Comparison of 10 Different Magnetic Resonance Perfusion Imaging Processing Methods in Acute Ischemic Stroke
Effect on Lesion Size, Proportion of Patients With Diffusion/Perfusion Mismatch, Clinical Scores, and Radiologic Outcomes

Ingrid Kane, MRCP; Trevor Carpenter, PhD; Francesca Chappell, MSc; Carly Rivers, PhD; Paul Armitage, PhD; Peter Sandercock, FRCPE, FMedSci; Joanna Wardlaw, FRCR, FRCP, FMedSci

Background and Purpose—Several methods are available to assess the magnetic resonance perfusion lesion in acute ischemic stroke. We tested 10 of these to compare perfusion lesion sizes and to assess the relation to clinical scores and final infarct extent.

Methods—We recruited patients with acute ischemic stroke, performed diffusion- and perfusion-weighted imaging, and recorded stroke severity at baseline, final infarct size on T2-weighted imaging at ≥1 month, and Rankin Scale score at 3 months. We calculated 10 perfusion parameters (6 of mean transit time, MTT; 3 of cerebral blood flow; 1 of cerebral blood volume; 7 relative and 3 quantitative), measured the perfusion-weighted imaging lesion and diffusion/perfusion mismatch volumes, and compared each with clinical and radiologic outcomes.

Results—Among 32 patients, the median perfusion lesion volume varied from 0 to 14 882 voxels ($P<0.0001$); the proportion of patients with mismatch varied from 9% to 72% ($P<0.05$), depending on the perfusion parameter. Five measures of relative MTT were associated with baseline National Institutes of Health Stroke Scale score; 1 (arrival time fitted) was also associated with clinical outcome. Final infarct size was most strongly associated with MTT measures, including arrival time fitted. There was no advantage of quantitative perfusion measures and no relation between mismatch presence/absence and infarct expansion with any of the 10 perfusion measures.

Conclusions—Perfusion lesion size differs markedly depending on the parameter calculated. Relative perfusion parameters performed as well as quantitative ones. Some parameters (mainly representing MTT measures) were correlated with clinical scores; others were correlated with final infarct size; and arrival time fitted was correlated with both. These findings should be validated in other datasets. A consensus is required on which perfusion measurement and processing methods should be used. (Stroke. 2007;38:3158-3164.)

Key Words: cerebral perfusion ■ diffusion imaging ■ magnetic resonance ■ stroke
PWI lesions that reflect CBF are generally smaller than those that reflect mean transit time (MTT).12–16 Different ways of estimating a single PWI parameter like MTT may yield differently sized PWI lesions.17 Comparisons of how well different relative and/or quantitative PWI lesions predict infarct growth yield differing results,17–19 possibly due to differences in patient case mix or the timing of scanning, as well as to variations in the combinations of PWI processing methods used.

What effect does this PWI lesion variability have on any relation between the presence or size of the PWI lesion or DWI/PWI mismatch and the neurologic severity of the stroke at baseline? Of previous studies reporting correlations between perfusion parameters and stroke severity at presentation,20–21 reported that TTP, a relative measure of MTT, was correlated with baseline National Institutes of Health Stroke Scale (NIHSS) score;21,22 suggested a correlation between qMTT and baseline NIHSS; and 23 suggested a correlation between qMTT and the Scandinavian Stroke Scale score.

If imaging is to guide clinical trials or routine practice, then it is important to know which baseline PWI lesion(s) best relates to the final infarct extent and clinical outcome. These 2 outcomes may have different baseline predictors, which may differ from PWI lesions that are correlated with baseline neurologic deficit. Several studies that compared acute PWI lesions and radiologic outcomes used outcome time points that were too early to determine the “final” infarct extent (24 hours to 1 week after stroke).24 Three studies that examined later time points only compared perfusion values, not lesion extent, but found associations between measures of MTT and 60- or 90-day T2 findings.20,21,25 A correlation between the acute PWI lesion and functional clinical outcome was found between TTP and modified Rankin Scale (mRS) score,21 relative (r) MTT and mRS,26 and qMTT and the Barthel Index.23

In view of these differences, we compared 10 different ways of processing the PWI data to quantify variation in PWI lesion size and DWI/PWI mismatch and to explore the association between each PWI parameter and the NIHSS score on admission, the mRS score at 3 months, the final infarct size on T2-weighted imaging at least 1 month after stroke, and infarct growth between baseline and final T2-weighted imaging.

Methods

Patients

We recruited patients presenting with their first-ever acute ischemic stroke who were able to undergo MRI as soon after stroke onset as possible and within an absolute maximum of 24 hours (the scanner was only available during normal working hours). A trained stroke physician assessed all patients as soon as possible, assigned a stroke subtype according to the Oxfordshire Community Stroke Project classification,27 and determined the stroke severity according to the NIHSS. Blinded to baseline features and imaging, we measured functional outcome at 3 months by the mRS. We included all ischemic stroke subtypes.

Image Acquisition

We performed all imaging on a GE Signa LX 1.5-T MRI scanner (General Electric, Milwaukee, Wis) with a birdcage quadrature coil and a standardized protocol for acute stroke (described previously).14 The spin-echo echoplanar imaging diffusion-tensor axial sequences and dynamic susceptibility contrast echoplanar imaging PWI had 15 axial slices each of 5-mm thickness with an interslice gap of 1 mm and an imaging matrix 128×128 encompassing a 240×240 mm field of view. Additionally for PWI, a gadolinium-based contrast agent (10 mL of 1 mol/L Gadovist or 20 mL of 0.5 mol/L Omniscan) was injected, with imaging starting 10 seconds after the start of contrast injection, continuing for 85 seconds, and collecting 34 volumes of 15 axial slices with an echo time of 30 ms and a repetition time of 2.5 seconds. Final follow-up T2-weighted imaging was performed at ≥1 month.

Image Processing

We performed all image processing blinded to clinical and any other imaging data. We coregistered the individual DWI and PWI data by using the open-access software FLIRT (www.fmrib.ox.ac.uk/fsl). We defined the AIF from the fitted data by averaging the concentration-time data from voxels corresponding to the lumina of the internal carotid arteries (to limit effects of any carotid stenosis). We chose this approach for several reasons: to be more relevant to an acute situation, wherein the only knowledge of infarct location (before DWI/PWI data processing) may come from the symptoms; to characterize brain blood supply as a global “normalizing” factor (the internal carotid arteries being before the circle of Willis represent the available blood supply minus the contribution from the basilar artery); and last because the internal carotid arteries are aligned perpendicular to the plane of imaging and hence avoid problems associated with partial volume. Care was taken to ensure that the regions drawn within the internal carotid arteries corresponded to the lumen (2 or 3 voxels per vessel).
that indicated reduced cerebral perfusion (reduced CBF, abnormal visible on printed color maps (Figure 2) by identifying areas of signal format.

We calculated maps of rCBV, rMTT, rCBF, arrival time fitted (ATF), peak time fitted (PTF), TTP, and FWHM of the concentration-time curve and the maximum value of the fitted concentration-time curve (Cmax). We normalized the parameter value in each voxel by the sample mean of the parameter value in the voxels used to define the AIF. Normalizing the CBF value by the rCBV sample mean of the voxels used to define the AIF results in qCBF; hence, this parameter is not mentioned later. We produced maps of qCBF and qMTT by deconvolving the peak voxel concentration-time curves with the concentration-time curve at the point halfway to the peak concentration; we normalized the parameter values obtained from the curve fitting procedure; rMTT

### Table 1. Volumes of PWI Lesions and Mismatch Tissue and No. of Patients With a PWI Lesion and PWI/DWI Mismatch by PWI Processing Method Used

<table>
<thead>
<tr>
<th>Definition</th>
<th>Mean (Median) PWI Lesion Volume</th>
<th>No. With No PWI Lesion</th>
<th>No. With Mismatch (%)</th>
<th>Median Volume of Mismatch</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATF</td>
<td>Estimated delay in arrival of contrast in a voxel obtained from the curve fitting procedure; rMTT</td>
<td>15 106 (5747)</td>
<td>11</td>
<td>18 (56)</td>
</tr>
<tr>
<td>PTF</td>
<td>Estimate of the time of maximum contrast concentration obtained from the fitted parameters; rMTT</td>
<td>21 185 (12478)</td>
<td>7</td>
<td>21 (66)</td>
</tr>
<tr>
<td>TTP</td>
<td>Peak time fitted minus arrival time fitted; rMTT</td>
<td>22 802 (14882)</td>
<td>9</td>
<td>20 (63)</td>
</tr>
<tr>
<td>FWHM</td>
<td>Width of the concentration-time curve at the point halfway to the peak concentration; rMTT</td>
<td>32 260 (13405)</td>
<td>7</td>
<td>23 (72)</td>
</tr>
<tr>
<td>First moment (ie, rMTT)</td>
<td>First moment of the concentration-time curve; rMTT</td>
<td>23 177 (13996)</td>
<td>7</td>
<td>23 (72)</td>
</tr>
<tr>
<td>Cmax</td>
<td>Maximum value of the fitted concentration-time curve; rMTT, rCBF and MTT</td>
<td>5993 (0)</td>
<td>17</td>
<td>7 (22)</td>
</tr>
<tr>
<td>rCBF</td>
<td>rCBV/rMTT</td>
<td>4162 (0)</td>
<td>17</td>
<td>5 (16)</td>
</tr>
<tr>
<td>qMTT</td>
<td>qCBF/qCBV</td>
<td>22 167 (8620)</td>
<td>13</td>
<td>18 (56)</td>
</tr>
<tr>
<td>qCBF</td>
<td>Maximum value of the scaled estimate of the voxel residue response</td>
<td>12 783 (0)</td>
<td>17</td>
<td>13 (41)</td>
</tr>
<tr>
<td>CBV</td>
<td>Area under the concentration-time curve; rCBV or qCBV</td>
<td>2446 (0)</td>
<td>19</td>
<td>3 (9)</td>
</tr>
</tbody>
</table>

Mean and median PWI volumes are shown to overcome the “0” medians. Lesion volumes are expressed in voxels. μ indicates proportional to.

*Negative values indicate that the median DWI lesion is larger than the median acute PWI lesion.

We compared the median PWI lesion and the PWI/DWI mismatch volumes with the Friedman test (multiple nonparametric related measurements). We compared the proportion of patients with or without DWI/PWI mismatch by PWI processing method by the χ² test. We compared the different PWI volumes to DWI lesion volumes with the Friedman test (multiple nonparametric related measurements). We compared the proportion of patients with or without DWI/PWI mismatch by PWI processing method by the χ² test. We compared the different PWI volumes to DWI lesion volumes with the Friedman test. We compared the proportion of patients with or without DWI/PWI mismatch by PWI processing method by the χ² test.

**Statistical Analysis**

The data were not normally distributed (Kolmogorov-Smirnov test). We compared the median PWI lesion and the PWI/DWI mismatch volumes with the Friedman test (multiple nonparametric related measurements). We compared the proportion of patients with or without DWI/PWI mismatch by PWI processing method by the χ² test.

An experienced stroke neuroradiologist outlined any PWI lesions visible on printed color maps (Figure 2) by identifying areas of signal that indicated reduced cerebral perfusion (reduced CBF, abnormal CBV, or increased MTT) compared with the normal perfusion distribution, taking account particularly of any differences between the 2 hemispheres or in the anteroposterior distribution and gray/white matter differences. We did not include areas of increased CBF or CBV in the “perfusion deficit.” Each PWI parameter was outlined separately, blinded to all clinical, other imaging, and other PWI data. We then traced the lesion outline onto the Analyze format images by using Analyze version 7.8 and derived PWI lesion volumes by counting the number of voxels within the lesion on all slices on which it was visible. All PWI lesions for a single patient were traced in Analyze in the same session but while blinded to all other information. We defined the DWI/PWI mismatch as the acute PWI volume minus the acute DWI lesion volume and infarct expansion as any increase in size from the acute DWI lesion to the final T2 lesion.
weighted final infarct volume, and mRS score as the independent variables. We transformed the PWI lesion volume data by taking the cube root to minimize the effect of outliers. We used Fisher’s exact test to investigate any correlation between the presence or absence of mismatch at baseline and the presence or absence of infarct expansion on the final T2 image. All analyses were performed in SPSS version 13 for Windows.

**Results**

We recruited 32 patients (13 female, 19 male), whose mean age was 70 years (range, 36 to 93 years). The median time to MRI was 7.3 hours (range, 1.4 to 24 hours). The time to imaging was <6 hours from symptom onset in 12 of 32 (38%), 6 to 12 hours in 8 (25%), and between 12 and 24 hours in 12 (37%). According to the Oxfordshire Community Stroke Project classification,27 there were 3 lacunar stroke (LACS), 19 partial anterior circulation stroke (PACS), and 10 total anterior circulation stroke (TACS). The median baseline NIHSS score was 7 (range, 1 to 25).

The PWI lesion size varied markedly with the method of calculating the PWI lesion (Table 1 and Figure 2). The median PWI lesion volume varied from 0 voxels (Cmax, CBV) to 14 882 voxels (TTP) (Friedman test 121.5, median PWI lesion volume varied from 0 voxels (Cmax, calculating the PWI lesion (Table 1 and Figure 2). The NIHSS score was 7 (range, 1 to 25).

For admission imaging, 14 patients (44%) were treated with tissue plasminogen activator (tPA) and 18 (56%) were not. The median baseline NIHSS was 7 (range, 1 to 25). The median time to imaging was 7.3 hours (range, 1.4 to 24 hours). The time to imaging was <6 hours from symptom onset in 12 of 32 (38%), 6 to 12 hours in 8 (25%), and between 12 and 24 hours in 12 (37%). According to the Oxfordshire Community Stroke Project classification,27 there were 3 lacunar stroke (LACS), 19 partial anterior circulation stroke (PACS), and 10 total anterior circulation stroke (TACS). The median baseline NIHSS score was 7 (range, 1 to 25).

**Discussion**

Different PWI parameters produce very different estimates of abnormal perfusion in the same data from the same patient and hence, very different estimates of the volume of “tissue at risk.” If patients with DWI/PWI mismatch only were to receive thrombolysis, then selection based on TTP would result in 20 of 32 (63%) patients receiving treatment, whereas selection on the basis of Cmax would result in only 7 of 32.

**Table 2. Association Between PWI Lesion Size (in Voxels) and Baseline Clinical Score (NIHSS), Functional Outcome at 3 Months (mRS), and Final Infarct Extent on T2-Weighted MRI Imaging (≥1 Month After Symptom Onset)**

<table>
<thead>
<tr>
<th>Perfusion Method</th>
<th>Baseline NIHSS</th>
<th>3-Month mRS</th>
<th>T2 Final Infarct Size at ≥1 Month</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATF</td>
<td>0.209 (0.006)</td>
<td>0.049 (0.035)</td>
<td>0.330 (0.002)</td>
</tr>
<tr>
<td>PTF</td>
<td>0.210 (0.005)</td>
<td>0.042 (0.068)</td>
<td>0.292 (0.007)</td>
</tr>
<tr>
<td>TTP</td>
<td>0.193 (0.006)</td>
<td>0.040 (0.066)</td>
<td>0.286 (0.004)</td>
</tr>
<tr>
<td>FWHM</td>
<td>0.180 (0.006)</td>
<td>0.021 (0.313)</td>
<td>0.214 (0.025)</td>
</tr>
<tr>
<td>First moment (ie, rMTT)</td>
<td>0.206 (0.005)</td>
<td>0.042 (0.067)</td>
<td>0.303 (0.004)</td>
</tr>
<tr>
<td>Cmax</td>
<td>0.147 (0.133)</td>
<td>0.018 (0.049)</td>
<td>0.263 (0.059)</td>
</tr>
<tr>
<td>rCBF</td>
<td>0.206 (0.057)</td>
<td>0.035 (0.285)</td>
<td>0.324 (0.036)</td>
</tr>
<tr>
<td>qMTT</td>
<td>0.050 (0.456)</td>
<td>0.017 (0.407)</td>
<td>0.162 (0.089)</td>
</tr>
<tr>
<td>qCBF</td>
<td>0.098 (0.195)</td>
<td>0.029 (0.202)</td>
<td>0.236 (0.025)</td>
</tr>
<tr>
<td>CBV</td>
<td>0.236 (0.066)</td>
<td>0.042 (0.278)</td>
<td>0.392 (0.032)</td>
</tr>
</tbody>
</table>

 Significant associations are highlighted in boldface type; P values are in parentheses.

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that these PWI lesions are a better indicator of the extent of MTT lesions with baseline NIHSS score presumably means associated with functional outcome. The correlation of large producing smaller lesions than noted earlier, ATF, was rCBF, qCBF, and CBV less so. However, the final T2 lesion extent may not reflect the total damage within the brain. Histologic evidence of damage may occur outside the T2-visible lesion.\textsuperscript{30,31} Functional outcome is more relevant to stroke services and patients. The true final damage being greater than just the T2-visible lesion might explain why, in this study, the correlations between baseline PWI lesion and functional outcome were strongest for rMTT measures.

Our results confirm previous observations that TTP and qMTT are correlated with baseline NIHSS score,\textsuperscript{15,20–22} but previous studies compared fewer PWI lesions than in the present study. The maximum PWI parameters compared in previous studies were 9,\textsuperscript{18} 6,\textsuperscript{12} 4,\textsuperscript{17,19} and 3,\textsuperscript{13,16} but these studies did not quantify the difference in visible lesion volume or the impact of that difference on DWI/PWI mismatch. Thus, in general, relative measures of MTT were correlated with both baseline stroke severity and clinical functional outcome. These are relatively quick to perform and easy to obtain (no deconvolution required) and therefore are practical in the acute setting.

The fact that we were unable to demonstrate a correlation between the presence/absence of mismatch and the presence/absence of infarct expansion suggests that the presence of mismatch per se is not an ideal criterion to use when selecting patients for acute stroke treatments. About half of the patients without mismatch (either on rMTT or rCBF) may develop infarct growth,\textsuperscript{14,32} so the mismatch concept may not identify all “tissue at risk”—DWI-abnormal tissue may recover, and most PWI parameters probably overestimate tissue at risk.

We used visual assessment of the PWI lesions because visual assessment is the fastest method for detecting the acute lesion in the clinical setting. We did not use thresholding/automated lesion edge detection because no consistent threshold has yet been identified.\textsuperscript{33} Furthermore, it was unclear how a threshold with NIHSS score or 3-month functional outcome should be derived. The threshold that matches the boundary of the final T2 lesion is relatively straightforward to determine but may not represent the final tissue damage and is of less clinical relevance. However, manual outlining introduces observer variation. Some might disagree on where the boundaries should be drawn. For example, in Figure 2, it would appear that the ATF has produced a large lesion compared with other MTT lesions, whereas Figure 3 indicates that, on average, the ATF produced the smallest of the MTT-like lesions. Similarly, Figure 2 suggests that the CBF lesions are quite large, whereas Figure 3 indicates that, on average, the CBF, CBV, and Cmax lesions were very small or nonexistent. Figure 2 is only intended to illustrate the variation in lesion appearance among the 10 parameters and was chosen because the CBF and CBV lesions were visible, so these may not be truly representative of the average in this cohort. This is a
further reason for validation of these findings in other datasets.

We did not use cross-calibration (scaling to a fixed value of presumed normal white matter) so as to preserve information in the perfusion maps about the underlying perfusion status of all tissue. Although scaling to presumed normal white matter may allow the different PWI parameter images to be scaled directly into the same windowing, in the typical elderly stroke population, the background white matter is often abnormal, so applying an arbitrary scaling factor might not improve image accuracy or interpretability. It might also skew the scaling of some parameters so as to actually reduce the visibility of some lesions. Instead, we normalized the individual perfusion parameter maps to the average value of that parameter in the region used to define the AIF because AIF (eg, maximum contrast value, area under the curve) is linearly associated with the corresponding tissue parameters Cmax, rCBV, etc. Thus, normalization by the average parameter value within the AIF region of interest attempts to counteract in the calculated relative perfusion parameters due to the differing arrival rate of contrast in the brain between patients, thereby more effectively achieving standardization, as would scaling to presumed normal white matter. We included data for all patients in the statistical analysis, whether there was a PWI lesion present or not, to be able to determine the relative predictive values of the different PWI processing methods, including those that less frequently produce a PWI lesion. Choosing a PWI parameter that has a high probability of not producing a visible lesion, while not knowing what the absence of a lesion means, is unlikely to be helpful. We did not use an explicit correction for multiple comparisons, but the effect of doing so can be seen by ignoring probability values >0.01 in Table 2. Other publications did not make clear whether all patients, or just those with visible PWI lesions, were included, which may explain previous discrepancies. Excluding patients without PWI lesions would result in a very skewed comparison; eg, in our series, some PWI parameters (eg, TTP) might contribute 23 of 32 patients, whereas others like rCBF or CBV might only contribute 13 of 32. Excluding patients without PWI lesions would provide no information on the relevance of a PWI-negative examination. In the acute situation, with limited time for multiple postprocessing attempts, one needs to use the PWI parameter that is most likely to inform decision making.

There is an urgent need to standardize methods for processing perfusion data. This includes deciding on not only which PWI lesion to measure but also how to measure it and which software should be used. Manufacturer processing algorithms may differ and could produce variations in lesion size between scanners, even when each center is producing maps of the same PWI lesion. Therefore, there is a need to standardize software also. Perhaps there is a need for a standard PWI test dataset that could be used to calibrate different software. This might at least reduce some of the variation between PWI lesions. Relative measures of MTT, which are quick to perform and are associated with stroke severity and functional outcome, may be more useful than PWI parameters that are related closely to radiologic surrogates. Similar variation may arise if computed tomography perfusion data are processed in different ways with different manufacturer’s software. Similar studies should be performed with computed tomography perfusion as a matter of urgency, as computed tomography perfusion is rapidly increasing in popularity and is much more accessible than MRI.

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Disclosures
None.

References


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