^{68}$Ge scan) followed by emission data (steady-state 10-minute $^2$H$_2^18$O infusion and $^18$O$_2$ inhalation and 5-minute $^{15}$O inhalation scans) were acquired (Advance scanner; GE Medical Systems, Milwaukee, WI). Images were reconstructed into 2.34×2.34×4.25-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 (spoiled 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 128×128, 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 128×128, 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 MTT$_{PET}$ 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 contralateral middle cerebral artery using block-circulant deconvolution, in which MTT$^{PWI}$=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).
MTT increase. Comparisons of means and ORs were performed also calculated to determine the risk of infarction for each 1-second MTT across VOIs that progressed to infarction versus VOIs that did not.

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

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**Image Coregistration**

Using SPM (Welcome Department of Imaging Neuroscience, London, UK), the PET and mean PWI maps (Cambridge data set) were coregistered to the acute T2 and the latter to the follow-up T1 spoiled gradient-recalled acquisition; the mean PWI image (I-KNOW data set) to the follow-up T1 spoiled gradient-recalled acquisition; and the latter to the acute images.

**Matrix Transformation**

To reduce both noise and data size for the analysis, all coregistered images were transformed into an 8×8×8-mm³ matrix to be referred as voxels of interest (VOIs).

**Regions of Interest (Both Data Sets)**

Using Analyze 7.0, DWI lesions were delineated manually on the b=945 or 1000-s/mm² images and infarct and affected and unaffected hemisphere masks on the follow-up fluid-attenuated inversion recovery and T2-weighted MRI. The DWI lesion, infarct and hemisphere regions of interest comprised all VOIs within the original masks across slices. VOIs that fell across contours were excluded if >50% of the original 1×1×1-mm³ pixels fell outside the mask. Otherwise, only the remaining fraction of the 8×8×8-mm³ VOIs was retained. Within VOIs, any 1×1×1-mm³ pixel with MTT=0 or classified as CSF based on T1 segmentation in SPM was considered artifactual and excluded from the mean VOI value. Finally, to make comparisons meaningful, small (≤1 VOI) DWI lesions or final infarcts caused post hoc subject exclusion.

**Data Handling and Statistical Analysis**

**Cambridge Data Set**

**Outcome of VOIs**

We determined on an individual basis the number of DWI-negative (DWI−) and DWI-positive (DWI+) VOIs that progressed or not to infarction. A comparison of these proportions was performed for each patient using χ².

**MTT as a Function of VOI Outcome**

Within patient, we then compared, among the DWI+ VOIs, the MTT across VOIs that progressed to infarction versus VOIs that did not. This analysis was repeated among the DWI− VOIs. ORs were also calculated to determine the risk of infarction for each 1-second MTT increase. Comparisons of means and ORs were performed using t tests. The analyses were carried out for the MTTPET and the MTTPWI data separately. The reliability of MTTPWI 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 Characteristics Curves**

To quantify the predictive value of MTTPET, 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 Ischemia1 to Thrombolysis In Myocardial Ischemia2 to 3 (nonrecanalizers) and Thrombolysis In Myocardial Ischemia1 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%.

**MTTPWI Versus MTTPET**

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, MTTPWI was significantly higher in the VOIs that infarcted as compared with those that did not.
in 3 patients ($P \leq 0.001$). MTTPET was significantly higher in the VOIs that infarcted in 2 patients ($P \leq 0.001$), in both of whom MTTPW1 was also significant. The results with the ORs were entirely consistent.

Among the DWI+ VOIs, MTTPW1 was higher in the VOIs that infarcted as compared with those that did not in 1 patient with moderate significance ($P = 0.01$); with MTTPET, the comparison was not significant in any patient; the results with the ORs were again consistent.

The good overall concordance of the findings between MTTPW1 and MTTPET for both DWI+ and DWI− VOIs indicated adequate reliability of the former for the present purposes. We therefore proceeded with the analysis of the I-KNOW data set.

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=1), 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 infarcted 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, MTTPW1 was 11.4±3.2 seconds and 6.9±1.9 seconds in the DWI+ and DWI− VOIs, respectively ($P < 0.001$). Across patients, MTTPW1 was higher in the DWI− VOIs that infarcted 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; $P = 0.01$).

ROC Analysis

Diffusion-Weighted Imaging− VOIs
Using all VOIs across patients, the AUC for MTTPW1 to predict infarction was 0.78 (95% CI, 0.77 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 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 MTTPW1 and MTTPET, indicating adequate reliability of the former for present purposes. Assessing MTTPW1 in a reasonably large sample of hyper-
acute patients, we then found, supporting our hypothesis, that MTT$_{\text{PWI}}$ 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, MTT$_{\text{PWI}}$ was significantly higher in VOIs that progressed to infarction in 3 of 4 patients, of which 2 showed similarly significant findings with MTT$_{\text{PET}}$, 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+ VOIs except in 1 patient using MTT$_{\text{PWI}}$ at a lowish P < 0.01. Importantly, therefore, these data showed satisfactory concordance between the 2 imaging modalities.

Although MTT$_{\text{PWI}}$ has been previously validated as a predictor of the penumbra threshold against Xenon CT and PET,11–13,21 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–PWI was performed within 6 hours in 85% of patients and reperfusion therapy administered in 79%.

Outside the DWI lesion, MTT$_{\text{PWI}}$ 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 MTT$_{\text{PWI}}$ in the “mismatch.”4,5,7–10 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 ≥0.77. This is consistent with 2 previous studies using ROC to assess the predictive value of MTT$_{\text{PWI}}$ independent of the DWI lesion3 or specifically in the “mismatch,”21 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 MTT$_{\text{PWI}}$ 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, MTT$_{\text{PWI}}$ 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 MTT$_{\text{PWI}}$ within than outside the DWI lesion. Nevertheless, the observed AUCs ≥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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**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>
<td>7</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>64</td>
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</tr>
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<td>F</td>
<td>84</td>
<td>R</td>
<td>10</td>
<td>21</td>
</tr>
<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>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Non-infarcted</td>
<td>Infarcted</td>
<td>Non-infarcted</td>
</tr>
<tr>
<td>1</td>
<td>104</td>
<td>286 (82%)</td>
<td>62 (18%)</td>
<td>9 (11%)</td>
</tr>
<tr>
<td>2</td>
<td>44</td>
<td>445 (99%)</td>
<td>5 (1%)</td>
<td>49 (56%)</td>
</tr>
<tr>
<td>3</td>
<td>101</td>
<td>346 (96%)</td>
<td>16 (4%)</td>
<td>23 (21%)</td>
</tr>
<tr>
<td>4</td>
<td>60</td>
<td>554 (97%)</td>
<td>19 (3%)</td>
<td>7 (15%)</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).