Viability Thresholds of Ischemic Penumbra of Hyperacute Stroke Defined by Perfusion-Weighted MRI and Apparent Diffusion Coefficient

L. Røhl, MD; L. Østergaard, MD, MSc, PhD; C.Z. Simonsen, MD; P. Vestergaard-Poulsen, PhD; G. Andersen, MD, PhD; M. Sakoh, MD, PhD; D. Le Bihan, MD, PhD; C. Gyldensted, MD, PhD

Background and Purpose—The penumbra of ischemic stroke consists of hypoperfused, but not irreversibly damaged, tissue surrounding the ischemic core. The purpose of this study was to determine viability thresholds in the ischemic penumbra, defined as the perfusion/diffusion mismatch in hyperacute stroke, by the use of diffusion- and perfusion-weighted MRI (DWI and PWI, respectively).

Methods—DWI and PWI were performed in 11 patients ≤6 hours after the onset of symptoms of acute ischemic stroke. Regions of interest (ROIs) were placed covering the ischemic core (ROI 1), the penumbra that progressed to infarction on the basis of follow-up scans (ROI 2), and the penumbra that recovered (ROI 3). The ratios of relative cerebral blood flow (rCBF), relative cerebral blood volume (rCBV), mean transit time (MTT), and apparent diffusion coefficient were calculated as lesion ROIs relative to the contralateral mirror ROIs.

Results—The post hoc analysis showed that the penumbra progressed to infarction at the following cutoff values: rCBF <0.59 and MTT >1.63. Higher sensitivity and accuracy in predicting outcome of the penumbra were obtained from the rCBF maps compared with the rCBV and MTT maps. The initial rCBV and apparent diffusion coefficient ratios did not differentiate between the part of the penumbra that recovered and the part that progressed to infarction. The mean rCBF ratio was optimal in distinguishing the parts of the penumbra recovering or progressing to infarction.

Conclusions—The thresholds found in this study by combined DWI/PWI might aid in the selection of patients suitable for therapeutic intervention within 6 hours. However, these hypothesized thresholds need to be prospectively tested at the voxel level on a larger patient sample before they can be applied clinically. (Stroke. 2001;32:1140-1146.)

Key Words: MRI, diffusion-weighted ■ MRI, perfusion-weighted ■ penumbra ■ stroke, acute

Diffusion-weighted MRI (DWI) and perfusion-weighted MRI (PWI) have recently become strong diagnostic tools for the assessment of acute stroke in humans. The ischemic penumbra is functionally impaired yet still viable tissue surrounding the ischemic core. Originally, the penumbra was defined as the condition of the ischemic brain in which flow lay between an upper threshold of electrical failure and a lower threshold of energy and ion pump failure. Alternatively, the penumbra has been defined simply as a region of limited blood supply in which metabolism is preserved. The time period during which the penumbra remains viable is debated. Today, recombinant tissue plasminogen activator is approved in the United States for thrombolytic therapy within 3 hours of ischemic stroke onset. Studies using positron emission tomography (PET) and MRI indicate that depending on the extent of energy depletion, the therapeutic window might be much longer, up to 48 hours in some cases. The definition of the penumbra is important in selecting patients suitable for therapeutic intervention. Several studies have indicated that for the purpose of defining the tissue at risk of infarction, the penumbra can be operationally defined as the mismatch between the lesion volume detected by PWI and DWI. Preliminary studies have already used this mismatch as a guideline for therapeutic intervention in ischemic stroke within 6 hours, with promising results. However, studies investigating the discrimination between potentially salvageable tissue from tissue that would recover spontaneously within the perfusion/diffusion mismatch are scarce. Most studies have determined thresholds between all ischemic tissue progressing to infarct (including the ischemic core) from tissue recovering spontaneously on the basis of cerebral blood flow (CBF) and cerebral blood volume (CBV) or the decrease in apparent diffusion coefficient (ADC), which reflects early cytotoxic edema.
The purpose of the present study was to define viability thresholds in the ischemic penumbra, operationally defined as the perfusion/diffusion mismatch, in hyperacute stroke patients (≤6 hours of symptom onset) by the use of combined DWI and PWI.

Subjects and Methods
Twenty-six patients (16 women and 10 men, mean age 64 ±14, range 30 to 89 years) presenting at our institution with symptoms of acute stroke within 6 hours of symptom onset underwent an acute CT scan to exclude intracranial or subarachnoidal hemorrhage. Then MRI, including DWI and PWI, was performed. Patients were excluded if the exact time of occurrence of the ischemic event could not be established. Three patients with transient ischemic attacks and 1 patient in whom PWI was impossible because of movement artifacts were excluded. Eleven of these 24 patients were characterized by a diffusion lesion volume >1.0 mL as well as a large (>15 mL) perfusion/diffusion mismatch, as defined from the maps of MTT. These patients were included in the following analysis of viability thresholds of relative CBF (rCBF), relative CBV (rCBV), mean transit time (MTT), and ADC. Final infarction size was measured by T2-weighted imaging after 1 month. None of these patients received thrombolytic or neuroprotective therapy. The project was approved by the Regional Danish Committee for Ethics in Medical Research and was performed with informed, written, prior consent from each patient or a close relative.

MRI Protocol
MRI was performed by use of a GE Sigma 1.0-T Imager (GE Medical Systems) retrofitted with a 1-MHz receiver. The entire protocol consisted of a sagittal scout, an axial DWI, an axial T1-weighted 3D scan, an axial T2-weighted scan, and an axial PWI. Total examination time was 30 minutes, which included preparation of the patient with the insertion of a venous catheter in a cubital vein.

Diffusion-Weighted MRI
Multislice DWI using spin-echo, single-shot, echo-planar imaging was performed by acquiring an unweighted image (S₀, b factor 0 s/mm², neglecting the contribution of the imaging gradients to the diffusion weighting), as well as 3 diffusion-weighted images with diffusion gradients in orthogonal directions: Sₓ, Sᵧ, and S𝑧 (b factor 1000 s/mm²). Fourteen to 16 axial slices were acquired, covering the entire brain. The acquisition parameters used for DWI were as follows: repetition time/echo time (TR/TE) 3000/109 ms, 96×96 matrix, 22×16.5-cm field of view (FOV), 5-mm slice thickness, and 2-mm slice gap. The acquisition time was 20 seconds. An average diffusion-weighted image was calculated from the diffusion-weighted images as the mean intensity of the 3 images. ADC was estimated as the mean diffusivity in the 3 orthogonal directions (from Le Bihan et al20): ADC = [ln(Sₓ/S₀) + ln(Sᵧ/S₀) + ln(S𝑧/S₀)]/3b, where S (i=x, y, z, 0) denotes DWI signal intensities for the 3 orthogonal directions and the unweighted image, respectively.

Perfusion-Weighted MRI
PWI was performed by dynamic gradient-echo echo-planar imaging, tracking a bolus of 0.1 mmol/kg gadodiamide (Omniscan, Nycomed Imaging), injected at a rate of 5 mL/s, by use of a magnetic resonance–compatible power injector (Medrad). This bolus was immediately followed by injection of an equal volume of physiological saline, also at a rate of 5 mL/s. Five slices (5 patients) or 10 slices (6 patients) covering the lesion on the diffusion-weighted images (pulsed sequences were optimized after the first 5 patients, allowing acquisition of 10 slices) were obtained. Fifty single-shot, gradient-echo, echo-planar images were obtained in each of the slices during the bolus passage, and accordingly, 250 or 500 images were obtained during the 1.16-minute acquisition time. The acquisition parameters were as follows: TR/TE 1500/45 ms, flip angle 60°, 96×96 matrix, 22×16.5-cm FOV, 5-mm slice thickness, and 2-mm slice gap. Maps of rCBV were calculated by integrating the first-pass concentration time curve.21,22 The rCBF and MTT maps were calculated by using a noninvasively determined arterial input function and singular value decomposition deconvolution, as described previously.23,24 Postprocessing was performed on a SUN SPARC 60 workstation.

T2-Weighted MRI
Approximately 30 days after acute stroke, a T2-weighted MRI scan was performed with the following acquisition parameters: TR/TE 4000/102 ms, 256×256 matrix, 22×22-cm FOV, 5-mm slice thickness, 2-mm slice gap, and 2.08-minute acquisition time.

Data Analysis
The DWI and ADC images, the maps of rCBF, rCBV, and MTT, and the final T2-weighted images were all transferred to a personal computer. Measurements of all the lesion volumes were performed by a planimetric technique using a commercially available software package (ALICE, Hayden Image Processing Solutions). This program has an autothreshold function, which we used to determine the borders of the ischemic core (on DWI) and final infarction (on chronic T2-weighted imaging), as described previously by Sorensen et al.25 We defined the penumbra as the difference between the volume with reduced blood flow, as shown at the maps of rCBF, and the ischemic lesion volume at the initial DWI image (ie, the perfusion/diffusion mismatch). Then, 3 regions of interest (ROIs) were placed manually on the rCBF maps as shown in Figure 1. ROI 1 covered the ischemic core, as detected from the diffusion-weighted images. ROI 2 covered the diffusion/perfusion mismatch volume that (by visual inspection) progressed to infarction, as defined by the final unaligned T2-weighted image. ROI 3 covered the mismatch volume that appeared normal on follow-up images. The ROIs were applied at all the affected rCBF slices, with a maximum number of 5 slices (5 patients) or 10 slices (6 patients). All 3 ROIs were mirrored to the contralateral unaffected hemisphere. Finally, all ROIs were copied to rCBV, MTT, and ADC maps. The ratios between physiological estimates (rCBF, rCBV, MTT, and ADC) of the lesion and of the contralateral mirror ROI were then determined. In 1 patient, the calculation of an ADC image failed, because DWI in only 1 direction was obtained, and accordingly, there were only 10 patients in the analysis of ADC.
### Results

The patient sample included in the analysis consisted of 11 patients (5 women and 6 men, mean age 67 years). Mean CT scan time was 4.2 hours after symptom onset, and mean magnetic resonance scan time was 4.9 hours after symptom onset. The patient data are summarized in Table 1.

Mean ratios for the 3 ROIs determined from the different perfusion and ADC maps are shown in Table 2. All lesion/contralateral ratios of the ROIs for the rCBF, rCBV, MTT, and ADC maps are shown in Figure 2. A low mean rCBF ratio of 0.26 was found in the ischemic core; a ratio of 0.42, in the penumbra progressing to infarction; and a ratio of 0.62, in the penumbra that recovered (Figure 2A). The 2-way ANOVA showed a highly significant difference between these 3 ratios (F = 60.83, \(P < 0.001\)), and the following t test also demonstrated a significant difference between all 3 ROIs (ie, the core, the penumbra that recovered, and the penumbra that progressed to infarction). From the ROC curve, we found the optimal cutoff value between the 2 parts of the penumbra to an rCBF ratio of 0.59 (Table 3), and with this ratio, the sensitivity was 0.91, the specificity was 0.73, and the accuracy was 0.82 (calculated as 0.5 \cdot \text{sensitivity} + 0.5 \cdot \text{specificity}).

The mean ratio of rCBV in the 3 ROIs showed markedly less reduction but followed the same pattern as rCBF (Figure 2B), and the difference was also highly significant (2-way ANOVA: \(F = 20.77, P < 0.001\)). The mean rCBF ratio was 0.55 in the core, 0.84 in the penumbra progressing to infarction, and 0.94 in the penumbra that recovered. However, there was no statistical difference between the part of the penumbra that recovered and the part that went on to infarction, by the use of the paired t test (\(P = 0.023\); the level of significance with Bonferroni correction is \(P = 0.05/12 = 0.004\)). From the ROC curves, the optimal cutoff value between the 2 parts of the penumbra was found to be an rCBF ratio of 0.85 (Table 3), with an accuracy of 0.68. Finally, there was a longer MTT ratio for the more severe ischemia (Figure 2C). The mean ratios of the 3 ROIs on the maps of MTT differed significantly (2-way ANOVA: \(F = 14.67, P < 0.001\)); however, there was no statistical difference between the core and the penumbra that progressed to infarction (\(P = 0.054\)). The cutoff value between the 2 parts of the penumbra was an MTT ratio of 1.63 (Table 3), with an accuracy of 0.68.

The comparison of the areas of the ROC curves of each of the 3 parameters showed that only the difference in rCBF was significant.
between the rCBF area (mean±SE 0.85±0.08) and the rCBV area (mean±SE 0.67±0.12) reached a statistically significant level (z=2.19, P=0.028). This suggests that rCBF is a better separator of viable and nonviable tissue than is rCBV. Furthermore, higher sensitivity and accuracy were obtained from the rCBF maps than from the rCBV and MTT maps (Table 3).

Including all hemodynamic parameters (rCBF ratio, rCBV ratio, and MTT ratio) in a multivariate discriminant function did not improve the sensitivity, specificity, or accuracy (Table 3).

The ratios of the ADC maps are shown in Figure 2D. The mean ADC ratio of the core was 0.62, and the mean ADC ratios of the parts of the penumbra that recovered or progressed to infarction were 0.89 and 0.93, respectively. There was a statistically significant difference between the mean ratios of the 3 ROIs according to the 2-way ANOVA (F=27.87, P<0.001), but no significant difference was found between the part of the penumbra that recovered and the part that progressed to infarction (P=0.47). From Figure 2, it appears that ADC ratios less than ~0.75 predict irreversible damage (ie, the core), because only 1 value below this range was seen in the penumbra.

In Figure 2A through 2D, there was a large overlap between individual values of ROI 1, ROI 2, and ROI 3.

Figure 3 illustrates the relationship between rCBF and MTT for the part of the penumbra that progressed to infarction (filled circles) and the part that recovered (open circles). The cutoff ratios for the rCBF and the MTT ratios are shown.

### Discussion

We found that the penumbra progressed to infarction when the mean rCBF ratio (lesion/contralateral side) was <0.59 and the mean MTT ratio was >1.63. The rCBV or ADC did not discriminate significantly between the 2 parts of the operationally defined penumbra. Furthermore, the critical ratio of rCBF was more sensitive in discriminating between

### Table 3. Cutoff Values of rCBF, rCBV, and MTT Ratios

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Cutoff Value</th>
<th>Penumbra→Infarct (Sensitivity)</th>
<th>Penumbra→Recovery (Specificity)</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>rCBF ratio</td>
<td>0.59</td>
<td>0.91</td>
<td>0.73</td>
<td>0.82</td>
</tr>
<tr>
<td>rCBV ratio</td>
<td>0.85</td>
<td>0.64</td>
<td>0.73</td>
<td>0.68</td>
</tr>
<tr>
<td>MTT ratio</td>
<td>1.63</td>
<td>0.73</td>
<td>0.64</td>
<td>0.68</td>
</tr>
</tbody>
</table>

Sensitivity, specificity, and accuracy of rCBF ratio, rCBV ratio, and MTT ratio in prediction of outcome of the penumbra are shown. Results of the multivariate discriminant analysis, including all hemodynamic parameters (rCBF ratio, rCBV ratio, and MTT ratio), are shown in the last row.
Using PWI and DWI, Schlaug et al. found the mean rCBF, and consequently, their mean ratios are somewhat higher. Thus, the infarct region was a phenomenon due to CBF increase in nonischemic tissue that later went on to infarction. With the use of different investigatory methods (PET, SPECT, and PWI), increased CBV in ischemic tissue has been demonstrated in experimental studies as well as in humans. In the present study, the mean rCBV value of the penumbra that recovered was 0.94, and accordingly, we found that an unaffected CBV in the penumbra to be a good prognostic sign, in accordance to previous findings. In the literature, the prognostic importance of a high CBV is uncertain. In a combined PWI/SPECT study of Hatazawa et al., increased rCBV had a protective effect on the evolving infarction, but rCBV reduction <0.70 predicted irreversible damage, as in our findings. This is in conflict with the studies of others, who found an increased rCBV ratio (calculated as the integral under the total tissue concentration-time curve) in the penumbra, which they defined as the hypoperfused tissue that later progressed to infarction. Accordingly, they concluded that increased rCBV is a predictor of stroke evolution. Finally, Liu et al., who used a design similar to ours, found mean rCBV ratios of the core, the area of infarct growth, and the eventually viable tissue of 0.25, 0.69, and 1.13, respectively, which are in good agreement with the present study. In summary, it remains uncertain whether increased CBV has a protective or destructive effect on the penumbra, whereas reduced CBV <0.70 indicates irreversible damage, according to the present study (Figure 2B) and others.

We found a longer MTT with more severe ischemia, in accordance with MTT being inversely related to the perfusion pressure. This may be because MTT increases monotonically with perfusion pressure even though the CBV changes are bimodal with a decrease in perfusion pressure. MTT is regarded an excellent measure of perfusion pressure and has potential as the parameter from which patients are selected for treatment. This has recently been demonstrated by Sunshine et al., who used combined DWI and maps of time to peak (which has a very similar appearance to maps of “true” MTT) to select patients for intravenous or intra-arterial thrombolytic therapy. We predict that patients...
potentially benefiting from treatment are those in whom the MTT ratio exceeds roughly 1.63.

We found a very low mean ADC ratio in the ischemic core (0.62). In the penumbra that recovered or progressed to infarction, the mean ADC ratios were almost identical (0.89 and 0.93, respectively). However, there was a remarkable resemblance between the thresholds found in animal studies and our thresholds. In an experimental rat study of middle cerebral arterial occlusion, an ADC reduction to 77% was found in the core (defined as tissue ATP depletion), and a reduction to 90% was found in the penumbra (defined as tissue acidosis). In other experimental studies, the ADC of the core was reduced to 0.60.43 In humans, ADC in ischemic tissue has been shown to decrease to minimum values of ∼50% to 60% of the contralateral side within the first 96 hours.2,44 Schlaug et al12 found that ADC was reduced in the ischemic core and in the penumbra (that latter went on to infarction) to 0.56 and 0.91, respectively. Liu et al45 found ADC reductions in the core, in the irreversibly damaged penumbra, and in the reversibly damaged penumbra of 0.53, 0.98, and 1.00, respectively. We conclude that it may not be possible to discriminate reversible and irreversible parts of the penumbra by the use of ADC.

There are some drawbacks of the present study. The most serious is that we used large ROIs instead of a voxel-based image analysis to determine the thresholds in the study. This is unfortunate, because therapeutic decisions would be based on voxel values, not on large ROIs as applied in the present study. Voxel-based analysis requires coregistration, possibly obscuring possible thresholds because of alignment inaccuracies and tissue shrinkage. Although promising progress has been made in this respect,29 in the present study, we chose a global ROI approach to establish the existence of perfusion thresholds. However, in future studies, the hypothesized thresholds found in the present study need to be prospectively tested at voxel level on a larger patient sample before they can be applied clinically.

The fact that we used DWI abnormality to determine the ischemic core might not be correct. However, although reversal of diffusion changes has been demonstrated in animals,43,46 this has not yet been proven in humans.

Finally, recent studies on the prediction of stroke outcome have used statistical models combining SPECT and PWI15 or all PWI, DWI, and structural images.47 This approach may prove to be necessary to predict the outcome after ischemic stroke in single patients.

In conclusion, the thresholds for rCBF (<0.59) and MTT (>1.63) found in the present study might guide the selection of patients suitable for therapeutic intervention within 6 hours, such as thrombolytic therapy. These are patients in whom considerable parts of the penumbra around the ischemic core (detected on DWI) will deteriorate spontaneously without treatment. Because these thresholds are hypothesized thresholds on a limited patient sample, they need to be prospectively tested at voxel level on a larger patient sample before they can be applied clinically.

Acknowledgments
This study was supported by the Danish Medical Research Council (L.O.). We thank Nycomed Imaging AS, Oslo, Norway, for providing the contrast agent used in this study.

References


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*Stroke.* 2001;32:1140-1146
doi: 10.1161/01.STR.32.5.1140

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/32/5/1140

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