Perfusion Magnetic Resonance Imaging Maps in Hyperacute Stroke

Relative Cerebral Blood Flow Most Accurately Identifies Tissue Destined to Infarct

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Background and Purpose—In ischemic stroke, perfusion-weighted imaging (PWI) and diffusion-weighted imaging (DWI) provide important pathophysiological information. A PWI>DWI mismatch pattern suggests the presence of salvageable tissue. However, improved methods for distinguishing PWI>DWI mismatch tissue that is critically hypoperfused from benign oligemia are required.

Methods—We investigated the usefulness of maps of relative cerebral blood flow (rCBF), volume (rCBV), and mean transit time (rMTT) to predict transition to infarction in hyperacute (<6 hours) stroke patients with PWI>DWI mismatch patterns. Semiquantitative color-thresholded analysis was used to measure hypoperfusion volumes, including increasing color signal intensity thresholds of rMTT delay, which were compared with infarct expansion, outcome infarct size, and clinical status.

Results—Acute rCBF lesion volume had the strongest correlation with final infarct size ($r=0.91, P<0.001$) and clinical outcome ($r=0.67, P<0.01$). There was a trend for acute rCBF>DWI mismatch volume to overestimate infarct expansion between the acute and outcome study ($P=0.06$). Infarct expansion was underestimated by acute rCBV>DWI mismatch ($P<0.001$). When rMTT lesions included tissue with moderately prolonged transit times (mean delay 4.3 seconds, signal intensity values 50% to 70%), infarct expansion was overestimated. In contrast, when rMTT lesions were restricted to more severely prolonged transit times (mean delay 6.1 seconds, signal intensity >70%), these regions progressed to infarction in all except 1 patient, but infarct expansion was underestimated ($P<0.001$).

Conclusions—The acute rCBF lesion most accurately identified tissue in the PWI>DWI mismatch region at risk of infarction. Color-thresholded PWI maps show potential for use in an acute clinical setting to prospectively predict tissue outcome. (Stroke. 2001;32:1581-1587.)

Key Words: ischemic stroke ■ magnetic resonance imaging, diffusion-weighted ■ magnetic resonance imaging, perfusion-weighted ■ stroke outcome

In recent years, combined diffusion-weighted imaging (DWI) and perfusion-weighted imaging (PWI) have become important strategies in the investigation of acute stroke. Although partial reversal of diffusion abnormalities has been reported with rapid reperfusion, acute DWI lesions typically evolve into infarction. PWI provides complementary information to DWI by detecting regions of impaired perfusion. At the hyperacute stage of stroke (within 6 hours), >75% of patients have perfusion lesions larger than corresponding diffusion lesions. These PWI>DWI mismatch patterns predict subsequent infarct expansion and therefore may identify at-risk but potentially salvageable tissue. Indeed, recent reports suggest that PWI>DWI mismatch may identify a subset of patients with the greatest potential to benefit from thrombolytic therapy. However, PWI might overestimate the “true” mismatch region, because current techniques may not distinguish between critically hypoperfused tissue at risk and areas with lesser perfusion abnormalities not destined to infarct. With bolus-tracking PWI, various hemodynamic indices can be calculated and displayed as maps. These include relative mean transit time (rMTT), time to peak (TTP), and relative cerebral blood flow (rCBF) and volume (rCBV) maps. Currently, TTP or rMTT maps are most widely used.
for lesion volume measurements as perfusion lesion boundaries are visually distinct.6,8,16 However, TTP and rMTT are indirect measures of tissue perfusion and do not distinguish between gray and white matter, and lesions may include benign oligemic tissue that is not at risk of infarction.8,14,17 Maps of rCBF and rCBV offer theoretical advantages as they provide more direct measures of tissue perfusion.14 Currently, rCBF and rCBV gray scale maps are less widely used for the measurement of perfusion deficits than are rMTT or TTP maps, because accurate distinction of the borders between hypoperfused gray matter and normal white matter is difficult.1 This reflects the 2- to 3-fold physiological difference in blood flow and volume between normal gray and white matter.18,19 Color rCBF and rCBV maps may address these problems by providing semiquantitative assessments of cerebral perfusion.20

There has been only 1 study that compared the use of rMTT, rCBV, and rCBF maps in prediction of the transition to infarction in stroke.14 This investigation found that acute rCBV maps had the strongest correlation with final infarct size. However, patients were imaged up to 12 hours after stroke onset, and some had PWI>DWI patterns. Such nonmismatch patterns identify patients who typically do not have subsequent infarct expansion.8 As a consequence, PWI does not provide additional information to DWI in prediction of the final infarct size in this group.8

We therefore investigated the use of the different PWI maps in hyperacute stroke patients. Analysis was limited to those with PWI>DWI mismatch because this is the group with tissue at risk of infarction and therefore most likely to respond to acute intervention.5,12,13 A novel semiquantitative color method of analyzing PWI maps was used. The primary aim was to determine which of the perfusion maps most closely delineates mismatch tissue likely to proceed to infarction and best correlates with final infarct size and clinical outcome. Such information could be potentially applied in the acute stroke setting, particularly in the selection of patients for thrombolysis.

Subjects and Methods

Patients

Patients with sudden focal neurological deficit, consistent with hemispheric ischemic stroke within 6 hours of onset, were recruited prospectively from the Stroke Service of the Royal Melbourne Hospital from January 1998 to January 2000. The patients in this report were part of a larger cohort of 66 patients recruited during the same period, who had DWI and PWI within 24 hours of stroke onset. Six of these patients have been the subjects of a previous report.21

Stroke onset was defined as the last time the patient was known to be without neurological deficit. PWI and DWI were performed within 6 hours of stroke onset in all patients. Outcome MRI was performed in surviving patients between days 30 and 90. Outcome clinical assessment was performed on the same day as the outcome MR study and consisted of the National Institutes of Health Stroke Scale (NIHSS) and the Modified Rankin Scale, a validated handicap scale. All patients were assessed by a neurologist or neurology resident blinded to the MRI studies.

Patients were excluded if they had lacunar stroke, cerebral hemorrhage, preexisting significant nonischemic neurological conditions (including dementia or extrapyramidal disease), or a history of prior stroke that would hamper interpretation of clinical and radiological data. There were no age, gender, or handedness exclusions. No patient received thrombolytic therapy. The study was performed with the approval of the Scientific Research and Ethics Committee at our institution, and written informed consent was obtained from the patient or next of kin.

MRI Protocol

Each MRI examination consisted of DWI, PWI, and conventional imaging using a standard protocol optimized to obtain high-quality images as rapidly as possible in ill and potentially uncooperative patients. The total imaging time was ~20 minutes. All scans were obtained using a 1.5-T MRI-equipped whole-body scanner (Signa Horizon SR 120; General Electric). Diffusion-weighted images were obtained using a multislice, single-shot spin-echo EPI sequence. Slice thickness was 6 mm with a 1-mm gap, with the number of slices set to include the whole brain (average of 16). Matrix size was 128×128, field of view was 24×24 cm, and TR/TE was 6000/107 ms. Diffusion gradient strength was varied between 0 and 22 mT/m, resulting in 3 b values of increasing magnitude from 0 to 1000 s/mm.

Perfusion-weighted images were obtained after a bolus of gadolinium-DTPA (0.2 mmol/kg) via a large-bore cannula in the antecubital fossa. The injection was performed at a speed of 5 mL/s with an MR-compatible power injector (Spectris; Medrad) and followed by a 15-mL bolus of saline. An EPI gradient-echo sequence with a TR/TE of 2000/70 ms and a flip angle of 60 degrees was used, as previously described.22 Twelve slices were obtained, centered on the DWI lesion. Slice thickness was 6 mm with a 1-mm gap, matrix of 256×128, and field of view of 40×20 cm. Images were obtained at 40 time points per slice with an imaging time of 1 minute 21 seconds.

Image Processing and Analysis

Postprocessing of perfusion raw images was performed on a Unix workstation using customized software developed in IDL (Interactive Data Language; Research Systems Inc). Tissue and arterial contrast agent levels were determined with the assumption of a linear relationship between transverse relaxivity (J2R2*) and intravascular concentration of Gd-DTPA.15 Correction for motion artifact was performed if necessary using 3-dimensional realignment of the images at each time point on a slice-by-slice basis.23 To calculate rMTT, rCBV, and rCBF maps, we used the nonparametric singular-value decomposition method described by Ostergard et al.18,19 This method involves deconvolution of the tissue concentration-time curve on a pixel-by-pixel basis with an arterial input function. The shape of the arterial input function was determined from pixels located over the proximal middle cerebral artery of the unaffected hemisphere. Maps of rCBF and rCBV were determined from the peak height and the area under the deconvolved curve, respectively. Maps of rMTT were generated from the ratio of rCBV to rCBF. The overall generation of these maps took 5 minutes.

All gray scale perfusion maps were converted to a red/green/blue (RGB) rainbow color scale (Figure 1). On this scale, peak signal intensity was red (on the RGB scale: red 100%, green 0%, blue 0%) with equal graduations, corresponding to reducing signal intensity, down to blue (RGB scale: red 0%, green 30%, blue 100%). Purple (RGB scale: red 30%, green 0%, blue 100%), which is the next color below blue on the signal intensity scale, was “stretched” from signal intensity 30% to 0%. The IDL software has a sliding bar that can perform this manipulation of the color scale between 2 signal intensities. Thus, purple occupies 0% to 30% (the lowest 30% of signal intensities) on the signal intensity scale. This particular thresholded color scale was stored in the postprocessing software; hence, the same scale was automatically applied to each patient’s PWI maps.

As a result of the application of the thresholded color scale to rCBV and rCBF maps, normal cortical mixed gray/white matter and deep gray matter were red/yellow (>70% signal intensities), and normal deep white matter was green/blue (30% to 70% signal intensities). Pixels with a signal intensity below that of normal white matter, corresponding to the lowest 30% of signal intensities, were therefore purple. Only these “purple” pixels were measured within
the lesion volume. Thus, the goal of this method of rCBV and rCBF map color analysis was to improve the objectivity in delineation between normal white matter and adjacent hypoperfused tissue. Furthermore, this technique was designed to identify only critically hypoperfused tissue on rCBV and rCBF maps.

For rMTT maps, the same RGB color scale was applied, but in reverse. Pixels with a signal intensity of <30% (thresholded to purple) were defined as normal tissue, and pixels with a signal intensity of >30% (blue, green, yellow, or red) were defined as having a prolonged contrast bolus transit time. Volumes and MTT of the varying severities of contrast delay were then measured. Mild MTT delay was defined as signal intensity of 30% to 50% (blue), moderate MTT delay was defined as 50% to 70% (green), moderately severe MTT delay was defined as 70% to 90% (yellow), and severe MTT delay was defined as >90% (red). The MTT of each of these regions was compared with the MTT of the contralateral middle cerebral artery territory on a corresponding high ventricular slice for each patient. This enabled the generation of an average contrast bolus delay in seconds for the 4 different regions of MTT delay, facilitating comparison with previous studies (Table 1).17,24

Four MTT lesion volumes were then calculated by adding the volumes for the different thresholds of signal intensity: MTT signal intensity >30% (blue+green+yellow+red), MTT signal intensity >50% (green+yellow+red), MTT signal intensity >70% (yellow+red), and MTT signal intensity >90% (red).

Volumetric analyses of all color and gray scale perfusion maps were performed by 2 independent observers, with knowledge of the side of the lesion but blinded to the DWI and clinical results. Regions of hypoperfused tissue were outlined using a semiautomated pixel-wise method on each image slice, as previously described.23 Known anatomic markings such as ventricles and cortical sulci were taken into account. The area of the outlined region of interest was multiplied by the slice thickness plus the interslice gap and then summed to give the total lesion volume. The average of the lesion volumes determined by the 2 blinded observers was used for subsequent analysis.23

Volumetric analysis of the DWI and T2-weighted imaging (T2-WI) was performed using the same software by a third observer with knowledge of the side of the infarct but blinded to the clinical and PWI data. The isotropic trace of the diffusion tensor was used to assess acute lesion volume, and the b=0 s/mm2 reference image was used to determine outcome infarct volume.8 We previously demonstrated that the intraobserver and interobserver variabilities for the measurement of DWI and T2-WI lesion volumes with this technique were <5%.8

Because the goal of the present study was to analyze patients with PWI>DWI mismatch, we defined a meaningful mismatch as an acute rMTT lesion volume that was 15% greater than the acute DWI lesion volume.14 A difference of 15% was used to account for the effects of volume averaging, possible head position changes, and errors in lesion volume measurement.

Statistical Analysis
Demographic data are presented as mean±SD. Nonparametric tests were used for comparisons because the data were not normally distributed. The Spearman rank correlation coefficient was used to measure the strength of association among PWI, T2-WI outcome infarct size, and outcome NIHSS and early signs. The Wilcoxon signed rank test was used to compare differences among acute PWI lesion volumes, acute DWI lesion volume, and outcome infarct size. In addition, each acute PWI>DWI outcome mismatch volume was compared with the volume of infarct expansion from acute to outcome study. Analysis was performed using a statistical software package (STATA statistical software: release 6.0 level 1999; STATA Corporation). Results were considered significant at the 5% level.

Results
There were 30 patients who had serial PWI and DWI within 6 hours of stroke onset. Of these, 23 patients had PWI>DWI mismatch (13 men, 10 women; age 69.9±12.3 years; age range 45 to 85 years). The other 7 patients were excluded from the analysis because they had PWI<DWI patterns. All 23 patients had cerebral ischemia limited to the middle cerebral artery territory. A summary of demographic and imaging data is presented in Table 2. Mean time to acute MRI was 3.6±1.3 hours after stroke onset. Outcome T2-WI and clinical assessment were performed at 75.1±29.4 days. Patient 2 died before outcome assessments could be performed,
with DWI lesion volume and NIHSS at day 5 used for outcome measures.

For the color PWI maps, we found that interobserver variability was 9% for the measurement of regions with mild MTT delay (blue), 8% for regions with moderate MTT delay (green), 10% for regions with moderately severe MTT delay (yellow), and 8% for regions with severe MTT delay (red). Interobserver variability was 9% for both rCBF and rCBV lesions. These values are similar to previous studies that used only TTP or rMTT maps.6,17 For the gray scale maps, interobserver variability was 11% for rMTT, 19% for rCBF, and 17% for rCBV lesions. Thus, the use of a standardized color scale improved the assessment of relative signal intensity change on rCBV and rCBF maps compared with gray scale maps (Figure 1).

Lesion volumes on gray scale rCBV maps were slightly larger than those on the color rCBV maps (36.3±45.6 versus 28.0±40.3 cm³, P=0.01, Wilcoxon signed rank test). Gray-scale rCBF lesions were larger than color rCBF lesions (111.9±81.3 versus 82.7±71.3 cm³, P<0.001). Lesion volumes on gray scale rMTT maps were very similar to rMTT >30% signal intensity color maps (174.3±116.6 versus 176.3±117.8 cm³, P=0.95). Further comparisons of gray scale PWI lesions with outcome measures were not performed due to the poor interobserver reliability of the rCBV and rCBF maps.

Correlations were found between lesion volumes measured from all 3 color PWI maps and final infarct size (Table 2). Acute rCBF lesions had the strongest correlation with final infarct size (r=0.91, P<0.001). Acute rCBV lesion volume was significantly smaller (P<0.001, Wilcoxon signed rank test) than eventual infarct size. Acute volumes of rMTT signal intensity >30% and rMTT signal intensity >50% were larger than final infarct size (P<0.001). Strong correlations between final infarct size and the acute volumes of MTT signal intensity >70% and >90% were observed. However, both of these rMTT lesions were smaller than the final infarct size (P<0.001). Acute rCBF lesion volume most closely approximated final infarct size, although rCBF lesions tended to be larger (mean volume difference 19.7 cm³, 95% CI 9.3 and 76.8 cm³, P=0.07). Correlations were also found between each of the 3 acute PWI lesion volumes and clinical

### Table 2. Summary of Patient Data

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Mean 69.9 3.6 31.8 27.9 82.7 176.3 148.5 53.1 31.9 74.6 8.7 2.9

SD 12.3 1.3 42.1 40.3 71.3 117.8 114.5 43.6 35.6 61.4 6.3 1.5

RS indicates Modified Rankin Scale.
outcome (Table 2). The strongest correlation was seen between acute rCBF lesion volume and neurological outcome (NIHSS, $r=0.69$, $P<0.001$; early signs, $r=0.67$, $P<0.001$). Thus, acute rCBF lesions were the best predictors of both final infarct size and clinical outcome.

All patients had acute rMTT>DWI mismatch of $\geq 15\%$ as defined by the inclusion criteria. In all 23 patients, rCBF lesions were also $\geq 15\%$ larger than associated DWI lesions. Within rMTT>DWI mismatch regions, there were varying degrees of prolonged contrast transit. The rMTT $>30\%$ and $>50\%$ volumes of PWI/DWI mismatch were larger than the extent of rCBF>DWI mismatch in all patients. Fifteen patients had rMTT $>70\%$ lesions exceeding the acute DWI lesion, whereas 11 of these 15 had rMTT $>90\%$ lesions exceeding the acute DWI lesion volume. In addition, rMTT>DWI mismatch regions with more severely delayed contrast transit ($>70\%$ signal intensity) were smaller than the region of rCBF>DWI mismatch in all except 1 patient.

In comparison, only 8 of 23 patients had an acute rCBV lesion $\geq 15\%$ than the DWI lesion. Furthermore, the region of rCBF>DWI mismatch was smaller than the volume of rCBF>DWI mismatch in each of these 8 patients. In the remaining 15 patients, the region of reduced rCBV was similar to the acute DWI lesion. Thus, all 23 patients had normal or increased rCBV in regions of rCBF>DWI mismatch (Figure 2). In addition, 22 patients had regions of rCBF>DWI mismatch with normal or increased rCBV that progressed to infarction (mean volume 45.9±41.4 cm$^3$).

Mean infarct expansion between acute DWI and outcome T2-WI was 42.9±41.6 cm$^3$. Of particular interest, the extent of infarct expansion was similar to the volume of acute rCBF>DWI mismatch (51.7±49.7 cm$^3$), although there was a nonsignificant trend for the volume of rCBF>DWI mismatch to overestimate the degree of infarct expansion (Wilcoxon signed rank test, $P=0.06$). In comparison, the PWI/DWI mismatch volumes of rMTT $>30\%$ (145.3±104.2 cm$^3$) and rMTT $>50\%$ (116.8±101.9 cm$^3$) were much greater ($P<0.001$) than infarct expansion. PWI/DWI mismatch volumes of rMTT $>70\%$ (23.0±31.4 cm$^3$) and rMTT $>90\%$ (1.1±28.5 cm$^3$) and the volume of acute rCBV>DWI mismatch (3.7±15.9 cm$^3$) were less than infarct expansion ($P<0.001$). Thus, the volume of acute rCBF>DWI mismatch most accurately predicted the extent of eventually infarcted tissue.

**Discussion**

The principal finding of the present study was that rCBF lesion volumes more accurately predict final infarct size than rMTT or rCBV lesions in patients with PWI>DWI mismatch patterns at the hyperacute stage of stroke. The rCBF lesions had the strongest correlation with eventual infarct size, with no significant difference seen between these volumes. Furthermore, the volume of tissue with rCBF>DWI mismatch closely matched the volume of infarct expansion between acute and outcome studies. Acute rMTT mismatch tissue volumes either overestimated or underestimated infarct expansion, whereas rCBV mismatch volume underestimated the extent of infarct expansion. These findings indicate that acute color rCBF maps in ischemic stroke are accurate at identifying PWI>DWI mismatch tissue at risk of progression to infarction.

The use of acute rCBF maps to identify tissue likely to infarct is similar to that previously demonstrated. However, only 1 other study directly compared the different acute

**TABLE 3. Spearman Rank Correlations of Acute PWI Lesion Volumes With Final Infarct Size (T2-WI) and Outcome Clinical Scales**

<table>
<thead>
<tr>
<th></th>
<th>T2-WI</th>
<th>NIHSS</th>
<th>RS</th>
</tr>
</thead>
<tbody>
<tr>
<td>rCBV</td>
<td>0.70†</td>
<td>0.58†</td>
<td>0.39*</td>
</tr>
<tr>
<td>rCBF</td>
<td>0.91†</td>
<td>0.69†</td>
<td>0.67†</td>
</tr>
<tr>
<td>MTT $&gt;30%$</td>
<td>0.80†</td>
<td>0.58†</td>
<td>0.49*</td>
</tr>
<tr>
<td>MTT $&gt;50%$</td>
<td>0.77†</td>
<td>0.51*</td>
<td>0.45*</td>
</tr>
<tr>
<td>MTT $&gt;70%$</td>
<td>0.87†</td>
<td>0.59†</td>
<td>0.60†</td>
</tr>
<tr>
<td>MTT $&gt;90%$</td>
<td>0.83†</td>
<td>0.62†</td>
<td>0.57†</td>
</tr>
</tbody>
</table>

RS indicates Modified Rankin Scale.

*P<0.05, †P<0.001.
TABLE 4. Color PWI Maps in Patients With PWI>DWI Mismatch

<table>
<thead>
<tr>
<th>Map</th>
<th>Description</th>
<th>Use</th>
<th>Prediction of Tissue Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>rMTT</td>
<td>Time for bolus of contrast medium to travel through microvasculature; delayed contrast transit in hypoperfusion</td>
<td>Perfusion deficits easy to identify and delineate; varying degrees of prolonged contrast transit may be observed</td>
<td>Region of rMTT&gt;DWI mismatch overestimates the amount of tissue at risk of progressing to infarction by including regions of benign oligemia</td>
</tr>
<tr>
<td>rCBV</td>
<td>Volume of contrast medium in microvasculature during first pass of bolus</td>
<td>Regions of reduced and increased blood volume can be identified</td>
<td>Regions of reduced rCBV&gt;DWI mismatch underestimate at risk tissue; normal or increased rCBV surrounding the DWI lesion may indicate compensatory vasodilation but may not protect from progression to infarction</td>
</tr>
<tr>
<td>rCBF</td>
<td>Ratio of rCBV to rMTT (ie, volume of contrast medium in microvasculature per unit time); may be quantified in mL · 100 g⁻¹ · min⁻¹ · ml/100 g/min</td>
<td>Improved ability to define regions with reduced blood flow compared with gray-scale maps</td>
<td>Region of rCBF&gt;DWI mismatch most accurately identifies tissue at risk of progressing to infarction</td>
</tr>
</tbody>
</table>

PWI lesion volumes in stroke. In contrast to our findings, this earlier study found that neither rCBF nor rMTT lesions correlated as strongly with final infarct size as rCBV lesion volumes. Possible explanations for this discrepancy involve the use of gray scale PWI maps and the inclusion of patients presenting beyond 6 hours, as well as those without a PWI>DWI mismatch pattern. Such patients are probably less likely to optimally respond to thrombolytic therapy. In patients with mismatch patterns (PWI<DWI), the DWI lesion has already expanded into the full extent of the hypoperfused tissue, or reperfusion has occurred. In these patients, rCBF lesions are likely to significantly underestimate outcome infarct size.

The color rMTT maps identify gradations of delay in contrast bolus transit (Figure 2). A previous study found that regions of moderate to severely delayed tissue transit were better predictors of outcome infarct size. We also attempted to improve the accuracy of rMTT maps in identification of critically hypoperfused tissue by measuring different thresholds of rMTT using the changes in signal intensity seen on the color maps. Our thresholds were comparable to those of previous studies, as the increase in mean contrast delay between each signal intensity gradation was 2 to 2.5 seconds (Table 1).

Most of the rMTT>DWI mismatch tissue had moderately prolonged transit times (signal intensity values 50% to 70%, mean delay in contrast transit 4.3 seconds). Despite a narrow range of contrast delay (2.02 seconds), these regions were equally likely to progress to infarction or to be salvaged. As found in a previous study, areas of more severely prolonged rMTT (signal intensity >70%, mean contrast delay 6.1 seconds) nearly always progressed to infarction. However, the regions of more severely delayed rMTT were smaller than rCBF lesion volumes and significantly underestimated final infarct size. This finding suggests that measures of contrast transit time may be less specific than measures of CBF at identifying the actual amount of tissue at risk of infarction. However, a limitation of the color rMTT maps we used is the inability to further discriminate between tissue in the signal intensity range of 50% to 70%, which may have more accurately defined tissue likely to progress to infarction.

Although rCBV lesions had moderately strong correlations with outcome infarct size, we found that the extent of reduced rCBV on these maps underestimated the extent of ischemic tissue. In most patients, volumes of reduced rCBV closely paralleled acute DWI lesion size (Figure 2). Thus, most of the rMTT and rCBF>DWI mismatch regions had relatively normal and, in some cases, increased rCBV (Figure 2). The finding of elevated CBV within hypoperfused but still viable regions suggests compensatory vasodilation in response to reduced cerebral perfusion pressure. It has been suggested that normal or increased CBV indicates tissue unlikely to infarct. However, in the present study, we found that normal or increased rCBV within rCBF and rMTT>DWI mismatch regions may progress to infarction.

The PWI maps were generated using a thresholded color scale to semiquantitatively assess relative perfusion abnormalities. The aims of this technique were to improve the usefulness of the maps for prediction of tissue at risk of progression to infarction and to more objectively define hypoperfused regions, particularly on rCBV and rCBF maps. For these reasons, we used a predefined relative rCBF and rCBV threshold (30% of signal intensity). The rCBF threshold was quite accurate in predicting conversion to infarction, which is consistent with another study that determined a relative CBF infarction threshold with the use of different methodology. Absolute quantification was not performed, because there are a number of issues to be resolved before truly quantitative PWI can be applied in a clinical setting in cerebrovascular disease. These issues include the optimal location for determining the arterial input function and the need for improved segmentation methods to distinguish between normal and hypoperfused gray and white matter on rCBV and rCBF maps. Thus, a disadvantage of our method is the inability to provide absolute CBF or CBV thresholds for conversion to infarction.

It is important to emphasize the hazards of relying on a single PWI parameter map, because the different PWI maps provide complementary physiological information about ischemic tissue (Table 4). Our technique allows the simultaneous comparison of regions of varying contrast delay on a single color rMTT map with easily visible, thresholded lesions on rCBF and rCBV maps. The use of these PWI maps to identify tissue at risk, combined with short postprocessing time and good interobserver agreement, suggests that this method could be used prospectively in an acute clinical setting to predict tissue outcome.
Acknowledgments

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References


Perfusion Magnetic Resonance Imaging Maps in Hyperacute Stroke: Relative Cerebral Blood Flow Most Accurately Identifies Tissue Destined to Infarct
Mark W. Parsons, Qing Yang, P. Alan Barber, David G. Darby, Patricia M. Desmond, Richard P. Gerraty, Brian M. Tress and Stephen M. Davis

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